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Opinion Paper

Linking laboratory and medication data: new opportunities for pharmacoepidemiological research

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Abstract

Transfer of automated laboratory data collected during routine clinical care from the laboratory information system into a database format that enables linkage to other administrative (e.g., patient characteristics) or clinical (e.g., medication, diagnoses, procedures) data provides a valuable tool for clinical epidemiological research. It allows the investigation of biochemical characteristics of diseases, therapeutic effects and diagnostic and/or prognostic markers for disease with easy access and at relatively low cost. To this end, the Utrecht Patient Oriented Database (UPOD), an infrastructure of relational databases comprising data on patient characteristics, laboratory test results, medication orders, hospital discharge diagnoses and medical procedures for all patients treated at the University Medical Centre Utrecht since January 2004, was established. Current research within UPOD is focused on the innovative linkage of laboratory and medication data, which, for example, makes it possible to assess the quality of pharmacotherapy in clinical practice, to investigate interference between laboratory tests and drugs, to study the risk of adverse drug reactions, and to develop diagnostic and prognostic markers or algorithms for adverse drug reactions. Although recently established, we believe that UPOD broadens the opportunities for clinical pharmacoepidemiological research and can contribute to patient care from a laboratory perspective.
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Keywords: clinical chemistry; clinical epidemiology; laboratory medicine; pharmacoepidemiology; research database.

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Introduction

Since the introduction of the first computers to process and capture laboratory data in the 1960s (1), enormous progress has been made in laboratory automation. Currently, the majority of biochemical laboratory tests are performed by fully automated analysers, and test results are processed and stored electronically within advanced laboratory information systems. These automated laboratory data are primarily used in patient care and for management purposes. However, transfer of data from the laboratory information system into a database format that allows questioning and linkage to administrative (e.g., patient characteristics) or other clinical data (e.g., disease and medical treatment) would provide a valuable tool for clinical epidemiological research, i.e., the application of epidemiological principles and methods to problems encountered in clinical medicine (2).

Until now, most clinical epidemiological research with laboratory data was only possible after elaborate gathering of data for a specific research question. A structurally available data linkage system that provides complete and well-defined research data that can be questioned at any time would increase the possibilities for conducting clinical epidemiological research with laboratory data. Therefore, the Utrecht Patient Oriented Database (UPOD), an infrastructure of relational databases comprising data on patient characteristics, laboratory test results, medication orders, hospital discharge diagnoses and medical procedures for all patients treated at the University Medical Centre Utrecht (UMC Utrecht) was recently established. In this paper the structure, current content and potential applications of UPOD are presented. Because of the innovative character and clinical relevance of the linkage of laboratory and medication data, which increases the opportunities to study the use and effects of drugs in a clinical setting (i.e., clinical pharmacoepidemiological research), this specific feature is used as an example to illustrate the potential of UPOD.

Table 1 Number of data within UPOD from the year 2005.

Type of data	Number
Inpatient admissions	28,561
Day-care treatments	15,305
Outpatient visits	333,858
Laboratory test results	3,812,756
Medication orders	289,878
Discharge diagnoses	88,216
Procedures	148,499

Utrecht Patient Oriented Database: UPOD

Setting

The UMC Utrecht is a 1042-bed academic medical centre located in the centre of The Netherlands. Approximately 165,000 patients are treated annually during more than 28,000 clinical hospitalisations, 15,000 day-care treatments and 333,000 outpatient visits (Table 1). At UMC Utrecht all administrative and clinical information on in- and outpatients is registered and processed electronically and stored at patient level within systems that are integrated in the hospital information system.

Research database

UPOD is a relational database infrastructure capturing complete and detailed data on patient characteristics, laboratory test results, medication orders, hospital discharge diagnoses and therapeutic procedures for all patients treated at UMC Utrecht since January 2004 (Figure 1). Periodically all relevant data are automatically transferred from the specific registration systems into tables in the management information system, which is an environment (SQL server) that allows checking, cleaning, storing, maintaining, questioning and linking of data (Figure 1). All data contain a patient identifier and an index date, allowing selection of unique patients or events and deterministic linkage between tables comprising different types of data. Researchers who are granted access to the data can make data selections in the management information system using SQL syntaxes. Subsequently, data can be downloaded from the management information system to the researcher's personal computer.

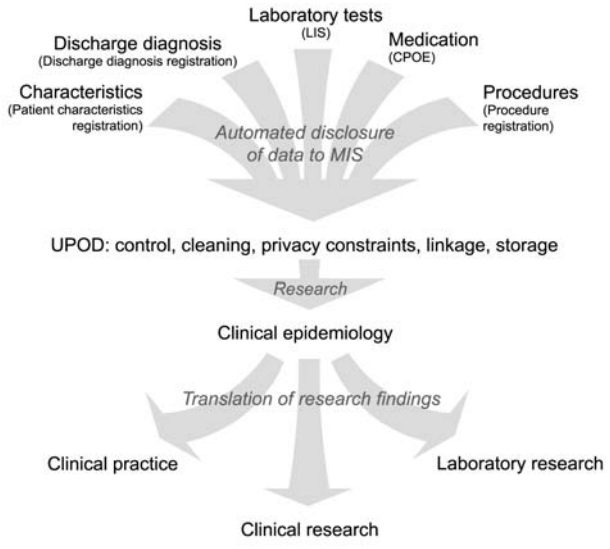

Figure 1 UPOD: clinical epidemiological research with a relational database system comprising patient-oriented clinical and administrative data.

Data on patient characteristics are extracted from the hospital's central electronic patient registry and consist of gender and dates of birth, death, hospitalisation and discharge. Laboratory data originate from the laboratory information system, and include all tests concerning clinical chemistry, haematology, endocrinology, immunology and therapeutic drug monitoring. The records contain information on the collection date, type of material and the result. Medication data concern drugs that are ordered in the computerised physician order entry (CPOE) system for medication. Medication records contain information on the start and stop date, duration, prescriber (type of medical specialty), amount administered, dosage regimen, and route of administration for each drug prescription. Drugs are coded with regard to the different national (generic product code, trade code) (3) and international (Anatomical Therapeutic Chemical classification, ATC) (4) classification schemes. Diagnostic data concern the full list of discharge diagnoses (up to 10 diagnoses per admission) that are registered primarily for reimbursement purposes. Discharge diagnoses are coded according to the International Classification of Diseases, 9th edition Clinical Modification (ICD-9-CM) (5). Likewise, data on therapeutic procedures performed by medical specialists are registered. Procedures are coded according to the Classification of Procedures by Medical Specialists, published by the Dutch CBV Foundation (6).

In addition to the laboratory data described above, UPOD contains a specific database with haematology data on automated blood cell analyses performed with Abbott Cell-Dyn Sapphire automated blood cell analysers used at UMC Utrecht. A feature of this type of blood cell analyser is that it not only reports the parameters requested by the physician, but all haematological parameters that it is capable of measuring (7). For example, when a physician requests a haemoglobin measurement, the analyser also automatically determines the platelet count. Although this platelet count is not reported to the clinician, the analyser stores the data. Periodically, all data captured within the blood cell analysers are manually downloaded to a database format, and are cleaned and checked for integrity, making the data available for research. These haematological data include the collection date, type of material and the results, including flagging parameters.

Ethical and privacy considerations

The collection, storage and use of administrative and clinical patient information for scientific research is subject to ethical and privacy regulations (8, 9). The establishment and utilisation of UPOD is in accordance with guidance of the Institutional Review Board (IRB) and privacy board of UMC Utrecht, which allows

the use of clinical data from patients who did not object to use of their data for scientific purposes, as long as the patients cannot be identified directly from the data.

Within UPOD, only data are captured that were initially registered during routine care and not for research purposes. Because no extra material, for example, blood samples, is taken from patients, there is not a requirement to obtain informed consent from individual patients or seek IRB approval for every study protocol.

At our institution, patients are informed at the time of admission that their data can be used for scientific research purposes. Patients can object to the use of their data within UPOD according to a general procedure for objecting to the use of data for scientific research that is available at UMC Utrecht.

To prohibit the identification of individual patients within the database, sensitive patient data must be encoded before they are processed outside the protective environment of the hospital and management information systems. For this purpose, the original patient identification number for UMC Utrecht is encrypted into a unique UPOD patient identifier within the database. Decrypting the patient identifier is possible in case it is essential to retrieve additional information from the patient's medical record. However, decryption is only possible after approval of the protocol by the IRB.

Linking laboratory and medication data

Laboratory data are often essential for selection, dosing and monitoring of drug therapy. Currently, many hospitals implement CPOE systems for ordering prescriptions or laboratory tests that contain decision support tools involving linkage of laboratory and pharmacy information at the time of ordering medication. This so-called real-time linkage of laboratory and medication information is considered an important contribution to reducing prescription errors and improving patient care (10) since, in the absence of such computerised support systems, patient safety hinges on the ability of the physician to recall a particular warning concerning a specific drug in relation to the clinical characteristics of the patient (11).

In addition to the benefits of real-time linkage for clinical practice, laboratory and medication data can also be linked retrospectively for research purposes within a database (10), as is done within UPOD. This innovative technique provides numerous opportunities to conduct pharmacoepidemiological studies in which the role of the clinical laboratory is considered. These include evaluating the quality of pharmacotherapy with regard to laboratory monitoring, studying therapeutic and adverse effects of drugs, and investigating drug-test interference (10).

In the following, examples of pharmacoepidemiological studies concerning the clinical laboratory are presented to illustrate the relevance of linking laboratory and medication data within a research database. We consider etiological (causality of an association between exposure and outcome), descriptive (pattern and frequency of the disease), prognostic (prediction of an outcome from factors that can be obtained before or at a certain time of treatment) and diagnostic (development of tests that allow accurate diagnosis of health status) epidemiological studies. Table 2 presents examples of pharmacoepidemiological studies currently being conducted within UPOD.

Etiological epidemiology: adverse drug reactions and drug-test interference

Adverse drug reactions Adverse drug reactions are considered a major threat to patient safety (17). Depending on the definition, adverse drug reactions occur in up to 5%–30% of hospitalised patients (18). Laboratory testing can be helpful in managing the risk of adverse drug reactions, as it has been shown that 60%–65% of clinically relevant adverse drug reactions can be detected with a biochemical test (13, 19–21). Several studies (22–25) have shown that linking laboratory and medication data for large groups of patients is a powerful tool for studying the association between adverse events that can be detected with a

Table 2 Examples of current research projects within UPOD.

Subject	Type of epidemiology	
Laboratory monitoring for heparin-induced thrombocytopaenia (HIT)	Descriptive	In patients at risk for HIT, close monitoring of the platelet count and an anti-heparin platelet factor 4 antibody test are advised to rule out HIT in case of suspicion (12); it is investigated if there is a need to intensify laboratory monitoring within our institution.
Epidemiology of drug-associated blood dyscrasias	Etiologic	Blood dyscrasias following exposure to non-cytotoxic drugs are rare; however, the outcome can be severe, especially since they are often unexpected and are diagnosed after symptoms occur; thrombocytopenia, agranulocytosis, and aplastic anaemia are among the most reported and fatal adverse drug reactions (13), but research into the frequency, risk factors and mechanisms is still scarce (14, 15).
Laboratory markers for early warning of drug-induced blood dyscrasias	Prognostic	Haematological parameters can possibly serve as early warning markers of drug-induced blood dyscrasias; some haematological parameters reflect blood dyscrasias in an early stage and thus may be useful as indicators for predicting drug toxicity (16).

biochemical test and drug exposure. Two recent examples are the assessment of the incidence of drug-induced liver injuries based on serum values for liver enzymes during hospitalisation (26) and the quantification of the association between hyponatraemia and the use of serotonergic antidepressants in elderly patients (27). In addition to evidence on the association between drug exposure and an adverse event, epidemiological studies can provide knowledge on risk factors for adverse drug reactions. An example of such a study is the recent identification of treatment-related risk factors for hospital-acquired hyponatraemia (28). Knowledge of risk factors is important for the identification of patients at high risk of adverse drug reactions (18) to initiate prophylactic treatment or close monitoring for the development of adverse drug reactions (29).

Drug-test interference With more than 40,000 drugs described that affect laboratory test results (30, 31), drug-test interference is a relevant issue in clinical chemistry (32). The interference can be due either to a biological effect, e.g., the increase in serum concentration of the thyroid hormone FT_4 by valproic acid (33), or to analytical interference, e.g., interference by aminoglycoside in total protein determination in urine (34). Drug-test interference can lead to misinterpretation of laboratory data, potentially resulting in unnecessary medical services and costs. Gronroos et al. extensively evaluated the literature on drug-test interference and recommended the development of a database system comprising linked laboratory and medication data for appropriate investigation of drug-test interference (35).

Descriptive epidemiology: quality of pharmacotherapy

In selecting a drug, the patient's physical condition can be a contraindication. By linking laboratory and medication data, it can be investigated whether the drug is appropriately prescribed to the patient. Using this approach, Schiff et al. revealed that at their institutions a large proportion of patients received potassium supplementation while hyperkalaemic (36). By linking prescription claim data and hospital admission records, Juurlink et al. showed that publication of the results of the Randomised Aldactone Evaluation Study (RALES) was associated with an abrupt increase in the rate of prescriptions for spironolactone and in hyperkalaemia-associated morbidity and mortality in heart failure patients also treated with ACE inhibitors (37).

On the other hand, laboratory measurements can also reveal conditions that require treatment. Schiff et al. uncovered patients who were not treated with levothyroxine after abnormal levels of thyroid-stimulating hormone (TSH) were found (38).

Patient groups with altered drug metabolism, such as patients with renal insufficiency, often require dose adjustments of specific drugs. Epidemiological studies can be used to evaluate the adherence to dosing instructions with regard to renal insufficiency, as shown by Chertow et al., who reported that 70% of medication orders were written for an inappropriately high dose or frequency (39), increasing the risk of developing adverse drug reactions.

For a number of drugs, laboratory monitoring for drug toxicity, e.g., drug-induced liver damage, blood dyscrasias and nephrotoxicity is warranted (40). In several cases of adverse drug reactions that have led to withdrawal of drugs from the market, a lack of appropriate laboratory monitoring played an important role (41). Several recent studies considering laboratory monitoring during drug exposure in outpatients showed that essential monitoring was performed in only a minority of patients at risk of severe adverse drug reactions (42–44).

Laboratory monitoring can also be warranted for efficacy of drug therapy, for example, measuring cholesterol goal attainment in statin treatment. Goettsch et al. linked outpatient laboratory data to prescription histories from community pharmacies and found that the percentage of patients who achieved the cholesterol level recommended in guidelines was low in practice (45).

Prognostic and diagnostic epidemiology: markers for drug effects

Several adverse drug reactions develop unexpectedly and are diagnosed when symptoms occur, for example, drug-induced thrombocytopaenia is often detected after spontaneous/excessive bleeding occurs (14). For the patient (irreversible harm) and for society (increased medical costs), it is relevant to investigate whether the risk of such adverse drug reactions can be predicted before initiation of the medication and hence even guide the choice of medication, or if these adverse drug reactions can be diagnosed at an early stage (i.e., before clinical symptoms occur). Laboratory parameters could potentially serve as prognostic or diagnostic markers for adverse drug reactions (46), for example, the occurrence of the typical drop in platelet count associated with heparin-induced thrombocytopenia (HIT) (47). Epidemiological studies within databases linking laboratory and medication data can contribute to the identification of predictive or prognostic markers and/or the development of algorithms for adverse drug reactions.

Discussion

Application of UPOD for clinical epidemiological research

Transfer of automated laboratory data from the laboratory information system into a relational database infrastructure makes laboratory data available for clinical epidemiological research. Linking laboratory data to other clinical data provides numerous opportunities to study the biochemical characteristics of diseased populations, the effects of medical therapy that can be detected with laboratory tests and contribute to the development of predictive and diagnostic markers and/or algorithms for disease.

The application of automated database systems comprising observational data on patient characteristics, diagnoses, disease and therapy is already an established and widely used approach in the study of the effects of drugs in clinical settings (48), in particular with regard to the detection, verification and quantification of adverse drug reactions (49). The linkage of laboratory and medication data is especially innovative for database systems comprising data on in-hospital patients, such as UPOD. With regard to the general population, laboratory data have recently become available within some of the automated database systems used in pharmacoepidemiological research, for example the insurance-based Kaiser Permanente database (40, 43) and the Dutch population-based PHARMO Record Linkage System (45). However, until recently, most database systems used to study drug use in populations comprised drug histories from community pharmacies or hospitals linked to registrations of morbidity or hospital-discharge diagnoses (48), but lacked laboratory data, thereby limiting the possibilities for conducting studies on adverse drug reactions that can be detected biochemically, as illustrated in a recent study carried out by our group (50). It was found that the underlying disease overshadows many clinical conditions and that comorbidity is seldom registered in the case of severe illness. This could result in underestimation of the number of cases and potential bias when using hospital discharge diagnoses only in (pharmaco)epidemiological research. Because laboratory data allow more sensitive detection of the outcome and thereby increase the study power, the potential of investigations regarding, for example, the association between drug exposure and hyponatraemia would be increased if cases were sampled from laboratory data (50). Taking this into account and considering the elevated risk of adverse drug reactions in hospitalised patients, the importance of laboratory information in drug therapy and the continuing introduction of new drugs with innovative mechanisms of action, a research platform that allows the linkage of laboratory and medication data for hospitalised patients promises to be a valuable tool for clinical epidemiological studies aimed at investigating the (adverse) effects of drugs.

Quality and data management

The use of database systems such as UPOD for clinical epidemiological research has several advantages. In contrast to ad hoc data collection, database systems allow the study of complete and validated data on a patient level for a large population over a prolonged period of time with relatively easy access and at low cost (51). Furthermore, the collection of data using electronic registration systems and by automated transfer can be considered less prone to mistakes and less expensive compared to manual data collection. In addition, the real-life setting makes the population representative of patients actually being treated in clinical practice (51).

Although the potential advantages of a database comprising clinical data are numerous, potential threats to epidemiological research using observational data should be considered, for example, missing data and misclassification that are to a certain extent inherent to the use of retrospectively gathered data (52). To ensure maximum completeness and integrity, the data within UPOD are collected automatically and are extensively checked by data processing experts, administrative personnel and researchers. Furthermore, a data dictionary in which the database content is described in detail is available for researchers.

UPOD was established after the introduction of a CPOE system for ordering medication in our hospital and currently comprises complete data for a period of 2 years for one institution. This may possibly limit the study of rare outcomes in the short term and the extrapolation of findings to other hospitals. However, the population covered will increase rapidly over time (Table 1), and cooperation with other hospitals will extend the possibilities.

We believe that the institutional basis of the database has several advantages. The setting within a large academic hospital guarantees optimal synergy between clinical and both diagnostic and basic research laboratories. In this way, the translation of research findings to clinical practice and the experimental laboratory becomes relatively easy and efficient. For example, when novel associations between drug exposure and abnormal blood-cell parameters reflecting damage to blood cells are found in epidemiological research, mechanistic hypotheses can be further investigated within the experimental laboratory setting using blood cell-specific in vitro systems (53). In addition, the institutional basis makes it possible to validate data relatively easily or gather additional data, for example, by retrieving information that is currently not available within UPOD, such as radiology reports or electrocardiograms, from the original patient chart or by contacting the patient through his or her physician.

UPOD can be further expanded with data on extramural patient care, e.g., medication histories from community pharmacies or visits to general practitioners, and potentially other important types of clinical information such as pathology and genetic data. With regard to the latter, worldwide initiatives are currently undertaken to collect genetic data within population databases to study gene-disease relationships to characterise individual patients with regard to disease subtype based on their genetic profile (54). Adding genetic data to UPOD will provide interesting research possibilities such as pharmacogenetics, i.e., investigating the role of genetic variation in the patient's response to pharmacotherapy (55).

Conclusions

Facilitating the linkage of laboratory data collected during routine clinical care within a database system to other patient-oriented records broadens the opportunities for clinical pharmacoepidemiological research. Although recently established, UPOD prom-

ises to be invaluable for this type of research and should be exploited fully.

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