Therapeutic Monitoring of Psychotropic Drugs

An Outline of the AGNP-TDM Expert Group Consensus Guideline

P. Baumann, C. Hiemke,† S. Ulrich,‡ I. Gaertner,§ M. L. Rao,‖ G. Eckermann,¶ M. Gerlach,# H.-J. Kuss,** G. Laux,†† B. Müller-Oerlinghausen,‡‡ P. Riederer,§§ and G. Zernig‖‖*

Abstract: TDM of psychotropic drugs is widely used, but there is little consensus regarding its optimal use in the clinical context. This prompted a multidisciplinary group comprised of clinical biochemists, clinical pharmacologists, and psychiatrists of the AGNP (Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie) to provide a consensus guideline. This will allow clinical psychiatrists, practitioners, and laboratory directors involved in psychopharmacotherapy to optimize TDM of antidepressants, antipsychotics, and opioid substituents. Recommendations are also given on the combined use of TDM and pharmacogenetic tests.

Key Words: therapeutic drug monitoring, psychotropic drugs, consensus statement

(*Ther Drug Monit* 2004;26:167–170)

Although psychotropic drugs were introduced in the 1950s, TDM of antidepressants and antipsychotics has been available for only about 30 years. The rationale for TDM is based on the putative plasma concentration–clinical effectiveness relationship that was observed for some drugs and on the observation that pharmacokinetic factors may be, in part, responsible for nonresponse of many patients or for the occurrence of adverse effects at usual doses. The development of sensitive analytic methods for drug analysis showed that there is a wide interindividual variability in the metabolism and pharmacokinetics of these drugs. However, therapeutic windows have been described only for some drugs such as tricyclic antidepressants. The demonstration of a genetically determined metabolism of antidepressants and antipsychotics was one of the next steps. Consequently, this encouraged clinicians to use TDM in combination with pharmacogenetic tests.[1,2]

Apparently, there has been only 1 consensus paper published on TDM of psychotropic drugs: the report of the Task Force on the Use of Laboratory Tests in Psychiatry,[3] which considered only TDM of tricyclic antidepressants. The state of the art of TDM of psychotropic drugs was summarized as a result of a meeting including psychiatrists, clinical pharmacologists, and biochemists.[4] However, there is definitely a lack of consensus on the optimal use of TDM in psychiatry, particularly involving new drug categories that have been introduced over the last few decades. A recent study showed that there is a wide interlaboratory variability in the reference value ranges that were reported by 31 laboratories in Europe and Australia.[5] The growing knowledge of the fate of drugs and their regulation in the human organism has also helped to redefine the indications for TDM and also to show its limits.

To monitor psychoactive drugs, the analytic methods must be highly sensitive and selective for accurate and precise quantification because, generally, plasma concentrations of psychotropic drugs are low, and patients are frequently comedicated with other drugs, which may interfere with the assay. Among the methods used, prepurification of the samples before chromatographic (HPLC, GC) separation of the drugs and interfering compounds is now widely carried out. Generally, detection and quantification of drugs are performed using UV or fluorescence detectors, but mass spectrometry (LC-MS, LC-MS-MS, GC-MS) is also increasingly available. Other methods including immunoassays and radioreceptor assays are also suitable, but for all methods, their advantages and their limitations need to be carefully defined before they are introduced into practice.

Received for publication October 1, 2003; accepted January 12, 2004.

From the *Unité de Biochimie et Psychopharmacologie Clinique, Département Universitaire de Psychiatrie Adulte, CH-1008 Prilly-Lausanne, Switzerland; †Psychiatrische Klinik der Universität Mainz, Untere Zahlbacher Str. 8, D-55101 Mainz, Germany; ‡Esparma GmbH, D-39171 Osterweddingen, Germany; §Psychiatric University Hospital, Tübingen, Germany; ‖Department of Psychiatry, University of Bonn, D-53105 Bonn, Germany; ¶Bezirkskrankenhaus Kaufbeuren, Kaufbeuren, Germany; #Klinik und Poliklinik für Kinder- und Jugendpsychiatrie und Psychotherapie der Universität Würzburg, D-97080 Würzburg, Germany; **Department of Psychiatry, University of Munich, Munich, Germany; ††Bezirksklinikuna Gabersee, D-83512 Wasserburg/Inn, Germany; ‡‡Drug Commission of the German Medical Association, Cologne/Berlin, Germany; §§Psychiatrische Klinik, Universität Würzburg, D-97080 Würzburg, Germany; and ‖‖Psychiatric University Hospital, Innsbruck, Austria.

Reprints: Prof. Pierre Baumann, Dr rer.nat, Unité de Biochimie et Psychopharmacologie Clinique, Département Universitaire de Psychiatrie Adulte, Hôpital de Cery, CH-1008 Prilly-Lausanne, Switzerland (e-mail: pierre.baumann@inst.hospvd.ch).

This situation prompted a multidisciplinary group comprising chemists, clinical biochemists, clinical pharmacologists, and psychiatrists of the AGNP (Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie) to develop consensus guidelines that will help clinical psychiatrists, laboratory practitioners, and heads of laboratories involved in psychotropic drug analysis to optimize the use of TDM of antidepressants, antipsychotics, and opioid substituents. An outline of these guidelines, which will be published elsewhere in extenso, is presented here.

TDM OF PSYCHOTROPIC DRUGS: OUTLINE OF A CONSENSUS

The aim of the consensus guidelines is to optimize the use of TDM of psychotropic drugs, including mainly antidepressants, antipsychotics, and opioid substituents, and to recommend when TDM and genotyping/phenotyping procedures may help to improve pharmacotherapy. Therefore, the indications for TDM, taking into account the different classes of drugs, had to be defined, the most relevant reports of the literature had to be selected, especially also with regard to reference values of plasma concentrations (therapeutic windows) and steady-state drug concentrations at clinically relevant doses. There was also a general need for recommendations regarding the practice of TDM in the clinical context and in the laboratory.

Global Indications for TDM of a Psychotropic Drug or Group of Drugs

Global indications for TDM include the following:

- Plasma concentrations are highly variable at a given dose (high pharmacokinetic variability)
- A therapeutic range of plasma concentrations has been established with a narrow therapeutic index (including latent toxicity), or a steep plasma concentration–therapeutic effect relationship was found
- Problems in the prediction of clinical effects and problems in dose titration
- Long-term treatment

Table 1 gives a summary of the indications for TDM of psychotropic drugs in frequently encountered clinical situations. Except for "suspicion of non-compliance," the validity of most of the other indications had to be examined separately for each drug category. Certainly, TDM should be requested only when required clinically and when there is a chance that the result will provide an answer to the relevant questions.

There is consensus to propose 5 levels of recommendation:

1. Standard of care: Established therapeutic window.
2. Recommended: Putative therapeutic window obtained from plasma concentration measurement at therapeutically effective doses (fixed-dose studies).
3. Probably useful: Suggested therapeutic ranges are plasma concentrations at therapeutically effective doses obtained from steady-state pharmacokinetic studies. *Level of evidence:* Clinical data from retrospective analysis of TDM data, single case reports, or non-systematic clinical experience.
4. Unclear: Therapeutic ranges from steady-state pharmacokinetic studies at therapeutically effective doses. *Level of evidence:* Valid clinical data so far lacking or inconsistent results.
5. Not recommended: Unique pharmacology of the drug, eg, irreversible blockade of an enzyme or flexible dosing according to clinical symptoms.

TABLE 1. Indications for TDM of Psychotropic Drugs with Respect to Individual Therapeutic Situations That are Often Encountered in the Clinical Setting

Suspected noncompliance
Lack of clinical response or insufficient response even if doses are considered adequate
Drugs, for which TDM is mandatory for safety reasons (eg, lithium)
Adverse effects despite the use of generally recommended doses
Suspected drug interactions
Patients with pharmacokinetically relevant comorbidities (hepatic or renal insufficiency, cardiovascular disease)
Combination treatment with a drug known for its interaction potential in situations of comorbidities, "augmentation," etc
Presence of a genetic particularity concerning the drug metabolism genetic deficiency, gene multiplication)
Problems occurring after switching from an original preparation to a generic form (and vice versa)
Relapse prevention in long-term treatments, prophylactic treatments
Recurrence despite good compliance and adequate doses
Children and adolescents
Elderly patients (>65 y)
TDM in pharmacovigilance programs
Forensic psychiatry

For all levels of recommendation, TDM is indicated in case of suspicion of non-compliance. Non-compliance seems to occur at a highly underestimated frequency and should therefore be tested for whenever suspicion is justified, eg, after nonresponse or only partial response. A recent study revealed that during a 3-month treatment with SSRIs, 72.5% of the patients missed at least 1 dosing day, and 29% of the patients had dosing lapses of 2 or more days.[6]

For psychoactive drugs such as lithium, TDM is a recommended standard of care (category 1), because if it is not considered, the risk for therapeutic failure or intoxication of the patient is high. Present experimental evidence justifies inclusion of tricyclic antidepressants and methadone in category 2. The allotment of drugs to categories 3 (eg, citalopram, amisulpride) and 4 (eg, moclobemide, pimozide, ziprasidone) may

rapidly change with increasing experimental evidence for a clear-cut plasma concentration–clinical effectiveness relationship. Tranylcypromine is an example of a drug included in category 5.

TDM Reference Values and Therapeutic Window

Most often, data are available in the literature on steady-state plasma concentrations of a psychotropic drug and its main active metabolite, which were obtained from studies with volunteers or selected patients who were treated with a fixed dose of the drug for a given period of time. However, clinical ratings (efficacy, adverse effects) were rarely carried out. These plasma concentration measurements may be considered helpful in clinical situations in which the clinician needs to know whether the patient is compliant, or whether his drug metabolism shows some particularity.

Studies on the plasma concentration–clinical effectiveness (efficacy, adverse effects) relationship are not available for all drugs.[7] They are needed to obtain reliable therapeutic plasma concentration ranges (therapeutic windows), but the quality of the studies varies widely if carried out at all (cf levels of recommendation with respect to TDM).

TDM is well established for tricyclic antidepressants, but the evidence for a significant relationship between drug concentration and therapeutic outcome of new antidepressants is poor.[8,9] Except for testing of compliance, the TDM of antipsychotic drugs is less mandatory than that of tricyclic antidepressants. However, for some antipsychotics such as clozapine and olanzapine, there is fair evidence for a therapeutic window. It is increasingly accepted that TDM is indicated in patients treated with methadone or *R*-methadone.[10]

Because many psychotropic drugs are metabolized by cytochrome P-450, phenotyping and/or genotyping patients for polymorphic forms of this enzyme system is recommended in well-defined situations (Table 1).

Practical Aspects of TDM

Recommendations for the Laboratory

The laboratories should carry out the assays in compliance with good laboratory practice (GLP). They need to be validated for linearity, selectivity, accuracy, precision, recovery, and sensitivity [limits of detection (LOD) and quantification (LOQ)]. The laboratory should carry out internal quality control and participate in an external quality assurance program. The concentrations of the psychoactive drug and its metabolite(s) should be reported with the reference concentrations range, in either mass or molar units (SI, International System of Units). The LOD should be indicated in situations where concentrations are too low to be reported. It would be an advantage for a laboratory to offer an interpretation and clinical pharmacologic advice provided with each report. However, the number of laboratories that can offer expert interpretation is probably small because of structural reasons. It is therefore recommended that the treating physician should ask a clinical pharmacologist for advice.

Recommendations for the Treating Physician

TDM does not appear to be justified for all patients and all situations, and TDM cannot replace clinical judgment. The physician should be aware that TDM is not available for all drugs and that its benefit depends on their level of recommendation for TDM, on the availability of established plasma concentration ranges at fixed doses, and on the therapeutic window. He/she should also take into consideration the recommendations of the laboratory in regard to information on anticoagulants, the timing of blood sampling (steady-state conditions, trough levels, etc), and conditions for shipment to the laboratory before sampling blood for TDM. To ensure quality of the analysis, indications on comedications, which may interfere with the assay, may be useful. The request form should be filled out properly. Finally, the physician should be aware that laboratories differ in their presentation of results with regard to the units in which they are expressed. Many recommendations deal with the interpretation of the results and suggestions for decision making by the physician.

Use of TDM Results in the Clinic

TDM is thus one aspect of the therapeutic strategy. It's results should be interpreted with expertise, especially in situations where drug interactions, pharmacogenetic particularities, or comorbidity may influence the fate of the drug in the organism. Recommendations by the laboratory are limited by the fact that the physician possesses adequate information on the patient's clinical situation. On the other hand, junior psychiatrists should get acquainted with the interpretation of results under supervision of an expert who is trained in clinical psychopharmacology and pharmacokinetics.

Admittedly, some important questions related to TDM are still waiting for an answer. Most studies on the plasma concentration–clinical effectiveness relationship were carried out with groups of patients. There is some preliminary evidence that individual patients may have their own optimal plasma drug concentration ranges, possibly because of clinical (diagnosis) or biologic (eg, individually regulated drug transport in the brain) particularities. With regard to the indications presented in Table 1, the blood collection and assay conditions developed for routine TDM may show their limits. As a rule, trough concentrations are measured, but in some situations peak concentrations would show a better correlation with adverse effects. In forensic psychiatry, when drug concentrations are either extremely high or very low, the standard calibration curve used for TDM may not be suitable.

In conclusion, the usefulness of TDM to optimize pharmacotherapy of psychiatric patients is now recognized. This

recognition is the consequence of the improvement of analytic procedures and the new quality standards introduced in the laboratories, but mainly of an increased knowledge on metabolism, pharmacokinetics, and pharmacogenetics of psychotropic drugs. Pharmacokinetic interactions have important consequences on the clinical outcome, and TDM is a powerful diagnostic tool to show the underlying pharmacokinetic causes. There is clearly a need for consensus guidelines because the field of TDM has experienced a dramatic development, but the harmonization of its practice has been neglected. These guidelines developed by an interdisciplinary group will contribute to an improvement of the use of TDM by laboratory practitioners and clinicians.

REFERENCES

1. Kirchheiner J, Brøsen K, Dahl ML, et al. CYP2D6 and CYP2C19 genotype-based dose recommendations for antidepressants: a first step towards subpopulation-specific dosages. *Acta Psychiatr Scand*. 2001;104:173–192.
2. Dahl ML, Sjöqvist F. Pharmacogenetic methods as a complement to therapeutic monitoring of antidepressants and neuroleptics. *Ther Drug Monit*. 2000;22:114–117.
3. Task Force on the Use of Laboratory Tests in Psychiatry. Tricyclic antidepressants-blood level measurements and clinical outcome: an APA task force report. *Am J Psychiatry*. 1985;142:155–162.
4. Laux G, Riederer P, eds. *Plasmaspiegelbestimmung von Psychopharmaka: Therapeutisches Drug-Monitoring. Versuch einer ersten Standortbestimmung.* Stuttgart: Wissenschaftliche Verlagsgesellschaft mbH, 1992.
5. Wilson JF. Survey of reference ranges and clinical measurements for psychoactive drugs in serum. *Ther Drug Monit*. 2003;25:243–247.
6. Meijer WEE, Bouvy ML, Heerdink ER, et al. Spontaneous lapses in dosing during chronic treatment with selective serotonin reuptake inhibitors. *Br J Psychiatry*. 2001;179:519–522.
7. Ulrich S, Schrödter I, Partscht G, et al. Therapeutisches Drug-Monitoring von Psychopharmaka: Eine allgemeine Einführung. *Psychopharmakotherapie*. 2000;7:2–14.
8. Hiemke C, Härtter S. Pharmacokinetics of selective serotonin reuptake inhibitors. *Pharmacol Ther*. 2000;85:11–28.
9. Rasmussen BB, Brøsen K. Is therapeutic drug monitoring a case for optimizing clinical outcome and avoiding interactions of the selective serotonin reuptake inhibitors? *Ther Drug Monit*. 2000;22:143–154.
10. Eap CB, Bourquin M, Martin J, et al. Plasma concentrations of the enantiomers of methadone and therapeutic response in methadone maintenance treatment. *Drug Alcohol Depend*. 2000;61:47–54.