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The dose–concentration–effect relationships—the basis for TDM. A critical appraisal

Lars F. Gram

Institute of Public Health, Research Unit of Clinical Pharmacology, Faculty of Health Sciences, University of Southern Denmark–Odense University, Odense, Denmark

Abstract

Therapeutic Drug Monitoring (TDM) is based on a series of theoretical assumptions, a clinical pharmacological rationale, scientific documentation and a practical implementation, respecting the theoretical and scientific basis. The clinical pharmacological rationale for TDM; a pharmacokinetic variability exceeding therapeutic index *and* dose titration on the basis of clinical or paraclinical measurements not being feasible, limits TDM to a minor fraction of all drugs available. The theoretical assumption that blood concentration measurements reflect/predict the tissue/receptor concentration and the clinical endpoints, requires several points to be considered such as concentration fluctuations, protein binding, active metabolites, etc. A relatively constant ratio between blood and tissue/receptor concentration is generally assumed, but the important role of transporter proteins, with inter- and intraindividual variability due to polymorphisms, inducers and inhibitors seriously challenge this basic assumption. Concentration–effect relationships concerns *groups* of patients and indicate the probability of a given response (therapeutic/toxic) at a given concentration. Dose–effect and concentration–effect studies of drugs like digoxin, lithium and antidepressants have shown that the dose–effect or concentration–effect curves for therapeutic effect and tolerability are flat and overlapping. Dose–effect studies, now standard in drug development, represent a unique possibility to examine dose–concentration–effect relationships of new drugs.

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E-mail address: if_gram@cefko.sdu.dk (L.F. Gram).

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1. Introduction

Therapeutic drug monitoring (TDM) is usually defined as the clinical use of drug blood concentration measurements as an aid in dose finding and adjustment.

A critical appraisal of this principle requires considerations of several aspects of TDM:

- The clinical rationale,
- The theoretical basis,
- The scientific documentation,
- The practical implementation,
- TDM in drug development, and
- Research applications of TDM.

2. The clinical rationale

TDM, as developed since the 1960s [1–3], is limited to a fairly small fraction of available drugs. This limitation is largely related to the clinical rationale for TDM.

Clinical rationale is essentially based on two clinical pharmacological features of the drug [1,2].

(1) TDM is only relevant when there is a pharmacokinetic variability that clearly exceeds the therapeutic index such that standard doses applicable to all patients cannot be defined.

(2) TDM is only considered when dose titration on the basis of clinical or paraclinical effect measurements is not feasible. This could be when rapid treatment is required and clinical endpoints are unacceptable for dose adjustment or the onset of action is slow and gradual and dose optimisation may speed up the recovery.

3. Theoretical basis

The often implicit assumption made in TDM is that a given drug concentration measurement reflects the tissue/receptor drug concentration and thereby the clinical effects. TDM thus may eliminate the pharmacokinetic variability causing poor correlation between drug dose and drug blood concentration. The use of TDM will, however, require theoretical considerations on the relationships between drug dose, blood concentration and clinical effects.

Table 1 summarizes the confounders that may violate the assumption of a straightforward concentration–effect relationship for a given drug. For drugs with short half-lives relative to the dose interval, the timing of blood sampling becomes critical. Inter- and intraindividual variation in serum/plasma protein-binding yields a variability in the ratio of measured total concentration and free concentration that most directly reflects tissue/receptor concentration [3,4]. If there are more than one active component in the form of metabolites or enantiomers, the contribution to the response of each component, relative to the blood concentration has ideally to be worked out. Indeed, the simple

Table 1
Confounders affecting the possible relationship between measurements of blood–drug-concentrations and clinical drug effects

Blood concentration measurements
• Fluctuations—C_{min}, C_{max}, C_{mean}, AUC?
• Protein-binding—total or free concentration?
• Active metabolites—relative potency
• Enantiomers—relative potency
Blood/tissue concentration ration constant?
• Transporter proteins (polymorphisms, inducers, inhibitors)
• Tissue drug metabolism (polymorphisms, inducers, inhibitors)
• Tissue protein-binding
Drug–receptor interaction
• Ligand/receptor interaction
• Selectivity/non-selectivity
• Receptor polymorphisms
• Up/down regulation
• Second messenger/effector
Clinical endpoints
• Therapeutic effect (measurements?)
• Tolerability (measurements?)
• Drop-outs (adverse reactions, lack of effect)

adding of concentration measures of two or more active components may be an oversimplification [5]. At least, for the free blood concentration, it is generally assumed that this reflects the free tissue/receptor concentration [4]. However, the recent demonstration of the role of transporter-proteins for the disposition kinetics of many drugs [6,7] seriously challenges this assumption. The kinetics of the lipid-lowering drug pravastatin, although not an obvious candidate for TDM, may serve as an example of how transporter-protein involvement may distort the relationship between drug concentration in blood and at the effector site. Pravastatin is actively transported from portal/sinusiodal blood into the liver cells, and actively transported from liver to bile via canalicular cells [8,9]. The result is a very effective entero-hepatic circulation, probably leaving little and variable amounts of drug for systemic circulation and distribution. Blood concentrations thus are unlikely to predict drug activity at the site of action in the liver. Digoxin, a classical TDM drug, is pharmacokinetically influenced by transporter proteins [10], which may influence its blood/tissue/receptor ratio. The transporter may vary in function due to polymorphisms as well as the effect of inducers or inhibitors and the potential of inter- and intraindividual variations in blood-tissue/receptor concentration ratios are probably much more than what had been assumed around 10 years ago [4].

Drug metabolism via the polymorphic CYP2D6 has been suggested to contribute to the differences between extensive and poor metabolisers of debrisoquine/sparteine in analgesic effect of codeine through the formation to morphine [11]. The presence of CYP2D6 in the brain might contribute to this difference [12], and similarly, the occurrence of

pronounced extrapyramidal effects of remoxipride in poor but not in extensive metabolism in spite of only moderate differences in systemic kinetics has been interpreted as an effect of active CYP2D6 in the brain [13]. However, direct evidence of significant drug metabolism in tissues like brain is limited. Finally, our knowledge of the confounding effect on TDM of inter/intraindividual variability of receptor activity is limited, although some studies suggest that monitoring of receptor polymorphisms may become an important supplement to TDM [14].

4. Scientific basis and practical implementation

The aim of TDM is to optimise drug dosing to achieve the maximal therapeutic effect with minimal tolerability problems. The theoretical confounders and the scientific basis for TDM have to be viewed in this context.

The practical implementation of TDM includes more or less rigorous principles for dosing and sampling schedules, conformant with the underlying scientific/clinical documentation of recommended drug concentrations. However, in some cases, indications or procedures may have changed since the original studies were made. For instance, for digoxin and the antipsychotic drug perphenazine, dosing has changed from three times to once daily and the dose-sampling interval from 8 to 12–24 h. Obviously, such changes may invalidate the TDM procedures if they are not carefully analysed for possible consequences.

5. Dose–concentration–effect relationships

The target concentration ranges employed in TDM are based on data concerning concentration–effect relationships. Such concentration–effect curves, related to therapeutic effect or tolerability, *represent groups of patients* and actually indicate *the probability of a given effect at a given drug concentration*. Large inter- and intraindividual variability in concentration–effect relationship will obviously limit the value of TDM. Furthermore, the concentration–effect curves for therapeutic effect and tolerability may be flat and overlapping. For two classical TDM drugs, digoxin and lithium, this problem has recently been emphasized [15,16].

The consequence of this pattern of dose–effect curves is that no drug concentration is optimal from a group-patient's point of view. Low concentrations will yield generally good tolerability but insufficient therapeutic/prophylactic (lithium) response; whereas high concentrations may yield a more consistent response but more patients with tolerability problems.

This pattern can also be seen in *dose–effect* studies that are now mandatory for the market authorisation of new drugs. Some data on antidepressants may exemplify this and elucidate the link between dose–effect and concentration–effect relationships. For the selective serotonin reuptake inhibitor (SSRI), fluoxetine, more than 1100 outpatients were included in large dose–effect studies, which, however, failed to demonstrate any dose–effect relationship when standard outcome measures in terms of depression ratings were

analysed [17]. However, analyses based on dropouts, yielded some indication of a dose–effect relationship: dropouts due to worsening or lack of effect (as a reverse proxy of antidepressant effect) was high on low doses and lower on higher doses, whereas dropouts due to adverse events increased with increasing dose [17]. However, one disturbing pattern was observed—these changes occurred over the same dose range, suggesting flat and overlapping dose–effect curves for therapeutic effect and tolerability. In a recent meta-analysis of dose–effect relationships for antidepressants including 33 studies on different antidepressants (tricyclics, SSRI, MAO inhibitors, atypical), Bollini et al. [18] found essentially the same pattern, concluding that "with a low dose of antidepressants, clinicians trade off a slightly reduced chance of improvement for a higher chance of avoiding adverse reactions". The Danish University Antidepressant Group carried out a study on clomipramine, comparing five doses of 25, 50, 75, 125 or 200 mg/day for 6 weeks with weekly measurements of clomipramine and primary metabolites [19]. Comprehensive analyses of the relationships between dose–effect, dose–concentration and concentration–effect thus were possible. A weak but statistically significant correlation between dose and depressive rating was found. However, endpoint analyses including the dropout showed the percentage of lack of effect declining from 53% at the lowest dose to 20% at the highest dose, and the percentage of study terminations due to adverse events increasing from 3% at the lowest dose to 27% at the highest dose. The total percentage of dropouts and of patients benefiting from the treatment thus was much the same at all doses. The influence of time on antidepressant response was analysed using the principle of "pattern analysis" as described by Quitkin et al. [20]. Of particular interest in this analysis are patients who show a "persistent response" defined by the rating score reaching a defined low value and remaining low for the rest of the study period. Further, "persistent response" could be classified as "early" (first or second week) or "late" (third or fourth week). Among the cases of early persistent response, 16 out of 18 were seen among patients on medium/high doses (75, 125 or 200 mg/day) whereas among the late persistent responses, 15 out of 20 were seen among patients on low doses (25 or 50 mg/day). This study thus suggests that low doses are associated with good tolerability but weak and/or slow antidepressant response, whereas medium or high doses are associated with more tolerability problems but stronger and/or faster antidepressant response.

In this study, the factor 8 variation in dose was translated into a 100-fold variation in drug concentrations (clomipramine + desmethylclomipramine). However, the blood concentrations correlated strongly with the dose ($R_S \approx 0.85$) and this explains why dose–effect and concentration–effect correlations (effect measured as final rating score) were about the same ($R_S \approx -0.25$).

Clomipramine + desmethylclomipramine blood serum levels below 200 μM were associated with high frequency of poor response, and such low blood levels were seen in 70–95% of patients on low doses (25–50 mg/day) but only in 0–14% in the higher dose groups (75–200 mg/day). The large range in blood concentrations relative to range in dose was not only due to interindividual variability, but as much a consequence of dose-dependent kinetics. The five doses varying with factors 1:2:3:5:8 thus were transformed into median blood concentrations (clomipramine + desmethylclomipramine) varying with factors 1:2:4:10:25 [19].

6. TDM in drug development and research

The dose–effect studies represent a unique possibility to examine the pharmacokinetics of new drugs, not only to explore the relevance of TDM but also to describe inter- and intraindividual variability and dose dependency in the relevant patient population given the relevant doses. Unfortunately, most of the dose–effect studies carried out on new drugs over the last decade have missed this opportunity [21].

TDM data collected in a routine setting may also serve research purposes such as population kinetic analyses [22] and identification of pharmacokinetic drug–drug interactions [23]. Networks of TDM laboratories should be established that can measure blood concentrations of essentially all drugs, not only TDM drugs, in order to facilitate identification of possible mechanisms underlying suspected drug–drug interactions. Then, in turn, the clinicians should be trained in "thinking pharmacokinetically" and ensure that blood samples are collected in suspected cases [24].

References

[1] A. Rickens, S. Warrington, When should plasma drug levels be monitored?, Drugs 17 (1979) 488–500.
[2] L.F. Gram, Plasma level monitoring of tricyclic antidepressant therapy, Clin. Pharmacokinet. 2 (1977) 237–251.
[3] F. Sjöqvist, O. Borgå, M.-L. Dahl, M.L.'E. Orme, Fundamentals of clinical pharmacology, in: T.M. Holford, G.H. Holford (Eds.), Avery's Drug Treatment, 4th Edition, ADIS, Auckland, New Zealand, 1997, pp. 1–73.
[4] M. Rowland, T.N. Tozer, Distribution, in: M. Rowland, T.N Tozer (Eds.), Clinical Pharmacokinetics, Concepts and Applications, 2nd Edition, Lee & Febiger, Beckenham, UK, 1989, pp. 131–147 (Chap. 10).
[5] L.F. Gram, N. Reisby, I. Ibsen, A. Nagy, S.J. Dencker, P. Bech, G.O. Petersen, J. Christensen, Plasma levels and antidepressive effect of imipramine, Clin. Pharmacol. Ther. 19 (1976) 318–324.
[6] P. Borst, R. Evers, M. Kool, J. Wijnholds, The multidrug resistance protein family, Biochim. Biophys. Acta 1461 (1999) 347–357.
[7] Y. Tanigawara, Role of P-glycoprotein in drug disposition, Ther. Drug Monit. 22 (2000) 137–140.
[8] B. Hsiang, Y. Zhu, Z. Wang, Y. Wu, V. Sasseville, W.P. Yang, T.G. Kirchgessner, A novel human hepatic organic anion transporting polypeptide (OATP2). Identification of a liver-specific human organic anion transporting polypeptide and identification of rat and human hydroxymethylglutaryl-CoA reductase inhibitor transporters, J. Biol. Chem. 274 (1999) 37161–37168.
[9] K. Niinuma, Y. Kato, H. Suzuki, C.A. Tyson, V. Weizer, J.E. Dabbs, R. Froehlich, C.E. Green, Y. Sugiyama, Am. J. Physiol. 276 (1999) G1153–G1164.
[10] K. Westphal, A. Weinbrenner, T. Giessmann, M. Stuhr, G. Franke, M. Zschiesche, R. Oertel, B. Terhaag, H.K. Kroemer, W. Siegmund, Oral bioavailability of digoxin is enhanced by talinolol: evidence for involvement of intestinal P-glycoprotein, Clin. Pharmacol. Ther. 68 (2000) 6–12.
[11] S.H. Sindrup, K. Brøsen, P. Bjerring, L. Arendt-Nielsen, V. Larsen, H. Angelo, L.F. Gram, Codeine increases pain thresholds to copper vapor laser stimuli in extensive but not poor metabolizers of sparteine, Clin. Pharmacol. Ther. 48 (1990) 686–693.
[12] S.H. Sindrup, L. Poulsen, K. Brøsen, L. Arendt-Nielsen, L.F. Gram, Are poor metabolisers of spar-teine/debrisoquine less pain tolerant than extensive metabolisers?, Pain 53 (1993) 335–339.
[13] L.F. Gram, K. Brøsen, S. Sindrup, E. Skjelbo, Genetic and interethnic variability in drug metabolism: what are the clinical consequences?, in: G. Alvan, L.P. Balant, P.R. Bechtel, A.R. Boobis, L.F. Gram, G. Paintaud, K. Pithan (Eds.), COST B1 Conference on Variability and Specificity in Drug Metabolism, DG-12, COST B1, European Commission, Bruxelles, 1995, pp. 235–245.
[14] M. Arranz, J. Munro, J. Birkett, A. Bolonna, D. Mancama, M. Sodhi, K.P. Lesch, J.F. Meyer, P. Sham,

M. Levy, R.M. Murray, R.W. Kerwin, Pharmacogenetic prediction of clozapine response, Lancet 355 (2000) 1615–1616.
[15] R. Jelliffe, Goal-oriented, model-based drug regimens: setting individualized goals for each patient, Ther. Drug Monit. 22 (2000) 325–329.
[16] A.J. Gelenberg, J.M. Kane, M.B. Keller, et al., Comparison of standard and low serum levels of lithium for maintenance treatment of bipolar disorder, N. Engl. J. Med. 321 (1989) 1489–1493.
[17] L.F. Gram, Fluoxetine, N. Engl. J. Med. 331 (1994) 1354–1361 (Review).
[18] P. Bollini, S. Pampallona, G. Tibaldi, B. Kupelnick, C. Munizza, Effectiveness of antidepressants, Br. J. Psychiatry 174 (1999) 297–303.
[19] Danish University Antidepressant Group (DUAG), Clomipramine dose–effect study in patients with depression: clinical endpoints and pharmacokinetics, Clin. Pharmacol. Ther. 66 (1999) 152–165.
[20] F.M. Quitkin, J.G. Rabkin, D. Ross, J.W. Stewart, Identification of true drug response to antidepressants: use of pattern analysis, Arch. Gen. Psychiatry 41 (1984) 782–786.
[21] L.F. Gram, Is there a right dose of psychotropic drugs?, in: L.P. Balant, J. Benitez, S.G. Dahl, L.F. Gram, R.M. Pinder, W.Z. Potter (Eds.), Clinical Pharmacology in Psychiatry: Finding the Right Dose of Psychotropic Drugs, COST B1, European Commission, Bruxelles, 1998, pp. 1–11.
[22] M. Jerling, M. Merlé, F. Mentré, A. Mallet, Population pharmacokinetics of nortriptyline during monotherapy and during concomitant treatment with drugs that inhibit CYP2D6—an evaluation with the nonparametric maximum likelihood method, Br. J. Clin. Pharmacol. 38 (1994) 453–462.
[23] M. Jerling, L. Lindström, U. Bondesson, L. Bertilsson, Fluvoxamine inhibition and carbamazepine induction of the metabolism of clozapine: evidence from a therapeutic drug monitoring service, Ther. Drug Monit. 16 (1994) 368–374.
[24] L.F. Gram, The role of the clinical pharmacologists in TDM, in: M. Levy (Ed.), Abstract from 3rd EACPT, Jerusalem, Br. J. Clin. Pharmacol. (1999) 4.