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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

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Changes in the defined daily dose; CYP2D6/CYP3A metabolism as an indicator for dose-setting problems

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Abstract *Objective*: Interindividual variability is common at all stages of drug absorption, distribution, pharmacodynamics, metabolism and elimination. In this study, we focused on two enzymes involved in phase-I drug metabolism as markers of pharmacological variability: the CYP3A and CYP2D6 subsystems of cytochrome P_{450}. The main aim of our study was to determine whether substrate drugs for CYP2D6 and/or CYP3A enzymes, showing high interindividual matabolic variability, are more prone to postmarketing adjustments of defined daily dose (DDD).
Methods: A case-control design was used. We identified all DDD changes between 1982 and May 2004 through the website of the WHO Collaborating Centre for Drug Statistics Methodology. Cases were drugs with a DDD change and controls were other drugs with unchanged DDDs. Information about metabolism pathway, introduction year, literature exposure and administration route was retrieved.
Results: We included 88 cases and 176 controls. Of the 88 cases, 51 were dosage decreases (58.0%). Overall, DDD changes were not associated with CYP2D6/CYP3A metabolism (OR 1.92; 95%CI 0.78–4.72). However, DDD decreases were associated with CYP2D6/CYP3A metabolism (OR 3.21; 95%CI 1.25–8.26). Adjusting for introduction year weakened this effect (OR 2.78; 95%CI 0.98–7.90).
Conclusion: Our study indicates that CYP2D6 and CYP3A substrates are more likely to require a DDD decrease after granting of market authorisation. However, this effect was diminished by adjusting for period of introduction. The implication of this finding is that variability indicators, as is demonstrated in this study for CYP2D6/CYP3A metabolism, can exert their influence on a wide variety of drug measures, such as the DDD.

Keywords Dosing changes · Pharmacoepidemiology · Cytochrome P_{450} · Pharmacogenetics · Label changes · Regulatory affairs

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Introduction

Various authors have stressed the provisional nature of assessments about effectiveness and safety of medicines at the time when a new active substance is introduced into clinical practice [1, 2]. The same holds for finding the right dose on the basis of pre-authorisation studies [3, 4].

Dosing of pharmaceuticals is a dynamic process, in which recommended dosages may undergo changes over time. When Cross et al. studied labelling changes of New Molecular Entities in the United States approved by the Food and Drug Administration between 1980 and 1999, they found that one in five compounds underwent a dosage change after marketing [3]. Our group has previously reported on 115 changes in the defined daily dose (DDD)—a dose measure developed and maintained by the World Health Organization (WHO)—and came basically to the same conclusion [4]. DDD increases were most frequently associated with antibiotics, while cardiovascular drugs underwent more dose decreases. An important finding from both studies was that newer drugs were more susceptible to postmarketing dose changes than older drugs [3, 4].

Thus, optimising dosage strategies remains an important challenge for drug development [5]. Causes for dosage changes may be found anywhere in the drug life-cycle. Both pharmaceutical, clinical and economical determinants of variability in dosing have been reported [6, 7]. A classic example is the postmarketing dose reduction of captopril, where the initially recommended dose was much higher than necessary for the vast

majority of patients being prescribed the drug in routine clinical practice [8].

In pharmacology, interindividual variability is common at all stages of drug absorption, distribution, pharmacodynamics, metabolism and elimination. For metabolism, interindividual variation in the phase-I metabolising enzymes of the cytochrome P_{450} (CYP) system is a widely recognized source of between-patient differences regarding drug therapy response [9] and plays an important role in drug safety.

Here, we want to focus on two enzymes involved in phase-I drug metabolism as markers of pharmacological variability, namely the CYP3A and CYP2D6 subsystems of CYP. The CYP2D6 and CYP3A enzymes together are responsible for about 60–75% of phase-I reactions undergone by all drugs metabolised through the CYP system and show extensive interindividual variation [9]. Also, these enzymes play an important role in many drug interactions.

The pathway from being a substrate of a metabolising enzyme system to complexity in clinical practice of finding the 'right' dose, and as a possible consequence a change in a dose measure such as the DDD, is long and may be full of erratic features (e.g. publication of new clinical trial results, marketing by the industry and changes in good practice guidelines). However, although the DDD is not an average recommended dose by definition, a DDD change can be seen as a reflection of 'noise' surrounding the dosing of drugs in daily practice, indicating situations where the actual prescribed dose has departed significantly from the labelled use at the moment of setting the DDD. Accordingly, we use the DDD as a measure for problematic dose setting in this study.

We hypothesize that drugs metabolised through these variable enzyme systems are more susceptible to changes in dosage after marketing authorisation and, consequently, the need for a DDD change.

Therefore, the main aim of our study was to determine whether substrate drugs for CYP2D6 and/or CYP3A enzymes are more prone to postmarketing DDD adjustments.

From a drug safety perspective, special interest goes out to postmarketing DDD decreases, since these represent cases where the average prescribed dose was lowered over time, possibly instigated by safety concerns or the 'overdosing' of the drug after introduction.

Methods

We used a design comparable to that used in the previously mentioned study on DDD changes [4]. Again, we made use of a case-control design for the analysis. Cases were drugs with a DDD change between 1982 and May 2004. Only the first DDD change of a drug was included. Controls were randomly selected from all other drugs for which a DDD was available. Excluded from the analysis were drugs with a topical action, laxatives, drugs acting on the respiratory tract and stomatological preparations, since these drugs probably have a limited systemic absorption. Products with multiple active ingredients and drugs that show a high between-patient dose variability due to a strong relationship between dose and disease state (e.g. insulin, anti-anaemic preparations) were also excluded. Furthermore, we excluded drugs with a low volume of use in Europe; only drugs that were marketed in The Netherlands were included in the analysis. For each case, two controls were randomly selected.

Information about the DDD changes, drugs and route of administration was retrieved from the website of WHOCC-DSM [10]. Year of global introduction of a drug was ascertained, since this was a determinant in the previous study [4]. Information on whether drugs were substrates of the CYP2D6/CYP3A enzymes was retrieved from the so-called 'Flockhart' CYP drug-interaction table [11].

To adjust for possible bias introduced by the prominence of a drug in the scientific literature, we calculated a measure of 'attention exposure' in medical journals. For all cases and controls, the sum of citations in MEDLINE as a fraction of the total number of MEDLINE citations in 2 years before an index year was ascertained.

All results were calculated using a logistic regression model and presented as odds ratios (ORs) with 95% confidence intervals (95%CI). In the model metabolism pathway, route of administration and decade of registration were entered as categorical variables, 'attention exposure' in medical journals as a continuous variable.

Results

We included 88 cases and 176 controls. Of the 88 cases, 51 were dosage decreases (58.0%). An overview of the cases and controls is displayed in Table 1.

The distribution of the fraction of MEDLINE publications (not shown in table) indicated that drugs with reported DDD changes were more widely covered than 'controls' in the medical literature ($P = 0.036$).

Being a substrate for either the CYP2D6 or CYP3A4 metabolism pathway was not significantly associated with any DDD change (OR 1.92; 95%CI 0.78–4.72). However, when we looked at only dosage decreases, the unadjusted OR for metabolism through CYP2D6 or CYP3A (9 of 51 cases versus 11 of 176 controls) was 3.21 with a 95%CI from 1.25 to 8.26. Table 2 shows the unadjusted and adjusted ORs for DDD decreases.

When CYP2D6/CYP3A metabolism results were entered into the regression model together with the influence of the administration route, the effect of the metabolic pathway on DDD decreases remained basically the same (OR 3.97; 95%CI 1.35–11.67). Adjustment for the number of publications on a specific compound had no large effect (OR 3.03; 95%CI 1.17–7.87). CYP2D6/CYP3A metabolism and decade of registration were also included in the logistic model, since

Table 1 Characteristics of cases of defined daily dose changes (all) and controls

	Case (88)	Control (176)	Crude odds ratio (95%CI)
Period of introduction			
≤ 1970	24 (27.3%)	105 (59.7%)	Ref
1971–1980	22 (25.0%)	24 (13.6%)	4.01 (1.94–8.31)
1981–1990	25 (28.4%)	25 (14.2%)	4.38 (2.15–8.90)
≥1991	17 (19.3%)	22 (12.5%)	3.38 (1.56–7.32)
Administration route			
Oral	59 (67.0%)	106 (60.2%)	Ref
Non-oral/multiple	29 (33.0%)	72 (39.8%)	1.34 (0.79–2.30)
Metabolised by CYP2D6 or/ and CYP3A	10 (11.4%)	11 (6.4%)	1.92 (0.78–4.72)
Metabolised by CYP3A4	6 (6.8%)	7 (4.0%)	1.77 (0.58–5.42)
Metabolised by CYP2D6	5 (5.7%)	4 (2.3%)	2.59 (0.68–9.90)
Metabolised by CYP3A4 and CYP2D6	1 (1.1%)	0 (0.0%)	NA

early registration may be associated with less information about the metabolic pathway, fewer changes in dosing due to more experience with the drug, and not having had a post-DDD-setting review by the WHO during the study period. In this variant, the effect of CYP2D6/CYP3A on dosage decreases lost significance (OR 2.78; 95%CI 0.98–7.90).

Discussion

Optimisation of drug dosing is key to successful drug development [5, 8]. We found that being a substrate for either CYP2D6 or CYP3A (i.e. combining the numbers for both groups) makes a drug about three times more prone to require its DDD to be decreased after market authorisation has been granted. Although this effect is diminished when adjusting for decade of introduction, a direction of effect remains. This implicates that patients with early prescriptions of these drugs immediately after introduction into clinical practice may be exposed to inappropriate dose regimens.

Phase-I metabolism is a process susceptible to a great amount of variance. Differences in metabolising activity and henceforth larger variability in plasma levels and half-life can result in a greater variation in patient responses. The nature of the variability is different for CYP2D6 and CYP3A metabolism: for CYP2D6 it is caused by different alleles, resulting in a multi-modal distribution of enzyme activity; the origin of variability in CYP3A metabolism is still the subject of discussion, but a multi-gene or gene-environment interaction is suggested by the unimodal nature of enzyme activity [12]. In this study, we have tried to link these intrinsic drug properties, while disparate in character, to outcomes that are relevant from both clinical and regulatory perspectives.

Table 2 Odds ratios for defined daily dose decreases in drugs metabolised by CYP2D6 or CYP3A4

Adjusted for	Odds ratio (95%CI)
Unadjusted	3.21 (1.25–8.26)
Route of administration	3.97 (1.35–11.67)
Exposure in medical journals	3.03 (1.17–7.87)
Period of introduction	2.78 (0.98–7.90)

Of course, there are many other sources of variability, besides CYP3A and CYP2D6, that influence dosing of drugs and that need to be explored further in the future. For example, variability in other metabolising pathways, in absorption, in distribution or in drug targets.

Recently, Kircheiner et al. [13] reviewed the influence of phenotype on drug response for antidepressants and antipsychotics and pointed to the complex nature and consequences that multigenic and gene-environment interactions at different stages may have on treatment recommendations; response to antihypertensive agents is also known to be dependent on phenotype [14].

For certain, there are other non-drug factors that are also of influence. In this study, the decade of registration was a strong predictor for undergoing a DDD change; this was also found in our previous study [4]. The reason for this could be that, because of the extensive experience with drugs marketed before 1970, good dosing strategies had already been developed in clinical practice long before the DDD methodology was introduced in the mid-1970s.

Although we consider the methodology employed here useful to gain insight into the studied process, there are some limitations that have to be addressed. First of all, the DDD changes included in this study possibly represent an underestimation of changes from the initial prescribed dose in daily practice. To minimize effects on drug utilization studies, the number of DDD changes is kept as low as possible. Often only changes in the average maintenance dose of 50% or more warrant a DDD change. For recently established DDDs and major drugs, an exception is made; here smaller DDD adjustments are possible, also some changes might be made for pragmatic reasons [10].

Bias may also have been introduced by the fact that well-known drugs are more likely to undergo a change in the DDD and also have their metabolism pathway elucidated. We tried to adjust for this by introducing the fraction of MEDLINE publications as a parameter, including the influence of the decade of registration and

excluding drugs not often used in Europe. Furthermore, the table used for determining enzyme substrates of drugs does not indicate the primary metabolic pathway, and may not be complete. However, the table is widely used as a reference guide and provides the evidence base for the reported metabolic pathways by referring to relevant publications.

One may argue that every need for adjustment of the dose after marketing is a failure of drug development and/or the regulatory system [4]. For sure, predictability of premarketing research with respect to patient outcomes after drug approval has improved significantly during the last decades. This paper warrants an ongoing strive to invest in the linking of in vitro data on, for example, metabolising properties of drugs with evaluations in real clinical practice [15].

Conclusion

In conclusion, our study indicates that CYP2D6 or CYP3A substrates are more likely to require a DDD decrease after granting of market authorisation. However, this effect was diminished by adjusting for period of introduction. The implication of this finding is that variability indicators, as is demonstrated in this study for CYP2D6/CYP3A metabolism, can exert their influence on a wide variety of drug measures, such as the DDD.

For the future, the interactions between variability in dosing and variability indicators, whether pharmacodynamic or pharmacokinetic, warrant further investigation.

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