LABORATORY MARKERS IN PERSONALIZED DRUG THERAPY

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Laboratory markers in personalized drug therapy

Laboratoriumwaarden bij het individualiseren van de farmacotherapie

(met een samenvatting in het Nederlands)

PROEFSCHRIFT

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door

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Tempus Praeteritum Nihil,
Futurum Incertum,
Preasens Instabile.
Cave Ne Perdas Hoc Tuum.

(The past is nothing, the future uncertain, the present unstable.
Ensure that you do not lose this time, which is yours alone)

Zonnewijzer van mijn ouders
(origineel zonnewijzer, Prinsenhof, Groningen)

Voor
Ingrid
Feike
Wietse
Jouke

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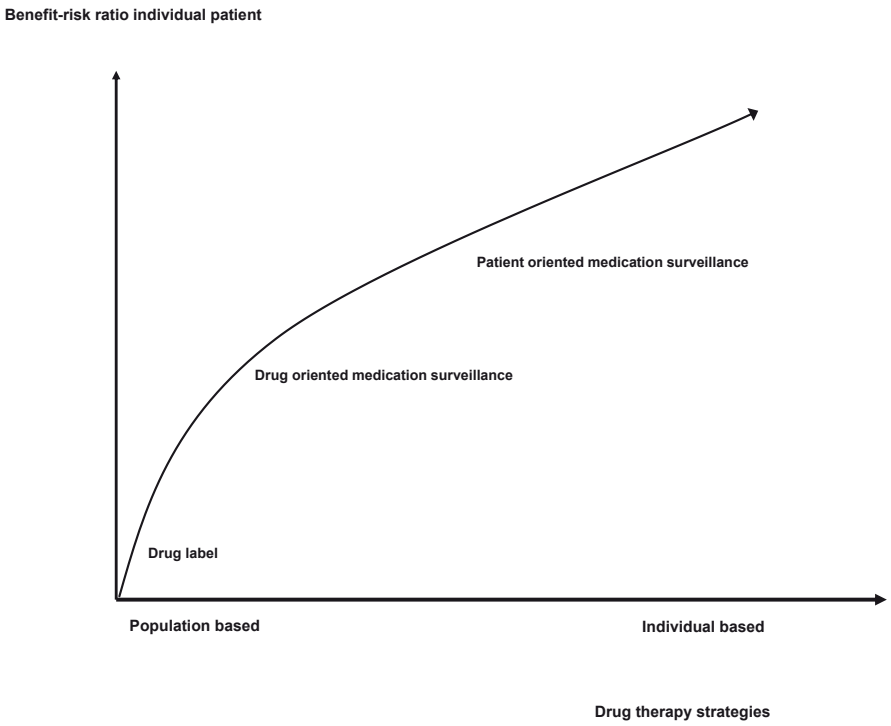
INTRODUCTION

Drug therapy is intended to cure, alleviate, prevent or diagnose a patient's disease, signs and symptoms. The downside of drug therapy is the risk of drug related problems such as adverse drug reactions. Drug regulatory authorities weigh on a population level the likelihood of benefit and harm of the product during its life cycle and these decisions regulate the access of prescribers and patients to medicines and the conditions thereof. During the last decade two major trends have influenced the thinking about the benefit-risk balance in drug therapy. Firstly, the landmark report "To err is human" of the Institute of Medicine,[1,2] showed that this balance is not only determined by the interaction of the pharmacological properties of the formulated molecule with the patient's (patho)physiological profile, but is also to a large extent modulated by the way the drug is handled by healthcare providers and by the patient. Medication errors have shown to be a major factor in drug induced harm and system flaws particularly contribute to these.[3-5] This awareness has triggered the development of mandatory risk evaluation and mitigation strategies on national and international levels to ensure that the benefits of a drug continue to outweigh certain risks in the general population.[6] The second trend regards the paradigm shift from a drug oriented approach towards a patient oriented approach. In pharmacy personalized drug therapy management induces major changes in the pharmaceutical care process (Figure 1). At the moment a drug is introduced at the market, drug regulatory authorities had approved the benefit-risk ratio of the drug by using information from pre-approval exposure experience (including clinical trials) in small homogeneous populations and information based on theoretical concerns. The actual drug label contains the information of evidence for harm. In the next step, this population based knowledge is incorporated into medication surveillance systems, which help the professional to manage and assess the benefit-risk ratio at a patient level. Traditionally, in this kind of medication surveillance systems a few common patient factors (age, gender) are recorded and the potential harm of the prescribed drug(s) is assessed one by one: single risk assessment.

Prescribing the drug in larger heterogeneous populations in the post-marketing surveillance phase generates more evidence for harm and therefore the individual potential risks for a patient becomes clearer. This new evidence for harm is translated into therapeutic recommendations in new versions of drug labels and medication surveillance systems which take into account the presence or absence of other patients' susceptibility factors like severity of disease, genetic variability, and attitudes and beliefs to drug therapy.[7,8] Personalized drug therapy will become achievable if these systems incorporate algorithms for multiple risk assessment of patient susceptibility factors and drug use. Recent studies underline the need for personalized drug therapy in different patients, but also recognize the complexity of obtaining evidence, replication of evidence and translating evidence into clinical practice.[9-13] In pharmacy, patient oriented medica-

Figure 1 Personalized drug therapy management



tion surveillance requires knowledge of patient susceptibility factors. This will help to manage and optimise the benefit-risk ratio for the individual patient by multifactorial risk assessment of patients' susceptibility factors. Clinical risk management provides a systematic framework to manage the multifactorial risks in clinical practice. It weighs the advantages and disadvantages of drug use for the individual patient and stratifies the potential benefit and harm in terms of evidence, probability and significance.[14,15] Clinical risk management consists of three steps that require monitoring, management and reassessment over time: the identification and assessment of risk, the development and execution of risk management strategies, and the evaluation of these risk management strategies.[16] In this thesis the term clinical risk management is narrowed to the more specific term Drug Therapy Management (DTM).

Biomarkers are considered important patient characteristics for the assessment of the individual risk factors in drug therapy. A biomarker has been defined as a characteristic which can be objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to therapeutic intervention.[17]

Table 1 provides examples of laboratory markers relevant in drug therapy.[18] For healthcare providers laboratory markers are considered especially important for taking evidence based decisions on drug effectiveness, risk of adverse events, medication adherence or medical necessity of a drug. More specifically they can play a role in appropriate drug selection and drug dosing and in the monitoring of drug-drug interactions, drug-disease interactions, and drug-laboratory interactions.[19,20] For example, in patients with impaired renal function starting with an angiotensin-converting-enzyme (ACE) inhibitor the potential drug-disease interaction is managed by starting with a low dose of the ACE-inhibitor and by monitoring levels of creatinine and potassium before the start of the ACE-inhibitor and within three weeks after the start.[21] A second example concerns a drug-drug (DDI) interaction in a patient using a potassium sparing diuretic in combination with an ACE-inhibitor. The potential risk of hyperkalaemia of this DDI-interaction is managed by close monitoring of potassium levels even at the discontinuation of the drug.[22] Finally, to avoid misinterpretation of laboratory test results, it is necessary that the laboratory has knowledge on what drugs the patient is using (drug-laboratory interactions). In 2009 an alert

Table 1 Biomarkers of drug effect or response[a]

Type of biomarker	Class	Category	Biomarker example
Laboratory markers	1. Biochemical	Electrolytes	Sodium, potassium
		Organs: • Liver	ALT, AST, Child-Pugh-score
		• Kidney	Creatinine
		• Thyroid	T4, TSH, T3
		Enzymes	Creatine Phosphokinase
		Lipids	HDL, LDL, triglycerides, cholesterol
		Glucose	Glucose
	2. Haematological	Blood Cell Count	Total blood count, leucocytes, thrombocytes, erythrocytes
		Coagulation	INR, PT
	3. Pharmacological		
	3a. endogenous	Pharmacogenetics	HLA-B*5701
	3b. exogenous	Drug monitoring	Digoxin, lithium, phenytoin
Physical markers	1. Clinical		Eye lid drooping
	2. Radiographic	Scans	MRI
Other markers	1. Histological	Biopsy	Jejunal biopsy
	2. Immunological	Antibodies	Anti-intrinsic factor
	3. Microbiological	Sensitivity tests	Pseudomonas aeruginosa
	4. Physiological		Blood pressure, body mass index

a: Adapted from Aronson[18] by permission of John Wiley and Sons.

from the Food and Drug Administration showed that 13 deaths were associated with the risk of falsely elevated blood glucose levels in patients using products containing non-glucose sugars influencing glucose levels.[23] So, laboratory markers may be helpful in the management of risks of drug therapy in the individual patient.

THESIS OBJECTIVES

There are three main objectives. The first one is to assess the evidence for the application of laboratory markers in DTM and to stratify the potential for harm in terms of evidence, probability and significance. The second objective is to investigate the development and execution of risk management strategies in patients with impaired renal function. The third objective is to examine the effects of drugs on laboratory test results.

THESIS OUTLINE

The specific objectives can be divided into the following categories:

Chapter 2: Laboratory monitoring in drug therapy management
In this part studies are presented about the necessity and clinical usefulness of laboratory markers in drug-drug interactions guidelines and in drug labels. Drug labels frequently provide instructions on laboratory monitoring but no review has collected all recommended laboratory markers and their applicability in clinical practice. Therefore, the clinical applicability of instructions on laboratory monitoring in 200 drug labels was reviewed (Chapter 2.1). To get insight into the nature, prevalence and clinical relevance of laboratory markers in the clinical risk management of potential drug-drug interactions a cross-sectional study was performed using drug-dispensing data (Chapter 2.2).

Chapter 3: Risk management strategies for patients with impaired renal function in community pharmacy
In this part the risk management strategies for the adjustment of drug therapy to impaired renal function of the individual patient are studied in clinical practice.
Chapter 3.1 describes an observational study in which the therapeutic advice formulated by pharmacists is based on the renal function of patients of 70 years or older with diabetes or cardiovascular disease and supported by a pharmacy medication alert system (PMAS).
Linking laboratory data to pharmaceutical data in primary care is still problematic and adherence to monitoring recommendations in clinical guidelines for patients at risk is also not optimal. Pharmacists need the information of laboratory test results for

optimal drug therapy management. To reduce current shortcomings the feasibility of point-of-care creatinine testing in ambulatory elderly was evaluated in a pilot study in three community pharmacies (chapter 3.2). In chapter 3.3 the effectiveness and safety of nitrofurantoin in patients with renal impairment in primary care was evaluated, to analyse the quality of the recommendations of the Dutch guidelines for drug dosing in renal impairment guideline recommendations.

Chapter 4: Effects of drugs on laboratory tests

A significant amount of evidence has been described in the literature about in vivo and in vitro effects of drugs on laboratory tests. To date pharmacists are not familiar with these effects and clinical guidelines have not yet incorporated this information. Information about the effects of a drug on laboratory test results in drug labels was compared with information in the international reference book on effects of drugs on clinical laboratory tests to describe the nature, frequency and quality of the information (Chapter 4.1).[24] Finally, a study in a database linking laboratory and pharmacy data of hospitalized patients was conducted as a proof of concept for detecting in vivo effects of drugs with the well-known effect of trimethoprim on creatinine test results as a proxy.

Chapter 5: General discussion

In Chapter 5 the results of the different studies are summarized and put into a broader perspective. In addition, challenges for the future are described.

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2

LABORATORY MONITORING IN DRUG THERAPY MANAGEMENT

2.1

INSTRUCTIONS ON LABORATORY MONITORING IN 200 DRUG LABELS

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ABSTRACT

Background

Monitoring drug treatment is important to assess the therapeutic effects and to prevent adverse drug reactions. Unfortunately, the clinical evidence for monitoring is often missing. To attain evidence-based laboratory monitoring and to improve patient safety it is mandatory for the clinical chemist to develop effective and rational methods for monitoring. The legal source for this evidence-based information is the drug label. We analysed frequency, nature, and applicability of instructions on laboratory monitoring described in 200 drug labels.

Methods

The applicability of instructions was assessed with an adapted Systematic Information for Monitoring score. Seven items of information were evaluated: why to monitor, what to monitor (essential), when to start or stop monitoring, how frequently to monitor, critical value (essential) and how to respond (essential). Each item scored one point when information was described specifically, otherwise the score was zero. Instructions were applicable if all three essential items scored.

Results

In 131 drug labels, 566 instructions on laboratory monitoring were identified, an average of 2.8 per drug label. Kidney, liver, electrolyte, and drug monitoring were important biomarker categories (71%). The median applicability score was 2.1 (0-6) and 95 (17%) instructions were applicable. Six determinants were associated with applicable instructions: kidney (OR 7.0; 95% CI 4.4-11.3), creatine phosphokinase (4.5; 1.5-13.6), drug selection (6.8; 4.0-11.7), dose adjustments (2.4; 1.5-3.7), year on the market 2000-2007 (2.6; 1.1-6.1) and statins (4.8; 2.5-9.0).

Conclusions

Drug labels frequently describe instructions on laboratory monitoring, but these are ambiguous and incomplete and clinical applicability for the professional is limited.

INTRODUCTION

The role of the clinical chemist in an integrated healthcare system becomes increasingly important and is transforming from the core business of diagnostic services to additional knowledge services provided to other healthcare professionals.[1,2] Preventing laboratory errors in the preanalytical, analytical and postanalytical phase is a part of evidence-based laboratory medicine, which will help to achieve high quality services, such as clinical guidelines, clinical decision support systems, and education and training of healthcare professionals with the ultimate goal to improve patient safety.[3-6]

One of the most critical issues of patient safety in laboratory medicine is the effect of drugs in the preanalytical phase. Monitoring drug treatment is important to assess the therapeutic effects and to prevent adverse drug reactions and subsequent hospital admission.[7,8] An important biomarker for the prevention of medication-related hospital admission is kidney function.[9] Close collaboration of the clinical chemists with other healthcare professionals is mandatory to develop effective and rational monitoring and to prevent laboratory errors. In many guidelines laboratory monitoring is recommended, although there is little clinical evidence.[10,11] This view is supported in a study on monitoring of renal function before and after initiation of angiotensin converting enzyme inhibitors. The protocols within the medical literature made no recommendation for detecting renal failure in vulnerable patients and as a consequence the guideline for angiotensin converting enzyme inhibitors in primary care management was not clear on this point.[12] In a review guideline recommendations were discussed for periodic monitoring of liver enzymes to prevent drug induced liver injury but the evidence for monitoring was sparse.[13] In a report about evidence-based laboratory guideline development one of the conclusions was that the evidence in laboratory diagnosis is often poor.[4] Besides the information in guidelines another driving force for clinical applicability of laboratory monitoring instructions is the drug label or Summary of Products Characteristics. Since the drug label is the legal source of information, evidence and information on laboratory monitoring evidence should be described in this. The regulatory agencies in the USA and Europe approve the scientific product information provided by the manufacturer according to the guidelines for drug approval.[14,15] Ideally, the monitoring information included in drug labels can be used to maximize benefits and minimise risks of an individual patient's drug therapy and for the treated population at large.[3,7,10] However, studies on information of specific biomarkers and laboratory monitoring in drug labels showed that the information was inadequate, incomplete, or difficult to access during pharmacotherapy.[16,17] These studies focused either on a single biomarker category (e.g., renal function, haematology) or on a specific section of the drug label (e.g., pharmacological properties).[18-21]

In this study all laboratory monitoring instructions were reviewed to evaluate the frequency, nature, and applicability of instructions on laboratory monitoring in drug labels of 200 commonly prescribed drugs in The Netherlands.

MATERIALS AND METHODS

Selection of drug labels

A representative sample of drug labels, the 200 most frequently prescribed drugs in primary care, was identified from dispensing data between July 2006 and July 2007 of 100 community pharmacies, covering a population of 720,000 patients. Drug labels of the selected products were obtained from the website of the Dutch Medicines Evaluation Board, which contains information on all medicinal products nationally approved for sale[22] or the related website of European Medicines Agency (EMA) for drugs authorised by the centralised authorisation procedure in the European Union.[23] The use of the drug-dispensing data was performed in accordance with current Dutch privacy and ethical regulations and approved by the Institutional Review Board of the Utrecht Institute for Pharmaceutical Sciences.

Selection of instructions on laboratory monitoring

The 200 drug labels were searched using keywords related to information on laboratory monitoring, on pharmacotherapy adjustments, or on concrete laboratory tests, e.g., 'control', 'determine', 'function', 'level', 'monitor', 'stop', 'cease', 'genotype' and specific laboratory tests, such as alanine aminotransferase, aspartate aminotransferase, creatinine or INR. For quality assurance, a pharmacist (FdK) read 10 drug labels to validate the keywords. Drug labels with information on laboratory monitoring were only included if the information was intended as an operational instruction to do something, e.g., 'the serum creatinine must be monitored before starting the therapy'. Instructions for monitoring the same biomarker in different sections of the drug label were counted separately, if the nature of the information was different. One of the authors (pharmacist AG) reviewed the paragraphs with the marked keywords and classified the relevant information. A second pharmacist (FdK) validated the classification in a random sample of 10% of the drug labels. Both pharmacists initially agreed in 95% of the random sample and consensus was reached in the classification for the rest.

Applicability of instructions on laboratory monitoring

To assess the applicability of instructions on laboratory monitoring for the healthcare professional an adapted Systematic Information for Monitoring (SIM) score was used[17] In an earlier study, the SIM score was developed and used to measure the adequacy of

Table 1 Items of information scored for instructions on laboratory monitoring in drug labels[a]

Items of information	Necessary content for score =1	Example scoring	Score
Why to monitor	Reason for monitoring is specified:	The drug is contra-indicated for patients with renal failure e.g.,	__ *b*
	1. drug selection	serum creatinine > 135 mmol/L (drug selection)	
	2. dose adjustments		
	3. monitoring for safety		
What to monitor	Laboratory test is specified	Liver tests must be monitored	0
		Liver tests (ALT, AST) must be monitored	1
When to start monitoring	Moment to start monitoring is specified:	Monitor patients with normal renal function	0
	1. before treatment	Before starting therapy and after starting at least once a year for	1
	2. at initiation	patients with normal renal function	
	3. during follow-up		
	4. after cessation		
When to stop monitoring	Moment to stop monitoring is specified:	Serum creatinine must be monitored	0
	1. when in reference range	Stop monitoring after the drug is stopped	1
	2. after stopping treatment		
	3. after explicit period		
How frequently to monitor	Frequency of monitoring is specified	Serum creatinine must be monitored	0
		Monitor frequently in patients with serum creatinine near critical value	1
Critical value	Critical value is specified	The drug is contra-indicated for patients with impaired renal function	0
		The drug is contra-indicated for patients with renal failure: e.g.,	1
		serum creatinine > 135 µmol/L	
How to respond	Therapy adjustment is specified:	In case of overdosing monitor liver tests	0
	1. drug selection: cease or change drug		
	2. dose adjustments: adjust dose, interval, frequency or titrate	Cease the drug for patients with renal failure (drug selection)	1
	3. monitoring for safety: add, cease or change drug to avoid adverse reactions		

ALT, alanine aminotransferase; AST, aspartate aminotransferase. a: Adapted from Ferner et al.[17]. b: Item why to monitor is obligatory for inclusion.

instructions to monitor for haematological reactions in drug labels from the UK and the information was compared with documents from the USA and Australia. The SIM-score values the information on seven items: 'why to monitor', 'what to monitor', 'when to start monitoring', 'critical value', 'how to respond', 'how frequently to monitor', and 'when to stop monitoring' (Table 1). In that study, four items were considered essential: 'what to monitor', 'how frequently to monitor it', 'critical value', and 'how to respond'. We defined the score for each item into, 1 (information item specifically described) or 0 (information item not available or not specifically described), except for the item why to monitor, because this item was obligatory for inclusion. Instructions on how frequently to monitor scored one point even when the information was not entirely specific, e.g. frequently, regularly. The total applicability score for each instruction was the sum of the scores for the six items of information therefore ranging from 0 to 6. The instructions were considered applicable if at least the three essential items ('what to monitor', 'critical value' and 'how to respond') all scored one point.

Data analysis

The strength of the association between applicable instructions (score of three on the three essential items) and the study variables what to monitor (biomarker category), why to monitor, year of introduction on the market, and therapeutic group was estimated with univariate logistic regression analysis and expressed as odds ratios (OR) with 95% confidence intervals (CI).

RESULTS

In 131 (65.5%) of the 200 selected drug labels, 566 instructions on laboratory monitoring were identified, an average of 2.8 (range, 0-15) per drug label. The other 69 drug labels had no instructions for laboratory monitoring.

With respect to the nature of the item 'what to monitor' 14 categories of biomarkers were identified, of which 'kidney' (28%), 'liver' (20%), 'electrolyte' (12%), and 'drug monitoring' (11%) represented the majority (71%) of the total number of instructions (Table 2). The names of the laboratory tests described were ambiguous, e.g., T4 for thyroid function and PT for clotting time. Overall, monitoring for safety (55%) was the most frequent reason for the item 'why to monitor' succeeded by 'dose adjustments' (33%) and 'drug selection' (13%). Instructions for monitoring for efficacy were described in a subcategory for 'dose adjustments', which is dose titration on the basis of glucose, lipids, thyroid, drug monitoring, and coagulation. 'Why to monitor' varied across biomarker categories. For 'kidney' and 'liver' most instructions were related to 'dose adjustments' (50% and 42% respectively) or to 'drug selection' (each 22%), while for other biomarker categories

Table 2 What to monitor and why to monitor in different biomarker categories

What to monitor:		Total instructions[a]		Why to monitor[b]					
				Drug selection		Dose adjustments		Monitoring for safety	
Biomarker category	**Example of laboratory test**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Kidney	Creatinine	157	(27.7)	35	(22.3)	79	(50.3)	43	(27.4)
Liver	ALT, AST, GGT	112	(19.8)	25	(22.3)	47	(42.0)	40	(35.7)
Electrolyte	Na, K, Ca, Mg	70	(12.4)	5	(7.1)	12	(17.1)	53	(75.7)
Therapeutic drug monitoring	Digoxin, Phenytoin, Lithium, Theophylline	63	(11.1)	1	(1.6)	8	(12.7)	54	(85.7)
Glucose	Glucose	46	(8.1)	1	(2.2)	20	(43.5)	25	(54.3)
Haematology	Leukocyte, Thrombocyte, Granulocyte	36	(6.4)	3	(8.3)	2	(5.6)	31	(86.1)
Coagulation	INR, PT	34	(6.0)	0	(0.0)	4	(11.8)	30	(88.2)
Creatine phosphokinase	CPK	13	(2.3)	1	(7.7)	1	(7.7)	11	(84.6)
Thyroid	TSH, T3, T4	7	(1.2)	0	(0.0)	5	(71.4)	2	(28.6)
Other biomarkers	HCG, Uric acid, Dexamethasone, Serum proteins, Urea, Lactate	7	(1.2)	0	(0.0)	2	(28.6)	5	(71.4)
Adrenal gland	Cortisol	6	(1.1)	0	(0.0)	0	(0.0)	6	(100.0)
Lipids	Cholesterol, LDL, HDL, Triglyceride	6	(1.1)	0	(0.0)	4	(66.7)	2	(33.3)
Urine test	Ketones, Glucose	5	(0.9)	1	(20.0)	0	(0.0)	4	(80.0)
Genotype	HLA-B, Cyp2C9, Cyp2C19	4	(0.7)	0	(0.0)	1	(25.0)	3	(75.0)
Total		566	(100.0)	72	(12.7)	185	(32.7)	309	(54.6)

a: presented as percentages of the total number of instructions (n=566). b: presented as percentages of the total number of instructions per biomarker category.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; Ca, calcium; CPK, creatine phosphokinase; HCG, human chorionic gonadotropin; GGT, gamma-glutamyl transferase; CYP2C9, cytochrome P450 2C9; CYP2C19, cytochrome P450 2C19; HLA-B, human leukocyte antigen, class 1, B; HDL, high density lipoprotein; INR, international normalized ratio; K, potassium; LDL, low density lipoprotein; Mg, magnesium; Na, sodium; PT, prothrombin time; TSH, thyroid stimulating hormone; T3, thiiodothyronine; T4, thyroxin.

instructions were primarily related to 'monitoring for safety', e.g., coagulation (88%), haematology (86%), and drug monitoring (86%).

Instructions for monitoring were described in nine different sections of the drug label, most frequently in the section 'special warnings and precautions for use' (42%), 'posology and method of administration' (21%), 'interaction with other medicinal products' (19%), and 'contraindications' (5%). The distribution for the variable 'why to monitor' also varied over different sections of the drug label. First, in the section 'contraindications' 96% of the instructions were given for the reason 'drug selection'. Second, in the sections 'pharmacokinetic properties' (92%) and 'posology and method of administration' (83%) instructions were predominantly given for the reason 'dose adjustments'. Third, in the sections 'special warnings and precautions for use' (61%), 'interaction with other medicinal products' (94%), 'undesirable effects' (95%), and 'overdose' (97%) instructions were

Table 3 Association between items of information and applicable instructions

	Not applicable (score < 3 on essential items) n=471 (100%)		Applicable (score = 3 on essential items) n=95 (100%)		Odds ratio	(95% CI)
1. What to monitor (biomarker category)						
Kidney	96	(20%)	61	(64%)	7.0	(4.36 -11.28)
Liver	96	(20%)	16	(17%)	0.8	(0.44 - 1.42)
Electrolyte	69	(15%)	1	(1%)	0.1	(0.01 - 0.45)
Therapeutic drug monitoring	60	(13%)	3	(3%)	0.2	(0.07 - 0.73)
Glucose	45	(10%)	1	(1%)	0.1	(0.01 - 0.74)
Coagulation	31	(7%)	3	(3%)	0.5	(0.14 - 1.55)
Haematology	35	(7%)	1	(1%)	0.1	(0.02 - 0.98)
Urine test	4	(1%)	1	(1%)	1.2	(0.14 - 11.24)
Other biomarkers	7	(1%)	0	(0%)	NE	
Thyroid	7	(1%)	0	(0%)	NE	
Creatine phosphokinase	7	(1%)	6	(6%)	4.5	(1.47 - 13.61)
Adrenal gland	6	(1%)	0	(0%)	NE	
Lipids	4	(1%)	2	(2%)	2.5	(0.45 - 13.91)
Genotype	4	(1%)	0	(0%)	NE	
2. Why to monitor						
Drug selection	37	(8%)	35	(37%)	6.8	(4.01 - 11.69)
Dose adjustments	138	(29%)	47	(49%)	2.4	(1.51 - 3.70)
Monitoring for safety	296	(63%)	13	(14%)	0.1	(0.05 - 0.17)

Essential items of information: what to monitor, critical value and how to respond. CI, confidence interval; NE, not estimable.

most frequently given for the reason 'monitoring for safety'. For the variable 'what to monitor' instructions for 'kidney' were primarily given in the sections 'pharmacokinetic properties' (75%), 'contraindications' (63%), and 'posology and method of administration' (46%). Instructions for 'liver' were given in the section 'undesirable effects' (52%), 'contraindications' (33%), and 'posology and method of administration' (30%). Instructions for 'electrolyte' were given in the sections 'overdose' (38%), and 'special warnings and precautions for use' (17%). Instructions for 'drug monitoring' were primarily given in the section 'interaction with other medicinal products' (45%). Finally, instructions for monitoring the same biomarker category (n = 130) for different purposes in different sections of the drug label were identified in 76 (38%) of the included drug labels.

Only specific instructions on laboratory monitoring scored one point per item of information. Instructions for the essential item 'what to monitor' were specifically described in 67%. For the second essential item 'how to respond', 75% of the instructions were

Table 4 Association between variables in the study and applicable instructions

Variable in the study	Not applicable (score < 3 on essential items) n=471 (100%)		Applicable (score = 3 on essential items) n=95 (100%)		Odds ratio	(95% CI)
1. Year of introduction on the market						
<1960	59	(13%)	11	(12%)		(reference)
1960-1969	75	(16%)	5	(5%)	0.4	(0.12 - 1.09)
1970-1979	67	(14%)	8	(8%)	0.6	(0.24 - 1.70)
1980-1989	103	(22%)	23	(24%)	1.2	(0.55 - 2.63)
1990-1999	130	(28%)	30	(32%)	1.2	(0.58 - 2.64)
2000-2007	37	(8%)	18	(19%)	2.6	(1.11 - 6.14)
2. Therapeutic groups (top 10)						
Agents acting on RAS	80	(17%)	13	(14%)	0.8	(0.41- 1.46)
Antibacterials (systemic)	41	(9%)	11	(12%)	1.4	(0.68 - 2.78)
Statins	25	(5%)	20	(21%)	4.8	(2.52 - 8.99)
Anti-inflammatory Antirheumatic drugs	30	(6%)	11	(12%)	1.9	(0.93 - 3.99)
Antidepressants	30	(6%)	3	(3%)	0.5	(0.14 - 1.60)
Diuretics	26	(6%)	3	(3%)	0.6	(0.17 - 1.88)
Drugs used in diabetes	26	(6%)	1	(1%)	0.2	(0.02 - 1.36)
Antiepileptics	24	(5%)	1	(1%)	0.2	(0.03 - 1.48)
Antithrombotic agents	14	(3%)	6	(6%)	2.2	(0.82 - 5.88)
Beta blocking agents	16	(3%)	3	(3%)	0.9	(0.27 - 3.25)

Essential items of information: what to monitor, critical value and how to respond. CI, confidence interval; RAS, renin angiotensin system.

specifically described, but for the third essential item 'critical value', the instructions were less specifically described (21%). The other items of information scored low: when to start monitoring 30%, when to stop monitoring 1% and how frequently to monitor 15%. The number of applicable instructions was low [n = 95 (17%); score = 3 on the three essential items] and the median applicability score was 2.1. Statistically significant determinants for applicable instructions were 'kidney' (OR 7.0; 95% CI 4.4-11.3), creatine phosphokinase (4.5; 1.5-13.6), drug selection (6.8; 4.0-11.7), dose adjustments (2.4; 1.5-3.7) (Table 3).The determinants electrolyte, drug monitoring, glucose, monitoring for safety, were statistically significant associated with not applicable instructions whereas thyroid, adrenal gland, genotype and other biomarkers did not have any applicable instruction at all. Introduction on the market (year 2000-2007) (2.6; 1.1-6.1), and statins (4.8; 2.5-9.0) were also statistically significant associated study variables (Table 4). Statins scored highest with 20 applicable instructions (21%).

DISCUSSION

A high mean frequency of instructions on laboratory monitoring of 2.8 per drug label was described. Regarding the nature of instructions, more than two thirds of the instructions were represented by four biomarker categories: 'kidney', 'liver', electrolyte, and drug monitoring. Furthermore, important reasons to monitor were dose adjustments, monitoring for safety and drug selection. Information on laboratory monitoring was scattered over nine different sections of the drug label. Therefore, to survey the information on one biomarker was difficult. The applicability of the instructions on laboratory monitoring for healthcare professionals was low (17%). Statistically significant determinants associated with applicable instructions were kidney, creatine phosphokinase, drug selection, dose adjustments, introduction on the market (year 2000-2007), and statins.
In an earlier study about linked laboratory and pharmacy data, an average frequency of 6.6 instructions per drug was found [24], which is in contrast with the lower frequency of 2.8 instructions per drug label in our study. However, these results are not directly comparable, because of differences in source of information, drug selection and the number of included drugs. Furthermore, in one-third of our drug labels there were no specifically described instructions to monitor at all and this could explain a lower frequency of instructions per drug label. Additional research is required to investigate why in some drugs instructions were described, while in other drugs from the same therapeutic group there were no instructions described. A good example in this study is the nine included benzodiazepines for which five drug labels had instructions for laboratory monitoring and four drug labels did not.

In addition, to commonly reported biomarker categories in other studies, such as 'kidney', 'liver', electrolyte, haematological factors, prothrombin time, or glucose, less frequently reported categories were also identified in this study because all biomarkers in all sections of the drug label were assessed, e.g., creatinine phosphokinase, adrenal gland, urine tests, and lipids.[25-28]

For the biomarker categories 'kidney' and 'liver' most instructions for monitoring are related to dose adjustments or dose selection, probably because of the elimination role of these organs. The remaining instructions are related to monitoring for safety and assessment for kidney injury or liver injury. Although for the biomarker 'liver' there is no evidence so far, that routine monitoring of liver enzymes prevents drug-induced clinically significant hepatotoxicity.[13] In other biomarker categories instructions to 'monitor for safety' predominates. A possible explanation for this observation is that these biomarker categories are more related to adverse reactions of a drug. As was expected, instructions for monitoring efficacy were found in the category 'dose adjustments' on the basis of glucose, lipids, thyroid, drug monitoring, and coagulation. Explicit instructions for coagulation, thyroid, adrenal gland, lipids, and genotype are missing for 'drug selection', but the number of instructions for these categories is very low. For genotype, this is in contrast with the increasing frequency of inclusion of information for pharmacogenetic monitoring in similar drug labels in the USA[29] and the up-to-date information of pharmacogenomics biomarkers in drug labels on the website of the U.S. Food and Drug Administration (FDA).[30]

Most instructions for monitoring were expected in the section 'special warnings and precautions for use', but this contained less than half of the number of instructions. Instructions for monitoring the same biomarker in different sections and for different purposes, more specifically dose adjustment, drug selection, or monitoring for safety were often seen for 'kidney' and 'liver'. Concentrating all information on monitoring in a separate laboratory-monitoring section as in FDA approved drug labels (e.g., carbamazepine drug label[31]) will elucidate for the professional what, why, when and how frequently to monitor, at which critical value and how to respond to abnormal values for each biomarker. There are other global differences between FDA and EMA approved drug labels. In the latter there is no separate section about drug abuse and dependence. EMA labels contain a section on the effects on ability to use machines and to drive. International cooperation of regulatory authorities and drug manufactures could reduce undesirable differences. The European Union centralized authorisation procedure is a good example of this desired cooperation. Additional research on systematic comparison with other sources could reveal and explain in more detail differences between countries and continents.

Monitoring instructions in drug labels should be at least specific and unambiguous for the three essential items of information 'what to monitor', 'critical value', and 'how

to respond' to be applicable. This information was described in two thirds for the item 'what to monitor', in three quarters for the item 'how to respond', but was incomplete for the essential item 'critical value' and the remaining three items of information. Six variables in this study were associated with applicable instructions. First, for the variable 'biomarker category' we found that, the determinants 'kidney' and 'creatine phosphokinase' were the most important predictors of applicable instructions. For these two biomarkers more detailed and specific information seemed to be described compared to other biomarker categories. Electrolyte, drug monitoring, glucose, haematology, thyroid, adrenal gland, genotype, and 'other biomarkers' were strongly related to inapplicable instructions, because these markers scored less than three points. In contrast to a study for haematological instructions on laboratory monitoring in which 47 from the 84 instructions were applicable, we found only one applicable haematological instruction out of 35.[17] The difference could be explained because in the haematological study less specific instructions were included and interpreted by a panel for applicability. Second, the determinant 'introduction on the market (year 2000-2007)' was strongly related to applicable instructions. A slight improvement of the odds ratios during the last 50 years towards more applicable instructions can be seen, probably due to a greater awareness of adverse drug reactions, medication safety, and the influence of regulatory authorities. Third, for the category 'why to monitor' we found that the determinants drug selection and dose adjustments were strongly related to applicable instructions. A possible explanation for this observation is the clear outcome to stop the drug for contraindicated drugs at a critical value for a biomarker or to adjust the dose at a less critical value. Finally, the therapeutic group statins was strongly associated with a higher chance of applicable instructions, because the instructions in the drug labels of simvastatin and atorvastatin were described nearly all specific for all items of information.

Besides the seven items of information of the adapted SIM-score two other items were observed in the drug labels: the incidence of abnormal laboratory values and patient related risk factors, e.g., age, race, disease, and genotype. These factors can be used in a more patient centered monitoring approach. Therefore, the development of a system to assess the comprehensiveness of laboratory monitoring management guidelines, could improve laboratory monitoring strategies.[32]

Clinical applicability of instructions on laboratory monitoring is not only defined by the quality of information in the drug label or guideline but by other criteria as well. These criteria can be assessed by using four components: analytical validity, clinical validity, clinical utility and ethical, legal and social implications.[33] Analytical validity defines a test's ability to accurately and reliably measure the outcome of interest. Elements within analytical validity include analytic sensitivity, analytical specificity, quality control and assay robustness. Clinical validity defines a test's ability to predict the associated outcome. Clinical utility defines the benefits and risks associated with a test and it has to

be demonstrated by well-controlled prospective studies. If clinical utility is established adoption of the test will be facilitated by incorporation of the information in drug labels by the manufactures and in guidelines by professional organisations. Ethical, legal and social implications identify opportunities to implement a test into clinical practice, e.g., adequate coding and reimbursement, cost effectiveness, involvement of a progressive treating physician group and widespread access to the test.[34] Although instructions on laboratory monitoring in drug labels are the legal sources of information it is not the only driving force for the clinical applicability of these instructions.

In conclusion, drug labels frequently describe instructions on laboratory monitoring, but these are ambiguous and often incomplete and therefore the applicability by the healthcare professional is limited. Introduction of a specific laboratory-monitoring section in drug labels with references to clinical guidelines for more detailed information would offer a better base for clinical decision making. A concerted effort of clinical chemists and other healthcare professionals warrants the development of evidence-based guidelines for monitoring drug treatment.

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2.2

LABORATORY TESTS IN THE CLINICAL RISK MANAGEMENT OF POTENTIAL DRUG-DRUG INTERACTIONS

A cross-sectional study using drug-dispensing data from 100 Dutch community pharmacies

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ABSTRACT

Background

Patient safety and the life cycle of a drug are negatively influenced by the still increasing occurrence of potential drug-drug interactions (DDIs). Clinical risk management of potential DDIs is required in patients using drugs to influence the benefit-risk profile positively. Information about laboratory test results, in particular, may be useful in the assessment of potential DDIs for the individual patient.

Objective

The objective of this study was to examine the frequency and nature of laboratory tests required for the assessment of clinical relevance of potential DDIs in Dutch community pharmacy. In addition, the nature and clinical relevance of these potential DDIs is analysed.

Methods

All patients from 100 Dutch community pharmacies using, according to dispensing information, two or more drugs concomitantly on a specified date (Wednesday, 4 April 2007), were included (n = 223 019). The anonymous dispensing data of the included patients were analysed against a list of DDIs requiring laboratory tests for the assessment of their clinical relevance. The number of patients at risk for these potential DDIs with severe adverse reactions was calculated. The frequency of potential DDIs requiring laboratory tests were stratified by age, sex and the degree of polypharmacy.

Results

Of the included patients, 24.4% had one or more potential DDIs (n = 54 427). In 9.0% of the included patients one or more laboratory tests for the assessment of clinical relevance of the potential DDI were required (n = 19 968).The frequency of DDIs requiring laboratory tests increased with increasing age and number of drugs, but was not related to sex. The most commonly required laboratory tests were renal function (42.2%), electrolytes (20.1%) and coagulation (13.1%).The percentage of patients at risk for potential DDIs requiring laboratory tests with adverse reaction category F (serious, irrecoverable disablement or death) was 2.5%, category E (increased risk of failure of life-saving therapy) was 0.6%, and category D (inconvenience with residual symptom and failure of therapy concerning serious but non-fatal diseases) was 3.8%.

Conclusions

A large number of patients in Dutch community pharmacies are at risk for potential DDIs requiring laboratory tests for the assessment of the clinical relevance of the interaction.

There is a strong relationship between the frequency of DDIs requiring laboratory tests and age and the number of drugs concomitantly used. In the clinical risk management of potential DDIs, information about laboratory test results is of additional value. Future research is necessary in order to obtain more evidence in using laboratory tests in terms of which tests should be linked to pharmacy data, in which patients they should be done, how often and what actions should be taken when an abnormal value is found.

INTRODUCTION

Drug-drug interactions (DDIs) have shown to contribute significantly to the negative consequences of drug treatment.[1-3] The prevalence of drug-drug interactions with potential serious adverse reactions in patients taking more than one drug concomitantly has been estimated at 6–14%.[4,5] In a study, carried out in an elderly population in the Netherlands, the prevalence of DDIs increased from 10.5% in 1992 to 19.2% in 2005.[6] In another study carried out in Sweden in people aged = 75 years the prevalence of type C (potentially clinically relevant) DDIs was 26% and of type D (potentially serious) DDIs 5%.[7] Clinical risk management of potential DDIs aims to protect the patient from drug-induced adverse reactions.[8]

DDIs are not only a threat to patient safety but may also negatively influence the life cycle of a drug. A high potential for DDIs may stop the development of a new drug and may contribute to the ever-growing development costs and decreasing clinical success rates.[9,10] In addition, newly detected and difficult-to-manage DDIs have significantly contributed to the withdrawal of approved drugs in recent years (e.g. cisapride and mibefradil).[11] Currently, guidelines for the management of several DDIs include the use of laboratory tests (laboratory tests) as risk modifier in the assessment of the DDI. For healthcare providers, monitoring of drug concentrations as well as clinical chemistry and/or hematologic tests could provide important information about the clinical relevance of the DDI for the individual patient.[12-14]

The objective of this study was to examine the frequency and nature of laboratory tests required for the assessment of clinical relevance of potential DDIs in community pharmacies. In addition, the nature and clinical relevance of these potential DDIs is analysed.

METHODS

Setting

At the end of 2006 there were 1825 community pharmacies in The Netherlands. For the present study, anonymous drug-dispensing data from 100 (5.5%) Dutch community pharmacies were received through the Foundation for Pharmaceutical Statistics (SFK), which collects exhaustive drug dispensing data in The Netherlands. The 100 participating pharmacies belonged to the franchise organisation 'Kring-apotheek' (n = 330) and included pharmacies from all over the country. The pharmacies within this scheme focus on pharmaceutical care projects with the aim of improving individual patient care and enhancing medication safety. In Dutch community pharmacies, the prescription medicine history of individual patients can be considered as nearly complete, because most patients visit only one single pharmacy.[15]

The drug-dispensing data included information about the patient (age, sex, unique anonymous identifier), dispensed drug, dispensing date, number dispensed and prescribed dosage regimen. Dispensed drugs were coded according to the Anatomical Therapeutic Chemical classification system.[16] The use of the drug-dispensing data was performed in compliance with Dutch privacy regulations and approved by the Institutional Review Board of the Utrecht Institute for Pharmaceutical Sciences.

Study population

The eligible study population consisted of all patients who had been dispensed at least two prescriptions by one of the 100 included pharmacies from July 2006 to July 2007. Patients were included if they were using two or more different drugs concomitantly on a fixed date (Wednesday, 4 April 2007). In this study, products with more pharmacologically active substances are considered as one dispensed drug. To assess whether drugs were used concomitantly on the specified date the theoretical duration of drug use was needed. For each dispensed drug the theoretical duration of drug use was estimated by dividing the number of dispensed units by the prescribed dosage regimen. If the dosage regimen was unknown (4.5%) or the estimated duration was less than 1 day (4.4%) or more than 1 year (0.2%) (e.g. antithrombotic agents), the duration was estimated by the calculated average of valid durations of that drug.[17] The duration of use was multiplied by 1.1 to correct for irregular drug use and early drug collection from the pharmacy.[18]

Patients of unknown sex (0.1%) or unknown age (0.09%), those over 99 years of age (0.06%), patients missing a unique identifier (0.003%) or those using more than 50 different drugs (0.002%) were excluded, because they probably reflect fictitious patients used for administrative purposes, e.g. drugs dispensed directly to a general practitioner. The final study population therefore consisted of 223 019 patients using at least two drugs on 4 April 2007.

Selection of potential drug-drug interactions

One of the study outcomes was the nature of potential DDIs requiring laboratory tests for the assessment of clinical relevance of the interaction. In the Netherlands, a working group of the Scientific Institute of Dutch Pharmacists developed and now maintain a computerized surveillance guideline for the management of DDIs.[19] In this surveillance guideline clinical relevance is described in more detail.[4,20] In brief, an alphanumerical code indicates the risk of a DDI using a 6-point scale for the seriousness of the potential adverse reaction (A-F) and by using a 5-point quality of evidence scale (0-4) (Table 1). Based on this clinical guideline, 329 potential DDIs have been classified as potentially significant because they should generate a direct interaction alert in the computerized DDI surveillance system in community pharmacies; the assessment of these combinations of drugs is considered necessary in daily patient care. For the clinical relevance of the

Table 1 Classification of drug-drug interactions in the Dutch surveillance guideline[4,20]

Category	Description
Quality of evidence	
0	Pharmacodynamic animal studies; in vitro studies
1	Incomplete, published case reports
2	Well documented, published case reports
3	Controlled, published interaction studies with surrogate endpoints
4	Controlled, published interaction studies with clinically relevant endpoints
Seriousness of potential adverse reactions	
A	Clinically irrelevant effect
B	Short-lived inconvenience
C	Inconvenience without residual symptoms; failure of therapy concerning non serious diseases
D	Inconvenience with residual symptoms; failure of therapy concerning serious but non-fatal diseases
E	Increased risk of failure of life-saving therapy
F	Serious, irrecoverable disablement or death

Table 2 Number of drug-drug interactions (DDIs) requiring laboratory tests in the Dutch surveillance guideline (June 2007)[19]

Interactions	No. of interactions (%)[a]
Clinical significant DDIs	329 (100)
DDIs not requiring laboratory tests	222 (67)
DDIs requiring one or more laboratory tests	107 (33)

a: The total number of laboratory tests (tables III and IV) is higher than number of DDIs requiring laboratory tests because each interaction can refer to more than one test.

Table 3 List of drug-drug interactions (DDIs) requiring clinical chemistry and haematological laboratory tests in the Dutch surveillance guideline (June 2007)[19]

Type of test	No. of tests (%)
Total	63 (100.0)
Coagulation	31 (49.2)
Renal function	11 (17.5)
Biochemical liver test	7 (11.1)
Electrolytes	5 (7.9)
Blood cell count	4 (6.3)
Blood glucose	3 (4.8)
Thyroid function	1 (1.6)
Creatine phosphokinase	1 (1.6)

Table 4 List of drug-drug interactions (DDIs) requiring drug monitoring in the Dutch surveillance guideline (June 2007)[19]

Therapeutic group	Test	No. of tests (%)
Total		62 (100.0)
Cardiac glycosides	Digoxin	6 (9.7)
	Quinidine	3 (4.8)
	Disopyramide	1 (1.6)
Immunosuppressants	Ciclosporin	8 (12.9)
	Tacrolimus	4 (6.5)
	Everolimus	3 (4.8)
	Sirolimus	3 (4.8)
	Mycophenolic acid	2 (3.2)
Antiepileptics	Phenytoin	9 (14.5)
	Carbamazepine	4 (6.5)
	Valproic acid	3 (4.8)
	Lamotrigine	2 (3.2)
	Phenobarbital	1 (1.6)
	Other antiepileptics	1 (1.6)
Antipsychotics	Lithium	4 (6.5)
	Clozapine	1 (1.6)
	Haloperidol	1 (1.6)
Tricyclic antidepressants	Antidepressants	1 (1.6)
Xanthines	Theophylline	5 (8.1)

combination, the Dutch alphanumerical code should be combined with the incidence and the existence of risk factors that increase the seriousness and/or the incidence of an adverse reaction.

To determine DDIs requiring a laboratory test, the documentation of each interaction in the surveillance guideline of June 2007[19] was screened for the words 'drug monitoring', 'clinical chemistry test' and/or 'haematological test'. All laboratory tests were included and their nature was classified into two categories: 'clinical chemistry and haematological tests' or 'drug monitoring'. The distribution of relevant DDIs requiring laboratory tests in the Dutch DDI surveillance system of June 2007 is presented in Tables 2, 3 and 4. We identified 107 potentially significant DDIs (33%) with at least one laboratory test mentioned in the documentation out of 329 potentially significant DDIs. Because each interaction can refer to more than one laboratory tests, the total of laboratory tests was 125. For example, in the documentation of drug-interaction 'methotrexate and NSAIDs'

Table 5 Characteristics of the study population in 100 Dutch pharmacies, 2007 (n = 223 019)

Characteristics of study population	No. of patients(%)	
Age (y)		
0-10	2 856	(1.3)
10-20	5 925	(2.7)
20-30	10 030	(4.5)
30-40	14 752	(6.6)
40-50	26 901	(12.1)
50-60	40 340	(18.1)
60-70	48 947	(21.9)
70-80	43 920	(19.7)
80-90	25 279	(11.3)
≥90	4 069	(1.8)
Sex		
Male	92 599	(41.5)
Female	130 420	(58.5)
No. of drugs concomitantly used		
2-4	159 290	(71.4)
5-7	46 958	(21.1)
8-10	12 900	(5.8)
11-13	3 067	(1.4)
14-16	639	(0.3)
17-19	135	(0.1)
≥20	30	(0.01)

Table 6 Most common potential drug-drug interactions in the study population

Interactions	Quality of evidence[a]	Frequencies/ 1000 patients
Type F (serious, irrecoverable disablement or death)		
Agents acting on the RAS + potassium-sparing diuretics	2	24
Tricyclic antidepressants + SSRIs/duloxetine	3	1
Potassium salts + potassium-sparing diuretics	3	1
Type E (increased risk of failure of life-saving therapy)		
Methotrexate + NSAIDs/acetylsalicylic acid	3	2
HMG-CoA reductase inhibitors (statins) + gemfibrozil	3	2
Lamotrigine + valproic acid	3	1
Type D (inconvenience with residual symptoms; failure of therapy concerning serious but non-fatal diseases)		
Diuretics + NSAIDs/acetylsalicylic acid	3	13
Agents acting on the RAS + NSAIDs/acetylsalicylic acid	3	11
Digoxin + verapamil/diltiazem	3	2
Acenocoumarol/fenprocoumon + amiodarone/propafenone	3	2
Acenocoumarol/fenprocoumon + SSRIs	1	2
Acenocoumarol/fenprocoumon + antibiotics	3	1
Acenocoumarol/fenprocoumon + phytomenadione	1	1
Acenocoumarol/fenprocoumon + allopurinol	1	1
Beta blocking agents, non-selective + insulins	3	1
Lamotrigine + other antiepileptics/rifampicin	3	1

a: Quality of evidence is assessed using a 5-point quality of evidence scale (0-4) developed by a working group of the Scientific Institute of Dutch Pharmacists.[20] Details can be found in table I.
RAS, renin-angiotensin system; **SSRIs,** selective serotonin reuptake inhibitors.

the advice is to monitor methotrexate concentration and also to check blood cells, renal function and biochemical liver tests.

Data analysis

To determine how many patients were at risk for potential DDIs requiring laboratory tests, the drug-dispensing data were analysed. The number of patients with a potential DDI requiring laboratory tests was used for the nominator. For patients with two or more potential DDIs the DDI with the highest risk code was selected. The number of patients in the study population was the denominator.

To determine the nature and frequency of laboratory tests, all potential DDIs were included and categorized by laboratory test subcategories, and classified by age, sex and number of dispensed drugs.

Table 7 Laboratory tests required for the assessment of clinical relevance of potential drug-drug interactions in the study population

Category		No. of tests (%)
Clinical chemistry + haematological tests		
Renal function	Serum creatinine; estimated glomerular filtration rate	13902 (42.2)
Electrolytes	Serum potassium	6602 (20.1)
Coagulation	International normalized ratio (INR)	4315 (13.1)
Blood glucose	Glucose	3143 (9.5)
Biochemical liver test	AST, ALT, γ-glutamyltransferase	1103 (3.4)
Blood cell count	Leukocytes, neutrophils, granulocytes,trombocytes, haemoglobin	596 (1.8)
Creatine phosphokinase	Creatine phosphokinase	507 (1.5)
Thyroid function	Thyroid-stimulating hormone	13 (0.04)
Subtotal		**30181 (91.7)**
Drug monitoring		
	Digoxin	776 (2.4)
	Immunosuppressants	57 (0.2)
	Antiepileptics	1283 (3.9)
	Antipsychotics	333 (1.0)
	Tricyclic antidepressants	209 (0.6)
	Theophylline	83 (0.3)
Subtotal		**2741 (8.3)**
Total no. of laboratory tests		**32922 (100.0)**

RESULTS

According to the dispensing data of the 100 selected pharmacies, 719 022 patients were served. Patients using two or more different drugs concomitantly on the specified date were finally included in the study (n=223 019) (Table 5).The mean age of the patients included in the study was 59.2 years (SD= 18.9, range 0-99) and, on average, patients had been dispensed 3.9 drugs (SD= 2.2, range 2-27).

Of the included patients, 24.4% (n = 54 427) used a combination of drugs with potential DDIs. In 36.7% of these patients, i.e. 9.0% (n = 19 968) of the study population, one or more laboratory tests were required for the assessment of clinical relevance of the potential DDI. The frequencies for category D, E and F were 3.8%, 0.6% and 2.5%, respectively; the most common of these potential DDIs are given in Table 6. The nature and frequencies of the nine different laboratory tests are given in Table 7. The frequencies of potential DDIs requiring laboratory tests increased with increasing age (Figure 1) and a higher number of dispensed drugs (Figure 2). For example, the overall mean frequency of potential DDIs

Figure 1 Frequencies of potential drug-drug interactions (DDIs) requiring laboratory tests by age and sex

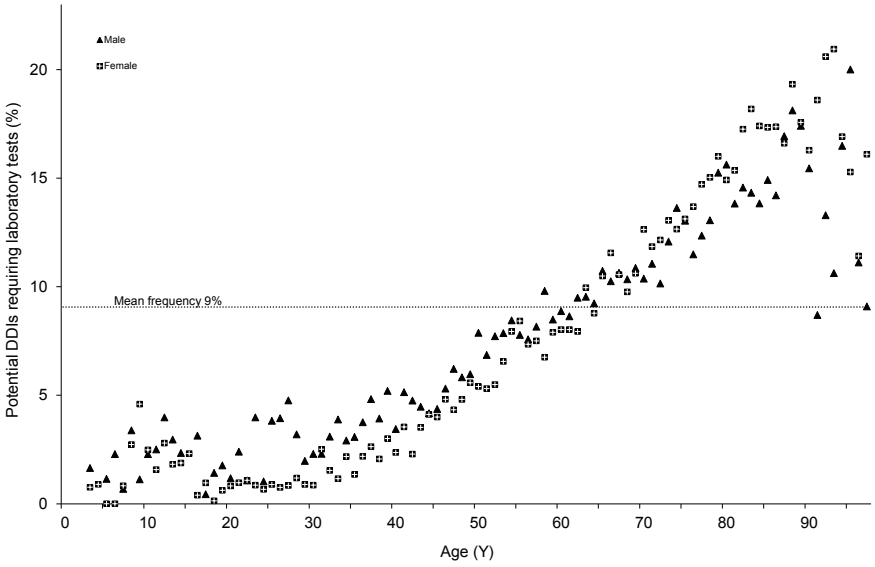
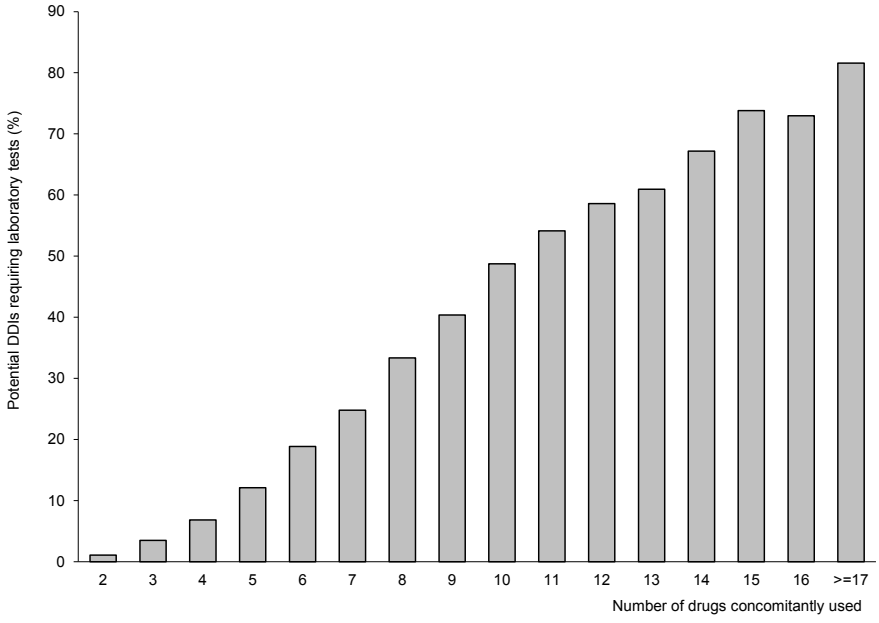


Figure 2 Frequencies of potential drug-drug interactions (DDIs) requiring laboratory tests by number of drugs concomitantly used



requiring laboratory tests 9.0%, with no difference between men or women, 3.1% in those aged 20-40 years and 13.4% in those aged over 65 years. In patients using 2-5, 6-10, >10 different drugs the mean frequency of potential DDIs requiring laboratory tests was 5.9 %, 33.2 %, 65.6 %, respectively. Illustrative of these results is the case of a 76-year-old woman who had been dispensed 15 drugs on the specified date. This patient was at risk for six potential DDIs (categories D, E and F). For the assessment of two potential high-risk combinations (category F), potassium levels were required, and for two category D interactions, the International Normalized Ratio and theophylline monitoring were recommended.

DISCUSSION

In our study, many patients were at risk for potential DDIs with potential serious adverse reactions (categories D, E and F), and results from laboratory tests were frequently required according to clinical guidelines for the assessment of their clinical relevance. Some of the most common DDIs in our results are in line with previous research.[4-6,21] Agents acting on the renin-angiotensin system (RAS), (potassium-sparing) diuretics, NSAIDs and aspirin (acetylsalicylic acid) were the most frequently involved drugs. Some less common combinations of drugs were also analysed. For example, 178 patients were at risk due to taking the the combination of lamotrigine and valproic acid, and 201 patients due to taking the combination of tricyclic antidepressants and SSRIs. In 9.0% of the patients, nine different laboratory tests were required for the assessment of clinical relevance. Information about renal function and electrolytes was needed most frequently. Almost 25% of the patients using two or more drugs concomitantly on the specified date were at risk for potential DDIs.

Other investigators have found different DDI frequencies because of differences in study population, period, setting and definition of DDI. In a Dutch study, the prevalence of DDIs in people aged ≥ 70 years increased from 10.5% in 1992 to 19.2% in 2005, largely due to increased use of spironolactone in this patient group. The prevalence of potentially life-threatening DDIs was 2.9% in people aged ≥ 70 years in 2005, but no prevalence for DDIs requiring laboratory tests for assessment was available.[6] In another study, the frequency of DDI alerts as a percentage of the total number of prescriptions was 6% and the overall frequency of potentially life-threatening DDIs was 0.7%.[4] A study carried out in Sweden in 1999 showed at least one potential drug interaction for 13.6% prescriptions[5] and, in a more recent study in people aged ≥ 75 years, the prevalence of type C potential DDIs was 26% and the prevalence of type D potential DDIs was 5%.[7] The prevalence of DDIs requiring laboratory tests increased with age and number of drugs concomitantly used, which was similar to other studies investigating the prevalence of potential DDIs.[6,7]

Detecting potential DDIs with a computerized surveillance system based on drug-dispensing data has some limitations. Interactions will only take place when the patient is actually using both drugs according to the prescribed dosage regimen. In addition, many potential DDIs never lead to an actual clinical adverse reaction in a patient. Since we were looking for potential DDIs, the prevalence of actual interactions will be much lower. In the risk estimation of potential DDIs, several factors have to be considered to determine the total risk of a DDI. These factors are clinical evidence, seriousness of the adverse reactions, incidence of the DDI, risk factors (other DDIs, mechanism of interaction) and patient characteristics (genotype, weight, age, race and co-morbidity). For example, the interaction between RAS-inhibitors + NSAIDs (category D) is only relevant when the indication is heart failure. Since the reason for use is unknown in community pharmacies, the frequency for this interaction is overestimated.

For effective clinical risk management, the Dutch surveillance guideline for computerized DDI surveillance systems should enhance the specification of laboratory tests and patient characteristics that are relevant for the clinical relevance assessment of DDIs and drug-disease interactions.

Laboratory tests are not always necessary in reducing the risk of potential DDIs. For example, in DDIs with digoxin, dose adjustment based on clinical symptoms is also recommended in the Dutch surveillance guideline as an alternative for laboratory monitoring, and therefore overestimates the frequencies of these kinds of interactions. Another limitation is calculation of the theoretical duration of use, based upon the number of dose units and the prescribed daily dose. If the prescribed daily dose was incomplete or missing we estimated the duration of use and could have included drugs not used concomitantly. We only used data from 5.5% of the Dutch pharmacies because these pharmacies provided the drug-dispensing data. The prevalence of DDI requiring laboratory tests for assessment could be underestimated for different reasons. The included pharmacies focus on pharmaceutical care projects with the aim of enhancing medication safety and to improve individual patient care, which may have led to selection bias. In addition, over-the-counter drugs and herbal drugs are not registered systematically, so the number of potential DDIs requiring laboratory tests for assessment could be underestimated. In the Netherlands, pharmacy shopping behaviour is limited and dispensing registers are relatively complete.[15] Prevalences may be even higher because the healthcare provider could have rejected prescriptions before dispensing as a result of adequate intervention of DDI alerts. Besides DDIs, other laboratory-pharmacy interactions are advised in the summary of product characteristics, i.e. drug-disease interactions, dose adjustment and monitoring toxicity. These interactions may require different biomarkers, e.g. pharmacogenetic testing, and they were not an objective of this study. Finally, modified or newly included DDIs were not reviewed, but the DDI surveillance

system is updated once every month; in the last year, 26 new DDIs have been added, thereby increasing the prevalence of DDIs.[22]

Therefore, a laboratory test could be a good marker for potential serious adverse reactions of DDIs, but in most countries laboratory testing is not a routine. Incorporating evidence in clinical rules could facilitate evidence-based decision making by the healthcare professional. For a start, healthcare providers could carry out laboratory tests to actively monitor renal function and electrolytes in order to prevent patient harm. For effective clinical risk management, the exchange of more patient characteristics between physicians and pharmacists might prevent more DDIs.

Just as in hospital pharmacies, automated laboratory linkage to medication data is a major new tool for healthcare providers in the risk management of avoidable DDIs and in the improvement of patient safety.[23,24]

CONCLUSIONS

A large number of patients are at risk for potential DDIs that require laboratory tests for the assessment of their clinical relevance in community pharmacies. There is a strong relationship between the frequency of DDIs requiring laboratory tests and age and the number of drugs concomitantly used. In the clinical risk management of potential DDIs, information about laboratory test results is of additional value. Future research is necessary in order to obtain more evidence in using laboratory tests in terms of which tests should link to pharmacy data, in which patients laboratory tests should be carried out, how often they are needed and what actions should be taken when an abnormal value is found.

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3

RISK MANAGEMENT OF PATIENTS WITH IMPAIRED RENAL FUNCTION IN COMMUNITY PHARMACY

3.1

A PHARMACY MEDICATION ALERT SYSTEM BASED ON RENAL FUNCTION IN OLDER PATIENTS

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ABSTRACT

Background

Patients with diabetes or cardiovascular disease are at risk for reduced renal function and frequently use drugs that interact with renal function. General Practitioners (GPs) monitor renal function in these patients. Computerised prescription systems produce alerts in patients labelled as having chronic kidney disease, but alerts are often ignored. If pharmacists use a pharmacy medication alert system (PMAS) based on renal function, they can provide the GP with therapeutic advice to optimise the medication. The extent of this advice and the feasibility in the clinical context are unknown.

Aim

To assess the therapeutic advice formulated by pharmacists with help of a PMAS based on the renal function of patients aged ≥70 years with diabetes or cardiovascular disease.

Design and setting

Observational study in primary health care in the Netherlands.

Method

GPs provided pharmacists with the renal function of older patients with diabetes or cardiovascular disease who were using target drugs, that is, drugs requiring therapeutic advice in patients with reduced renal function. With the help of a PMAS, pharmacists assessed the actual medication. The GP weighed the advice in relation to the clinical context of the individual patient.

Results

Six hundred and fifty patients were prescribed 1333 target drugs. Pharmacists formulated 143 therapeutic recommendations (11% of target drugs) concerning 89 patients (13.7% of study population). In 71 recommendations in 52 patients (8.0% of study population), the GP agreed immediately.

Conclusion

The use of a PMAS resulted in therapeutic advice in 11% of the target drugs. After weighing the clinical context, the GP agreed with half of the advice.

INTRODUCTION

Chronic kidney disease (CKD) is a growing health problem, with a prevalence from 4.9% in general practice in the UK to up to 13% in the US population.[1-3] The medical consequences of CKD are not only the risk of end-stage renal disease and cardiovascular morbidity, but also an increased risk of adverse drug events and medication-related hospital admissions.[4,5]

When renal function is reduced, the dosage of drugs that depend on renal excretion should be adjusted and nephrotoxic drugs should be avoided.[6-8] Patients with diabetes and cardiovascular disease have an augmented risk of CKD and frequently use renally cleared drugs.[1,9] Medication alerts systems warn prescribers of medication that can interact with impaired renal function, but these alerts are often ignored.[10-13] A medication alert system that weighs the actual renal function of the patient could help to reduce medication errors.[14-16]

This observational study assessed the therapeutic advice formulated by the pharmacist with help of a medication alert system based on the renal function of patients aged ≥70 years with diabetes or cardiovascular disease.

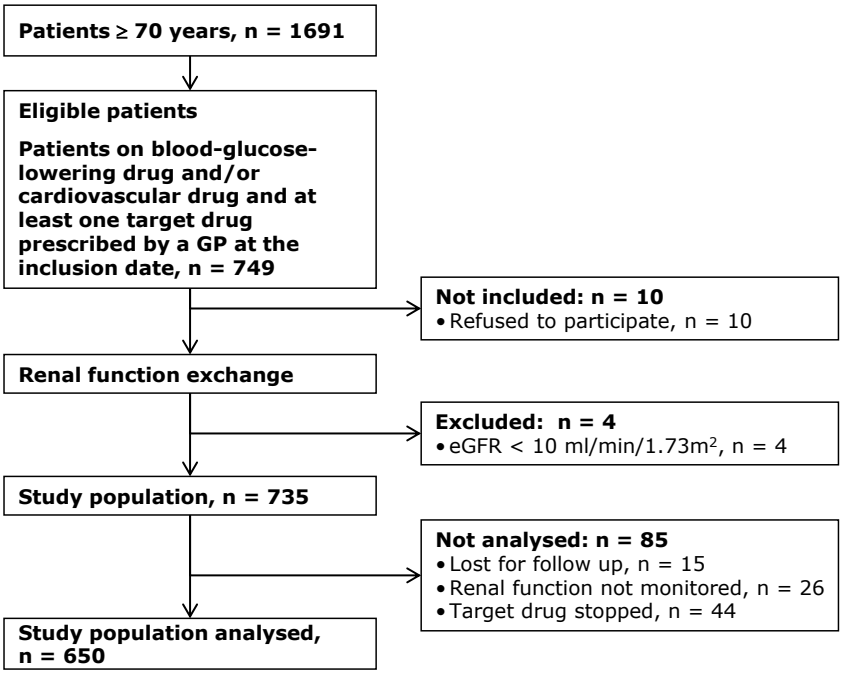
METHOD

Setting and study population

The study was conducted in Arnhem, a city in the East of the Netherlands with nearly 148 000 inhabitants. Seven GPs, belonging to the same pharmacotherapy audit meeting group, participated in the study. Five pharmacists who worked in close collaboration with this group selected the patients in their pharmacy computer system. Patients aged ≥ 70 years in the care of the participating GPs were eligible if they were on GP-prescribed maintenance therapy of blood-glucose-lowering or cardiovascular drugs (for example, digoxin, diuretics, or inhibitors of the renin-angiotensin system (RAS), including angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs)). Patients also used at least one 'target drug' on the inclusion date of 4 January 2010. 'Target drugs' were defined as drugs requiring therapeutic advice in patients with decreased renal function considering the Dutch dosing guideline for impaired renal function.[17] Patients with an estimated glomerular filtration rate (eGFR) < 10 ml/min/1.73m^2 were excluded (Figure 1).

The GPs already used a computerised medication monitoring system. This system generated an alert when the GP prescribed a target drug in patients labelled as having CKD, but it could not consider the eGFR level.

Figure 1 Selection of the study population



The use of drug dispensing data and laboratory test results in this study complied with Dutch privacy regulations.

Renal function monitoring

Actual eGFR was defined as an eGFR value measured within the last 12 months. If an actual eGFR was unknown, the GP requested the patient to undergo a blood test for renal function. The laboratory provided serum creatinine and an eGFR (ml/min/ 1.73m^2) calculated by the normalised four-variable Modification of Diet in Renal Disease (MDRD).[18] Serum creatinine was measured enzymatically (Modular, Roche diagnostics) and was IDMS (isotope dilution mass spectrometry) calibrated. The actual values of eGFR data were provided to determine drug-specific risk.

Assessment of renal function alerts

In this study, the pharmacists used a pharmacy medication alert system (PMAS) built by one of the authors (AG) in a Microsoft® Access database. The system, which was an addition to the current pharmacy computer system, assessed the medication in relation to the reported eGFR and provided an alert for target drugs according to the Dutch

guidelines for drug administration in reduced renal function.[17] These guidelines include drug-specific cut-off values for eGFR, accompanied by a therapy-adjustment advice.
After receiving a data file from the GP with the eGFR of the included patients, the pharmacists linked the eGFR in the PMAS. Simultaneously, the patient's actual medication was electronically imported from the usual pharmacy computer system into the PMAS. An alert was generated to stipulate action if the eGFR was lower than the cut-off value of the target drug (Table 1). The software could not correct for invalid dose or dose interval, so the pharmacist assessed the alerts for these aspects based on the guideline recommendations presented in a text box. The pharmacist formulated therapeutic advice for either dosage adjustment, to stop the drug, or to substitute it by a non-contraindicated drug. Once a week, the pharmacist communicated the therapeutic advice to the GP by a list. The GP evaluated the therapeutic advice in relation to the clinical context of each individual patient, and responded with agreement or disagreement. Predefined reasons for disagreement could be checked on the list and the GP was asked to give supplementary comments in a free-text box. The list was returned to the pharmacist.

Table 1 Predefined cut-off values top 10 target drugs with truncated guideline advice

Therapeutic group	Drug name	Cut-off values ml/min	Guideline advice
Blood-glucose-lowering drugs	Metformin	30-50	Initial dose 2x 500 mg
		<30	Contraindicated
	Glimepiride	10-50	Initial dose 50%
Cardiac glycosides, digoxin	Digoxin	10-50	Intial dose 50%
Low-ceiling diuretics, thiazides	Hydrochlorothiazide	30-50	Initial dose 12.5 mg
		<30	Contraindicated
High-ceiling diuretics	Furosemide	10-30	Dose higher
Potassium-sparing diuretics	Spironolactone	10-50	Monitor potassium
	Amiloride	30-50	Monitor potassium
		<30	Contraindicated
Diuretics combinations	Triamterene	30-50	Dose 50%, monitor potassium
		<30	Contraindicated
	Epitizide	<30	Contraindicated
Beta-blockers	Sotalol	30-50	Max dose 160 mg/day
		10-30	Max dose 80 mg/day
Angiotensin-converting enzyme inhibitors	Enalapril	30-50	Intial dose 5 mg
		10-30	Intial dose 2.5 mg

Outcome

The outcome of the study was the frequency of therapeutic advice formulated by the pharmacist (expressed as a proportion of the total number of target drugs). The management of the therapeutic advice by the GP was also studied.

Statistical analysis

All relevant patient data were entered into a Microsoft Access 2003 database and further analysed with SPSS Statistics (version 17.0) for descriptive statistics (mean, frequency, range).

RESULTS

On the inclusion date 650 patients were included and analysed (Figure 1). These patients were prescribed 1333 target drugs (Table 2). An actual eGFR had been determined in 78.5% (n = 510) of the patients (range per GP 66-89%). In the remaining patients, eGFR was determined after the inclusion date.

Table 2 Characteristics of the analysed study population

Characteristics	**n**	**%**
Patients	650	100.0
Female	433	66.6
Target drugs	1333	
	Mean	**SD [range]**
Age, years	81	6.7 [70-101]
eGFR, ml/min/1.73m^2	63.3	17.0 [13- >95]
Number of drugs	5.8	2.8 [1-17]
Number of target drugs	*2*	1.1 [1-7]
Patients prescribed target drugs by therapeutic group	**n**	**%**
Blood-glucose-lowering drugs	156	24.0
Cardiac glycosides digoxin	73	11.2
Low-ceiling diuretics thiazides	259	39.8
High-ceiling diuretics	164	25.2
Potassium sparing diuretics	49	7.5
Diuretics combinations	46	7.1
Beta-blocker sotalol	33	5.1
Beta-blockers atenolol/bisoprolol	31	4.8
RAS-inhibitors	224	5.1

eGFR = estimated glomerular filtration rate. RAS = renin-angiotensin system. SD = standard deviation

Assessment of renal function alerts

The computer software generated 212 alerts (15.9%) in a total of 1333 target drugs, because the eGFR was lower than the predefined cut-off value of the target drug. After the pharmacist assessed the actual medication for correct dose and dose interval, 93 alerts (7.0%) appeared to be correct and seven alerts (0.5%) were missing. Therefore, action to adjust therapy was considered necessary in 112 prescriptions in 74 patients (8.4% of the target drugs, 11.4 % of the patients). Additionally, pharmacists gave advice in 31 prescriptions of target drugs, even though the eGFR was just above the cut-off value. Eventually, 143 therapeutic recommendations (10.7% of the target drugs) concerning 89 patients (13.7% of analysed study population) were included for analysis of the GP responses. The drugs most frequently involved were diuretics (41.3% of therapeutic advice), blood-glucose-lowering drugs (14.0%), digoxin (11.2%), and RAS inhibitors (10.5%). Almost all prescriptions that received an alert were chronic prescriptions taken by the patient for a longer period of time.

GP response to pharmacist advice

The GP immediately agreed with 71 recommendations (49.7% of the therapeutic advice) concerning 52 patients (8.0% of the study population).The GP most frequently disagreed with the advice on diuretics, blood-glucose-lowering drugs, digoxin, and RAS inhibitors. Within each of these therapeutics groups, the GP immediately disagreed in one-third of the advice. The responses of the GPs are shown in Table 3.

DISCUSSION

Summary

The use of a PMAS based on renal function resulted in therapeutic advice for a substantial number of drugs in older patients with diabetes or cardiovascular disease. The GP immediately agreed with half of the advice. Overall, in 5% of the prescriptions, the GP agreed to rectify the prescription.

The GPs used a medication monitoring system based on the Dutch G-standard,[17] the national drug database, which is used by all professional parties in Dutch health care. Despite this monitoring system, pharmacists still formulated additive therapeutic advice in 11% of the target drugs. What could be the reasons for this? First, it is known that a high number of medication alerts may cause 'alert fatigue' in the prescriber.[10] In the case of repeat prescriptions in particular, alerts were ignored. The extra effort to seek a renal function and to weigh the choice and dosage of the drug may cost too much time. Second, this observation could be explained because at the time of prescription, an actual eGFR was not available in more than 20% of the patients. Finally, it is important

Table 3 GP response

Response	n (total N=143)	%	Comments
Immediate agreement	71	49.7	52 patients, 8% of study population
Postponed reaction	20	14.0	-
• GP first wants to consult specialist	12	8.4	-
• GP first wants to speak to patient	6	4.2	-
• Further monitoring biomarker(s)	2	1.4	Potassium, creatinine
Disagreement	38	26.6	-
• No standard reason indicated	17	11.9	No adverse reactions (n=1), already low dose (n=2)
• Potassium normal	5	3.5	
• Disease is stable	16	11.2	Diabetes (n=5), heart failure (n=7), hypertension (n=3), renal function (n=1)
Specialist is treating patient	14	9.8	Specialist was responsible for the drug therapy (GP only prescribed the refill prescriptions)

to consider the prescribing context. The alerts concerned chronic medication that the patient may have been using for a longer period of time, with an established clinical effect and with the patient accustomed to take them. Change of drug choice under these circumstances may disrupt the flow of treatment.

The use of PMAS reduced the number of alerts compared to the current pharmacy computer system. A more sophisticated clinical decision support system could further reduce the number of irrelevant alerts by incorporating invalid dose or dose- interval algorithms that can weigh comorbidity and other patient-related risk factors that may affect the reliability of the eGFR,[19] and by linking laboratory to pharmacy data. Currently, some of these principles are already incorporated in new versions of medication monitoring systems.

Strengths and limitations

This study revealed the benefit of therapeutic advice automatically generated by a PMAS based on renal function. The clinical relevance is substantial: prescribing of target drugs to older patients with diabetes of cardiovascular disease is a daily activity in primary care, and the risk of complications related to renal function is high.[4] Primary care studies on compliance to dosing guidelines in patients with CKD are rare.[6] Recently, Bhardwaja et al demonstrated in a large US study of 32 917 patients with an eGFR below 50 ml/min/1.73m^2, that an alert system in the pharmacy can result in a reduction of medication errors from 49% to 33%.[14]

The data may not be generalisable to other settings because of the small number of participating practices, but the underlying problem of medication safety in relation to renal function and the intervention of a PMAS is of general interest.
The advice given was based on a single eGFR value obtained not more 1 year previously. This was for pragmatic reasons: renal function of patients who are in a diabetes or hypertension control system should be monitored yearly. However, variability in serum creatinine measurements necessitates at least two creatinine measurements,[20,21] and even more frequent monitoring of renal function is needed in patients who are not stable.[22]

Comparison with existing literature

GPs immediately agreed with half of the therapeutic advice. This is in accordance with the acceptance rate in a study in which clinical pharmacists gave therapeutic recommendations to GPs based on the medical records of 200 patients with diabetes or hypertension.[23] In a hospital setting, the acceptance rate was the same: 55% of the pharmacist advice was accepted by the clinician.[15]
Besides the predefined reasons for disagreement, the GPs were not very explicit with their comments in the free-text box. Disagreement could be explained by a difference between the dosage guidelines and clinical practice. An example is the advice to start with low doses of RAS inhibitors to prevent adverse drug reactions, whereas current clinical practice guidelines do advise to prescribe RAS inhibitors in high doses in order to protect kidney function (with monitoring of renal function and serum potassium).[24-26] Meanwhile, the advice in the Dutch dosage guidelines has been adjusted to clinical practice.

Implications for research and practice

To optimise drug prescribing in patients with decreased renal function, many steps need to be taken: systematic renal function monitoring in patients on target drugs, linking the laboratory to the pharmacy, assessment of the alerts by both pharmacist and GP and communication with the patient on the proposed prescription change. When implementing a PMAS, all above-mentioned steps deserve attention.
A PMAS based on renal function resulted in therapeutic advice in one of every nine target drugs in older patients on blood-glucose-lowering or cardiovascular drugs. After weighing the clinical context, the GP agreed with half of the advice. Collaboration between GP and pharmacist, using their clinical and pharmacological expertise respectively, can contribute to patient safety.

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3.2

FEASIBILITY OF POINT-OF-CARE CREATININE TESTING IN DRUG THERAPY MANAGEMENT OF AMBULATORY ELDERLY IN COMMUNITY PHARMACY

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ABSTRACT

Background

In elderly patients with renal impairment it is often necessary to adjust drug therapy to establish effective and safe use. Clinical guidelines recommend regular monitoring of renal function in patients with diabetes and cardiovascular disease, but adherence to these recommendations varies from 28-75%. To assess appropriateness of drug therapy, pharmacists should have access to an actual renal function test result. Near patient testing and direct management of creatinine levels could have added value.

Objective

In this study feasibility of point-of-care creatinine testing (POCCT) was evaluated in drug therapy management of ambulatory elderly patients in community pharmacy.

Methods

Elderly on maintenance therapy with renally cleared drugs for diabetes or cardiovascular disease were eligible for POCCT. After consent, testing was performed by well-trained point-of-care operators. A pharmacist assessed the clinical relevance of electronically generated drug alerts based on actual renal function and the Dutch guidelines for drug-dosing in chronic kidney disease. If applicable, the GP of the patient was consulted and therapy adjustments were communicated to the patient. Feasibility was evaluated using questionnaires for patients and healthcare professionals.

Results

Of the 338 identified patients, 149 patients received an invitation letter for study participation because of unknown renal function (44%). In the study period 46 patients (31%) of this study population visited the pharmacy and underwent POCCT. Response rates for completing the patient and professional questionnaires were 87% and 100% respectively. Adherence to monitoring recommendations of creatinine improved with 13% in the selected population. More than half of the patients with POCCT had mild to moderate renal impairment. Evaluation of the questionnaires showed that POCCT was feasible for patients as well as for professionals.

Conclusions

POCCT has added value for effective drug therapy management by the pharmacist. It is a feasible technique in community pharmacy for patients, physicians and pharmacists.

INTRODUCTION

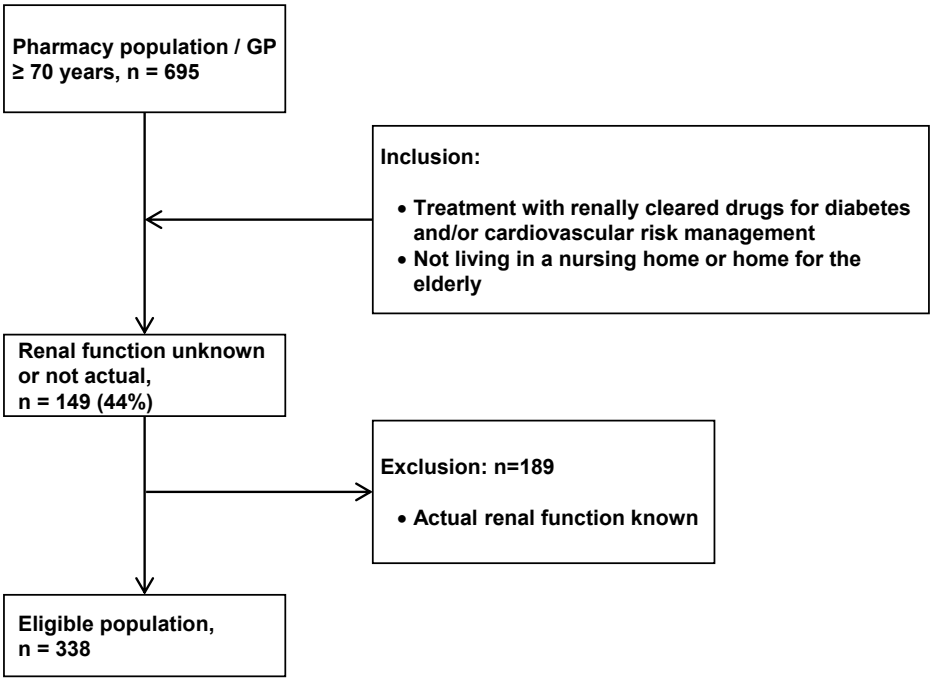
Chronic kidney disease (CKD) is a prevalent and growing health problem.[1-3] Adverse outcomes of CKD are mainly end stage renal failure and cardiovascular disease.
Important risk factors for the development of CKD are age, diabetes, obesity and hypertension. Elderly patients with diabetes and/or cardiovascular disease frequently use renally cleared drugs (RCD).[1,4] Dosage adjustment, or choosing an alternative drug, is often necessary in patients with renal impairment.[5] Therefore, regular monitoring of renal function is necessary for optimal drug therapy in these patients. CKD is a patient-related risk factor for medication-related hospital admissions.[6] In Dutch patients discharged from hospital, dosage adjustments were missing in 40% of the patients with CKD.[7]
Although the monitoring of renal function is frequently recommended in labels of RCD (28%)[8] and clinical guidelines [4,9-11], adherence of health care professionals to these recommendations varies from 28-75%.[12-17] Non-adherence can lead to preventable drug induced harm. All health care professionals involved in drug therapy management (DTM) should have access to actual renal function data to reduce the risk of harm in patients with CKD. Collaborative DTM by pharmacists can contribute to a safer use of medication by using their clinical pharmacological knowledge, skills and abilities to perform patient assessments, ordering laboratory tests, administering drugs, and selecting, initiating, monitoring, continuing and adjusting drug regimens.[18] Therefore, if actual renal function is unknown, not actual or unavailable at the moment a patient at risk for CKD visits the pharmacy, point-of care creatinine testing (POCCT) and DTM in pharmacy practice could have added value. Testing creatinine in capillary blood is a simple and fast method with the same clinical validity as central laboratory testing if quality issues are guaranteed by laboratory professionals.[19,20] Therefore in an integrated healthcare setting also laboratory professionals are required to guarantee efficiency and quality of point-of-care testing in primary care.[21,22] [23,24] Having access to immediate test results through point-of-care testing is well known in general practice and is associated with patient and healthcare professional's satisfaction and acceptability.[25-27] To our knowledge it has not been studied yet in community pharmacy. In this study we investigated the feasibility of POCCT in DTM of ambulatory elderly in community pharmacy.

METHODS

Setting and study population

The study was conducted during January-May 2011 in three community pharmacies in collaboration with five general practitioners (GPs) in two cities located in the South of The Netherlands**.** All ambulatory patients of 70 years or older who were treated with

Figure 1 Flow diagram of the study design



renally cleared drugs for diabetes and/or cardiovascular disease were identified from the pharmacy's patient management system (Figure 1). The GP indicated for which of these patients actual (defined as an eGFR value measured within the last 12 months) renal function was unknown. Patients were excluded if the GP indicated the patient had end-stage renal failure. The pharmacist sent a letter containing study information to all patients without an actual renal function and asked for informed consent. Patients who gave consent and visited the pharmacy during the study period were included for POCCT. There were no additional costs for the patient for POCCT. Ethical approval was obtained for this study from the Medical Ethics Committee of the University Medical Center Utrecht (NL32180.041.10).

Point-of-care creatinine analysis

Point-of-care operators (pharmacists or pharmacy technicians) in the participating pharmacies were trained by certified technicians of the department of Clinical Chemistry and Haematology at the University Medical Center Utrecht. These operators analysed creatinine in a capillary blood sample (finger prick, 65 µL) using the i-STAT® System and the CHEM8+ cartridge (Abbott Point-of-care, Wiesbaden, Germany), according to standard procedures. i-STAT® performance claims were verified and bias estimated by use of

CLSI protocols EP15-A2 and EP09-A2 by the above mentioned department. Potassium was simultaneously analysed and used as an indicator for collection-induced haemolysis, and therefore the difficulty of blood collection. Glomerular filtration rate (GFR) was estimated from capillary creatinine levels using the 4-variable Modification of Diet in Renal Disease (MDRD) equation.[3] If MDRD results were difficult to interpret because the value was within 10% of a drug specific threshold value, the patient was asked to participate in a second POCCT after one week. The GPs received the POCCT-results on a daily basis. Classification of renal function groups was according to the European dosing guidelines for drugs in renal impairment: no renal impairment (> 80 ml/min/1.73m^2), mild renal impairment (50-80 ml/min/1.73m^2), moderate renal impairment (30-49 ml/min/1.73m^2), severe renal impairment (10-29 ml/min/1.73m^2) and end stage renal failure (< 10 ml/min/1.73m^2).[5]

Drug therapy management

Generation of computer alerts and the additional background information on the therapeutic adjustment advice were standardized by using a pharmacy medication alert system (PMAS) instead of the current pharmacy patient management systems. By use of this system the actual medication of the patient was assessed in relation to the monitored eGFR and an alert was provided for renally cleared drugs according to the Dutch guidelines for drug-dosing in chronic kidney disease.[9] These guidelines include drug-specific eGFR-threshold values accompanied by information for DTM on selecting, initiating, monitoring, continuing and adjusting drug regimens and are based on the same European classification system.[5] Pharmacists assessed the clinical relevance of the computer generated alerts for correct dose, dosing frequency, initiation of a drug, chronic use, and the pharmacotherapeutical context. If applicable, the GP of the patient was consulted and therapy adjustments were communicated to the patient.

Questionnaire development

Feasibility of POCCT in community pharmacy was evaluated for each of the three stakeholders: patient, GP, and pharmacy operators, based on a self-administered structured questionnaire. Since a validated questionnaire regarding satisfaction and acceptation in relation to point-of-care testing in pharmacy was not available, we developed our own. The items were based on validated questionnaires about satisfaction with point-of-care testing in general practice [26], and commonly used methods for the development of questionnaires. [28-31]

The questionnaire for the patients consisted of 11 questions in two domains of point-of-care testing. There were two questions in the domain "Information in advance" and nine questions in the domain "Perception". Participants were asked to score the degree of satisfaction for each question on a 5-point Likert scale from poor (1 point) , moderate (2

points), sufficient (3 points), good (4 points), to very good (5 points).[28,32] Two additional questions about the handling of the intervention, assessed patients' preferences on the intervention. In a free text box at the end of the questionnaire patients were asked to give any supplementary comments. One week after the last POCCT patients got the questionnaire for self-administration by mail. It was not given directly to the patient at the moment of testing, because we expected patients to be more objective after one week, resulting in less social desirability bias.

Structured questionnaires to evaluate the GPs and pharmacy operators' views on POCCT consisted of 9 questions in three domains of point-of-care testing. Two questions in the domain "Information in advance", three questions in the domain "Efficiency", and four questions in the domain "Perception". There were two additional questions about the handling of the intervention that evaluated professionals' views on the intervention. The professionals were asked to give any supplementary comments in a free text box. The questionnaires were handed over at the end of the study period.

Table 1 Characteristics of the study population

Characteristics	**n = 149 (100%)**	
	n	**(%)**
Female gender	83	(55.7)
Age groups (years)		
70-79	108	(72.5)
80-89	38	(25.5)
90-99	3	(2.0)
Renal function at inclusion		
Unknown	45	(30.2)
Not actual (older than 1 year)	104	(69.8)
Comorbidity		
Diabetes mellitus	6	(4.0)
Cardiovascular diseases	115	(77.2)
Both	28	(18.8)
	Median	**Range (SD)**
Age (years)	76	70-95 (5.2)
Drugs (frequency)	5	1-12 (2.7)
Renally cleared drugs (frequency)	2	1-5 (1.1)

SD = standard deviation

Data analysis

POCCT in community pharmacy was considered feasible for each stakeholder if 60% of the responses per question were scored with three or more points, indicating that the majority was satisfied with the item. The comments of the stakeholders in the free text box were summarized qualitatively.

Data were analysed using SPSS Statistics 18.0 for descriptive statistics (mean, frequency, 40th percentile, range, standard deviation). The patients' questionnaire was validated by using the proportion of missing data to test acceptability. Cronbach alpha was used to test the internal reliability after factor analysis, and the face validity was assessed by the research group. Group differences between the GPs and the point-of-care operators were tested with the Mann-Whitney U test.

Table 2 Quantitative outcomes of POCCT

Outcome	**POCCT (n=44)***	
	n	**(%)**
Renal function group (ml/min/1.73m²)		
1. Normal (> 80)	20	(45.5)
2. Mild (50-80)	19	(43.2)
3. Moderate (30-49)	5	(11.4)
Renal function at inclusion		
Unknown	10	(22.7)
Not actual (older than 1 year)	34	(77.3)
Comorbidity		
Diabetes mellitus	2	(4.5)
Cardiovascular diseases	38	(86.4)
Both	4	(9.1)
Patients with therapeutic advice	1	(2.3)
Number of alerts (max n = 84)	9	(10.7)
	Median	**Range (SD)**
MDRD (ml/min/1.73m²)	77	37-149(26.0)
Potassium (mmol/L)	4.4	3.7-5.3(0.4)
Duration of testing (minutes)	15	7-47(6.7)

* Data of two patients not available because POCCT failed.

CKD = chronic kidney disease; MDRD = modification of diet in renal disease; POCCT = point-of-care creatinine testing.

Table 3 Patients' view on feasibility of POCCT in community pharmacy

Items[a]	Responders n = 38*			Percentiles
	Valid	Mean	(SD)	40
Information in advance (Cronbach α = 0.843)				
1. Was the written information in advance comprehensible?	36	4.08	(0.604)	4.0
2. Was the information in advance complete?	36	4.14	(0.683)	4.0
Perception (Cronbach α = 0.895)				
3. What do you think of the information at the start of testing?	37	4.43	(0.603)	4.0
4. What do you think of the personal attention of the POC operator?	37	4.62	(0.545)	5.0
5. What do you think of your privacy during the visit?	37	4.59	(0.498)	4.2
6. How did you experienced the POCCT testing?	37	4.43	(0.502)	4.0
7. What do you think of the explanation of the test result?	37	4.30	(0.661)	4.0
8. What do you think of the opportunity of POCCT testing in pharmacy?	38	4.53	(0.557)	4.0
9. Would you participate in the future again?[b]	37	4.76	(0.435)	5.0
10. What is your final assessment of the testing and advice?	38	4.50	(0.507)	4.0
11. What is your final assessment of the time that it takes?	38	4.34	(0.534)	4.0
Additional questions on the handling of the intervention				
• What is your impression about the consult between pharmacist and general practitioner?	5	4.20	(0.447)	4.0
• With whom do you prefer to discuss the test result?	general practitioner (n=4) no opinion (n=1)			

* Data of two patients not available because POCCT failed.

a: Scored on a 5-point Likert scale ranging from 1= bad to 5 = very good.
b: Scored on a 5-point Likert scale ranging from 1= strongly disagree to 5= strongly agree.
SD = standard deviation; POCCT = point-of-care-creatinine testing.

RESULTS

Of the 338 identified patients, 149 patients received an invitation letter for study participation because of unknown renal function (44 %; Figure 1). The majority of the study population was prescribed drugs for cardiovascular diseases (Table 1). In the study period 46 patients (31%) of this study population visited the pharmacy and underwent POCCT. In two patients in one pharmacy the POCCT failed due to technical problems (Table 2). Adherence to monitoring recommendations of creatinine improved therefore with 13% in the selected population. Of the patients with POCCT 55% had mild to moderate renal impairment and therefore at risk for therapy adjustment.
Validation of the creatinine assay by the department of Clinical Chemistry and Haematology at the University Medical Center Utrecht showed that its performance in this study setting was suitable. No collection-induced haemolysis occurred, suggesting capillary

Table 4 Professionals' view on feasibility of POCCT in the pharmacy

Items	General Practitioners (n=5)				Point-of-care operators (n=5)				T-test
	Valid	Mean	(SD)	Percentiles 40	Valid	Mean	(SD)	Percentiles 40	p
Information in advance [a]									
1. Was the written information in advance comprehensible?	4	4.25	(0.500)	4.0	5	4.00	(0.707)	4.0	0.571
2. Was the written information in advance complete?	4	4.00	(0.816)	4.0	5	3.80	(1.095)	4.0	0.771
Efficiency [b]									
3. How do you assess the ease of POCCT in the pharmacy?	5	3.20	(1.483)	3.0	5	4.40	(0.548)	4.0	0.128
4. How do you assess the time saving/ the time it takes?	5	3.20	(1.483)	3.0	4	3.25	0.500)	3.0	0.951
5. How do you assess the quick availability of test results for the patient?	5	3.80	(1.095)	3.0	5	4.60	(0.548)	4.4	0.195
Perception [b]									
6. How do you assess the feedback of test results/ availability of a test results?	5	3.80	(0.837)	3.4	5	4.60	(0.548)	4.4	0.111
7. How do you assess the continuing POCCT in pharmacy?	4	3.50	(1.291)	3.0	5	4.60	(0.548)	4.4	0.125
8. How do you assess the applicability in practice?	4	4.00	(0.816)	4.0	5	3.80	(1.304)	3.4	0.798
9. What is your final assessment of POCCT in community pharmacy?	5	3.60	(1.140)	3.4	5	4.00	(0.707)	4.0	0.524
Additional questions on the handling of the intervention [b]									
• Ad hoc consultation.	5	4.00	(0.707)	4.0	3	4.67	(0.557)	4.6	0.220
• Collaboration between pharmacist and general practitioner.	5	4.20	(1.304)	4.4	5	4.20	(0.837)	4.0	1.000

a: Scored on a 5-point Likert scale ranging from 1= poor to 5 = very good.

b: Scored on a 5-point Likert scale ranging from 1= strongly disagree to 5= strongly agree, and no opinion (0).

SD = standard deviation; POCCT = point-of-care-creatinine testing.

blood sampling went well. Repeated testing after one week was necessary for three patients. In one patient the second MDRD result had increased above the threshold and assessment of drug therapy was not necessary anymore. In two patients the first MDRD result was not registered in PMAS and, therefore, could not be used to calculate the change in MDRD. PMAS generated in seven patients nine alerts (11%) out of 84 RCDs used in the patients with POCCT. In one case the pharmacist had to give a therapeutic advice which was accepted by the GP. In two cases the dosage of the drug was already appropriate and in six cases the recommendations of the guideline were intended for initial dosage schemes and not for maintenance.

The numbers of responders to the questionnaires were 40 patients (87.0%), five GPs (100%), and five point-of-care operators (100%). After analysis of the responses, POCCT was deemed feasible in community pharmacy because more than 60% of the responses per item scored three or higher for each of the stakeholders (Tables 3 and 4). The GPs scored lower on the items in the domain "Efficiency", but this was not statistically significant compared to the point-of-care operators. The patients' questionnaire was valid because face validity and acceptability were appropriate and Cronbach alpha was high for the domains "Information in advance" and "Perception", 0.843 and 0.895 respectively, representing good internal reliability.

In the free text box ten patients (25%), three GPs (60%) and three point-of-care operators (60%) made statements on POCCT. Five patients wrote down a positive reaction of POCCT and two patients in whom the test failed were interested in the reason why. Two GPs postulated they had to test and communicate with the patients themselves, but they appreciated the therapeutic advice. One point-of-care operator postulated that a fee for this care is needed in the future, immediate availability of the test result is vital, and the software tool that generated the alerts was very helpful.

DISCUSSION

In this observational study, patients, GPs and point-of-care operators in the pharmacy considered POCCT as feasible in ambulatory elderly in community pharmacy. At the index date actual renal function (i.e. MDRD value) was unknown for four out of ten eligible patients at risk for chronic kidney disease and using RCDs.

Introduction of a high quality point-of-care testing service in primary care warrants certification by laboratory professionals to guarantee efficiency and quality. [23,24] It is increasingly being used and frequently applied in diabetes managed care programs, lipid monitoring, and anticoagulant therapy.[25,26,33-35] In this study the point-of-care operators in the pharmacy performed high-quality analyses of creatinine after training by hospital-based technicians. In two cases analysis failed, probably due to the use of

non-acclimatized cartridges or insufficient sample volume. No collection-induced haemolysis occurred, suggesting high quality capillary sampling.

The patient questionnaire showed good internal reliability, face validity and applicability, and high response rates. It was therefore considered appropriate for use in community pharmacy patients. Participating patients were very satisfied with this kind of service, and the pharmacist could immediately assess their medication(s) in relation to their renal function. One reason for not giving consent or not visiting the pharmacy could be the inhibitory effect of the study design in which patients first had to give written consent. Other reasons could be that patients preferred their hospital specialist to initiate or to repeat creatinine testing, patients were not able to visit the pharmacy or were not interested in their renal function. Further research is necessary to investigate the reasons why patients at risk for CKD did not gave consent and why actual renal function was still unknown for 44% of the eligible patients at risk for CKD. Of the monitored patients more than half had renal function group mild or moderate renal impairment while they used at least one RCD and in 86% of the monitored patients renal function was known but not actual at the moment of inclusion. These patients used mostly drugs for cardiovascular disease while in patients with diabetes renal function was regularly monitored because of the implemented diabetes managed care program in this setting. The Dutch general practitioners clinical guideline for cardiovascular disease recommend monitoring renal function at least once a year in patients at risk for chronic kidney disease and in patients with heart failure every half year.[36,37] Therefore, the potential for advice by the pharmacist concerning drug therapy adjustment was high in patients using cardiovascular drugs despite the actual clinical outcome of a single advice.

The professionals' satisfaction and acceptation of POCCT was sufficient to good, but two GPs were reserved in their opinion and would rather perform POCCT and the communication with the patient themselves. A reason for this view could be that GPs have the final responsibility for drug therapy adjustment. However, in an integrated care setting GPs and pharmacists have to collaborate and take advantage of each other's' clinical and pharmacological expertise with the mutual objective to improve patients' medication safety. In addition, four patients preferred to discuss the test result with their GP probably because of the confidential relationship. Although a creatinine testing service for patients with unknown renal function in community pharmacy has potential advantages including immediate availability of test results, well-adjusted drug therapy and improved patient satisfaction, these advantages could also be accomplished if testing is done in general practice. Also in this case, good collaboration between healthcare professionals is obligatory and it requires that the test results are shared real-time by linking laboratory data to medical and pharmacy data.[38,39]

One point-of-care operator in the pharmacy was concerned about the cost implications of implementing POCCT in the pharmacy. The median time to perform the assay and to

assess drug therapy was 15 minutes. A fee for care is needed for this professional service, also covering the costs of the materials. The use of PMAS was time saving and more efficient in DTM by the pharmacists. Generating alerts based on a simple algorithm, MDRD is lower than the threshold value of the RCD, reduced considerably the number of alerts. In current pharmacy patient management systems an alert is generated for each RCD in patients over 70 years old. More sophisticated clinical decision support systems with algorithms for the prescribed dose or discriminating between initial or chronic dosages can further reduce the number of alerts, making the alerts more clinically relevant and individualized.[40-42] Although, other studies raise concerns about the ability of health information technology to alter the quality of patient care.[43,44]

A limitation of our study is that the number of GPs and point-of-care operators was low and the internal reliability and applicability of the professionals' questionnaire could not be tested.

Besides the earlier recommendation to investigate why many patients did not gave consent or visited the pharmacy we also recommend to perform a cost-effectiveness analysis before implementing POCCT in community pharmacy. Meanwhile a managed care program for cardiovascular disease focusing on regularly monitoring renal function could improve health outcomes in these patients.

In conclusion, availability of actual renal function has added value for effective DTM by the pharmacist. It has the potential to improve monitoring in patients at risk for CKD and using RCDs. POCCT is a feasible technique in community pharmacy for patients, physicians and pharmacists.

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3.3

INEFFECTIVENESS AND ADVERSE EVENTS OF NITROFURANTOIN IN WOMEN WITH URINARY TRACT INFECTION AND RENAL IMPAIRMENT IN PRIMARY CARE

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ABSTRACT

Background

Nitrofurantoin is a systemic antibacterial often used to treat uncomplicated urinary tract infections (UTIs). According to the drug label nitrofurantoin is contraindicated when the estimated glomerular filtration rate (eGFR) is less than 60 mL/min/1.73m^2. New evidence indicates that nitrofurantoin in patients with lower eGFRs may be effective and safe.

Objective

To determine whether treatment with nitrofurantoin in women with UTI and renal impairment in primary care is ineffective and/or causes more adverse events.

Design, Setting, and Participants

A cohort of 21320 women treated with nitrofurantoin identified from the Pharmo Record Linkage System was analysed.

Measurements

The primary outcome was ineffective treatment of nitrofurantoin defined as the start of a second antibacterial within one month after the start of nitrofurantoin. The secondary outcome was the occurrence of serious pulmonary and neurotoxic adverse events diagnosed during hospital admission within ninety days. The association between renal impairment and the risk of these outcomes was determined with Cox proportional hazard ratios (HRs).

Results

Overall, the incidence density for ineffectiveness was 5.4 per 1000 person-days and moderate renal impairment was not associated with ineffective treatment (HR: 1.1; 95% confidence interval, 0.74-1.51). The overall incidence density for adverse events was 0.03 per 1000 person-days. In a multivariate model the HR for adverse events in patients with moderate renal impairment was not significantly increased (3.2; 0.91-11.4).

Conclusions

Nitrofurantoin treatment is effective in women with UTI and moderate renal impairment. These data confirm that the threshold value for use of nitrofurantoin in renal impairment can be lowered. Although renal impairment was not associated with adverse events of nitrofurantoin, further research is needed for the safety of nitrofurantoin in women with renal impairment.

INTRODUCTION

Acute uncomplicated lower urinary tract infection (UTI) is common in otherwise healthy, non-pregnant women of all ages.[1] More than 30% of all women will experience at least once a UTI during their lifetime.[1] Nitrofurantoin is an antibacterial for systemic use and is considered a treatment of first choice for the treatment of uncomplicated UTI in different guidelines.[2-4] It has been used as an antibacterial drug since 1953 and has a broad spectrum of activity against most gram-negative bacilli and many gram-positive organisms. Gram-negative organisms cause approximately 90% of uncomplicated UTIs.[1,5] A recently published Cochrane review suggested that nitrofurantoin is a good choice as a first line drug for treating uncomplicated UTI in women, because nitrofurantoin has less risk of developing rash than alternative treatment with trimethoprim-sulfamethoxazole and does not share cross-resistance with other commonly prescribed antibacterials.[1] However, there is concern about the effectiveness of nitrofurantoin in patients with renal impairment. According to the information in the Dutch drug label, nitrofurantoin is contraindicated when the creatinine clearance is less than 60 ml/min.[6] In patients with normal renal function nitrofurantoin is concentrated many-fold in the urine and urine concentrations reach a much higher level than the minimum inhibitory concentration (MIC).[7] In renal impairment the excretion of nitrofurantoin is decreased, and effective antibacterial levels in the urine may not be achieved. [8-10] However, the evidence from clinical research to support the recommendations in renal impairment is limited due to very small patient samples. Therefore, it is unclear how relevant the contraindication of nitrofurantoin in renal impairment is in daily practice in relation to its effectiveness.

Another important concern is that nitrofurantoin entails a greater risk of adverse events in patients with renal impairment. Due to decreased renal excretion of nitrofurantoin its serum levels increase, which may lead to a higher risk for the development of adverse events, such as peripheral neuropathy. Felts et al. described six patients, four with severe renal impairment (10-30 ml/min), who developed neuropathy during the use of nitrofurantoin. All these patients had used nitrofurantoin for at least 14 days, which is longer than the recommended standard treatment of 5-10 days.[8]

Recently, Bains et al. conducted a retrospective observational study in 356 hospitalized patients in which the efficacy and safety of the use of nitrofurantoin was compared between patients with an estimated glomerular filtration rate (eGFR) ≤ 50 ml/min (renal impairment group) and an eGFR > 50 ml/min (control group). [5] This retrospective study demonstrated that in hospitalized patients with an eGFR of 50 ml/min or less, nitrofurantoin appeared to achieve acceptable clinical recovery and was well tolerated. A large epidemiological study was conducted to determine whether these results can be confirmed in an outpatient population.

METHODS

Setting

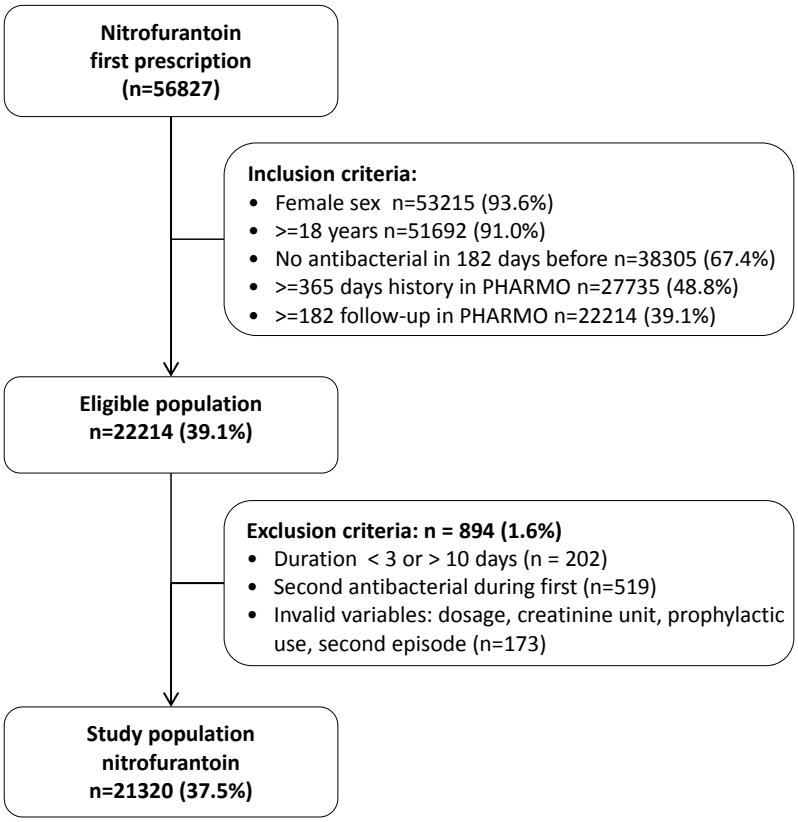
Data were obtained from the Dutch PHARMO Record Linkage System (RLS) a database with linked drug dispensing records from community pharmacies to general practitioner data, hospitalisation records and clinical laboratory data from individual patients.[11] This system includes the demographic details and complete medication history of more than three million community-dwelling residents from 1986 onwards. For this study drug dispensing data and hospitalization data were used. The computerized drug dispensing histories contain information concerning the dispensed drug, dispensing date, the prescriber, amount dispensed, prescribed dosage regimen, and the estimated duration of use. Drugs are coded according to the Anatomical Therapeutic Chemical (ATC) classification.[12] The hospitalization register comprises all hospitalizations in the Netherlands, including detailed information concerning the primary and secondary discharge diagnoses, diagnostic, surgical, and treatment procedures, type and frequency of consultations with medical specialists and dates of hospitalization and discharge. All diagnoses are coded according to the International Classification of Diseases, 9th edition (ICD-9-CM). All PHARMO RLS linked research is in accordance with Dutch privacy and ethical regulations.

Study design and population

A retrospective cohort study was conducted with a sample of the PHARMO RLS. Patients were eligible for inclusion in the study population when they were female, 18 years or older and had received a prescription for nitrofurantoin for 3 to 10 days between 1 January 2005 until 31 December 2010 (Figure 1). These patients had not received any antibacterial prescription at least half a year prior to the start of nitrofurantoin. In addition, they had at least one year of medication history prior to the start of nitrofurantoin and six months follow-up after the start of nitrofurantoin. Patients were excluded if a second antibacterial had been prescribed before the course of the first antibacterial had been completed, since it was impossible in such cases to ascertain whether the second antibacterial had been given because of ineffectiveness, intolerance or other side effects.

Both nitrofurantoin users with an actual creatinine value - measured between the day of the start of nitrofurantoin to one year before the start- and users without a known creatinine value were included in the study population. In the Netherlands the recommended dosage regimen of nitrofurantoin is 50 mg 4 times a day or 2 times daily 100mg for extended release preparations.[13] The recommended normal duration of uncomplicated UTI treatment is 5 days.[2]

Figure 1 Flowchart of the study population



Outcome

The primary outcome was ineffective treatment of nitrofurantoin defined as the start of a second antibacterial for treatment of UTI other than nitrofurantoin within one month after the start of nitrofurantoin. The secondary outcome was the occurrence of serious pulmonary and neurotoxic adverse events of nitrofurantoin leading to hospitalization as described in Meyler's side effects of drugs.[14] ICD9 codes were included if diagnosed during subsequent hospital admissions during 90 days after start of antibacterial treatment: neurotoxic adverse events: ICD9 = 357, 356, 729.5, or pulmonary adverse events ICD9 = 780.6, 782.5, 786.

Renal impairment

Outcome measures were computed separately for patients per renal function group using estimated glomerular filtration rates (eGFR) estimated from creatinine levels us-

ing the original 4-variable Modification of Diet in Renal Disease equation.[15] An eGFR of < 50 ml/min/1.73m^2 was considered to reflect renal impairment. The predefined renal function groups were > 80 ml/min/1.73m^2 (no renal impairment), 50-80 ml/min/1.73m^2 (mild renal impairment), 30-49 ml/min/1.73m^2 (moderate renal impairment), 10-29 ml/min/1.73m^2 (severe renal impairment) and < 10 ml/min/1.73m^2 (end stage renal failure), as derived from the European dosing guidelines for drugs in renal impairment.[16] Patients without creatinine values were classified as 'unknown'.

Potential confounding factors

The following factors were studied to control for potential differences between groups in predisposition to (recurrent) UTIs: age, use of immunosuppressive drugs (decreased immunity), use of urinary antispasmodics (incontinence), use of blood glucose lowering drugs (diabetes mellitus), use of acetylsalicylic acid in combination with dipyridamole (stroke), tamsulosin (kidney stones), rivastigmine or galantamine (cognitive impairment), distigmine or carbachol (incomplete bladder emptying), and sodium phosphate, magnesium citrate, potassium citrate/phosphate, citric acid, or allopurinol (urolithiasis).[17]

Data analysis

Descriptive statistics (mean, min, max, sum) were used to describe frequencies and incidence density ratios in the study population. The strength of the associations between renal function and ineffective treatment and serious adverse events respectively was evaluated with multivariate Cox regression analysis and expressed as hazard ratios (HR) with 95% confidence intervals (95%CI). Covariates were included in the multivariate analysis if they induced a change in the crude regression coefficient of at least 10%. Age is an important covariate in the analysis of adverse events, because elderly have a higher risk of pulmonary and neurotoxic adverse events, and nitrofurantoin is not recommended in these patients.[18,19] Data analysis was performed with IBM SPSS Statistics 19.0 for windows (IBM Inc., New York).

RESULTS

Of the 21320 included female patients, 3888 patients (18.2%) could be classified according predefined renal function groups because their creatinine value was known (Table 1). Renal impairment (<50 ml/min/1.73m^2) was observed in 4.8% (n=187) of these patients. Among the risk factors for UTIs, diabetes was most prevalent. Most patients were treated with nitrofurantoin for 4 or 5 days (80.5%).

Table 2 shows the association between renal impairment and the risk of a second antibacterial (ineffective treatment) within one month after start of nitrofurantoin. Overall

Table 1 Baseline characteristics of the study population

	Nitrofurantoin		eGFR (ml/min/1.73m2)									
	Total		> 80		50-80		30-49		10-29		<10		unknown	
	n=21320 (100%)		n=1859 (100%)		n=1842 (100%)		n=166 (100%)		n=20 (100%)		n=1 (100%)		n=17432 (100%)	
Age; Mean, Years (range)	47.8 (18-103)		46.5 (18-103)		64.7 (18-100)		78.9 (49-103)		79.1 (50-97)		80.0 (80)		45.8 (18-100)	
18-29	5116	(24.0)	469	(25.2)	58	(3.1)	0	(0)	0	(0)	0	(0)	4589	(26.3)
30-44	5161	(24.2)	457	(24.6)	159	(8.6)	0	(0)	0	(0)	0	(0)	4545	(26.1)
45-64	5938	(27.9)	542	(29.2)	650	(35.3)	16	(9.6)	1	(5.0)	0	(0)	4729	(27.1)
> 64	5105	(23.9)	391	(21.0)	975	(52.9)	150	(90.4)	19	(95.0)	1	(100.0)	3569	(20.5)
Risk factors														
Diabetes	857	(4.02)	86	(4.6)	185	(10.0)	29	(17.5)	5	(25.0)	0	(0)	552	(3.2)
Immunosuppressive drugs	87	(0.41)	14	(0.8)	14	(0.8)	4	(2.4)	1	(5.0)	0	(0)	54	(0.3)
Urolithiasis	57	(0.27)	2	(0.1)	18	(1.0)	4	(2.4)	0	(0)	0	(0)	33	(0.2)
Stroke	144	(0.68)	7	(0.4)	27	(1.5)	10	(6.0)	1	(5.0)	0	(0)	99	(0.6)
Antispasmodic drugs	138	(0.65)	11	(0.6)	15	(0.8)	2	(1.2)	1	(5.0)	0	(0)	109	(0.6)
Kidney stones	9	(0.04)	0	(0.0)	2	(0.1)	1	(0.6)	0	(0)	0	(0)	6	(0.0)
Cognition	29	(0.14)	3	(0.2)	7	(0.4)	1	(0.6)	0	(0)	0	(0)	18	(0.1)
Incomplete bladder emptying	17	(0.08)	2	(0.1)	3	(0.2)	1	(0.6)	0	(0)	0	(0)	11	(0.1)
Duration of antibacterial treatment; Mean, Days (range)	5.2 (3-10)													
3	1195	(5.6)	48	(2.6)	48	(2.6)	4	(2.4)	0	(0)	0	(0)	1095	(6.3)
4,5	17156	(80.5)	1557	(83.8)	1516	(82.3)	129	(77.7)	17	(85.0)	0	(0)	13937	(80.0)
6-10	2969	(13.9)	254	(13.7)	278	(15.1)	33	(19.9)	3	(15.0)	1	(100.0)	2400	(13.8)
eGFR; Mean, (range)	82.9 (9-200)		102.3 (81-200)		67.9 (50-80)		42.4 (30-49)		23.2 (10-29)		9.0 (9)		NA	

eGFR = estimated glomerular filtration rate; NA = not applicable.

Table 2 Association between renal impairment and ineffectiveness of nitrofurantoin

	Second antibacterial n (%)		Follow-up time (person-days)	Incidence density (per 1000 person-days)	Crude HR (95%CI)		Adjusted[a] HR (95% CI)	
eGFR (ml/min/1.73m2)								
>80	291	(15.7)	49497	5.88	1.00	reference	1.00	reference
50-80	314	(17.0)	48277	6.50	1.10	(0,94-1,29)	0.92	(0.78-1.08)
30-50	35	(21.1)	4191	8.35	1.41	(0,99-2,00)	1.06	(0.74-1.51)
10-30	6	(30.0)	456	13.16	2.12	(0,95-4,76)	1.57	(0.70-3.53)
< 10	0	(0)	30	NA	NA		NA	
Unknown	2431	(13.9)	469598	5.18	0.89	(0.78-1.00)	0.89	(0.79-1.01)
Overall	3077	(14.4)	572049	5.38				

HR= hazard ratio; 95%CI = 95% confidence interval
a: adjusted for age and use of blood glucose lowering drugs.

Table 3 Association between renal impairment and adverse events of nitrofurantoin

	Adverse event n (%)		Follow-up time (person-days)	Incidence density (per 1000 person-days)	Crude HR (95%CI)		Adjusted[a] HR (95% CI)	
eGFR (ml/min/1.73m2)								
>80	7	(0.38)	166941	0.04	1.00	reference	1.00	reference
50-80	13	(0.71)	165091	0.08	1.88	(0.75-4.71)	1.18	(0.47-3.01)
30-50	4	(2.41)	14719	0.27	6.46	(1.89-22.1)	3.22	(0.91-11.4)
10-30	0	(0.00)	1800	NA	NA		NA	
< 10	0	(0.00)	90	NA	NA		NA	
Unknown	29	(0.17)	1567283	0.02	0.44	(0.19-1.01)	0.46	(0.20-1.06)
Overall	53	(0.25)	1915924	0.03				

HR= hazard ratio; 95%CI= 95% confidence interval
a: adjusted for age and use of blood glucose lowering drugs.

incidence density for ineffectiveness was 5.4 per 1000 person-days. Renal impairment was not associated with ineffective treatment, although a non-significant trend for higher incidence densities was observed as renal function declined: 5.9 per 1000 person days for no renal impairment (>80 ml/min/1.73m^2) and 13.2 per 1000 person-days for moderate renal impairment (30-49 ml/min/1.73m^2) (HR: 1.1; 95%CI: 0.74-1.51), respectively. Table 3 shows the association between renal impairment and the risk of a serious adverse event of nitrofurantoin. Neurotoxic adverse events were not observed in the three months follow-up after the start of nitrofurantoin. Overall incidence density for adverse events was 0.03 per 1000 person-days. The HR (95%CI) for adverse events after the start

of nitrofurantoin in patients with moderate renal impairment compared to patients with no renal impairment was 6.5 (1.89-22.1). After adjustment for age and diabetes renal impairment was not significantly associated with these adverse events: 3.2 (0.91-11.4). Patients with unknown renal function have lower point estimates for ineffectiveness and adverse events than patients with renal function.

DISCUSSION

Overall, renal impairment was not associated with ineffective treatment of nitrofurantoin in women with UTI. A non-significant trend for higher incidence densities was observed with decreasing renal function. Renal impairment was not associated with adverse events of nitrofurantoin. A non-significant trend between renal impairment and adverse events of nitrofurantoin was observed.

Nitrofurantoin is considered a treatment of first choice for treating uncomplicated UTI in women.[1] The amount of nitrofurantoin excreted into the urine is directly related to renal function and therefore nitrofurantoin may be ineffective for treatment of UTI patients with reduced renal function.[7,9,10] Nevertheless, Baines et al. reported that in hospitalized patients with renal impairment (< 50 ml/min) nitrofurantoin is effective and well tolerated. In this study frequencies for starting a second antibacterial were comparable for the renal impairment group (29%) and control group without renal impairment (24%). In our study we showed that the frequency of patients with ineffective nitrofurantoin treatment was the same in patients with renal impairment. In patients with unknown renal function ineffective treatment occurred even less (14%). However, these results are not directly comparable with previous studies, because of differences in study design, patient population and number of patients.

The total incidence rate for serious adverse events of nitrofurantoin including pulmonary, neurotoxic, hepatic and haemolytic reactions is less than 0.003%.[8]

In our study, no neurotoxic adverse events were diagnosed, except one diagnosis for pain in the limb, which can be related to polyneuropathy. Most frequently pulmonary abnormalities were diagnosed in the three months after nitrofurantoin treatment (0.24%), However, causality between nitrofurantoin and these adverse events is difficult to establish.

In order to study the association between renal impairment and adverse effects of nitrofurantoin we used the Pharmo database. The registration of adverse effects in the Pharmo database is limited to adverse effects leading tot hospitalization which only encompasses the tip of the iceberg of all adverse effects. Therefore, the occurrence of adverse effects of nitrofurantoin use in relation to renal impairment may be underestimated. Although, we conducted our study in a large study population, the total number

of events, and the power therefore, was limited. To elucidate what happens on micro level studies with more sensitive markers for adverse events are needed. In addition, the number of patients with renal impairment less than 30 ml/min/1.73m^2 was limited. An explication could be that not all laboratories provide data to the Pharmo database. A bias could also occur because physicians are aware of the contraindication for nitrofurantoin. Although, renal impairment was not significantly associated with adverse events of nitrofurantoin, generalisation of the results for patients with renal impairment is therefore difficult.

In patients with unknown renal function we observed lower point estimates for ineffective treatment and/or ADE than in patients with a known renal function. An explanation could be that patients with an unknown renal function are "healthy survivors".[20]

The strength of this study is that it was conducted in a large study population with a relative long follow-up time in general practice.

This retrospective cohort study demonstrates that nitrofurantoin treatment is effective in women with UTI and moderate renal impairment. These data confirm that the threshold value for use of nitrofurantoin in renal impairment can be lowered. The Dutch guidelines for drug-dosing in chronic kidney disease has been lowered the threshold value, accordingly.[13] Although, renal impairment was not associated with adverse events of nitrofurantoin, further research is needed for the safety of nitrofurantoin in women with renal impairment.

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4

EFFECTS OF DRUGS ON LABORATY TESTS

4.1

INFORMATION COMPARISON OF THE EFFECTS OF DRUGS ON LABORATORY TESTS IN DRUG LABELS AND IN YOUNG'S BOOK

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ABSTRACT

Background

Effects of drugs on laboratory tests may lead to misinterpretation of laboratory data, unnecessary tests, higher costs and missed diagnoses. This study compared the information on drug-laboratory effects (DLE) described in 200 drug labels with that in Young's book.

Methods

Information on DLE was searched in the drug labels of 200 frequently prescribed drugs using the keywords 'interfer*', 'influence', and 'laborator*'. This information was compared with the information in Young's book. Each item of information scored 1 point if it was specific and exactly the same. Primary outcome was the percentage of DLE with completely the same information.

Results

In 23 (11.5%) of the 200 drug labels 83 DLE were described. Most DLE were described in drug labels of contraceptives (71%) and antibacterials (15%). The most frequently affected laboratory tests were adrenal gland (17%), urine tests (15%), liver tests (10%) and renal function tests (10%). Comparison of six DLE with Young's book was not possible because the information was not described in the book. Twelve (14.5%) DLE of the information in the drug label was identical to that in Young's book. Detailed information about nature of the effect, strength of the effect and body fluid was not described in the drug labels.

Conclusions

In a limited number of DLE in the drug labels the information was the same as in Young's book. Overall, the information on DLE provided in drug labels is unclear, inconsistent and incomplete and does not support healthcare professionals in making evidence-based monitoring decisions.

INTRODUCTION

It is well known that drugs can affect laboratory test results. This may lead to misinterpretation of laboratory data, unnecessary tests, additional costs and missed or incorrect diagnoses.[1] An alert from the Food and Drug Administration in 2009 showed the potential risk of falsely elevated blood glucose levels in patients using products containing non-glucose sugars, when using test strips with the enzyme glucose dehydrogenase-pyrroloquinoline quinone.[2] Thirteen deaths were associated with this drug-laboratory test interference. Extensive information on Drug-Laboratory Effects (DLE) is available that describes the effects of drugs on laboratory test results and incorporated in the book of Young.[3] Two other sources of information on DLE are commonly used in clinical practice. Clinical chemists also use the manual of the analyser provided by instrument manufacturers, but this information is insufficient, not standardised and difficult to access and interpret for clinical decision making.[1,4] Physicians and pharmacists are more focused on the information on DLE in the drug label or the Summary of Product Characteristics (SPC) of the drug manufacturer. However, little research is available about the information on DLE in drug labels. Therefore, the objective was to compare the information on DLE described in drug labels of 200 commonly prescribed drugs in the Netherlands with that in Young's book.

MATERIALS AND METHODS

Selection of drug labels

The 200 most frequently prescribed drugs in the Netherlands were identified from dispensing data between July 2006 and July 2007 of 100 Dutch community pharmacies, covering a population of 720,000 patients.[5] The corresponding drug labels were obtained from the website of the Dutch Medicines Evaluation Board, which contains information on all medicinal products nationally approved[6] or the related website of European Medicines Agency for drugs authorised by the centralised authorisation procedure in the European Union.[7] The use of the drug-dispensing data was performed in accordance with current Dutch privacy and ethical regulations[8] and approved by the Institutional Review Board of the Utrecht Institute for Pharmaceutical Sciences.

Information on DLE in drug labels

Two different mechanisms are distinguished in which drugs can affect laboratory tests. In vitro by analytical interference which affects the laboratory test result of a specific measurement procedure or by physiological influence of the drug on the concentration of a biomarker in vivo.[9] Information on DLE, both in vitro and vivo effects, was searched in the drug labels using the keywords 'interfer*', 'influence', and "laborator*". One of the

authors (pharmacist AG) screened the drug label with the marked keywords and classified the information into affected laboratory test and direction of the effect (increase, decrease).[10] A second pharmacist (FdK) validated the classification of these items of information in a random sample of 10% of the drug labels. Both pharmacists initially agreed in 95% of the random sample and consensus was reached in the classification for the rest.

Comparison of information

The items of information on DLE from the drug label were compared with the standard source of information on this particular subject: Young's book.[3] In this book information is provided about effects of drugs on clinical laboratory tests. The information is classified by the interfering drug name or drug class, and laboratory test. Each DLE is further classified by body fluid, nature of effect, and direction of effect (increasing, decreasing, no effect). Two items of information, the affected laboratory test and the direction of effect, which are included in both sources, were compared. If the item of information in the drug label was exactly the same as in Young's book, this scored 1 point. So, each DLE in the drug label could maximally score 2 points. When information in the drug label was not specific enough, the score was 0 points, e.g. in the drug label one of the described laboratory tests was liver tests, but this information was not specific enough to compare with the information in Young's book (alanine transaminase, aspartate transaminase, or gamma glutamyl transpeptidase). If a drug name or drug class was not described in Young's book comparison was not possible and therefore not applicable.

Data analysis

Descriptive statistics was performed to evaluate the frequency of drug labels DLE and the number of DLE by laboratory test, drug name and direction.

Primary outcome was the percentage of DLE with completely the same information (score = 2) compared with Young's book, calculated as the number of $DLE_{score=2}$ divided by the total number of DLE in the drug labels.

RESULTS

Eighty three DLE in twenty three drug labels (11.5%) were identified, an average of 3.6 DLE (range: 1 – 9) per drug label. Most DLE were described in drug labels of contraceptives (71%) and antibacterials (15%), whereas the affected laboratory test most frequently concerned was adrenal gland (17%), urine tests (15%), liver tests (10%) and renal function tests (10%). Table 1 summarizes the scores of 83 DLE after comparison of the information on DLE in drug labels and in Young's book. Twelve (14.5%) DLE scored the maximum of 2

Table 1 Comparison of information on drug-laboratory effects in drug labels and in Young's book

Drug name or class	Laboratory test	Number of DLE	Score* for item laboratory test	Score* for item direction of effect	Total
Amoxicillin/Clavulinic acid	estriol	1			NA
Amoxicillin/Clavulinic acid	glucose (urine)	1	1	1	2
Amoxicillin/Clavulinic acid	urobilinogen (urine)	1	1	0	1
Captopril	ketones (urine)	1	1	1	2
Contraceptives	adrenal gland (x6)	6	0	0	0
Contraceptives	aldosterone/renin (x1)	1			NA
Contraceptives	carbohydrate metabolism (x6)	6	0	0	0
Contraceptives	coagulation (x6)	6	0	0	0
Contraceptives	corticosteroid binding globulin (x6)	6	1	0	1
Contraceptives	fibrinolysis (x6)	6	0	0	0
Contraceptives	lipids (x5)	5	1	0	1
Contraceptives	liver tests (x6)	6	0	0	0
Contraceptives	renal function (x6)	6	0	0	0
Contraceptives	thyroid function (x6)	6	0	0	0
Cotrimoxazole	creatinine	1	1	0	1
Cotrimoxazole	methotrexate	1	1	1	2
Digoxin	therapeutic drug monitoring	1	1	0	1
Doxycycline	glucose (urine)	1	1	0	1
Medroxyprogesterone	coagulation factors	1	1	1	2
Medroxyprogesterone	glycoproteins	1	1	1	2
Medroxyprogesterone	liver tests	1	0	1	1
Medroxyprogesterone	steroids	1	0	1	1
Meloxicam	creatinine	1	1	1	2
Meloxicam	urea	1	1	1	2
Meloxicam	aminotransferases	1			NA
Methylphenidate	amphetamine	1	1	1	2
Metronidazole	color (urine)	1	0	0	0
Minocycline	glucose (urine)	1	1	0	1
Nadroparin	thyroid function	1			NA
Naproxen	5-hydroxyindoleacetic acid (urine)	1	1	0	1
Naproxen	cortisol	1	1	0	1
Nitrofurantoin	glucose (urine)	1	1	1	2
Norethisterone	lipids	1	0	0	0
Norfloxacin	17-ketosteroids (urine)	1			NA
Norfloxacin	glucose (urine)	1	1	1	2
Norfloxacin	vanilyl mandelic acid (urine)	1			NA
Sotalol	metanephrines (urine)	1	1	1	2
Spironolactone	cortisol	1	1	0	1
Valproic acid	ketones (urine)	1	1	1	2
Total		83	22 (26.5%)	14 (16.9%)	

* score = 1 point if information is the same in the drug label and in Young's book, otherwise score = 0. NA= not applicable; DLE= drug-laboratory effects.

points. The same information in different contraceptives was combined. Comparison of six DLE with Young's book was not possible because the information was not described in the book. In 38 DLE (46%) the information on direction was inconsistent in Young's book, e.g. in the section of the laboratory test glucose of the contraceptives the direction was described as an increase as well as no effect. In the drug label detailed information about nature of the effect, strength of the effect and body fluid was not described.

DISCUSSION

Accurate laboratory test results are important in clinical decision making and therefore good information on DLE is mandatory. We found that the information on DLE in drug labels was incomplete and frequently missed essential information on specific laboratory test, strength of the effect, direction of the effect, body fluid and nature of the effect. DLE was frequently described in one of every nine drug labels. Previous studies demonstrated that information on DLE in general provided by instrument manufacturers was inadequate.[4,11]

DLE in drug labels for contraceptives were extensive, up to seventy percent of the DLE. However, a connotation in the drug label mentioned that changes in laboratory test results were within the normal range and so the clinical relevance of these DLE seems irrelevant. This was in contrast with previous studies of significant DLE of estrogens on laboratory tests.[12-14] Also, in Young's book the DLE was described, and additional information about direction and nature of the effect was provided, but quantification of the strength or clinical significance of the DLE was scarce.[3]

Furthermore, for antibacterials false positive test results for serum creatinine are well known in literature, but comprehensive information in the drug labels was lacking. Finally, false positive glucose tests in urine, for example for nitrofurantoin, is scarcely described in literature, but in several drug labels this DLE was described.

These three examples illustrated that the information on DLE in drug labels of commonly prescribed drugs was unclear, inconsistent, and incomplete.

Information on direction was difficult to interpret. In nearly half of the DLE it was inconsistent in Young's book, because all effects described in the references were mentioned without a conclusion of the overall effect on direction. In addition, not all DLE were described in this standard source because it was published in the year 2000.

Information on the strength of the effect is essential to assess the clinical relevance of the biological effect or the analytical interference. The strength of the effect highly depends on different factors like the concentration of the drug or its metabolites, time of sampling, the concentration of analyte, or the measurement procedure. Therefore, no

specific limit exists for each clinically relevant effect.[1] Limits for the presence of an effect can range from 5-30%.

Despite the enormous information available on DLE it still leads to medication safety issues. To bridge the information gap between professionals, a more extensive transfer of knowledge from the laboratory specialist to other health care professionals is mandatory to ensure medication safety in the future.[4] It is necessary to transform information from analyser manuals, drug labels, and literature into digitally applicable clinical decision support systems (CDSS) which can generate clinical relevant computer alerts by linking of laboratory, clinical and pharmaceutical data.[15] One free online searchable database for effects of drugs on clinical laboratory tests, Young's Effects Online, is no longer accessible and therefore books or commercial databases on DLE must be consulted manually for each DLE.[3,10,16] To handle the overload of potential DLE a CDSS could support laboratory specialists, clinicians, and pharmacists to manage the extensive knowledge on this subject and helps them in making evidence based decisions.[10,16]

In conclusion, in a limited number (15%) of the drug labels the information on DLE was the same as in the book. Overall, the information on DLE provided in drug labels is unclear, inconsistent and incomplete and does not support healthcare professionals in making evidence-based monitoring decisions. To improve medication safety we recommend a concerted effort of clinical chemists, physicians and pharmacists developing a CDSS with extensive and clear information on DLE.

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4.2

EFFECTS OF TRIMETHOPRIM ON CREATININE LEVELS IN HOSPITALIZED PATIENTS

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ABSTRACT

Background

Effects of drugs on clinical laboratory tests are well known. Trimethoprim can induce an increase of creatinine levels by inhibiting the tubular secretion of creatinine without affecting glomerular filtration rate. This can lead to the wrong clinical conclusion that renal function is decreased and consequently to incorrect adjustment of drug therapy.

Aims

In this 'proof of concept' study, the in vivo effect of trimethoprim on creatinine levels was studied using a database of linked pharmacy and laboratory data of hospitalized patients without impaired renal function.

Methods

A cohort of 414 patients treated with trimethoprim or other antibacterial drugs during hospital admission, selected from the Utrecht Patient Oriented Database, was analysed. The primary outcome was an increase of creatinine levels of 10% or more after start of the antibacterial treatment. The secondary outcome was a decline of renal function group.

Results

Trimethoprim was significantly associated with a creatinine increase over 10%: 21.9 per 100 person-days (HR: 2.61; 95%CI: 1.64-4.18).
The number of patients of 16 years and older with a decline of renal function group was significantly higher in patients treated with trimethoprim than in patients with other antibacterials, 18.4% vs. 9.6% (RR: 1.92; 95%CI: 1.10-3.36), respectively.

Conclusions

This study demonstrates that trimethoprim use is associated with a significant increase in creatinine levels in hospitalized patients without impaired renal function. This effect of trimethoprim on the creatinine level was associated with a double number of decline of renal function group in patients on trimethoprim compared to patients on other antibacterials.

INTRODUCTION

It is known that drugs can affect the results of clinical laboratory tests.[1-3] Falsely increased or decreased laboratory test results may lead to wrong diagnostic and therapeutic decisions and unnecessary harm and costs. Although for many drugs, in vivo and in vitro effects on laboratory tests have been described, the extent of these drug-laboratory interactions have rarely been quantified in terms of incidence in clinical practice and the clinical relevance thereof.[4] Two different mechanisms are distinguished by which drugs can affect laboratory tests: (a) in vitro by an analytical interference affecting the laboratory test result of a specific test or (b) by a physiological effect of the drug on the concentration of a biomarker in vivo.[5]

By use of standardised procedures in clinical laboratories it is possible to compensate or correct for most drug induced analytical interferences.[6] In contrast, in vivo effects are more difficult to correct because the test result truly reflects the concentration of the laboratory marker in the patient. For example, the antibacterial agent trimethoprim can significantly increase creatinine levels by inhibiting the tubular secretion of creatinine, resulting in a reversible and rapid (2-6 h after intake) increase of creatinine of 13-23% in patients without chronic kidney disease (CKD) [7-12] and even more frequently in patients with CKD (>35%).[8,10,13] Trimethoprim induces increase of creatinine levels without affecting glomerular filtration rate, leading to the wrong clinical conclusion that renal function is decreased and consequently to incorrect adjustment of drug therapy. In this 'proof of concept' study, the in vivo effect of trimethoprim on creatinine levels was studied in a database of linked pharmacy-laboratory data of hospitalized patients without impaired renal function.

METHODS

Setting

This study was a retrospective follow-up study in the University Medical Center Utrecht (UMCU), a 1042-bed academic medical centre located in the centre of the Netherlands with approximately 33 000 hospitalizations each year. Data were obtained from the Utrecht Patient Oriented Database (UPOD). The UPOD system is an infrastructure of relational databases comprising administrative data of patient characteristics, laboratory test results, medication orders, hospital discharge diagnoses and medical procedures for all patients treated at the UMCU since 2004. All UPOD research is in accordance with current Dutch privacy and ethical regulations and is also in accordance with guidance of the institutional review board. A more detailed description of UPOD has been published elsewhere.[14]

Study design and population

Patients were selected from UPOD in several consecutive steps, as illustrated in Figure 1. All patients of 2 years (renal function is predicted to be over 90% of the adult renal function from this age onwards)[15] and older hospitalized for more than 24 hours in the study period between 1 January 2007 and 31 December 2010 were eligible for inclusion. Patients who were prescribed trimethoprim (or the combination drug cotrimoxazole) during hospital admission were included if two plasma creatinine (Pcr) test result were available. These patients were compared with a reference group of patients who had been prescribed other antibacterials (OABs) not known to have an effect on Pcr levels: tetracyclines, macrolides and clindamycin. Only the first admission period was used for analysis. Intraindividual creatinine change was computed by calculating the difference between a creatinine value before the start of the antibacterial ($Creat_B$), defined as the creatinine test result obtained within 0.25–30 days before the start, and the first creatine value during treatment ($Creat_{First}$), defined as the first creatinine test result that had been determined within the period between six hours after start of the antibacterial and eight hours after it had been stopped (Figure 2). Patients with a $Creat_B$ level ≥ 150 µmol/L were excluded, because this represented renal impairment.[16] Other exclusion criteria were admittance to the nephrology and dialysis ward, intensive care ward, any co-medication, and admittance registration with specific ICD9 codes that refer to diseases that affect creatinine test results (Attachment A).[17]

In vivo effects of drugs on laboratory tests can only occur after drug exposure, so the moment of starting the drug in relation to the time of testing is crucial to observe a

Figure 1 Flowchart of the study population

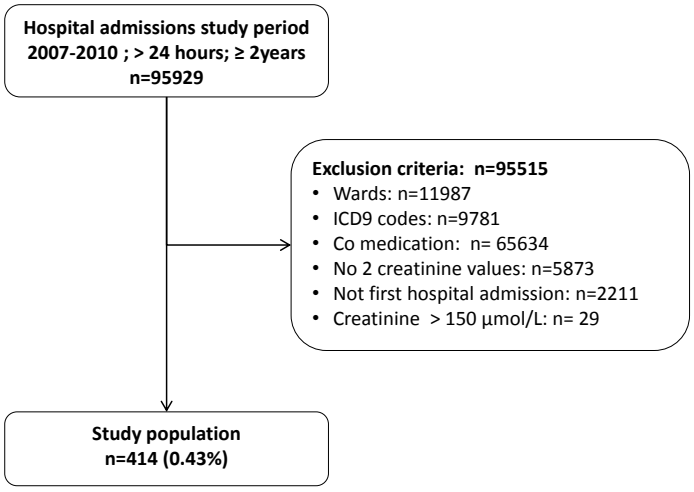
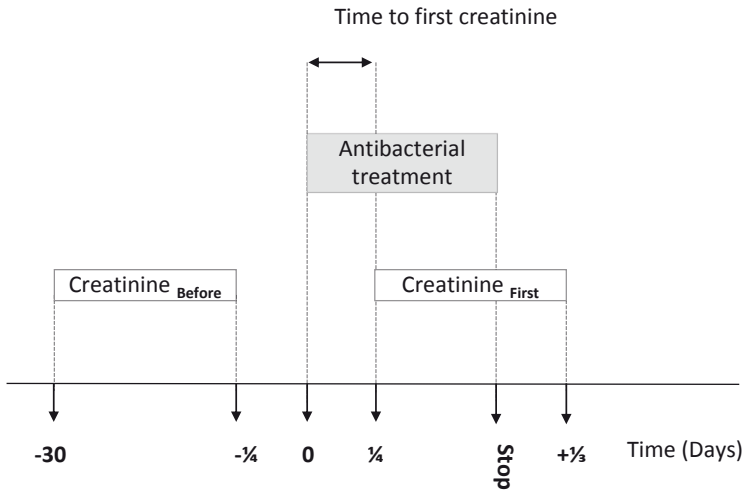


Figure 2 Schematic representation of the inclusion criteria



potential effect. The time to the first creatinine test result was defined as the difference between the laboratory test time of $Creat_{First}$ and the start of the drug (T=0) in the hospital (Figure 2). The reference range for Pcr in the UMC Utrecht is 74-120 µmol/L for men and 58-103 µmol/L for women. All laboratory tests were performed using the Beckman DxC 800 analyser.

Outcome

Primary outcome was an increase in creatinine levels of 10% or more after the start of the antibacterial treatment ($Creat_{First}$- $Creat_{B}$).

Also, the frequency of patients with a decline in renal function group after the start of the antibacterial compared to the renal function group before start was determined. Renal function groups were defined according to the European dosing guidelines for drugs in renal impairment: no renal impairment (> 80 ml/min/1.73m^2), mild renal impairment (50-80 ml/min/1.73m^2), moderate renal impairment (30-49 ml/min/1.73m^2), severe renal impairment (10-29 ml/min/1.73m^2) and end stage renal failure (< 10 ml/min/1.73m^2).[18] Since we did not include body length in our dataset, eGFRs for children could not be calculated. eGFRs for patients of 16 years and older were calculated from creatinine levels using the 4-variable Modification of Diet in Renal Disease (MDRD) equation.[19]

Potential confounding factors

The following covariates were studied to control for individual differences in predisposition to creatinine increase over 10%: age, sex, length of hospitalization, duration of

antibacterial treatment, time to first creatinine test result, and C-reactive protein (CRP) test result. This last covariate was included if CRP analysis was performed between -36 and +36 hours before or after the start of the antibacterial. CRP is a marker used in the diagnosis and follow-up of infectious and inflammatory diseases.[20]

Data analysis

Outcome measures were computed separately for patients starting with trimethoprim and for patients starting with another antibacterial. Descriptive statistics (median, min, max,) were used to determine the in vivo effect and to describe frequencies and incidence density ratios. The strength of the association between creatinine increase over 10% and antibacterial treatment was evaluated with Cox regression analysis and expressed as hazard ratios (HR) with 95% confidence intervals (95%CI). Covariates were included in the multivariate analysis if they induced a change in the crude regression coefficient of at least 10%. Because a significant fraction of CRP values was missing, these data were dummy coded using the missing indicator method to estimate HR for infection in the pooled data.[21] This method of modelling missing data assumes data are missing at random. Data analysis was performed with IBM SPSS Statistics 19.0 for windows (IBM Inc., New York).

RESULTS

The basic characteristics of the study population are shown in Table 1. Trimethoprim was prescribed as monotherapy in 48 patients (19.3%) and as a combination with sulfamethoxazole in 201 patients (80.7%). Median time to first creatinine test result (23 vs. 41h) and CRP (26 vs. 58 mg/L) were significantly lower in the trimethoprim cohort than in the OAB-cohort. Median creatinine change was significantly higher in the trimethoprim cohort than in the OAB cohort, 2.6% vs. -6.7%, (95%CI: 3.74-16.91).Trimethoprim was prescribed for more than half of the cases at the neurology, cardiology and haematology wards (57.1%), while more than half of the OABs were prescribed at surgery and cardiology wards (68%).

The association between antibacterial treatment and the risk of a creatinine increase over 10% is showed in Table 2.Overall incidence density for creatinine increase over 10% was 15.0 per 100 person-days. In the multivariate Cox regression analysis treatment with trimethoprim was significantly associated with creatinine increase over 10%: 21.9 per 100 person-days (HR: 2.61; 95%CI: 1.64-4.18). Overall, in patients with a creatinine increase over 10% the median increase in trimethoprim users and OAB users was 24.4% (10-244%) and 22.0% (10-243%), respectively. A non-significant trend for lower incidence densities was observed for prolonged duration of treatment and duration of hospital stay. Survival plots of time to first creatinine test result to creatinine increase over 10% demonstrated

a significant difference of the proportion of patients with creatinine increase over 10% between trimethoprim and OAB (Figure 3).

The number of patients of 16 years and older with a decline of renal function group (n =53) was significantly higher in patients treated with trimethoprim than in patients with OAB, 18.4% and 9.6% (RR: 1.92; 95%CI: 1.10-3.36), respectively. The number of patients that declined to a moderate or severe renal function group was 16.

Table 1 Characteristics of the study population

	Trimethoprim		Other antibacterials		
	n=249	**(100%)**	**n=165**	**(100%)**	***p* value[a]**
Female	127	(51.0)	75	(45.5)	0.269
Age; Median, Years (range)	56.2 (2-90)		57.9 (3-92)		0.052
2-18	52	(20.9)	10	(6.1)	
19-64	116	(46.6)	97	(58.8)	
>64	81	(32.5)	58	(35.2)	
C-reactive protein; Median, mg/L (range)	26.0 (2-410)		58.0 (2-343)		0.001
> 10	89	(35.7)	51	(30.9)	
<=10	51	(20.5)	8	(4.8)	
unknown	109	(43.8)	106	(64.2)	
Hospital duration; Median, days (range)	8.0 (1.0-103.1)		9.2 (1.7-60.7)		0.517
1-5	85	(34.1)	39	(23.6)	
6-10	73	(29.3)	54	(32.7)	
11-15	22	(8.8)	31	(18.8)	
>15	69	(27.7)	41	(24.8)	
Treatment duration; Median, days (range)	4.8 (0.5-68)		4.4 (0.2-48.8)		0.744
1-3	86	(34.5)	65	(39.4)	
4-5	72	(28.9)	39	(23.6)	
6-8	45	(18.1)	31	(18.8)	
>8	46	(18.5)	30	(18.2)	
Time to first creatinine; Median, hours (range)	23.0 (6-207)		41.0 (6-353)		0.001
6-18	85	(34.1)	36	(21.8)	
19-36	56	(22.5)	40	(24.2)	
37-54	42	(16.9)	24	(14.5)	
55-72	39	(15.7)	34	(20.6)	
>72	27	(10.8)	31	(18.8)	

a: The p values were calculated using t-tests for continuous variables and chi-square tests for nominal categorical variables

Table 2 Association between creatinine increase over 10% with antibacterial treatment

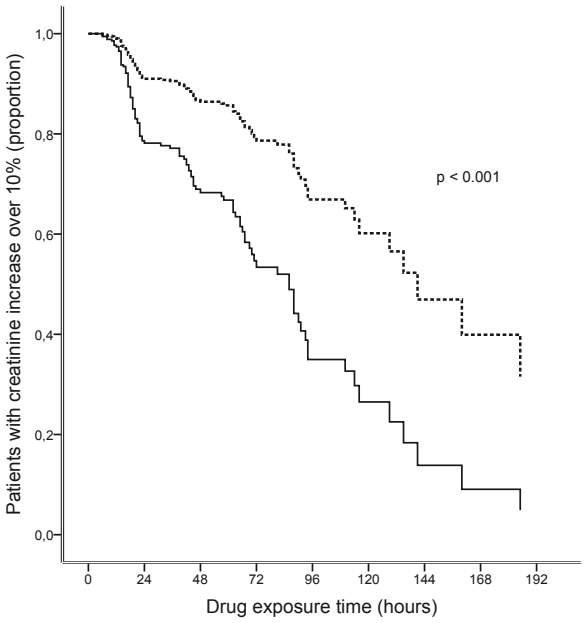
	Creatinine increase over 10%		Follow-up	Incidence density	Crude		Adjusted[a]	
	n	(%)	(person-days)	(per 100 person-days)	HR	(95%CI)	HR	(95%CI)
Antibacterial								
Other antibacterials	26	(15.8)	359.1	7.2	1	Reference	1	Reference
Trimethoprim	87	(34.9)	396.4	21.9	3.26	(2.08-5.10)	2.61	(1.64-4.18)
Sex								
male	55	(25.9)	414.9	13.3	1	Reference	1	Reference
female	58	(28.7)	340.6	17.0	1.17	(0.80-1.71)	1.21	(0.83-1.77
Age (years)								
2-18	20	(32.3)	100.8	19.9	1	Reference	1	Reference
19-64	49	(23.0)	387.7	12.6	0.84	(0.50-1.41)	0.94	(0.55-1.60)
>64	44	(31.7)	267.1	16.5	0.98	(0.57-1.67)	1.29	(0.74-2.21)
Hospital duration (days)								
>15	39	(35.5)	283.7	13.7	1	Reference	1	Reference
11-15	10	(18.9)	97.5	10.3	1.03	(0.50-2.10)	1.08	(0.53-2.20)
6-10	25	(19.7)	225.3	11.1	0.97	(0.57-1.63)	0.86	(0.51-1.45)
1-5	39	(31.5)	149.1	26.2	2.20	(1.35-3.61)	1.80	(1.08-2.97)
Treatment duration (days)								
>8	17	(22.4)	198.6	8.6	1	Reference	1	Reference
6-8	16	(21.1)	166.5	9.6	1.27	(0.62-2.57)	1.33	(0.65-2.71)
4-5	27	(24.3)	221.0	12.2	1.41	(0.73-2.73)	1.48	(0.76-2.87)
1-3	53	(35.1)	169.4	31.3	5.21	(2.77-9.81)	4.96	(2.63-9.36)
Overall	113	(27.3)	755.5	15.0				

OR= odds ratio; 95%CI= 95% confidence interval
a: adjusted for C-reactive protein according to missing indicator method.

DISCUSSION

The results of this study demonstrate that trimethoprim use in hospitalized patients is associated with a higher risk of creatinine increase than in patients treated with other antibacterials and that the number of patients with a decline of renal function group is double that of patients on trimethoprim compared to patients on other antibacterials. To our knowledge this study is the first large epidemiological study designed to quantify the effect of trimethoprim on the creatinine concentration in hospitalized patients without impaired renal function. This well-known effect was investigated in UPOD as a first step to proof that the signal can be detected and used for future development of automatic reminders of drug effects on laboratory tests. Up to date, little research has

Figure 3 Multivariate Cox regression analysis plot of time to creatinine increase over 10% Trimethoprim ( ); Other antibacterials (-----)



been done on the clinical outcomes of computer applications with automatic monitoring of drug effects on laboratory tests.[1]

The reported strength of the effect of trimethoprim (24.4%) corresponds with earlier studies in patients without chronic kidney disease.[7-12] Decline of renal function group was high in trimethoprim users and it was used to quantify the chance of a potentially wrong clinical conclusion that renal function is decreased and that drug therapy should be adjusted accordingly.

The strength of this study lies in the use of complete and validated automated data available within UPOD. [14] However, a limitation is that UPOD comprises data from only one hospital, so careful extrapolation of our findings to other settings is necessary.

A limitation of this study was the use of the CRP dummy coded missing indicator method to estimate HR for infection in the pooled data.[21] This method of modelling missing data assumes data are missing at random, but routine use of CRP is not recommended.[20] CRP levels were used as a marker for inflammation just before or shortly after the start (± 36 h) of antibacterial treatment. In patients with trimethoprim, CRP was monitored more often and the median levels were lower than in the OAB cohort. A possible explanation for this difference can be that more than half of the OABs were prescribed at surgery wards, most likely as prophylaxis. CRP levels normally rise within 2 to 6 hours of surgery

and normalize by the third day after surgery.[20] Surgery itself can also cause creatinine increase and recovery of the patients over time could explain the decrease in the proportion of patients with a creatinine increase in both cohorts.[22,23] However, information about surgery was not registered in the database, so the association of high CRP levels and/or higher creatinine levels with surgery remains an unconfirmed assumption.

Another limitation is the nature of cohort studies in which covariates may be not adequately documented, although almost all covariates, such as diseases and co medication, that can affect creatinine levels were excluded. The effect of creatinine increase due to trimethoprim treatment is associated with the inhibition of the tubular secretion of creatinine, but not exclusively. During antibacterial treatment this effect should maintain, however the proportion of patients with creatinine increase over 10% was reduced by 50% in the trimethoprim and OAB cohort within 3-4 days and 5-6 days, respectively. Apparently, the positive effect of antibacterial treatment and other factors patient related factors like dehydration, fever, and blood pressure affect creatinine levels thereby intertwining with the in vivo effect of trimethoprim. In addition, creatinine levels can also be increased due to normal biological variability of creatinine and nutritional or supplemental intake of creatine.[24] Further research is needed to unravel the association between trimethoprim and creatinine increase in these patients.

In conclusion, this 'proof of concept' study has demonstrated that trimethoprim treatment increases creatinine levels in hospitalized patients. If this effect is caused by the inhibition of the tubular secretion of creatinine alone, it could lead to more incorrect adjustments of drug therapy in patients with trimethoprim compared to patient with OABs.

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Attachment A ICD9 codes for exclusion[17]

ICD9 code	Diagnosis
179	Malignant neoplasm of uterus, part unspecified
185	Malignant neoplasm of prostate
188	Malignant neoplasm of bladder
203	Multiple myeloma
249; 250	Diabetes Mellitus
276.5	Volume depletion
277.3	Amyloidosis
283.11	Hemolytic-uremic syndrome
403	Hypertensive chronic kidney disease
404	Hypertensive heart and chronic kidney disease
580 - 589	Nephritis, nephrotic syndrome and nephrosis
585.1 – 585.5	CKD stage 1 -5
585.6	Renal End stage
590	Pyelonephritis
593.4	Other ureteric obstruction
634 - 639	Renal failure due to abortion or miscarriage
669.3	Acute renal failure following labor and delivery
710	Systemic lupus erythematosus
788.9	Prerenal and extrarenal uremia
958.5	Traumatic anuria
997.5	Urinary complications

5

GENERAL DISCUSSION

INTRODUCTION

During the last decade two major trends have influenced the thinking about the benefit-risk balance in drug therapy.[1] The first trend is the awareness that a major factor in drug-induced harm relates to well-known adverse drug reactions, that these are often preventable and that system flaws particularly contribute to these.[2-4] This awareness has triggered the development of mandatory risk evaluation and mitigation strategies on national and international levels to ensure that the benefits of a drug continue to outweigh the risks on a population and individual patient level.[5] The second trend regards the paradigm shift from a drug oriented population based approach towards an individual patient based approach in drug therapy. In the pharmacy setting this personalized drug therapy induced and further requires major changes in the pharmaceutical care process. Assessing, integrating and managing drug related risks in the context of the patient's status of the (patho)physiological biosystem, behavioural aspects, expectations and attitudes towards disease and treatment, are of critical importance. Drug therapy management (DTM) provides healthcare professionals with a tool for a proactive systematic approach to manage and implement these changes into daily clinical practice. It weighs the advantages and disadvantages of drug use for the individual patient and stratifies the potential benefit and harm in terms of evidence, probability and significance.[6,7]
Laboratory markers may play an important role in personalizing drug therapy, since these markers reflect the homeostasis of the patient and may function as biomarkers to indicate necessity, dose, effects and adverse effects of drug therapy.[8,9] In this thesis several studies are presented which elaborate this role of laboratory markers in personalized drug therapy.

The objective in *Chapter 2* of this thesis was to assess the available evidence for the application of laboratory markers in DTM and to stratify the potential for harm in terms of evidence, probability and significance. Two studies show the necessity of laboratory monitoring in drug therapy and identify the laboratory markers which are most frequently needed. In the study presented in *Chapter 2.1* an average of 2.8 instructions on laboratory monitoring per drug label was found. However, these instructions were ambiguous, incomplete and the clinical applicability for the professional was limited, because essential information was frequently missing about why to monitor, what to monitor, when to start or stop monitoring, how frequently to monitor, what to look for, and how to respond to an abnormal test result. In this study the most frequently described laboratory markers in drug labels are renal function, liver tests, electrolytes, and drug monitoring. The second study (*Chapter 2.2*) showed that laboratory markers are frequently required in the clinical risk management of potential drug-drug interactions for on average 9% of the patients and for 13% in those aged over 65 years. Important laboratory tests concerned renal function, electrolytes and coagulation.

Overall this chapter makes clear that laboratory markers are frequently needed during drug therapy and more comprehensive information is needed for appropriate monitoring in clinical practice.

In the third chapter of this thesis several studies on the development and execution of risk management strategies demonstrate how the risk of patients with impaired renal function can be reduced in community pharmacy. Monitoring of renal function which is frequently recommended in drug labels and DDI-guidelines (*Chapter 2*) was used as a case model for the introduction of a new laboratory marker in community pharmacy. The first risk reduction strategy was the use of a self-developed pharmacy medication alert system (PMAS) that specifically assessed the appropriateness of prescribed dosage regimens based on an actual renal function in high risk patients (elderly, cardiovascular disease, diabetes) (*Chapter 3.1*). In every one out of nine renally cleared drugs the pharmacist advised to adjust therapy and the general practitioner (GP) agreed on half of these advices. This study highlights the need to improve medication safety by close collaboration between GPs (with their clinical expertise), the community pharmacists (with their pharmacological expertise) and clinical chemists (with their biochemical and analytical expertise).

The second risk reduction strategy focused on the feasibility of point-of-care creatinine testing (POCCT) in community pharmacy of patients at risk for chronic kidney disease with an unknown or expired renal function laboratory test (*Chapter 3.2*). Renal function was unknown for four out of ten of the eligible patients. POCCT was found to have added value for effective DTM in these patients because an actual renal function was measured at the moment the patient visited the pharmacy. From a patient's perspective point-of- care testing was considered more convenient and saved time because the patient did not have to visit a central laboratory before his drug was dispensed. Another advantage of point-of-care testing is the availability of an actual renal function of a patient at risk for chronic kidney disease at the moment the physician prescribes a drug and the pharmacist wants to perform medication surveillance. Participating patients, GPs and community pharmacists considered POCCT feasible. Clinical chemists trained the POCCT operators and validated the POCC-system by standardized procedures.

A third risk reduction strategy evaluated ineffectiveness and adverse events of nitrofurantoin in women with urinary tract infection and renal impairment in primary care (*Chapter 3.3*). This study confirms that the recommended threshold value for use of nitrofurantoin in renal impairment can be lowered from 50 to 30 ml/min/1.73m^2.

Overall, assessment of renal function which is frequently recommended in drug labels and DDI-guidelines was used as a case model for the introduction of a new laboratory marker in community pharmacy. Collaboration between GP's, community pharmacists and clinical chemists is a key issue in DTM. Development of more patient oriented medication surveillance systems will help to implement laboratory markers more effectively

by generating fewer alerts of higher clinical relevance. Retrospective cohort studies can generate more evidence of threshold values for drug dosing in renal impairment.
In *Chapter 4* of this thesis the objective was to examine the effects of drugs on laboratory test results. In one study we showed that there is enough evidence of these effects but that the information of effects of drugs on laboratory tests in drug labels was unclear, inconsistent and incomplete, and that it does not support practising healthcare professionals in making evidence-based monitoring decisions (*Chapter 4.1*). In the second study we showed that in a database of linked pharmacy-laboratory data of hospitalized patients, trimethoprim is associated with a creatinine increase over 10%, and may lead to potentially incorrect dosage decisions. Overall, this chapter shows that the information in drug labels is incomplete. Furthermore, the effects of drugs on laboratory test results can be detected, but is difficult to interpret and the awareness of pharmacists of these effects of drugs on laboratory test results has to be raised. Clinical chemists need to know what medication the patient is actually using, so they can advise other healthcare professionals about the risks of drug effects.

In this general discussion the results of the individual studies will be put into a broader perspective by discussing challenges and barriers that are relevant to the translation of laboratory markers into personalized drug therapy. The following themes will be discussed:

- evidence for use of laboratory markers
- implementation of laboratory markers in drug therapy management
- personalized drug therapy.

Finally, recommendations for regulatory and clinical practice will be presented.

EVIDENCE FOR USE OF LABORATORY MARKERS

Effective and safe implementation of laboratory markers in personalized drug therapy is still not widespread, particularly not in community pharmacy, despite the multiple applications for laboratory markers when laboratory data and pharmacy data are linked (Table 1).[10] As a case model renal function in patients with chronic kidney disease shows clearly the benefits of laboratory markers in DTM and their applications in drug selection, dosing, monitoring, interpretation of laboratory test results and improvement. What conditions have to be met before a laboratory test can be successfully implemented in clinical practice? The most important condition is obtaining evidence and to evaluate the scientific information. A model was developed to provide a framework for evaluation of genetic test information, but this model can also generalized to other predictive tests with laboratory markers. The ACCE model consists of four criteria:

Table 1 Ten ways laboratory-pharmacy linkage can help in drug therapy management of patients with chronic kidney disease[a]

Category	Concept	Special role for the computer/ linkage	Example	
			Lab	Drug
Drug selection	Lab contraindicates drug	prevents prescription writing or dispensing	potassium increasing	potassium saving diuretics
	Lab suggests indication for drug	generates timely reminders, tracking interventions	eGFR decreasing and albuminuria	ACE inhibitor
Dosing	Lab affecting drug dose	performs dose calculations based on age, sex, lab value and weight	eGFR < 50 ml/ min/1.73 m2	digoxin
	Drug requiring lab for titration	statistical process control dosing adjustment charts	drug levels	lithium
Monitoring	Abnormal lab signalling toxicity	trigger alerts, assesses likelihood	eGFR < 80 ml/ min/1.73 m2	tobramycin parenteral
	Drug warranting lab monitoring for toxicity	oversees scheduling of both baseline and serial monitoring tests	eGFR decreasing	colchicine and clarithromycin
Lab interpretation	Drug influencing or interfering with lab	warns against/interprets false positive and false-negatives	increase of creatinine levels	sulfamethoxazole
	Drug impacting on response to lab finding	resets alarm threshold for treated patients	increase of creatinine levels	trimethoprim
Improvement	Drug toxicity/Effects surveillance	data mining of lab and drug data to generate new hypotheses of drug effects	acute renal failure	statins
	Quality oversight	monitors time interval between lab testing and prescription change, adequacy/ appropriateness of lab monitoring	eGFR at least once a year	chronic users of blood-glucose lowering drugs

a: Adapted from Schiff et al.[10] By permission of the American Medical Association
eGFR: estimated glomerular filtration rate; lab: laboratory

Analytical validity, Clinical validity, Clinical utility and associated implications (ELSi: ethical, legal, and social issues), which are described in greater detail below.[11]

Analytical validity of a marker test is defined by the ability to measure accurately and reliably the characteristic of interest. Elements within analytic validity include analytic sensitivity, analytic specificity, quality control and assay robustness. Nowadays, most laboratories meet these criteria for analytical validity by complying with Good Laboratory Practice (GLP). Testing outside the laboratory (GP-practice, pharmacy, patient) requires certification by laboratory professionals to guarantee efficiency and quality. The point-of-care system used in our study to monitor creatinine in capillary blood in

community pharmacy was validated by a department of clinical chemistry to meet the same quality standards as for laboratory monitoring of creatinine (Chapter 3.2).
A second criterion to evaluate is clinical validity, defined as the ability to detect or predict consistently and accurately the characteristic of interest. There are two aspects to clinical validity that are important to understand: evidence to show the marker-disease association and proving test performance in terms as sensitivity, specificity, positive and negative predictive values, and area under the receiver-operator curve.[12] Traditionally well known in pharmacy practice is therapeutic drug monitoring of drugs with a narrow therapeutic range (lithium, phenytoin, theophylline). Another example of a prominent clinically valid laboratory marker in the Netherlands is monitoring clotting time of patients using anticoagulants (coumarins) which is done by specialized anticoagulation clinics.
The third criterion to evaluate is clinical utility which describes the relevance and usefulness of the intervention in patient care.[13] An example of a clinically successful introduction of a pharmacogenetic marker is HLA-B*5701 testing to prevent potential severe hypersensitivity reactions of the HIV drug abacavir. In this particular case widespread adoption of this test increased as soon as its clinical utility had been demonstrated.[14] Another successful example is the concurrent introduction of a new drug trastuzumab, which is a humanized antibody approved for treatment of HER2-positive metastatic breast cancer, and the HER2 protein test. Adoption of the test into clinical practice was accelerated because treatment with trastuzumab is indicated only in patients with overexpression.[8]
The fourth criterion, the associated implications of the ACCE model named ELSi, will be discussed in more detail in the implementation section.

Health care professionals will more easily adopt laboratory markers in drug therapy once evidence for all three criteria of ACC is evaluated and warranted. Analytical validity is sufficiently guaranteed in professional laboratories complying with GLP. The same quality requirements are also necessary for assays used beyond the control of a clinical chemist, such as point-of-care systems[15] and home care tests. It is the responsibility of the regulatory authority of these assays to require manufactures the same quality. Evidence for clinical validity can only be obtained by performing research about marker-disease associations by assay or drug manufacturers and research about test performances by laboratory professionals according to standardized procedures. Clinical utility of many laboratory markers in drug therapy is not yet structurally evaluated and more research has to prove the relevance and benefits for health outcomes. For example, implementation of renal function as a marker in drug therapy management should be evaluated by clinical and observational studies. It may elucidate the effects of therapy adjustments on outcomes of harm such as adverse drug reactions, GP visits, hospital admission and outcomes of effectiveness, for example adherence to monitoring recommendations, adherence to drug therapy, and number needed to monitor.

IMPLEMENTATION OF LABORATORY MARKERS IN DRUG THERAPY MANAGEMENT

Ethical, legal, and social issues (ELSi) can have an enormous impact on any implementation process and in this process various stakeholders can be distinguished, which are responsible to guide this process. Therefore, we will discuss the ELSi implications for different stakeholders: regulatory authorities (inspection for public health, drug approval agencies, legislative authority) and policymakers (health insurance, clinical guideline developers, and professional organisations).

Chapter 2.2 shows that laboratory markers were frequently required in the clinical risk management of potential drug-drug interactions. This result partly led to an amendment of the Dutch medicines act initiated by the Royal Dutch Association for the Advancement of Pharmacy (KNMP). Pharmacists are now qualified, after consent of the patient, to request the physician for the test results of six laboratory markers: renal function, sodium and potassium, PT- INR, pharmacogenetic parameters and monitoring of drugs with a narrow therapeutic index. This first legal step will promote the exchange between physicians and pharmacists of important laboratory markers and it can thereby improve medication safety.

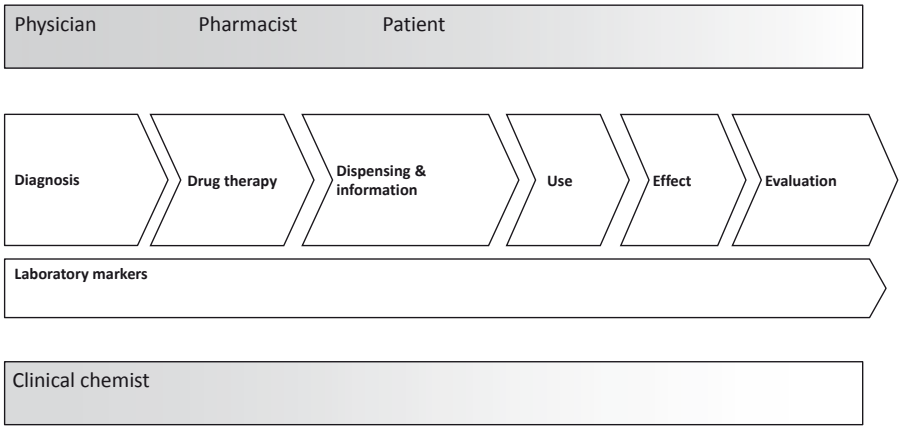
Health insurance and legislative authorities may also strengthen utilisation of laboratory tests by reimbursement as soon as there is enough evidence from cost-effectiveness studies. Simultaneously, ethical considerations need to be addressed specifically in genetic testing, such as implications of testing for relatives, the possibility of insurance discrimination or denunciation based on genotype.[16]

Drug regulatory authorities need to give clearance of an assay and to supervise consecutive update of the information in the drug label by the drug manufacturer.

Professional organisations can be the driving force for implementation and incorporation of knowledge and evidence into clinical guidelines as well development of educational strategies.[17] New evidence on the ineffectiveness of nitrofurantoin in women with renal impairment showed that the recommended threshold value in current guidelines for drug dosing in renal impairment can be lowered (*Chapter 3.3*). Standardized models for reporting guidelines are warranted to ensure the quality of guidelines.[18,19] The professional organisation KNMP fully put in motion on a national level the incorporation of laboratory markers into clinical guidelines, but implementation by the professionals in clinical practice has just started.

Besides the stakeholders as described above, four other stakeholders are directly involved in the pharmaceutical care process, each with their own responsibilities for effective and safe use of a drug (Figure 1). The physician is responsible for the diagnosis by obtaining relevant information from the patient, carrying out physical examination and by taking care of appropriate diagnostic and laboratory testing. Interpretation of the test results

Figure 1 Stakeholders directly involved in the pharmaceutical care process



will take place in close collaboration with the clinical chemist, who is responsible for the analytical quality and interpretation of the test result. When the physician prescribes a drug in a high risk patient with multiple diseases and co-medication consultation of a pharmacist can be necessary to optimize drug therapy. The pharmacist in turn is responsible for adequate dispensing and to provide the patient with clear information about how to use the drug and on what important aspects to focus during use (precautions and symptoms of adverse reactions). Finally it is the patient's responsibility to use the drug in concordance with the advice and to report any changes in use or in the effect of the drug. For each stakeholder I will discuss its role in more detail.

Healthcare professionals

Once clinical validity and analytical and clinical utility of a laboratory marker is determined close collaboration of the healthcare professionals involved in the pharmaceutical care process is a key issue in establishing personalized drug therapy by sharing and applying knowledge based on each expertise. In this multidisciplinary approach each professional will still have his or her own legal responsibilities as stated before, but in the ever growing complexity of patients with multiple diseases, drugs and laboratory markers clinical decision making will benefit from the acknowledgement of different professional expertises. Physicians have the final responsibility in treatment decisions, but other professionals can contribute to this responsibility. The need for collaboration throughout the pharmaceutical care chain is demonstrated in this thesis in *Chapter 3.1* and *3.2*. In these chapters we used renal function as a case model and several challenges and barriers can be seen when renal function is implemented in primary care.

The first challenge for effective implementation of renal function in daily practice is to focus on patients at risk, because they will benefit most. The age-independent prevalence of chronic kidney disease (CKD) in the Netherlands is high (11%)[20] and when these patients use renally cleared or nephrotoxic drugs dose adjustment or selection of another drug could be necessary. Elderly patients with diabetes or cardiovascular disease are more at risk for CKD and regular monitoring of renal function in these high risk patients is recommended in Dutch guidelines for general practitioners (diabetes, cardiovascular risk management and heart-failure).[21-23]

A second challenge is to select high risk drugs. To date the Dutch guidelines for drug-dosing in chronic kidney disease include over 250 drugs with a recommendation to undertake action when renal function is impaired.[24] Prioritizing for high risk drugs with severe potential adverse outcomes and a high frequency of use will limit the number of medication surveillance alerts. In *Chapter 2.1* we identified that blood-glucose lowering drugs and cardiovascular drugs were frequently prescribed in primary care. In *Chapter 3.1* physicians most frequently disagreed with half of the therapeutic advices on diuretics, blood glucose-lowering drugs, digoxin, and RAS-inhibitors because the clinical effect in chronically ill patients overrules the potential disadvantages of mild adverse drug reactions. So, a barrier to overcome is to achieve consensus about the differences in clinical advice of physicians and pharmacists. Professional organisations have to take the lead to solve this problem.

A third challenge is to identify and manage several critical processes during implementation of renal function: test ordering, laboratory measurement, and medication surveillance systems. Physicians are responsible for appropriate diagnostic and laboratory testing in the Netherlands. GPs often order tests at collaborative GP laboratories, while medical specialist order tests at the department of clinical chemistry and laboratory medicine in the hospital. Therapeutic drug monitoring is ordered at hospital pharmacies as well as at the clinical chemistry laboratory. Clotting time of patients using anticoagulants is closely monitored by specialized anticoagulation clinics or by patients with self-monitoring. A prerequisite for collecting all these data is electronic linking of laboratory data of all these parties on a national level, which is not yet realised. Up to date, it is difficult for the general practitioner to achieve a complete overview of all test results and to interpret test results of the same laboratory marker from different laboratories with various assays, test codes and reference ranges. Clinical chemists can play an important role in consulting other healthcare professionals in standardising these processes and to register uniformly the test results in medication surveillance systems.

Another critical process is harmonisation of laboratory measurement of renal function. Differences among clinical laboratories in calibration of serum creatinine assays can account for errors in glomerular filtration rate (eGFR) as high as 10-20%.[25,26] The best overall indicator of the level of renal function for use in daily practice is an eGFR. It can be estimated from serum creatinine levels by using different prediction equations that also take into account age, gen-

der, race, and body size.[27,28] Creatinine can be analysed in different body fluids such as plasma, serum, urine, and capillary blood and each is measured with different assays, which leads to a variety of laboratory test results. Therefore, to interpret these laboratory data correctly it should be clear, what assay and kind of standardisation was used, what prediction equation was applied, and what reference range is valid in that laboratory. Simply using a test result without knowledge of these parameters can lead to misclassification of the renal function of the patient. Important in this aspect is that the pharmacist obtains knowledge in order to be able to interpret these laboratory parameters. On the one hand professional organisations are responsible to guide this process, but on the other hand professionals are responsible themselves to acquire this expertise. We strongly recommend collaboration between the pharmacist and the clinical chemist in this matter. Education how to use and interpret the test results is essential for professionals and also for patients who practice monitoring.

A third critical process is the use of a medication surveillance system. In the Netherlands several medication surveillance systems are used in clinical practice, each based on the clinical information of either of the two national guidelines. Personalized drug therapy requires patient oriented medication surveillance systems with linked information about patient susceptibility factors and drug use.[29,30] Effective multifactorial risk assessment of patients' susceptibility factors is only achievable for healthcare professionals if these systems incorporate clinical decisions support systems (CDSS) that produce clinically relevant alerts. By using our PMAS the number of alerts was substantially reduced in the pharmacies participating in our studies in contrast to the traditional medications surveillance systems without CDSS (*Chapter 3.1* and *3.2*). Additional advantage of PMAS was that the alerts were identical with consistent background information to undertake action. A major challenge is to design medications surveillance systems with CDSS as a tool for multifactorial risk assessment that produce standardized alerts for each professional. Such a system can also produce timely alerts for appropriate monitoring to improve adherence to monitoring recommendations in clinical guidelines. Another advantage of linking laboratory data to medical and pharmacy data is the feedback of these data to the clinical chemist to provide insight in potential effects of drugs on laboratory tests results (*Chapter 4.2*). Clinical chemist can advise other professionals in making evidence-based decisions when relevant effects of drugs on laboratory tests are detected. They may provide more comprehensive information about these effects than the inconsistent and incomplete information provided in drug labels (*Chapter 4.1*)

Patients

Eventually, all steps in the pharmaceutical care process described above are intended to improve the benefit-risk balance of drug therapy in the individual patient. Beside the healthcare professionals the patient has his/her own responsibilities to use the drug safely. Informing the patient with clear and comprehensible information by each of the profes-

sionals may convince the patient to use the drug accordingly the advice and not to change the dose regimen or even to stop the drug without consulting the physician. Furthermore, it is important that patients understand to share information with the professionals about crucial susceptibility factors like intolerances, nutrients, natural products, alcohol intake, smoking behaviour, or OTC drugs. Even information about the results of health checks or home-tests can play an important role in believes and disbelieves of a patient. A large number of patients with diabetes mellitus regularly monitor their blood glucose levels with home tests. This home testing is widely acknowledged, because strict glycaemic control may prevent hypo or hyperglycaemia and it may lead to a reduction or postponement in diabetes-related health complications. Self-management may motivate patients to adhere to drug therapy and professional health advice. New developments are home testing of INR or lithium and a challenge is to exchange these home test results with the healthcare professionals. E-health information technology may provide a solution to exchange this kind of information in a structured and two-way manner between the patient and professionals. Make it as convenient as possible for the patient and provides high quality primary care services with point-of-care monitoring, self-monitoring, and E-health technology to motivate the patient to take responsibility for his own health outcomes.

PERSONALIZED DRUG THERAPY

In this final chapter we discussed the evidence for use of laboratory markers and the challenges and barriers of the implementation of laboratory markers in drug therapy management. Is personalized drug therapy a dream or inevitable reality?[8,9,31-33]

Each person is unique in the status of the (patho)physiological biosystem, behavioural aspects, expectations and attitudes towards disease and treatment. Population based risk/benefit recommendations help the professional to classify patient's health-care question and to make treatment decisions, but the risk/benefit for each individual patient can be different. Laboratory markers are considered important patient characteristics in personalized drug therapy in all steps of the pharmaceutical care process (Figure 1). However, the presence or absences of other patients' susceptibility factors are other critical factors to take into account (Table 2).[29,30 34,35] Healthcare professionals should take these factors into account when assessing and managing drug related risks in personalized drug therapy, because they are effect modifiers of the outcomes of treatment. A major challenge for the near future in personalized drug therapy is integrating clinically relevant patient's susceptibility factors into the pharmaceutical care process in an ever increasingly busy practice working with high quality standards.[36]

DTM provides a tool to establish an integrated drug therapy model that systematically helps the healthcare professionals to prioritize and to identify high risk processes, high

Table 2 Patient susceptibility factors in drug therapy management

Susceptibility factor		Action in DTM	Primary source of information	Duration of monitoring
Intrinsic				
	Patient: age, gender, race	initiation, dose adjustment or change DT	patient	variable
	Patient: BMI, pregnancy	initiation, dose adjustment or change DT	patient	temporarily
	Patient: intolerances, sensitivity to ADR	dose adjustment or change DT	patient	variable
	Disease: renal impairment, diabetes, heart failure	dose adjustment or change DT	physician	variable or continuously
	Molecular: laboratory marker value	change DT	clinical chemist	variable or continuously
	Genetic: polymorfism	initiaton DT	clinical chemist	one time only
Extrinsic				
	Administration factors: drug dosage, dosing time, order and route of administration, duration of therapy	dose adjustment or change DT	physician and pharmacist	continuously
	Drug: (concomitant) use, interaction, OTC, natural products (herbs)	dose adjustment or change DT	physician and pharmacist	temporarily
	Environment: cultural, regulatory authorities	dose adjustment	physician and pharmacist	variable
	Behaviour: smoking, alcohol, nutrition, diet	dose adjustment	patient	temporarily
	Medical practice: operation	dose adjustment or stop DT	patient	temporarily
	Attitude: compliance, beliefs, cognition	dose adjustment	patient	variable

ADR: adverse drug reaction; BMI: body mass index; DTM: drug therapy management; DT: drug therapy.

risk patients and high risk drugs. Linking information from external sources into electronic health records with clinical decision support systems is a second tool that can help to prioritize. In Table 2 four primary sources for information of patient susceptibility factors are distinguished: physician, pharmacist, clinical chemist and patient. Linking the data from the first three sources is since decades an issue of intense debate. Recently, policy decided to cancel the nationwide project for integration of medical, laboratory and pharmaceutical data in a final stage, because privacy of the patients was not sufficiently guaranteed. New efforts to restart this project are undertaken, but it will take years before this is fully implemented. Fortunately, on a regional and local level linkage of pharmacy and medication data is often realised as a first step of integrating data. However, incorporation of laboratory data in electronic health records and clinical decision support systems is not yet structural implemented and the development of an integrated multifactorial risk management model in primary care is one of the challenges. The last source of information of patient susceptibility factors is the patient himself and to attain his information is an even greater challenge. There are two sides of this coin. One side of the coin is the development of patient empowerment and participatory healthcare to enlarge patient's involvement in drug therapy assuming this will lead to better understanding, compliance, attitudes and beliefs, and therefore better health. The other side of the coin is the quality of the information. Most healthcare professionals prefer not to integrate the information of the patient directly in their professional systems; however exchange of information through web-based solutions (E-health technology) is a challenge for the future. Once linkage is realised highly validated medication surveillance systems with CDSS will provide healthcare professionals with a tool to prioritize in high risk patients and high risk drugs.

A third tool is education of health care professionals. It is one of the challenges, as described above, that professionals have to acquire basic knowledge of integrated multifactorial risk management. Furthermore, close collaboration of healthcare professionals is a key issue in establishing personalized drug therapy by sharing and applying knowledge based on the expertise of each professional.

A concerted effort is required of all stakeholders to make the shift from a drug oriented approach towards a personalized approach. Prioritizing will help to manage the overload of information and gradually achieve the inevitable reality of personalized drug therapy, for example as a first step by focussing on high risk patients and high risks drugs.

RECOMMENDATIONS FOR REGULATORY AND CLINICAL PRACTICE

This thesis leads to the following recommendations:

1. Drug labels and clinical decision support systems should contain more comprehensive information on laboratory monitoring: why to monitor, what to monitor, when to start or stop monitoring, how frequently to monitor, what to look for, and how to respond to an abnormal test result. Introduction of a specific laboratory-monitoring section in drug labels with references to clinical guidelines for more detailed information would offer a better base for clinical decision making.
2. Drug labels and clinical decision support systems should contain more comprehensive information on effects of drugs on laboratory test results.
3. Clinical decision support systems should incorporate algorithms for timely reminders of laboratory monitoring in patients at risk.
4. Models for laboratory marker management guidelines should be developed to ensure the quality of guidelines. A comprehensive instrument for guiding the development and evaluation of guidelines for laboratory monitoring is needed to improve the recommendations in these guidelines for the use of laboratory markers in drug therapy.
5. Clinical guidelines should only incorporate recommendations for dosage adjustments based on renal function if both physicians and pharmacists agreed on the clinical relevance of the recommendation.
6. Clinical studies with more patients should be conducted to find out if point of care creatinine testing in primary care is cost effective.
7. Point-of-care testing in primary care is a feasible method to gain actual test results at the moment of prescribing and dispensing a drug with a high convenience for the patient. To assure the quality of testing involvement of a clinical chemist is essential.
8. Extension of the list of laboratory markers that are needed in drug therapy management. At the moment current six laboratory markers are implemented: renal function, sodium and potassium, PT- INR, pharmacogenetic parameters and monitoring of drugs with a narrow therapeutic index.
9. Linkage of medication, pharmacy, laboratory and patient data in a national electronic health record should have the highest priority to improve implementation of laboratory markers in personalized drug therapy and to give clinical chemist insight into the prescribed medication.
10. Professionals need more information about the laboratory procedure (assay, standardisation method, equation applied, interference, reference range) before correct interpretation of test results from different laboratories is possible.
11. Validated medication surveillance systems with clinical decision support systems should be developed to provide healthcare professionals with a tool to prioritize

effectively high risk patients and high risk drugs. These systems should generate identical and clinically relevant alerts regardless the guideline that was adopted.

12. The patient should have his own electronic patient record independently from the professional systems. Through web based technologies certain information can be exchanged in two-way sided manner. The patient can update his record with crucial information that is not implied in the current electronic health record (test results from health check or self-monitoring). Vice versa the professional can access these data and provide the patient with health information.
13. Professional education and development on the clinical consequences of using laboratory tests should be a part of the continuous education program.
14. Clinical studies should be conducted to assess the health benefits outcomes of the application of laboratory markers in personalized drug therapy.

CONCLUSIONS

The findings from the studies presented in this thesis have demonstrated that laboratory markers are important in personalized drug therapy. Information about laboratory test results is essential for pharmacists to identify patients at risk for adverse drug events. Drug therapy management provides healthcare professionals with a tool for a proactive systematic approach to manage and implement personalized drug therapy into clinical practice. It weighs the advantages and disadvantages of drug use for the individual patient and stratifies the potential benefit and harm in terms of evidence, probability and significance. Mandatory for effective multifactorial risk assessment is linkage of medication, pharmacy, laboratory and patient data. Furthermore, a multidisciplinary collaboration of physicians, pharmacists and clinical chemists is required to achieve evidence based monitoring.

On a national level the incorporation of renal function into clinical guidelines is accomplished, however implementation by the professionals in clinical practice has just started. By monitoring only risks with proven clinical validity and clinical utility in patients at high risk, the use of laboratory markers will lead to improved medication safety and evidence based monitoring

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SUMMARY

Chapter 1

In the introductory chapter the scope, objective and outline of this thesis are described. It provides an overview of two major trends which have influenced the thinking about the benefit-risk balance in drug therapy during the last decade. One trend showed that this balance is not only determined by the interaction of the pharmacological properties of the drug with the patient's (patho)physiological profile, but is also to a large extent modulated by the way the drug is handled by healthcare providers and by the patient. Medication errors have shown to be a major factor in drug induced harm and system flaws particularly contribute to these. It has triggered on national and international levels the development of mandatory risk evaluation and mitigation strategies. The second trend regards the paradigm shift in pharmacy from a drug oriented approach towards a patient oriented approach. In the post-marketing surveillance phase the drug is prescribed in larger and more heterogeneous populations which generates more evidence for harm and therefore the potential risks for the individual patient becomes clearer. This new evidence for harm has to be translated into therapeutic recommendations which take into account the presence or absence of other patients' susceptibility factors like severity of disease, genetic variability, and attitudes and beliefs to drug therapy. Drug Therapy Management (DTM) provides a systematic framework to manage the multifactorial risk assessment in clinical practice. It weighs the advantages and disadvantages of drug use for the individual patient and stratifies the potential benefit and harm in terms of evidence, probability and significance. For healthcare providers laboratory markers are considered important patient susceptibility factors for taking evidence based decisions on drug effectiveness, risk of adverse events, medication adherence or medical necessity of a drug.

There are three main objectives in this thesis. The first one is to assess the evidence for the application of laboratory markers in DTM and to stratify the potential for harm in terms of evidence, probability and significance. The second objective is to investigate the development and execution of risk management strategies in patients with impaired renal function. The third objective is to examine the effects of drugs on laboratory test results.

Chapter 2

Two studies show the necessity of laboratory monitoring in drug therapy and identify the laboratory markers which are most frequently needed. In the study presented in *Chapter 2.1* an average of 2.8 instructions on laboratory monitoring per drug label was found. However, these instructions were ambiguous, incomplete and the clinical applicability for the professional was limited, because essential information was frequently missing about why to monitor, what to monitor, when to start or stop monitoring, how frequently to monitor, what to look for, and how to respond to an abnormal test result.

In this study the most frequently described laboratory markers in drug labels are renal function, liver tests, electrolytes, and drug monitoring. The second study (*Chapter 2.2*) showed that laboratory markers are frequently required in the clinical risk management of potential drug-drug interactions for an average 9% of the patients and for 13% in those aged over 65 years. Important laboratory tests were renal function, electrolytes and coagulation. Overall these studies make clear that laboratory markers are frequently needed during drug therapy and more comprehensive information is needed for appropriate monitoring in clinical practice.

Chapter 3

In the third chapter of this thesis several studies on the development and execution of risk management strategies demonstrate how the risk of patients with impaired renal function can be reduced in community pharmacy. Monitoring of renal function which is frequently recommended in drug labels and DDI-guidelines (Chapter 2) was used as a case model for the introduction of a new laboratory marker in community pharmacy. The first risk reduction strategy was the use of a self-developed pharmacy medication alert system (PMAS) that specifically assessed the appropriateness of prescribed dosage regimens based on an actual renal function in high risk patients (elderly, cardiovascular disease, diabetes) (*Chapter 3.1*). In every one out of nine renally cleared drugs the pharmacist advised to adjust therapy and the general practitioner (GP) agreed on half of these advices. This study highlights the need to improve medication safety by close collaboration between GPs (with their clinical expertise), the community pharmacists (with their pharmacological expertise) and clinical chemists (with their biochemical and analytical expertise).

The second risk reduction strategy study focused on the feasibility of point-of-care creatinine testing (POCCT) in community pharmacy of patients at risk for chronic kidney disease with an unknown or expired renal function laboratory test (*Chapter 3.2*). Renal function was unknown for four out of ten of the eligible patients. POCCT was found to have added value for effective DTM in these patients because an actual renal function was measured at the moment the patient visited the pharmacy. From a patient's perspective point-of- care testing was considered more convenient and saved time because the patient did not have to visit a central laboratory before his drug was dispensed. Another advantage of point-of-care testing is the availability of an actual renal function of a patient at risk for chronic kidney disease at the moment the physician prescribes a drug and the pharmacist wants to perform medication surveillance. Participating patients, GPs and community pharmacists considered POCCT feasible. Clinical chemists trained the POCCT operators and validated the POCC-system by standardized procedures.

A third risk reduction strategy evaluated ineffectiveness and adverse events of nitrofurantoin in women with urinary tract infection and renal impairment in primary care

(*Chapter 3.3*). This study confirms that the recommended threshold value for use of nitrofurantoin in renal impairment can be lowered from 50 to 30 ml/min/1.73m^2.
Overall, assessment of renal function which is frequently recommended in drug labels and DDI-guidelines was used as a case model for the introduction of a new laboratory marker in community pharmacy. Collaboration between GP's, community pharmacists and clinical chemists is a key issue in drug therapy management. Development of more patient oriented medication surveillance systems will help to implement laboratory markers more effectively by generating fewer alerts of higher clinical relevance.

Chapter 4

In Chapter 4 of this thesis the objective was to examine the effects of drugs on laboratory test results. In one study we show that there is enough evidence of these effects but that the information of effects of drugs on laboratory tests in drug labels was unclear, inconsistent and incomplete, and that it does not support practising healthcare professionals in making evidence-based monitoring decisions (*Chapter 4.1*). In the second study we show that - using a database of linked pharmacy-laboratory data of hospitalized patients - trimethoprim is associated with a creatinine increase over 10%, and may lead to potentially incorrect dosage decisions (*Chapter 4.2*). Overall, this chapter shows that the information in drug labels is incomplete. Furthermore, the effects of drugs on laboratory test results can be detected, but is difficult to interpret and the awareness of pharmacists of these effects of drugs on laboratory test results has to be raised. Clinical chemists need to know what medication the patient is actually using, so they can advise other healthcare professionals about the risks of drug effects.

Chapter 5

In *Chapter 5*, the general discussion, the results of the individual studies are put into a broader perspective by discussing challenges and barriers that are relevant to the translation of laboratory markers into personalized drug therapy. These topics are:

- evidence for use of laboratory markers
- implementation of laboratory markers in drug therapy management
- personalized drug therapy
- recommendations for regulatory and clinical practice.

In conclusion, the findings from the studies presented in this thesis have demonstrated that laboratory markers are important in personalized drug therapy. Information about laboratory test results is essential for pharmacists to identify patients at risk for adverse drug events. By monitoring only risks with proven clinical validity and clinical utility in patients at high risk, the use of laboratory markers will lead to improved medication safety and evidence based monitoring by assessing the benefit-risk balance for the individual patient.

SAMENVATTING

Het inleidende **Hoofdstuk 1** beschrijft hoe gedurende de laatste decennia twee ontwikkelingen het denken over de balans tussen werkzaamheid en risico's van geneesmiddeltherapie hebben beïnvloed. Een van de ontwikkelingen is dat deze balans niet alleen wordt bepaald door de interactie van de farmacologische eigenschappen van het geneesmiddel met de biochemische status van de patiënt, maar dat deze ook voor een groot gedeelte wordt beïnvloed door de manier waarop zorgverlener en patiënt met het geneesmiddel omgaan. Medicatiefouten blijken een belangrijke bron te zijn bij het ontstaan van geneesmiddel geïnduceerde schade. Systeemfouten dragen in het bijzonder hieraan bij. Dit heeft op nationaal en internationaal niveau geleid tot de ontwikkeling van verplichte evaluaties van geneesmiddelrisico's en strategieën om deze risico's te beperken.

Een tweede ontwikkeling is dat er in de apotheek een paradigmaverschuiving plaats vindt van een geneesmiddel georiënteerde benadering naar een meer patiënt georiënteerde benadering, omdat ieder mens anders reageert op een geneesmiddel. Op het moment dat het geneesmiddel is toegelaten tot de markt is de balans tussen werkzaamheid en de altijd bestaande risico's op bijwerkingen in de onderzochte studiepopulatie positief bevonden. In de klinische praktijk blijkt echter vaak dat bij gebruik in andere en grotere heterogene patiëntpopulaties nog niet eerder bekende bijwerkingen kunnen optreden ten gevolge van verschillen in de biochemische status van de individuele patiënt. Deze verschillen kunnen ontstaan zowel door inwendige factoren (genetische, metabolische en eliminatie processen) als ook door uitwendige factoren die samenhangen met de omgeving en cultuur (voeding, roken, alcohol, zorgverlener, houding en overtuiging ten aanzien van geneesmiddelgebruik). Nieuw bewijs voor de aan- of afwezigheid van bepaalde vatbaarheidsfactoren (risicofactoren) moet vervolgens opgenomen worden in behandelrichtlijnen.

Geneesmiddeltherapiemanagement zorgt voor een systematische aanpak om meervoudige risicobeoordeling van risicofactoren in de praktijk te kunnen uitvoeren. Geneesmiddeltherapiemanagement weegt de voor- en nadelen van het gebruik van een geneesmiddel in de individuele patiënt af en maakt onderscheid tussen potentiële werkzaamheid en mogelijke schade. Verder kwantificeert het de balans tussen voor- en nadelen naar mate van bewijs, waarschijnlijkheid en significantie. Laboratoriumwaarden zijn voor zorgverleners een belangrijke bron van informatie over de potentiële risicofactoren van de patiënt en helpen om tot evidence-based beslissingen te komen op het gebied van geneesmiddeleffectiviteit, risico op bijwerkingen, therapietrouw of de medische noodzaak van geneesmiddeltherapie.

In dit proefschrift wordt de plaats van laboratoriumwaarden bij het individualiseren van de farmacotherapie onderzocht aan de hand van drie doelstellingen. De eerste doelstelling is het beoordelen van het bewijs voor het gebruik van laboratoriumwaarden in geneesmiddeltherapiemanagement, onderscheid te maken tussen de potentiële

werkzaamheid en mogelijke schade, en kwantificeren van de balans tussen de voor- en nadelen. De tweede doelstelling is het bestuderen van de ontwikkeling en uitvoering van risicomanagementstrategieën in patiënten met verminderde nierfunctie. De derde doelstelling is het effect van geneesmiddelen op de laboratoriumuitslagen te onderzoeken.

In **Hoofdstuk 2** tonen twee onderzoeken de noodzaak aan van het monitoren van laboratoriumwaarden bij het gebruik van geneesmiddelen en welke laboratoriumwaarden daarbij frequent worden gebruikt. Een onderzoek (*Hoofdstuk 2.1*) toont aan dat er gemiddeld 2,8 aanbevelingen per geneesmiddelbijsluiter worden gevonden om laboratoriumwaarden te monitoren. Alleen waren deze aanbevelingen onduidelijk, onvolledig en de klinische toepasbaarheid voor de zorgverlener was beperkt omdat essentiële informatie regelmatig ontbrak. Deze essentiële informatie gaat over de verschillende aspecten van monitoren: waarom, wat, wanneer te beginnen of te stoppen, hoe frequent, waar op te letten en wat te doen bij een afwijkend resultaat. De meest beschreven laboratoriumwaarden in de bijsluiters zijn de bepalingen van nierfunctie, leverfunctietesten, elektrolyten en geneesmiddelspiegels. Het tweede onderzoek (*Hoofdstuk 2.2*) toont aan dat laboratoriumwaarden regelmatig nodig zijn tijdens het klinische risicomanagement van potentiële geneesmiddelinteracties bij 9% van de patiënten en oplopend tot 13% bij patiënten ouder dan 65 jaar. Belangrijke laboratoriumwaarden in deze studie zijn de bepaling van de nierfunctie, elektrolyten en stolling.
Samengevat kan worden gesteld dat deze studies duidelijk maken dat laboratoriumwaarden regelmatig nodig zijn tijdens geneesmiddeltherapie en dat er meer uitgebreide informatie nodig is om dit in de klinische praktijk doelmatig te kunnen toepassen.

In **Hoofdstuk 3** beschrijven verschillende onderzoeken de ontwikkeling en uitvoering van risicomanagementstrategieën die het risico op bijwerkingen van patiënten met verminderde nierfunctie kunnen verminderen in de openbare apotheek. Bepaling van de nierfunctie, dat regelmatig wordt aanbevolen in geneesmiddelbijsluiters en geneesmiddelinteractierichtlijnen (*Hoofdstuk 2*), is hier gebruikt als voorbeeld van de introductie van een nieuwe laboratoriumwaarde in de openbare apotheek. De eerste risicoreducerende strategie richt zich op het toepassen van een in eigen beheer ontwikkeld 'Pharmacy Medication Alert System' (PMAS) dat op basis van een actuele nierfunctie geneesmiddelbewaking uitvoerde op de voorgeschreven dosering van het geneesmiddel in hoog-risico patiënten (ouderen, cardiovasculaire ziekte, diabetes) (*Hoofdstuk 3.1*). Voor één op de negen renaal geklaarde geneesmiddelen gaf de apotheker een advies aan de huisarts om de therapie aan te passen. De huisarts ging met de helft van het aantal adviezen akkoord. Dit onderzoek benadrukt dat samenwerking tussen de huisartsen (met hun klinische expertise), de openbare apothekers (met hun farmacologische

expertise) en de klinisch chemici (met hun biochemische en analytische expertise) noodzakelijk is om de medicatieveiligheid te kunnen verbeteren.
De tweede risicoreducerende strategie richt zich op de haalbaarheid van de point-of-care meting van creatinine (POCCT) in de openbare apotheek van patiënten met een verhoogd risico op chronische nierschade, waarbij de nierfunctiewaarde onbekend of niet meer actueel is(*Hoofdstuk 3.2*). De nierfunctiewaarde was onbekend bij vier van de tien patiënten die beschikbaar waren voor het onderzoek. POCCT heeft een toegevoegde waarde om tot een effectief geneesmiddeltherapiemanagement te komen bij deze patiënten, gezien het feit dat de nierfunctie gemeten kan worden op het moment dat de patiënt de apotheek bezoekt. Vanuit patiëntperspectief is point-of-care meting een meer geschikte en tijdbesparende methode, omdat de patiënt immers niet een centraal laboratorium hoeft te bezoeken voordat het geneesmiddel kan worden afgeleverd.
Een ander voordeel van point-of-care meting is de beschikbaarheid van een actuele nierfunctiewaarde van de patiënt op het moment dat de arts een geneesmiddel voorschrijft en de apotheker medicatiebewaking wil uitvoeren. De deelnemende patiënten, huisartsen en apothekers beschouwen POCCT haalbaar. Het deelnemend klinisch-chemisch laboratorium trainde de medewerkers van de apotheek die de POCCT uitvoerden en het laboratorium valideerde het apparaat volgens gestandaardiseerde procedures.
Een derde risicoreducerende strategie evalueert de ineffectiviteit en bijwerkingen van nitrofurantoïne in vrouwen met een urineweginfectie en verminderde nierfunctie in de eerstelijnszorg (*Hoofdstuk 3.3*). Dit onderzoek bevestigt dat de aanbevolen drempelwaarde voor het gebruik van nitrofurantoine bij verminderde nierfunctie verlaagd kan worden van 50 naar 30 ml/min/1.73m^2.
Samenvattend zien we dat de nierfunctie een goed voorbeeld is van de introductie van een nieuwe laboratoriumwaarde in de openbare apotheek. Een belangrijk punt hierbij is goede samenwerking tussen huisartsen, apothekers en klinisch chemici om tot geneesmiddeltherapiemanagement te komen. Ontwikkeling van meer patiënt georienteerde medicatiebewakingssystemen zal bijdragen aan de effectieve implementatie van laboratoriumwaarden door het genereren van minder waarschuwingssignalen van hogere klinische relevantie.

In **Hoofdstuk 4** van dit proefschrift is het effect van geneesmiddelen op laboratoriumuitslagen onderzocht. Het eerste onderzoek toont aan dat er genoeg bewijs is over deze effecten, maar dat de informatie in geneesmiddelbijsluiters over het effect van een geneesmiddel op laboratoriumuitslagen onduidelijk, tegenstrijdig en onvolledig is en dat het praktiserende zorgverleners niet helpt om evidence-based beslissingen te nemen (*Hoofdstuk 4.1*). Het tweede onderzoek toont aan dat trimethoprim gebruik geassocieerd is met een stijging van de creatininespiegel van meer dan 10% in een populatie van ziekenhuispatiënten waarbij de gegevens van apotheek en klinisch chemisch

laboratorium zijn gekoppeld. Dit kan leiden tot een potentieel verkeerde aanpassing van de dosering.
Samenvattend toont dit hoofdstuk aan dat de informatie over het effect van geneesmiddelen op laboratoriumuitslagen in geneesmiddelbijsluiters onvolledig is. Dit effect kan worden aangetoond, maar is moeilijk interpreteerbaar. Apothekers dienen zich meer te realiseren dat dit effect op de laboratoriumuitslag door geneesmiddelen kan ontstaan. Klinisch chemici moeten inzicht hebben in wat voor geneesmiddelen de patiënt gebruikt, zodat zij andere zorgverleners kunnen adviseren over de risico's van dit effect.

In **Hoofdstuk 5** worden de onderzoeken in dit proefschrift, aan de hand van vier thema's in een bredere context geplaatst door de uitdagingen en barrières te bespreken die relevant zijn bij gebruik van laboratoriumwaarden bij het individualiseren van de farmacotherapie. De thema's zijn:

- bewijs voor het gebruik van laboratoriumwaarden
- implementatie van laboratoriumwaarden in geneesmiddeltherapiemanagement
- individualiseren van de farmacotherapie
- aanbevelingen voor regelgeving en de klinische praktijk.

Er kan worden geconcludeerd dat de resultaten van de onderzoeken in dit proefschrift laten zien dat laboratoriumwaarden belangrijk zijn bij het individualiseren van de farmacotherapie. Informatie over laboratoriumuitslagen is essentieel voor de apotheker om patiënten te kunnen identificeren met risico op geneesmiddelenbijwerkingen. Door alleen risico's te monitoren met bewezen klinische validiteit en relevantie in patiënten met hoog risico, zal het gebruik van laboratoriumwaarden leiden tot verbeterde medicatieveiligheid en evidence-based monitoren door het beoordelen van de balans tussen de voor- en nadelen van geneesmiddeltherapie in de individuele patiënt.

DANKWOORD

DANKWOORD

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Thereafter, he worked as a community pharmacist at 'Apotheek Gennep' in Gennep. In 1985 he started as a pharmacist at 'Apotheek Hatert' in Nijmegen and in 1993 he became owner of this pharmacy. In the period 2001-2011 he worked for the franchise organisation 'Kring-apotheek BV' at the department of Research & Development of pharmaceutical care as a developer of the quality care system and as a pharmaceutical care manager, successively. In this period (2002-2003), he also worked as a lead auditor at KEMA Quality BV in Arnhem. In 2007, he started his PhD research at the Division of Pharmacoepidemiology and Clinical Pharmacology of the Utrecht Institute for Pharmaceutical Sciences (UIPS) of Utrecht University.

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Arjen is happily married to Ingrid Buis and lives in Malden. They are the proud parents of three sons Feike, Wietse and Jouke.