Dose-response relationships in clinical pharmacology
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DOSE RESPPONSE RELATIONSHIPS IN PSYCHOPHARMACOLOGY

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INTRODUCTION

Drug therapy in psychiatry encompasses basically four main treatment modalities, neuroleptics, antidepressants, lithium and benzodiazepines. The first development within these main groups took place some 25-35 years ago, and it is fair to say that these four groups in principle still remain the corner stones in psychiatric pharmacotherapy. Within each group, except lithium, several new compounds have been developed, but the the basic therapeutic principles have remained the same as the prototypes, chlorpromazine, imipramine and diazepam. The modifications achieved by development of analogues mainly concern pharmacokinetic properties, pharmaceutical preparations (depot neuroleptics, etc., 1), and side effect/adverse reaction profile.

Whereas several studies have established some relationships between dose and acute responses of benzodiazepines (2) the picture is much less clear for the three other classes of treatments. Common for neuroleptics and antidepresants is that the therapeutic response is delayed, reaching maximum after 2-8 weeks. The following discussion will concentrate on these two classes of drugs. Dose-response studies with these drugs are important because the therapeutic range is narrow with toxic doses being only 3-6 times higher than therapeutic doses in individual patients. The aims of dose-response studies thus are to improve efficacy and/or reduce the risk of adverse reactions.

DOSE-RESPONSE STUDIES WITH NEUROLEPTICS AND ANTIDEPRESSANTS

The clinical effects observed in studies with usual therapeutic doses have largely been the following:

Neuroleptics:	antipsychotic
	unspecific calming
	extrapyramidal
Antidepressants:	antidepressive
	sedative-anxiolytic
	autonomic-cardiovascular

The antipsychotic or antidepressive effect clearly is the primary objective of the treatment. The unspecific calming effect of neuroleptics may be of considerable

importance in the treatment of acute psychoses. Likewise, the anxiolytic-sedative effect may often be useful in the early phases of the treatment of depressions. The extrapyramidal effects of neuroleptics have by some been considered closely associated with the antipsychotic effect, but recent research indicates that the two effects might indeed be separated by appropriate individualized dose adjustment (see below). The autonomic and cardiovascular effects of tricyclic antidepressants may often be disturbing and limiting for their use in some patients, in particular the elderly.

Neuroleptic antipsychotic effect is excerted gradually and both the dose and time factor thus are important variables. This means that dose-response studies within patients usually are not possible. The analysis must be based on comparisons of groups of patients on different doses. Baldessarini et al. (3) recently review a series of studies comparing different doses of neuroleptics in a controlled, prospective way. The studies were characterized by marked differences in doses employed within each patient group of the trial (varying by a factor 2-7). In spite of this the results were far from clear-cut and in strict statistical terms the differences between doses appeared uncertain. As an overall result of their analyses of short-term treatment studies the authors suggested that doses of chlorpromazine below 200 mg/day or haloperidol/fluphenazine below 4 mg/day were ineffective, doses of chlorpromazine of 300-600 mg/day (or haloperidol/-fluphenazine 12-18 mg) were optimal, and higher doses did not provide additional benefits. On the contrary, a poorer therapeutic response on higher doses was suggested, the role of adverse reactions, in particular extrapyramidal symptoms, was not clear.

In long-term maintenance treatment, methodological shortcomings in trial design precluded any conclusions concerning dose-response relationship for intended or unintended effects. On the basis of the available data the authors concluded that there appeared to be no benefit of particularly high doses and that in long-term treatment lower doses than commonly used, probably are as effective (3).

Antidepressants act gradually over several weeks and dose-response studies can only be based on group comparisons. In many clinical trials with flexible doses it is indicated that dose is adjusted according to clinical (therapeutic?) effect. In the light of the gradual onset it is difficult to evaluate the validity of such procedures, in particular when the criteria for choice of dose are poorly defined. The literature on tricyclic antidepressant contains remarkably little concern about the dose-response problem, although this would be of obvious relevance in relation to the 30-40% rate of treatment failure reported in most studies (4). One explanation might be that early experiences in terms of toxicity with higher doses influence subsequent practice. In an early controlled imipramine/placebo study (5) it thus was stated that "at the beginning of the study the dosage was increased to a maximum of 400 mg/day of imipramine, but because of several serious toxic reactions it was decided not to exceed 200 mg in the cases treated thereafter". The unfavourable results in a smaller number of patients thus have

determined the dose policy for the whole group of patients. In retrospect one may speculate if some of the patients have been sparteine/debrisoquine poor metabolizers, i.e. slow metabolizers of imipramine. The comprehensive analysis of Smith et al. (4) on study variables determining the outcome of clinical trials with tricyclic antidepressants did not include the dose as a variable of interest. The lack of strong data on the dose-response relationship for tricyclic antidepressants is also apparent from a recent authorative review (6) that states: "Dose has been almost always determined empirically, the patients tolerance most often being the limiting factor. ... The effective dose varies widely, depending on many factors. Undertreatment has been thought to be a frequent cause for an apparent failure of drug therapy ...".

For newer antidepressants, developed during the last decade, the interest in dose-response studies has been more pronounced. This is due partly to the requirements from regulatory bodies, partly to the problems in proving an efficacy comparable to that of the tricyclic antidepressants.

PROBLEMS IN STUDIES OF DOSE-RESPONSE RELATIONSHIP

The paucity of convincing data on dose-relationships for neuroleptics and antidepressants can be related to several methodological factors:

Firstly, the clinical endpoint may often be difficult to define due to the gradual onset of action, problems with validity and reliability of effect measurements (usually achieved by use of rating scales), and confusion of true therapeutic and side effects.

Secondly, diagnostic heterogeneity may be a problem which so far only is suggested in the literature. Unawareness of the existence of different dose requirements for different diagnostic subgroups of a given nosological entity thus may preclude relevant conclusions.

Thirdly, the study design and setting may be critical in several ways e.g. in terms of concurrent therapy (other drugs, psychotherapy etc.), control of drug compliance which in particular is an inherent problem in outpatients, sensitivity of side effects, i.e. to which extent side effects result in dose changes etc.

Fourthly, the interindividual pharmacokinetic variability seems to provide the best explanation of the difficulties in describing a dose-response relationship. It thus may be logical to discuss the drug concentration-response relationship rather than the dose-response relationship.

PHARMACOKINETIC VARIABILITY OF NEUROLEPTICS AND ANTIDEPRESSANTS

For all tricyclic antidepressants and the majority of classical neuroleptics a vast literature documents a very pronounced pharmacokinetic variability (7, 8, 9,). Patients given identical doses thus develop steady state blood levels that vary by a factor 10-30.

In our study on imipramine (10) we found a variation by a factor 60 for imipramine (6-360 µg/l) and 28 for the primary metabolite, desipramine (25-700 µg/l).

The sources of this variability are listed below:

The hepatic cytochrome P450db1 drug oxidation:

genetic polymorphism (sparteine/debrisoquine)

dose-dependent kinetics

interactions

Binding to plasma proteins

Age - Disease

Oxidation by the sparteine/debrisoquine oxygenase (P450db1) has been shown to be the rate-limiting step in the elimination of all the major tricyclic antidepressants (11) and recently this also has been shown for two neuroleptics, thioridazine (12) and perphenazine (13). Sparteine/debrisoquine poor metabolizers thus have a clearance of these drugs that is only 5-15% of that of the extensive metabolizers.

For imipramine it has been shown that the oxidation via the P450db1-isozyme (2-hydroxylation) exhibits saturable kinetics related to the first pass through the liver (14). The isozyme also is the site of the strong inhibitory effect of neuroleptics on the oxidation of tricyclic antidepressants (15).

Interindividual variations in protein binding may explain some of the variability in steady state levels and may in particular be important as a confounding factor in drug concentration-response studies.

DRUG CONCENTRATION RESPONSE RELATIONSHIPS

Drug concentration monitoring has been an indispensible part of lithium treatment ever since its earliest days more than thirty years ago. This was mainly due to the very severe, sometimes life-threatening toxicity seen in patients with doses/drug concentrations only 100-200% above their therapeutic levels. The correct lower therapeutic concentration limit is still debated.

For antidepressants and neuroleptics applicable methods for drug concentration measurements in plasma became available in the early 1970s and since then a large number of studies have been carried out examining the relationship between steady-state concentration of drug plus at least some active metabolites and the clinical outcome in terms of therapeutic and undesired effects. In spite of the large number of studies, the conclusions that can be drawn from these studies are uncertain. For some of the tricyclic antidepressants, notably imipramine and nortriptyline, different groups have reported concentration/effect relationship in reasonable agreement (16). As an example our results from three different studies with imipramine are compiled in the figure. The

studies were carried out in three clearly different diseases: endogenous depression (17), nocturnal enuresis (18) and painful diabetic neuropathy (19). The plasma concentration data suggest that therapeutic effect in the two latter conditions is achieved at drug levels clearly below those required for the successful antidepressant treatment in endogenously depressed patients. The effect in nocturnal enuresis and diabetic neuropathy pain treatment also occur much faster than in depression treatment, and these differences indicate that different response mechanisms are involved.

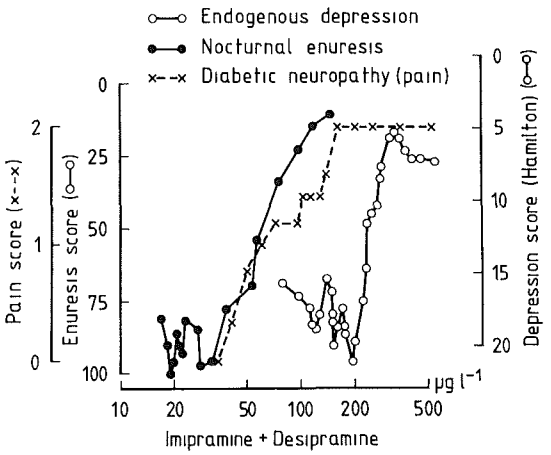

Figure: Summary of studies on the relationship between steady-state concentration (imipramine + desipramine) and the therapeutic effect of imipramine in three different conditions. The curves were constructed by rank-ordening the patients according to steady-state concentration and calculation of corresponding mean rating scores by use of a moving average technique (n = 5). The depression and enuresis scores represent residual values and the pain scores change in rating values (17, 18, 19).

The imipramine studies describe a lower effective plasma level of imipramine + desipramine such that with increasing steady-state concentrations some patients will respond above 150 µg/l and when a level above 250 µg/l is reached a maximum of efficacy is seen. For nortriptyline the most striking and best documented finding is an upper concentration limit of about 170-200 µg/l above which the therapeutic effect is poor. For amitriptyline similar but less consistent data have been reported, and for several other antidepressants (desipramine, clomipramine), the picture is still unclear. The more common side effects, such as anticholinergic effects and orthostatic

hypotension, appear to occur at drug levels that are lower than the therapeutic levels. These effects thus can not be avoided totally by concentration monitoring or dose adjustment. However, to achieve optimal therapeutic results and to avoid the risk of serious toxicity, drug level monitoring appears to be an important tool. As discussed below, this problem deserves further attention and carefully excerted prospective studies.

The results obtained with neuroleptics are as yet far from being conclusive. Either the drugs have only been studied systematically by one group or the results are unclear with disagreements between different reports, and with several studies failing to find any relationship at all (9). For some neuroleptics, such as chlorpromazine, perphenazine and haloperidol, the available data may suggest the existence of a lower concentration threshold for antipsychotic effects that is 1.5-3 times lower than the concentrations at which extrapyramidal symptoms are seen. A therapeutic range thus may be defined, and in some centers these results have created a basis for routine use of concentration monitoring of some neuroleptics.

The present literature on drug concentration-response relationship of antidepressants and neuroleptics is thus still not very conclusive. A major reason for this appears to be the complex interaction between several confounding methodological factors.

CONFOUNDING METHODOLOGICAL FACTORS IN DRUG CONCENTRATION-RESPONSE STUDIES IN PSYCHOPHARMACOLOGY

The pharmacokinetics of a drug may in several ways preclude the demonstration of a concentration-effect relationship: The steady-state level may for some drugs and in some patients be achieved very slowly, sometimes over several weeks (20). In these cases it may be difficult to define which drug level has been effective in the preceding weeks during which the drug excerted its effect. The same applies to the situation when the levels fluctuate considerably. This may reflect compliance problems, and therefore such studies are not suited for an outpatient setting. The plasma protein binding of neuroleptics and antidepressants varies between drugs and between patients for a given compound. Some drugs such as chlorpromazine and clomipramine has an extremely high degree of binding ($\geq$ 99%) and in these cases it may be methodologically difficult to assess the interindividual variability. For other drugs with a higher free fraction, the interindividual variability has usually been found to range from a factor 2 to 4 (7). The total plasma concentration (free + bound) thus may not very well reflect the free concentration and thereby the receptor concentration. The more pronounced the interindividual variability is, the more flat the (log) concentration-response curve will be, and this may reach a degree where no conclusions can be drawn. It has been claimed that a stronger concentration/effect relationship for some neuroleptics can be achieved

when free concentration or CSF concentration measurements are used (21). Assuming that drug binding in erythrocytes is relatively constant among individuals, the erythrocyte levels might be a useful measure of drug concentration better reflecting the free drug concentration (21).

Several antidepressants and neuroleptics have measurable plasma levels of metabolites. To which extent these are active metabolites can be settled by receptor studies for neuroleptics, whereas the therapeutic receptor(s) for antidepressants still is a matter of considerable debate. In any case it has to be considered how these metabolites behave in terms of being agonists or antagonists, their potency relative to parent compound and plasma levels, including correction for differences in protein binding, and the specificity of the assay.

The problems arising from the drug or its metabolites being present as 2 or more isomers or enantiomers have been increasingly underlined in recent years (22).

Stereoselectivity in drug binding to receptors and enzymes may result in markedly different pharmacodynamic effects and rates of elimination of isomers or enantiomers. Assay methods not differentiating between the different compounds in a racemic mixture may lead to meaningless results and conclusions.

Clinical pharmacodynamics of the neuroleptics and antidepressants play a role in drug concentration response studies, firstly, because different subtypes of a disease may require different drug concentrations and different duration of therapy. Very few data elucidating these possibilities exist. It is well known that the rate of response of both antidepressants and neuroleptics is highly variable, but a relationship with diagnostic classification has not been established.

In our study on imipramine (17) we found a very clear drug concentration/outcome relationship in those patients classified (by diagnostic inventories) as endogenously depressed. In the remaining "non-endogenous" group the relationship was less clear and it appeared that some of these patients responded at lower drug levels not being effective in the endogenously depressed patients. The number of patients was however small and these findings need confirmation.

Different effects of the drug may exhibit different (log) concentration-response curves. For neuroleptics the concentration-response curves for antipsychotic and extrapyramidal effects appear to be separated whereas the unspecific calming effect may be different, perhaps with a less steep course such that maximum effect is achieved at very high levels. This may result in a higher dose of neuroleptic drug in the early phases of acute psychoses, and the relationship between drug concentration and truly antipsychotic effects may be difficult to discover. In these patients it is rational to reduce the dose after some time and a concentration-effect relationship may be titrated at this point, unless the influence of concurrent non-pharmacological factors causes other problems in deriving clear conclusions. The complex concentration-

response relationships, e.g. the curvilinear relationship as described for nortriptyline (23) may indeed be a confounding factor in studies of this kind.

With one exception (23) all the studies in this field have in principle been retrospective. The results obtained as discussed above thus may be considered largely as hypothesis-generating. What now is needed are prospective studies testing the hypothesis concerning drug concentration-response relationships derived from the earlier studies. Future studies should take the many confounding factors into account and be designed in principle as randomized trials comparing in a double-blind fashion the efficacy and toxicity of different steady state levels. These are demanding projects in terms of planning and implementation, but the result can be expected to provide a long needed basis for better use of existing drugs and a better basis for testing new psychotropic drugs.

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Discussion - Dose-response relationships in psychiatry

A.N. Nicholson

If I have it correct, your opinion is that we have failed to establish dose-response relationships on mood with antidepressants. But we know that drugs which are used as antidepressants have obvious effects on the central nervous system and that these do relate very clearly to dose. For instance, antidepressants decrease or increase nocturnal wakefulness, they modify daytime alertness, and they suppress REM sleep. All these responses are dose-related. We also know that we can establish dose-response relations with subjective effects of centrally acting drugs. With antidepressants we seem to have a very special situation and that is that dose relations can be established on their central activity, but not so easily on what is believed to be their main therapeutic effect which is mood elevation. So the question that I would like to put to you is: does our inability to establish dose-response relationships on mood suggest that we may not be able to measure mood accurately and therefore we should be much more cautious in using these drugs? Or it is that we are trying to measure an effect of these drugs which may not exist. It may be that we are confusing changes that occur in behaviour other than mood, such as alertness?

L.F. Gram

I think the effects that you mentioned can be dose-related within subjects, because they are immediate and that is the difference. You cannot do within subject studies on the antidepressant effect, because you have varied time effects, you have gradual onsets and you can't just go up and down in a randomized fashion with a dose because the treatment given in the first two weeks would have some consequence on what you see afterwards. I don't think there is any particular problem in measuring the depression or defining that we are really treating depression. And I wouldn't say that dose-effect relationships cannot be demonstrated. I only stress it has not been demonstrated and that is the difference. Fear of toxicity may have been in part responsible for this and, on the other hand, the study of concentration-response relationships has proven to be a more

rewarding approach, because of the great pharmacokinetic variability in this group of drugs.

P.L. Morselli

I wonder whether we are overemphasizing the pharmacokinetic variability and not paying enough attention to the problem of diagnosis. It seems to me that in the case of schizophrenia and depression we are using single labels for diseases that may have similar forms of expression but that obey to quite different mechanisms. It looks as in schizophrenia, as well as in depression, we were in a situation similar to that of epilepsy many years ago, when the sophisticated diagnostic tools now available had not yet provided the means to distinguish among the different syndromes.

L.F. Gram

I agree, but the point is that one should not make a choice between stressing the kinetic variability or the diagnostic problems, One really has to face them all.

L. Lasagna

It seems to me that we know some things about dose response that are quite useful as a basis for medical practice. We know that if one does not flexibilize doses of the tricyclics, for example, one gets into trouble. If one gives routinely high doses, unpleasant adverse effects will develop in a lot of people, leading to poor compliance, and occasionally mania will develop. If one gives too low doses, there are some people who will respond, but many will not. We also know that a very common occurrence is for people to move from the out-patient setting into the in-patient setting, and as a result of having their dose increased they will then respond. We also unfortunately know that no matter how big a dose one uses of a given drug for some patients they will not respond, and sometimes, in these cases, switching to another class of antidepressant may work.

D.G. Grahame-Smith

I wonder whether we are using antidepressant drugs in the way in which they actually need to be used. If you look at the

neuropharmacological changes that occur, at least in animal brains, after treatment with antidepressants or after electroconvulsive shock you find that they produce extraordinarily similar changes. It might be that if you gave the brain a push with a dose of an antidepressant, waited 3 or 4 days, gave another dose, and perhaps another one after 3 or 4 days, you would have a similar therapeutic effect. Certainly I do not know how these drugs work and whether in fact the plasma levels, as we measure them, have any meaning in regard to their effect whatsoever. So when we have an inconclusive discussion of the sort we are having, I am not surprised.

A.N. Nicholson

Sleep deprivation is used as a treatment for depression, and many antidepressants, particularly the 5HT uptake inhibitors disturb sleep. They produce continuous wakefulness overnight, at least in the early days of their administration, it may well be that part of their therapeutic effect is related to sleep deprivation.