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Therapeutic Drug Monitoring Databases for Postmarketing Surveillance of Drug-Drug Interactions

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Abstract

Drug-drug interactions can be associated with patient morbidity due to either increased toxicity or a potentially ineffective concentration. Because interactions cannot always be anticipated during drug development and actual patients receiving a drug for therapeutic use often differ from those included in clinical trials, postmarketing surveillance is essential. Therapeutic drug monitoring (TDM) databases offer a unique opportunity in this respect.

Prerequisites for TDM databases to provide valid information in a pharmacoepidemiological perspective include the following: precise description of exposure to the potentially interacting drugs; measurement of parent compound and active metabolites through accurate and precise analytical techniques; documentation of relevant patient characteristics that may act as confounding factors (e.g. gender, age, smoking habits); repeated assessments over time if possible; and sound pharmacokinetic framework for data selection, analysis and interpretation.

The contribution of TDM to the documentation of drug-drug interactions takes advantage of different possible study designs, discussed on the basis of recently published studies. The single case report plays an important role as an alert signal. It is illustrated for a patient on long-term treatment, who displayed an unexpectedly high clozapine concentration after the introduction of ciprofloxacin comedication. The prospective on and off comedication panel study shows advantages in terms of carefully selected inclusion criteria and control of treatment modalities. A study of the thioridazine-fluvoxamine interaction is presented, with patients followed on thioridazine monotherapy, after introduction of fluvoxamine and after its discontinuation. The main advantage of the retrospective large-scale TDM database screen is representativeness of patients actually treated, whereas drawbacks are related to quality of data and suitability for valid interpretation. Such an approach is illustrated by a review of data collected over 10 years of routine TDM that allowed documenting induction of nortriptyline metabolism by carbamazepine and inhibition by several phenothiazines. Finally, population pharmacokinetics is well suited to observational data collected for TDM purpose, provided quality is ascertained. Focus is placed on interindividual variability and relationship between pharmacokinetic parameters and patient characteristics,

including comedication. The population approach is discussed with respect to a study that documented a 32% increase of haloperidol clearance associated with anticonvulsant comedication, in addition to effects of age and bodyweight.

Among factors to consider for improved effectiveness in the use of TDM databases for postmarketing surveillance of drug-drug interactions, integration of efficacy and safety data in future studies and communication of expert recommendations to prescribing physicians are essential.

Concurrent use of multiple drugs is common and drug-drug interactions are responsible for considerable patient morbidity. Various estimates of the prevalence of multiple drug use have been published. Polypharmacy has been estimated to occur in 10% of the total population in a Danish study,[1] the proportion increasing in elderly and more dependent, institutionalised patients.[2] Furthermore, a medication database screening in a Finnish hospital revealed that 57.3% of patients taking two or more drugs concurrently were exposed to potential interactions of minor clinical importance and 7.4% had combinations which might have led to serious clinical consequences.[3] These combinations were potentially hazardous because of either increased toxicity (4.8% of patients) or potentially ineffective concentration (2.2% of patients). The search for efficient and valid means of conducting drug-drug interaction studies and of conveying the information to prescribing physicians is thus a priority. Therapeutic drug monitoring (TDM) databases offer a unique opportunity in this respect.

Guidelines have been provided for the design of interaction studies during drug development, from early *in vitro* and *in vivo* investigations to subsequent rationally designed studies in healthy volunteers or patients.[4,5] However, careful postmarketing surveillance remains essential to identify previously unexpected interactions in populations that often differ from the ones considered in premarketing studies.[6] Whereas an interaction can occur at a pharmacodynamic level through a variety of mechanisms, this article focuses on pharmacokinetic interactions, i.e. alterations of absorption, distribution, metabolism and elimination caused by concomitant drug treatment. As emphasised in the European note for guidance on the investigation of drug-drug interactions, it is important to differentiate between detectable interactions and clinically relevant interactions.[4] An interaction is clinically relevant when the therapeutic activity and/or toxicity of a drug is changed to such an extent that a dosage adjustment of the medication may be required.

The goal of TDM is to optimise the patient's clinical outcome by managing the medication regimen with the assistance of measured drug concentration.[7] TDM is particularly valuable if therapeutic concentration range is narrow and intra- and interindividual pharmacokinetic variability is pronounced. Evaluation of possible drug-drug interactions has long been advocated as an appropriate indication for TDM and has been recognised as such in the standards of practice recently published by the US National Academy of Clinical Biochemistry.[8] TDM has been used to minimise toxicity and improve efficacy in the presence of potentially interacting drugs in many areas, including cardiology (e.g. digoxin, amiodarone), infectious diseases (aminoglycoside antibacterials), asthma therapy (theophylline) and thyroid hormone replacement therapy.[9] Areas where TDM is promising, although still controversial, include antiretroviral therapy,[10] cancer therapy[11] and antituberculosis chemotherapy.[12] Anticonvulsant and psychotropic drugs deserve particular focus.[13-15] Some of these drugs have been considered among the best candidates for TDM because their safety margin between therapeutic and toxic levels is small, polytherapy is frequent and the likelihood for drug-drug interactions is important. Indeed, these drug classes include some potent inducers [e.g. phenytoin, phenobarbital (phenobarbitone), carbamazepine] or inhibitors [e.g. fluoxetine, fluvoxamine, phenothi-

azines, valproic acid (sodium valproate)] of drug-metabolising enzymes of the cytochrome P450 (CYP) system.[16,17] This review focuses largely, though not exclusively, on psychotropic drugs, for which published data are abundant and the authors have accumulated experience over 20 years of TDM at the Department of Psychiatry, University of Geneva, Switzerland.[18,19]

This article proceeds in two stages. First, it reviews the prerequisites for TDM databases to provide valid information for documenting drug-drug interactions in a pharmacoepidemiological perspective, i.e. sound pharmacokinetic background and quality of the collected data. Secondly, it addresses four different methodological approaches that have been used to document drug-drug interactions, i.e. the single case report, the on and off comedication panel study, the TDM database screen and population pharmacokinetics. In each case, an example is illustrated and discussed in detail.

1. Pharmacokinetic Background

TDM data are generally interpreted within the framework of the following linear pharmacokinetic model. Assuming a 1-compartment open model, the average steady-state concentration (C^{ss}) of a drug administered at a fixed dose and constant dosing interval is provided by the following equation:

$$C^{ss} = \frac{F \cdot dose}{CL \cdot \tau} \quad \text{(eq. 1)}$$

where CL is total systemic clearance of the compound and τ is dosing interval. F is systemic availability, which equals 1 for intravenous administration and is less than 1 for orally administered drugs that display incomplete absorption and/or intestinal or hepatic first-pass metabolism.

If an active metabolite is measured together with parent compound, the following equation applies:

$$C^{ss,metabolite} = \frac{F \cdot dose}{CL_{metabolite} \cdot \tau} \cdot \frac{CL_{formation}}{CL_{parent}} \quad \text{(eq. 2)}$$

where CL_{parent} and $CL_{metabolite}$ are total systemic clearances of parent compound and metabolite, respectively, and $CL_{formation}$ is the partial clearance reflecting biotransformation of parent compound to metabolite. The metabolic ratio is thus as follows:

$$\frac{C^{ss,metabolite}}{C^{ss,parent}} = \frac{CL_{formation}}{CL_{metabolite}} \quad \text{(eq. 3)}$$

The extent to which TDM measurements truly reflect average steady-state concentrations depends on the compound half-life. For a drug with a relatively long elimination half-life ($t_{½}$ = 24 hours) that is administered twice a day (τ = 12 hours), fluctuation over one dosing interval is relatively modest, with a maximum to minimum concentration ratio less than 1.4. For a drug with a short elimination half-life ($t_{½}$ = 2 hours) administered three times a day (τ = 8 hours) maximum fluctuation is about 16-fold.[20] Implications with respect to drug-drug interaction studies are 5-fold:

- The timing of blood samples relative to last dose is an important parameter and accuracy is critical for short half-life drugs. Trough levels obtained immediately before next intake are generally recommended to facilitate interpretation.[13]
- Attention should be given to obtaining blood samples under steady-state conditions whenever possible, i.e. after 4 to 5 half-lives have elapsed since the most recent dose adjustment.[8]
- Straightforward interpretation of elevated or reduced concentration in terms of altered clearance and/or bioavailability is not allowed unless the validity of such an approximation is carefully assessed for each specific drug.
- Alternatively, the population pharmacokinetic approach makes it possible to take advantage of data obtained over the full dosing interval and before steady state is achieved.[21,22] This is particularly relevant for short half-life drugs. Dosing history over several days (or weeks) is generally required.
- Measuring active metabolites may be an efficient means to understand the nature of an interaction and its effect on different metabolic pathways.[23,24]

2. Therapeutic Drug Monitoring (TDM) Database Requirements

The quality of data necessary for proper interpretation of TDM data has been emphasised in recent publications.[8,25] The principles of epidemiological research have contributed to setting validity criteria for postmarketing surveillance of drug safety on the basis of automated databases.[26-28] These criteria may as well apply to surveillance of drug-drug interactions on the basis of TDM databases. First, exposure and outcome need to be properly defined. Exposure refers to the two (or more) potentially interacting drugs. Posology, dosing schedule and time interval since introduction, dose adjustment or discontinuation need to be fully documented for both compounds. Complete medication history over the last week may be required. Indeed, the time interval before onset of induction ranges from 2 to 7 days and the time to maximum inhibition depends on the involved mechanism, from 24 to 48 hours for competitive binding to much longer for decreased biosynthesis.[29] Outcome refers to measurement of parent drug and active metabolites through an accurate and precise analytical technique. Secondly, possible bias and confounding factors should be documented. Provided that TDM databases collect routine data, no procedure can be set up to control for such factors, but their careful measurement is necessary for proper data interpretation. Thus, TDM request forms should include information such as gender, age, bodyweight, renal or hepatic diseases, smoking and drinking habits, and comedication other than the drugs suspected to interact. Complementing these data with information about phenotype or genotype of individuals with regard to specific metabolic pathways has been advocated to allow differentiation between pharmacogenetic and environmental (e.g. comedication) determinants of altered drug metabolism.[30] Thirdly, repeated measurements over time increase the validity of results by increasing coherence and allowing assessment of a possible relationship between dose, duration of exposure and magnitude of interaction.

Statistical power, i.e. probability of detecting an interaction if present, should be adequate and thus the number of included patients should be sufficient. A specific aim of TDM-based studies should be to identify interactions sufficiently large not only to necessitate but also to permit dose adjustment by the prescribing clinician, for a given formulation. Focus also needs to be placed on large effects because routine TDM is nothing like a carefully controlled experiment, any weak effect being conceivably attributable to unidentified sources of variability. For comparison of patient groups exposed and nonexposed to comedication, sample size calculation suggested that about 15 to 20 patients per group may be sufficient to detect a 2-fold concentration increase or decrease for psychotropic drugs. If exposed and nonexposed patients were matched for possibly influencing characteristics, such as gender and age, this number may decrease to about 8 to 10 patients per group.[19]

Interaction studies performed during drug development and during therapeutic use differ in terms of primary objective, and thus in terms of statistics. For premarketing studies, the use of confidence intervals and acceptance ranges is recommended by regulatory authorities to document the size of expected effects or to support a no interaction claim.[4,5,31] In postmarketing studies, focus is placed on detection of unsuspected interactions and significance tests are generally performed.

For a postmarketing surveillance system to be effective, computerised TDM database management should aim at reaching a reasonable standard of validity and allowing rapid assembly of patient populations at low cost. As illustrated below, TDM databases have demonstrated potential for effective documentation of drug-drug interactions, using methodologies of variable complexity, from simple case reports to sophisticated population pharmacokinetic modelling.

3. The Single Case Report

Case reports have played a major role in postmarketing surveillance of drug safety and as an alert system for drug-drug interactions.[28] They

represent a simple and low cost method for generating hypotheses and stimulating subsequent studies on a larger scale. TDM data represent a unique and ever-growing source of information in that respect, with some patients receiving treatment for prolonged periods of time and assessed before a possibly interacting comedication is introduced, during comedication and after discontinuation.

Figure 1 illustrates the as yet unpublished case of a 46-year-old man who was prescribed clozapine for the long-term treatment of schizophrenia and had blood samples taken for TDM on 17 occasions during the year 2000. Inter-occasion 2-fold variability in clozapine concentrations was observed over about 5 months of treatment at a fixed 400mg/day, suggesting partial or irregular compliance during that period. In September 2000, the patient had a urinary tract infection and started ciprofloxacin treatment. Last monitoring performed before comedication was introduced showed concentrations of 354 μg/L for clozapine and 194 μg/L for desmethylclozapine at a clozapine dosage of 500 mg/day. Metabolite formation ratio desmethylclozapine/clozapine was 0.55. After introduction of ciprofloxacin 1500 mg/day, with a 775mg/day dose of clozapine, concentrations increased to 1218 and 371 μg/L for clozapine and desmethylclozapine, respectively, with the metabolic ratio decreasing to 0.30. The 3.4-fold concentration increase for clozapine largely exceeded the 1.6-fold dose increase, so that an interaction was suspected. Monitoring was repeated 3 days later while the patient was receiving ciprofloxacin 3000 mg/day and clozapine 775 mg/day, providing a similar picture with 1197 and 475 μg/L measured for clozapine and desmethylclozapine, respectively. Nine days after discontinuation of ciprofloxacin, concentrations decreased to 730 μg/L for clozapine and 256 μg/L for desmethylclozapine with a 600mg/day of clozapine. The metabolic ratio was 0.35 and still relatively low when compared with values measured before antibacterial treatment.

The likelihood of a clozapine-ciprofloxacin interaction was supported by different observations. On the one hand, the metabolism of clozapine is dependent on enzymes CYP1A2 and CYP3A4,[32] and ciprofloxacin is known to inhibit CYP1A- and CYP3A-mediated biotransformation.[33] On the other hand, a clinically significant interaction was expected from a recent study with a low dose of ciprofloxacin.[34] Reviewing TDM request forms, nevertheless, revealed that other factors might have contributed to variability. The patient was a smoker[35] and had received up to seven comedications on some occasions, including omeprazole and valproic acid (sodium valproate), which induce and inhibit, respectively, clozapine metabolism.[16,36] This complex situation emphasises the need to have all relevant information recorded for adequate evaluation of a case report and to replicate the observation to rule out the influence of uncontrolled or insufficiently controlled factors.

TDM-documented case reports of suspected drug-drug interactions have been numerous for many classes of drugs. As an example, the metabolic interaction between selective serotonin reuptake inhibitors (SSRI) and tricyclic antidepressants has been the object of repeated case reports from 1988 to the present.[37-42] They have been accompanied by numerous *in vitro* and *in vivo* studies aimed at quantifying the inhibitory potential of each individual SSRI with regard to the different CYP enzymes.[14,43]

4. The On and Off Comedication Panel Study

In the context of drug-drug interaction studies, panel studies refer to cohorts of patients followed over time before, during and after exposure to medication suspected to interact with ongoing treatment. They resemble formal interaction studies performed during drug development, with a selected group of patients included in a research protocol and drug treatment at least partially controlled. However, TDM-like steady-state concentrations are measured instead of full pharmacokinetic profiles and are used for intraindividual comparisons, each patient serving as his/her own control.

An example of such a panel study has been published recently by Carrillo et al.[44] They measured

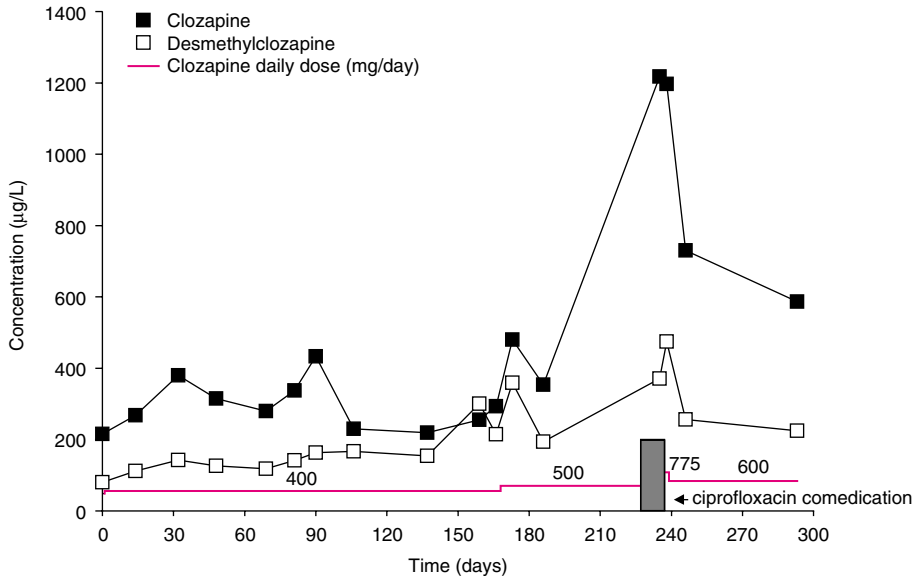

Fig. 1. Therapeutic drug monitoring data for a 46-year-old man prescribed clozapine for the long-term treatment of schizophrenia. Introduction of ciprofloxacin 1500 mg/day for the treatment of a urinary tract infection was associated with a 3.4-fold increase in clozapine concentrations, not accounted for by the 500 to 775mg increase in clozapine daily dose. The desmethylclozapine to clozapine formation ratio decreased from 0.55 to 0.30.

thioridazine and its active metabolites mesoridazine and sulforidazine in 10 male inpatients with schizophrenia on three occasions: during monotherapy with thioridazine at a flexible dose, 1 week after introduction of fluvoxamine at a low dose (25mg twice a day) and 2 weeks after fluvoxamine discontinuation. After addition of fluvoxamine, concentrations increased significantly, with mean percentage change of 225% for thioridazine, 219% for mesoridazine and 258% for sulforidazine. Two weeks after fluvoxamine discontinuation, mean concentration decreased, but a few patients continued to show elevated concentrations when compared with initial values. Results for thioridazine are illustrated in figure 2. It should be noted that inclusion and exclusion criteria were rigorous in this study; e.g. patients were not alcohol drinkers, had no abnormal laboratory values at baseline and received no concomitant medication other than the investigated drugs. Drug intake and blood sampling times were carefully controlled to reduce unexplained variability.

Such a prospective, experimental design clearly offers great potential to assess drug-drug interactions in a causal perspective. It has been used with success,[45-48] sometimes allowing investigation of a dose-effect or duration-effect relationship as well.[49] The literature indicates that careful review of TDM databases may allow retrospective collection of panels of well documented cases. Intraindividual comparison of concentrations obtained on monotherapy and while on comedication has demonstrated its value for documenting drug-drug interactions.[50-52]

5. The TDM Database Screen

In this review, the screen approach refers to retrospective studies performed on routinely assembled TDM databases to identify subgroups of patients exposed to comedication and at risk for elevated or reduced concentration of the target drug when compared with a control group. Advantages of such a study include better representativeness of patients actually treated and abundance of data

available at low cost. Drawbacks are mainly related to the nature and quality of data and their suitability for valid analysis and interpretation.[21,22] First, for pharmacokinetic reasons, only steady-state trough concentrations are generally analysed, with precise selection criteria actually depending on drug half-life. Secondly, classical statistics for group comparisons does not allow advantage to be taken of unequal numbers of repeated measurements in different patients, so that some data need to be discarded. Finally, increasing scientific validity of comparisons may lead to additional inclusion and exclusion criteria for increasing the homogeneity of the patient group exposed to comedication and the comparability of the nonexposed group. Most often, an independent control group is selected and checked for similarity with the exposed group with respect to possible bias or confounding factors.[50,53] Pairwise matching of exposed and nonexposed patients with respect to gender, age and possibly other factors known to influence the pharmacokinetics of the target drug (e.g. smoking, pharmacogenetic characteristics) has been advocated as a means to increase the power of group comparisons.[19] Another strategy is to address interindividual variability by multiple regression analysis, with comedication as well as other influencing variables included in the model.[23,24,54,55]

The potential of TDM database screening for documenting drug-drug interactions is best illustrated by the study of Jerling et al.[50,56] Data collected over 10 years of routine TDM for amitriptyline (2431 analyses for 1718 patients) and nortriptyline (1847 analyses for 1219 patients) were screened for groups of patients exposed to different comedications and a reference group of patients on monotherapy. Non-steady-state data were excluded, as well as outpatient data in order to minimise the influence of possibly erratic compliance. For each patient who had repeated measurements, the sample taken at the highest dose of the concomitant drug and, in a second stage, at the highest dose of antidepressant drug was selected. Comparability of exposed and nonexposed groups with respect to gender, age, dosing schedule, sampling time and treatment duration with current dose was carefully assessed. For some comedications, such as dextropropoxyphene, a subset of the original control group was selected to obtain similar age distributions. Results for nortriptyline are provided in figure 3. Group comparison of patients on monotherapy (n = 194) with patients exposed to comedication (n = 8 to 25) confirmed the induction of nortriptyline metabolism by carbamazepine and its inhibition by the phenothiazines perphenazine, thioridazine and levomepromazine. It revealed an inhibitory effect of dextropropoxyphene not previously described. For perphenazine, thioridazine and levomepromazine, data analysis also revealed an interaction more pronounced at low than at high doses of nortriptyline.

Gender and age pairwise matching of patients exposed to comedication with patients randomly selected from a pool of nonexposed patients has similarly demonstrated its value to quantify known interactions and to identify as yet undocumented

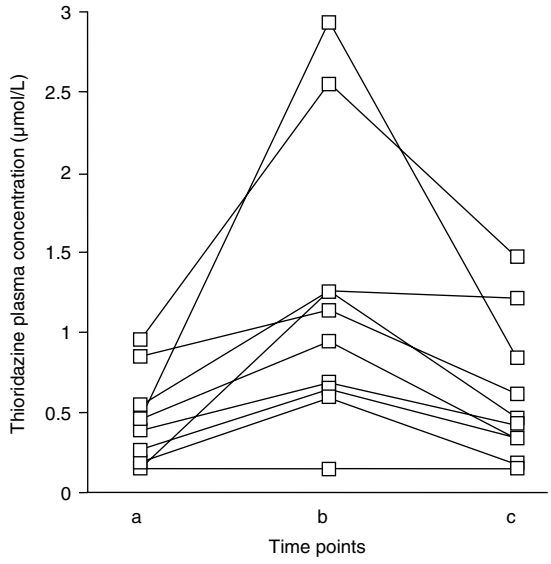

Fig. 2. Steady-state plasma concentrations of thioridazine in 10 patients with schizophrenia, measured at three different time points: (**a**) while receiving monotherapy with thioridazine (88 ± 54 mg/day); (**b**) after the addition of fluvoxamine (25mg twice a day) for 1 week; and (**c**) after discontinuation of fluvoxamine for 2 weeks (reproduced from Carrillo et al.[44] with permission)

ones.[19] Assuming a therapeutic range has been defined for the target drug, the interaction can be quantified by increased relative risk of a patient to remain at a subtherapeutic level or to reach excessively high, possibly toxic concentration when receiving comedication.[18]

From the earlier reports of TDM-based studies in the early 1990s,[23,57] and in parallel with a more widespread use of computerised databases, the number of publications has been increasing in recent years.[54,55,58-62] A few features of these recent studies are worth emphasising. The specific objective of studying interactions in actual patients as a complement to formal studies performed during drug development has been highlighted.[60,62] The added value of measuring metabolites for distinguishing between different metabolic pathways that may be influenced differently by interacting substances has been emphasised.[24,63] Real-time TDM-based surveillance of interactions has demonstrated its clinical relevance for drugs usually prescribed in combination.[10,61] The experience of Back et al.[10] with protease inhibitors indicated that trough concentrations of saquinavir (hard gel formulation) displayed marked interindividual variability, with a large proportion of patients below the therapeutic threshold. Coadministration of ritonavir was associated with markedly increased concentrations and a majority of patients above minimum target level. Given that rapid resistance emerges with the use of too low doses and that excessive toxicity occurs at high concentration, this study emphasises the need for early detection and adequate management of interactions that are part of combined treatment.

6. Population Pharmacokinetics

Whereas the approaches considered so far have concentrated on measured concentrations, population pharmacokinetics focuses on estimation of parameters such as absorption rate, systemic clearance and volume of distribution, and their quantitative relationship with demographic, pathophysiological and exposure variables, including comedication. Unexplained interindividual variability of pharmacokinetic parameters and residual

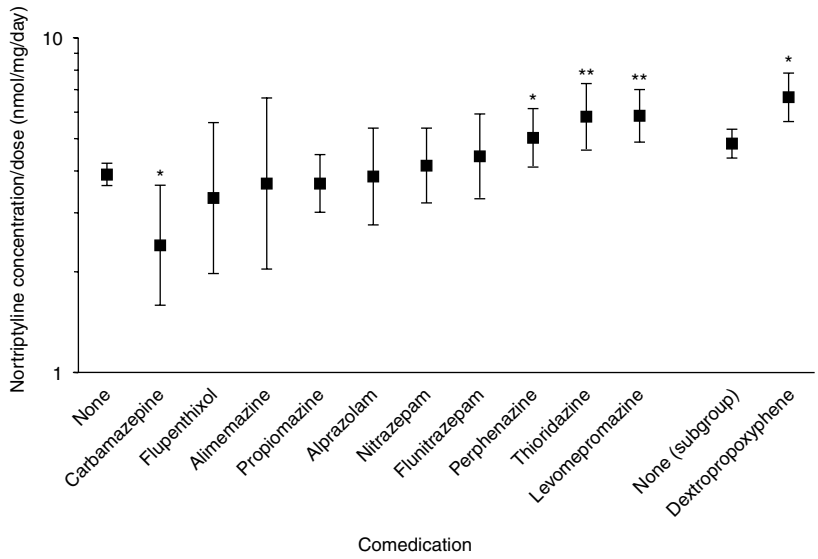

Fig. 3. Nortriptyline concentration to dose ratio at steady state (logarithmic mean ± standard deviation) in patients receiving monotherapy (n = 194) and in patients with concomitant intake of other drugs (n = 8 to 25). Analysis of variance was used for group comparisons (* $p < 0.05$, ** $p < 0.005$) [reproduced from Jerling et al.,[50,56] with permission].

intraindividual variability are explicitly integrated in the pharmacostatistical model. Such an approach is well suited to the nonstringent, observational data collected for TDM purposes, as long as their quality can be ascertained. More specifically, blood samples randomly spread over the full dosing interval or obtained before steady state is reached are important if complete description of the population pharmacokinetic profile is to be performed. Several blood samples from each patient are an advantage, and unequal numbers of measurements for different patients (imbalance) are accounted for.[21,22] Heterogeneity of the patient population is generally regarded as an advantage with respect to the role of serendipity in identifying factors associated with altered kinetics, even though *a posteriori* criteria for grouping patients may be considered as a drawback for reaching definitive conclusions.[64] Data analysis according to sometimes elaborate population models requires specific software. The NONMEM software has represented pioneering advances in the population methodology and remains the most frequently cited program.[65] However, software development continues to be an active area of investigation, with reliability, ease of use and level of support cited among the factors to consider in making a choice between different products.[66]

Several studies have shown the feasibility of detecting drug-drug interactions through population approaches during phase III clinical trials or during post-approval therapeutic use.[67-71] Results were often expected from available knowledge about metabolic processes or confirmed those of formal drug-drug interaction studies during drug development. In some cases, as yet undocumented drug-drug interactions have been detected. An example is the increase in caffeine clearance associated with dexamethasone comedication, identified on the basis of TDM data in neonates and infants.[72] Ludden[70] pointed out that population approaches have sometimes failed to detect expected interactions. Among possible explanations, one may cite a low number of patients for a particular combination of drugs and the numerous uncontrolled sources of variability that are particularly relevant for TDM data, such as patient compliance, inaccuracies in dosing histories and sampling time, or unreported use of over-the-counter drugs. Antal et al.[73] emphasised that analysis of retrospectively collected data can lead to markedly upward biased estimates of both interindividual and residual variability when compared with prospective studies. The quality of TDM databases may thus limit its potential for detecting smaller interactions but detection of large, clinically meaningful interactions is likely.

Recent use of the population approach for postmarketing surveillance of drug-drug interactions on the basis of TDM data is exemplified by studies by Yukawa et al. on lithium,[74] carbamazepine,[75] digoxin,[76] valproic acid,[77] phenobarbital[78] and haloperidol.[79] This recent study focused on 270 serum concentrations of haloperidol retrospectively collected from 191 patients during routine treatment.[79] All patients had been taking a constant dose of haloperidol for at least 10 days so that steady state was assumed. Blood samples were drawn before the morning dose. A steady-state pharmacokinetic model was selected, as described by equation 1. The authors emphasised that a relative rather than true average clearance was estimated on the basis of measured trough concentrations. The influence of a variety of factors on clearance was investigated, including gender, age, bodyweight, daily dose of haloperidol, and comedication with anticonvulsant drugs, antiparkinsonian drugs and substrates of CYP2D6. Between-patient variability in total body clearance and within-patient residual variability of concentration were described according to a proportional error model. The final relationship between haloperidol relative clearance, dose and patient characteristics was as follows:

$$CL\ (L/h) = 0.74 \cdot BW^{0.594} \cdot dose^{0.326} \cdot 1.32^{COMED} \cdot 0.867^{ELDERLY} \quad \text{(eq. 4)}$$

where BW is total bodyweight in kilograms, dose is in μg/kg/day, COMED is 1 if anticonvulsant comedication is present and 0 otherwise, and ELDERLY is 1 if age is ≥55 years and 0 otherwise. A

significant 32% clearance increase was associated with comedication with anticonvulsant drugs (phenytoin, phenobarbital or carbamazepine), in keeping with previously reported low concentrations in the presence of carbamazepine comedication.[19,80] The combined effect of total bodyweight, age and comedication is illustrated in figure 4. Interindividual variability was 33.6% and residual variability was 15.5%.

An important aspect of population pharmacokinetic models is their potential for prospective individualisation of dosage regimen, on the basis of TDM data and Bayesian forecasting.[21,81,82]

7. Perspectives

With postmarketing surveillance recognised as necessary to detect interactions of potential clinical relevance[6] and increasing reliance placed by regulatory authorities on population methods,[4,5] the future of TDM-based studies can be envisaged positively. Additional incentive arises from their suitability for subpopulations generally excluded from clinical trials, such as children, frail elderly patients and individuals with concomitant diseases who are receiving complex combined treatment.[2,83] The contribution of TDM databases takes place at different levels, from the alert signal based on a single case to the large-scale pharmacokinetic screen and the experimental on and off comedication panel study. It should be viewed as part of a dynamic process, which reflects changes in prescription habits and use of comedication over time and allows for serendipity in the detection of effects.

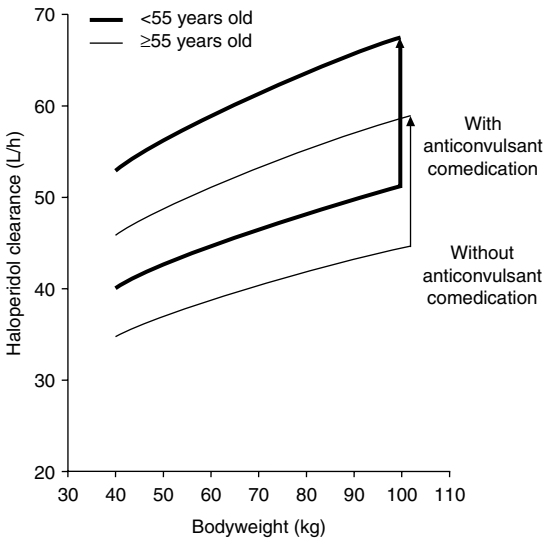

Fig. 4. Relationship between haloperidol relative clearance, bodyweight, age group and comedication with anticonvulsant drugs. A population pharmacokinetic model was developed by Yukawa et al.[79] on the basis of therapeutic drug monitoring data for 191 Japanese patients. It led to equation (4), which was used to draw this figure. A fixed 10mg daily dose was postulated. The arrows indicate clearance increase associated with anticonvulsant comedication.

Despite the increasing number of well performed studies documenting drug-drug interactions, a major discrepancy persists between available knowledge and factors actually taken into account when prescribing.[18,84] An explanation might be insufficient information or sometimes conflicting results about the relationship between concentration, therapeutic effect and adverse drug reactions. However, failure to effectively communicate expertise gained from TDM material to prescribing clinicians can also be invoked. Improved effectiveness in the use of TDM databases for postmarketing surveillance of drug-drug interactions asks for increased awareness of clinicians about the need to provide accurate and complete information about patient and treatment. It relies on intensive ongoing scientific activity to exploit TDM data fully and integrate efficacy and safety data if feasible. Equally important are efforts to communicate to clinicians expert recommendations for safe management of drug-drug interactions.

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