REVIEW OF CLINICAL PHARMACOLOGY AND
PHARMACOKINETICS, INTERNATIONAL
EDITION 18: 23-24 (2004)

The Practice of TDM: The Dialogue between the Clinical Pharmacological Laboratory and the Prescriber

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Therapeutic Drug Monitoring (TDM) means monitoring a therapy by measuring the concentration of drugs in serum or plasma. One important prerequisite for TDM is the existence of a relationship between the concentration of drug in serum and its pharmacological effect. TDM is recommended for drug which exhibit certain pharmacokinetic properties. These properties include: narrow therapeutic range, overlapping between therapeutic and toxic range, non linear dose-response curve, therapeutic or toxic effects can clinically not be detected at all or only with great difficulty, extreme toxicity, administration during long-term therapy, administration in life-threatening diseases. The determination of drug levels is recommended in different situations, which, however, do not apply to every drug: insufficient therapeutic results, optimizing the therapy, suspected overdosage. In the 30 years TDM has moved from an abstract consideration to a routine intervention.

There are three possibilities of drug monitoring: DCM (plasma concentration measurement or monitoring). Only plasma level of the drug is sent to the clinician without any interpretation. GLP (good laboratory practice) but not GCP (good clinical practice) is provided. DCM seems to be more collection of the stamps than clinical medicine, because special questionnaire, interpretation and feedback with the clinician are very often missing. TDM (therapeutic drug monitoring) includes both GLP and GCP (using special questionnaire, pharmacokinetic analysis, feedback with the clinician). For correct interpretation we need the following information: age, sex, pregnancy, height, weight, accompanying disease, additional drugs taken, clinical picture, dosing pattern, interval between blood sample collection and last intake. The Department of Clinical Pharmacology provides both GLP and GCP, every patient and every plasma level is interpretated by a Clinical Pharmacologist and Clinical Pharmacist. After the control by a senior Clinical Pharmacologist, a written recommendation with the picture from the pharmacokinetic software (e.g. MW-Pharm) is sent to the clinician. If the recommendation is accepted by the clinician the process is repeated. The TDM process involves the decision to request a drug level, the biological sample, the request, laboratory measurement, communication of results by the laboratory with clinical interpretation and therapeutic management. Clinical interpretation transforms drug concentration monitoring (DCM) into a TDM service and should be distributed to the requesting clinical as rapidly as possible. The ideal TDM should consist of clinical pharmacologists, clinical pharmacists and analytical scientists. Pharmacokinetic interpretive services improve patient care. The dosage prediction, including a graph are ideally suited for incorporation into the report form issued by a TDM service. The clinician caring for a patient will modify a drug dosage regimen. If the members of TDM team are well respected, many physicians will accept and implement their recommendations for dosage adjustment and seek their further advice. The third step of drug monitoring should be named ATDM (advanced TDM). It includes the estimation of the free fraction of the drugs, metabolites, pharmacogenetics, pharmacogenomics, interpretation bad-side etc.

To the drugs useful for TDM belong: antibiotics (aminoglycosides, vancomycin), antiepileptics (carbamazepine, clonazepam, ethosuximide, lamotrigine, phenobarbital, primidone, topiramate, valproic acid), theophylline, antineoplastic (methotrexate), cardiac agents (amiodarone, digoxin), immunosupressants (cyclosporine A, tacrolismus, mycophenolate), psychoactive drugs (amitriptyline, imipramine, diazepam, lithium). Metabolites useful for TDM: 10,11-epoxicarbamazepine, desethylamiodarone, 7-hydroxymethotrexate, desmethyldiazepam, metabolites of cyclosporine A (M17, M21, M1 and other).

TDM has been provided by the Department of the Clinical Pharmacology, University Hospital in Ostrava for twenty years. 16 thousands laboratory analyses, 8 thousands written recommendations and 2 thousands pharmacokinetic analyses are performed by our department every year. The introduction of the pharmacokinetic service of TDM digoxin decreased the number of toxic levels about 60% (1).

We developed HPLC method for the estimation of CSA and its three main metabolites (2) and compared through levels obtained by HPLC and specific RIA method (3). We did not find significant differences. Comparison of plasma levels during twelve hours after administration of CSA showed significant overestimation between 1-5 hours (40-60%) using specific RIA method. Using C2 or limited sampling strategy for TDM of CSA seems to be incorrect (4,5). The importance of TDM of paternal drug and its metabolite we described for carbamazepine and 10,11-epoxicarbamazepine (therapeutic range 4-12 mg/l). Patients with triple combination (carbamazepine, valproic acid and lamotrigine) showed 88% of plasma levels at the therapeutic range and no level above the therapeutic range. When we added to carbamazepine epoxy-metabolite, 25% of the patients had the plasma levels above therapeutic range, often with side effects.

TDM is a new medical discipline based on interdisciplinary cooperation of the clinician, analyst and clinical pharmacologist and it is able to improve therapeutic management of the patient.

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