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Review Article

THERAPEUTIC DRUG MONITORING IN PSYCHIATRY: AN IMPORTANT STEP IN CLINICAL PRACTICE

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ABSTRACT

TDM in psychiatry is a tool to optimize the therapeutic regimens in clinical practice. Psychopharmacology encompasses those drugs which metabolize and their metabolites also are active in the body. CYP-450 of antipsychotics is unique as the drugs are lipid soluble and the heterogeneous class of drugs act on different types of receptors and produce variable responses. Various techniques are involved to estimate the drug levels of those drugs. HPLC is a golden standard to assay the serum drug concentration of these drugs. The metabolites can also be assayed along with the parent drug. TDM of these drugs if applied at tertiary care, individualization of dosage regime of these drugs can help the outcomes of therapy and even drug-drug interaction can display the PK/PD nature of such drugs.

Keywords: TDM, PK/PD, ICD, DSM-IV, CYP, PM, CYP3A4, CYP2C19

INTRODUCTION

Basic aspects of pharmacodynamics (PDs), pharmacokinetics (PKs), as well as clinical outcome of a drug, are investigated during the phases of drug development before approval for general prescription by drug regulatory agencies [1].

In order to standardize the description and interpretation of psychiatric disorders, diagnosis and classification systems have been established. The ICD-10 is the most frequently used system worldwide for all general epidemiological purposes and for clinical diagnosis, whereas DSM-IV is the most frequently used system for research[2]. The point prevalence of unipolar depressive episodes estimates to be 1.9 % for men and 3.2 % for women, and that 5.8 % of men and 9.5 % of women will experience a depressive episode in a 12 month period [3]. Clinically useful psychoactive drugs act by interacting with brain neurotransmitters and receptors[4].

PHARMACOKINETICS

Pharmacokinetics describes the time-course of the various events that a dose of drug, and its metabolites in the body, may undergo: absorption, distribution, metabolism and excretion.

Psychoactive drugs have their main site of action in the brain. The majority of psychoactive agents are lipophilic (lipi-soluble), leading to the ability to penetrate the membrane, to be absorbed and to enter into the target organ. However, to be eliminated principally by the kidney from the body, they have to be converted to a hydrophilic (water-soluble) substance. The most important enzymatic systems are the cytochrome P-450 (CYP) enzymes that are responsible for more than 80 % of phase I reactions[5]. These enzymes prepare very lipophilic molecules for phase II reactions by creating a conjugation site, often a reactive group such as a hydroxyl group. In the phase II reactions, the conjugation with a glucuronyl sulphate- or acetyl groups forming a more polar and water soluble molecule that can be more easily excreted in the urine and/or bile[6].

Several psychoactive drugs, as well as their metabolites, are stereoisomers/enantiomers. In a race mate, the enantiomers may also have different PD properties [7].

Sources of Pharmacokinetic Variability

A broad variety of physiological, pathological, genetic and environmental factors might affect the PKs of a drug

Drug metabolism –CYP enzyme system and genetic variation

The major CYP enzymes that contribute to the metabolism of drugs in man are CYP3A, CYP2D6, CYP2C9, CYP2C19 and CYP1A2[8]. The potential of a drug to inhibit the metabolism of other drugs almost always exits for drugs metabolized by the same pathway but can also be present for entirely separate pathways [9].

The population is divided, based on the polymorphisms of drug metabolism, into at least two phenotypes: poor metabolizers (PM), lacking enzyme activity, and extensive metabolizers (EM), among the majority of individuals, who have a normal metabolic activity. Subjects with extremely high enzyme activity are referred to ultra-rapid metabolizers (UM) [10]. The proportion of different metabolizers in a population varies with ethnicity.

CYP2D6 is of particular importance in psychopharmacology as it is implicated in the metabolism of various antidepressants and antipsychotic drugs. CYP2D6 may be inhibited by therapeutic concentrations of various drugs [11].

Age

Adolescence is associated with major changes in hormone secretion, growth and behaviour. Although the hormonal changes associated with puberty might be expected to produce alternations in drug disposition, there is little evidence that this constitutes a major problem [12].

PK differences, which may be clinically important, can be seen between the elderly (65-79 years old) and the oldest olds (80-92 years old) [13]. Age does not alter drug absorption in a clinically significant way (passive diffusion is not changed). Among the factors that can influence PK changes in older people are decreased percentage of total body water (≈50 %), increased percentage of body fat, decreased liver mass and blood flow, decreased cardiac output, and reduced renal function [14].

There is preliminary evidence that CYP3A4 activity is lowest in neonates and increases to maximal levels in adults and that the activity of CYP3A4 (but not CYP2D6 or CYP2C19) appears to decrease between 20 and 80 years of age [15].

Gender

Differences in physical constitution (body water, muscle mass, organ blood flow and organ function) and physiology (menstruation, pregnancy and menopause) can result in differences in PKs (and PDs) between men and women [16]. Controversial findings may be found. Studies into the effects of gender on enzyme activity in humans suggest that females have higher activity of CYP2C19 compared with males, while activity of CYP2D6 does not differ between the sexes. CYP3A4 activity in females is greater *in vitro* compared with males, and is similar or greater in clinical studies [17].

Smoking and diet

Life style appears to have considerable influence on expression or activity of CYP enzymes. The majority of PK interactions with smoking are the result of induction of hepatic CYP, primarily CYP1A2. Smoking may increase CYP1A2 activity (and possibly CYP2E1 and glucuronide conjugation) (Kroon, 2007). Caffeine from dietary sources (mainly coffee and tea) is the most frequently and widely

consumed CNS stimulant in the world. CYP1A2 participates in the metabolism of caffeine, this means there is a potential for PK interactions due to inhibition of drugs that are metabolized by, or bind to, this enzyme [18].

Nutritional status

Underweight

Malnutrition can be associated with variable but potentially important effects on the bioavailability, binding, hepatic metabolism, and renal clearance of drugs. In mild to moderate malnutrition, changes in metabolism may be minimal or of limited clinical significance. However, clinical data to support this conclusion are very limited [19].

Concomitant medication

Oral contraceptives

The PK and clinical significance of the major drug interactions seen with oral contraceptives (OC) are that drugs may impair the OC efficacy, leading to breakthrough bleeding and pregnancy, and situations where OC may interfere with the metabolism of other drugs. The molecular basis of these interactions seems to be inhibition or induction of CYP3A and 2C families [20].

Herbal medicines

The concomitant use of herbal medicines and pharmacotherapy is wide spread. Approximately 25 % of patients hospitalized in internal medicine wards have been shown to consume some kind of herbal or dietary supplement [21]. Many herbs and natural compounds isolated from herbs have been identified as substrates, inhibitors, and/or inducers of various CYP enzymes [22].

Polypharmacy

Polypharmacy is widespread in populations around the world, especially among the elderly [23]. Age-related changes make the elderly, especially those with chronic conditions, susceptible to many drug adverse effects. Polypharmacy increases the risk of adverse drug reactions (ADR), interactions and incorrect drug use [24]. A new psychoactive drug is studied as a single drug *versus* either a placebo and/or a comparator agent. Experience with any new psychiatric medication in combination with another medication is limited to a few short-term drug-drug interaction studies, usually conducted in healthy young volunteers before drug registration and marketing [25]. Despite this, the use of combinations of psychoactive drugs has been common practice in adults [26]. The use of combination therapy has expanded even in youths [27].

Compliance

Poor compliance is an important cause of both therapeutic failure and drug toxicity. Adherence to medication plays a crucial role in the ultimate effectiveness of psychopharmacological interventions and in preventing relapse [28]. Noncompliance is extensive within medication for schizophrenia and mood disorders. Patients receiving antipsychotic medication take an average of 58 % of the recommended amount of medications and patients receiving antidepressant medication take an average proportion of 65 %, compared to patients with physical disorders who take 76 % of the recommended amount [30].

Individualized drug dosage

A complete patient evaluation and correct diagnosis remains important for ensuring proper treatment and selection of an appropriate psychoactive drug. There is a common practice of administering a standard dose to all patients but, in order to give the right dose to the right patient, the drug dosage should be determined individually. Although the drug concentration is important for the clinical response, it is not the sole determinant (e.g. co-morbid conditions, receptor sensitivity). Response in psychiatry is based on subjective assessment. Nevertheless, objective data, such as drug concentration, can assist in the clinical decision, in absence of relevant biological measures [31].

Therapeutic Drug Monitoring (TDM)

The blood is a unique body fluid in that it stays in intimate contact with all tissues. The drug concentration in the blood will depend on absorption, distribution and elimination of the drug, and will continuously mirror the fate of the drug in various tissues and organs. The basic assumptions underlying TDM are that drug metabolism, as well as other factors that affect the drug PKs, varies from one patient to another and that the blood level of a drug is more closely related to the drug's therapeutic effect or toxicity than is the dosage. TDM comprises the assessment and communication of drug levels in blood as well as recommendations for dose adjustments [32].

The foundation of modern TDM was established in the early 1970s, with monitoring of epileptic patients on phenytoin [33]. The TDM is by tradition based on concentration intervals (therapeutic range or index) within which most subjects are

expected to have their optimal response (high enough to give the desired effect but enough to avoid toxicity). Recommended dosing regimens are designed to generate blood concentrations within a therapeutic range. Therapeutic ranges, however, are only intermediate endpoints that must be used in the context of additional criteria to assess the clinical efficacy of any given drug therapy. The therapeutic goal must be individualized.

The field of TDM in psychiatry began with the tri-cyclic antidepressants and is based on indications of the existence of blood concentration-effect relationships for a drug and motivated by a therapeutic range (changes in systemic concentration can lead to significant change in PD response, i.e. sub-therapeutic or toxic effects). For some of the TCAs, therapeutic ranges have been established [34]. The lack of easily defined therapeutic range among the new psychoactive drugs has not been shown convincingly for TDM [35]. But a number of specific situations have been defined in which determination of blood concentrations has been proven useful, such as control of compliance, drug interactions, and identification of genetic peculiarities of drug metabolism [36]. A new way of looking at TDM when a psychoactive drug becomes available for prescription and no definitive concentration-effect relationships have been demonstrated is considered [37]. The first outcome of a patient's TDM should thereby be in "reference" to whether the patient has the "expected" amount of drug in relation to dose prescribed compared with inter-individual PKs data as reference values. If a second TDM sample is drawn from the same patient after a period of treatment, this outcome is compared with the previous one. This strategy provides a PK instrument to answer some questions related to the dosage of the patient. Therefore, if the metabolite of the parent compound has also been determined, the compliance may be scrutinized with the TDM-procedure based on metabolite/parent compound (M/P) ratio stability within individuals over time [38].

Finally, the simple act of ordering a blood drug level does not guarantee that the information will be meaningful or useful. The interpretation of blood concentrations can be profoundly influenced by factors such as the timing of the sample, the patient's clinical state, the drug's pharmacokinetics and metabolism, as well as the tube type and analytic methodology used. The likelihood of obtaining clinically meaningful and useful results can be maximized when these factors are taken into account [39]. TDM must include sampling organization, measurement of psychoactive drugs and interpretation of the blood concentration, for individual dose adjustment. A TDM service connotes an organized system of care to ensure that the serum drug concentration will have maximal positive impact on patient care [40].

Genotyping

Pharmacogenetics is the use of genomics to determine a subject's drug response and depends on the availability and reliability of genetic testing as well as the ability of providers to interpret test results [41]. The genotype is the genetic constitution of an individual, either overall or at one or more specific loci. Genotyping is the determination of specific genetic sequence variations, of functionally important polymorphism, in the gene encoding of a specific protein [42].

In short, subjects who carry 2 copies of a functional allele are genetically classified as EM, while those carrying two defective alleles, are PM [43]. Moreover, in the case of *CYP2D6*, subjects carrying more than two copies of a functional allele are classified as UM. Fairly recently, a novel allelic variant of *CYP2C19* associated with UM status has been described and denoted *CYP2C19*17* [44]. The allelic frequency of *CYP2C19*17* was different between Swedish and Chinese subjects being 18 % and 4 % respectively, but lower in the Japanese population, 1.3 % [45].

Indications for genotyping may be: identify patients who are PM (a decreased metabolic capacity may lead to high blood levels and increased risk of toxicity or, if the main compound is a pro-drug that needs to be activated, to therapeutic failure), differentiate between patients who are UM (may lead to low blood levels of the drug causing therapeutic failure) or have noncompliance, and differentiate between genetic or environmental factors that affect drug metabolism (phenotype=genotype?). Additionally, dose adjustments would compensate for genetically caused differences in blood concentrations [46].

Blood samples

Drug serum concentrations fluctuate after drug therapy has begun until there is an equilibrium, or steady-state, between intracellular and serum concentrations. The t1/2 provides an approximation of how long it takes to attain a steady-state

after initiation of the therapy. In general, steady-state blood concentrations of a drug are reached after the drug doses have been given for a length of time equal to 5 half-lives of the drug [47]. The timing of the sample in relation to the previous dose influences the interpretation of a drug concentration measurement. When a patient takes a dose of a drug, the amount in the blood rises for a time period, peaks and then began to fall usually reaching its lowest level (trough) just before the next dose. Peak levels should be below toxic concentrations and trough levels should remain in the therapeutic range.

CONCLUSION

Valuable and reliable information may be extracted from TDM collected samples [48]. The TDM databases are valuable tools for collecting new PK-data from large-scale heterogeneous clinical populations after the introduction of a drug into the market. Thus the development of a drug should be seen as a continuous process. The data collected by the TDM service may improve reference data for the evaluation of therapeutic response, as well as toxicological information concerning psychoactive drugs [49].

The relationships found in these TDM based studies between the drug serum concentration and the clinical information obtained simultaneously cannot be taking as being conclusive but may point towards future hypothesis testing studies. Variability of drug concentrations of psychoactive drugs is expected in TDM data, as a consequence of several factors that exist in the complex scenario in clinical practice.

The TDM samples with the correct interpretation of results in order to answer the question of whether a concentration of a psychoactive drug is in the expected range with respect to drug dosage (or therapeutic range), together with complementary CYP genotyping, may be a tool for dose optimization of the psychoactive drug since resistance or tolerance towards the drug may be disclosed. The optimization of treatment may be aided by the use more or less regularly of TDM, for maintaining/adjusting doses that may increase rates of drug response and for questionable compliance (compare the TDM metabolite/parent compound ratio between the samples). However, the TDM service may provide support to the prescribing physician at the off-label prescribing, which was found in this thesis, already in the early times of the introduction of a new psychoactive drug onto the market.

TDM is also a valuable tool to optimize further drug medication and drug safety when the selection of doses requires a consideration of PK parameters as well as in the elderly and pediatric populations.

The findings in this thesis have been awareness of the usefulness of the TDM service. In summary, the benefits of TDM data were individual dose optimization and providing research information for the TDM service, as well as toxicology. A more frequent clinical use of TDM and pharmacogenetic testing in clinical practice would contribute to better quality in treatment with psychoactive drugs.

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