Drug load in clinical trials: A neglected factor

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Combinations of drugs are increasingly being used on pharmacologic grounds. Examples of the use of these combinations include cancer chemotherapy treatment and hypertension treatment.1-3 The goal of using two or more drugs instead of one is to achieve greater efficacy with the same or fewer adverse effects or equal efficacy with fewer adverse effects.4,5 In pharmacologic terms this would signify supraadditive efficacy with additive or infraadditive toxicity and additive efficacy with infraadditive toxicity, respectively. Consequently, numerous clinical trials are being undertaken to compare combination regimens with their individual constituents.

However, the total drug load (i.e., the amount of drug exposure for a certain indication) is a neglected factor in many of these trials. When differences in effects are found in these trials, they are attributed to the pharmacodynamic properties of the therapeutic regimens instead of to a possible difference in drug load between the groups. However, the drug loads of two regimens should be equal before conclusions are reached on differences of intrinsic efficacy or toxicity.

Many examples of neglecting drug load can be found in the literature. MacKay et al.6 evaluated the effects of 50 mg losartan alone, 12.5 mg hydrochlorothiazide alone, a combination of 50 mg losartan and 6.25 mg hydrochlorothiazide, and a combination of 50 mg losartan and 12.5 mg hydrochlorothiazide for essential hypertension and concluded that the combination of 50 mg losartan and 12.5 mg hydrochlorothiazide produced an additive and safe reduction. However, for a clinically relevant evaluation they should have included a high-dose hydrochlorothiazide group and a high-dose losartan group, or they should have used lower doses of both drugs in the combination regimen (i.e., to compare regimens with a more equal drug load). This would have challenged the merits of the combination of losartan and low-dose hydrochlorothiazide. Similarly, studies by Faarvang et al.7 on the possible advantages of combining antirheumatic drugs and by Nelson et al.8 on the possible advantages of combining antidepressive drugs also did not include high-dose monotherapy groups or lower dosages for the combinations.

Another frequently encountered manner in which drug load is neglected is the habit of not taking baseline medication into account. Onghena and van Houdenhove9 reviewed 39 placebo-controlled trials on antidepressant-induced analgesia for chronic nonmalignant pain and found that the use of other analgesic agents, ergotamine, or antirheumatic drugs was permitted in these trials. For example, in one of the reviewed articles, a study by Loldrup et al.,10 patients were allowed to have up to 30 mg oxazepam and up to 3 gm acetaminophen (INN, paracetamol) in addition to the study medication, without taking between-group differences of oxazepam and acetaminophen into account. In an antihypertension drug trial research, Avanzini et al.11 compared the effects of four different drug regimens, but one regimen began with a considerably higher drug load than the others.

This problem is also important in add-on studies of antiepileptic drugs. The first trials to establish efficacy of a new antiepileptic drug are conducted by comparison of the new drug plus the existing, insufficiently effective, medication to placebo plus the
existing medication. This is necessary because it is unethical to give only new antiepileptic drugs or placebo to patients with newly diagnosed epilepsy; thus the effects of the new compound are evaluated as though only the new drug were given. However, we found that the total drug loads of baseline medication of the active and placebo groups sometimes differ, and therefore it is unclear whether observed differences in toxicity are really the result of the new antiepileptic drug or whether they are related to drug load. 

Polytherapy is being avoided in epilepsy treatment because of the fear of adverse effects. This is based on studies published around 1980 in which patients who were switched back from polytherapy to monotherapy experienced a decrease in toxicity. However, the patients in these studies had not only a reduction in the number of antiepileptic drugs but also in drug load. Comparison of toxicity between patients receiving monotherapy and patients receiving polytherapy with equal drug loads has shown that toxicity does in fact not differ between these groups.

Although the concept of drug load is intuitively obvious, little has been published about a method to evaluate drug load in polytherapy. Such a method should be helpful in the planning and analysis of clinical trials and should enable determination of the role of drug load as a prognostic factor. In experimental settings, fractions of drug exposure are already used in the isobole method. This is the preferred method to detect synergy, zero interaction, or antagonism. The dosages of a drug combination \((d_a, d_b)\) are determined that have the same effect as certain dosages of the drugs alone \((D_a, D_b)\). The equation for the zero interaction line for two agents is as follows: \(d_a/D_a + d_b/D_b = 1\). When the sum is less than one, the combination is judged to be supraadditive; when the sum is more than one, the combination is judged to be infraadditive. The interaction can thus be evaluated for the dosages used, irrespective of the dose-response curves of the individual drugs. We have developed a method to assess drug load that is analogous to the isobole method.

Methods

The unity of drug load can be defined as the average amount of drug needed to obtain the desired effect in the general population. To approximate the unity drug load, the defined daily dose as published by the World Health Organization may be used.

Table I. Defined daily dose values of antiepileptic drugs as assigned by the World Health Organization (1996)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Defined daily dose (mg)</th>
</tr>
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<tbody>
<tr>
<td>Carbamazepine</td>
<td>1000</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>300</td>
</tr>
<tr>
<td>Valproate</td>
<td>1500</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>100</td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>1250</td>
</tr>
<tr>
<td>Vigabatrin</td>
<td>2000</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>300</td>
</tr>
</tbody>
</table>

The defined daily dose was introduced by the World Health Organization Drug Utilization Research Group as a tool to convert drug consumption data from different sources into comparable units. The World Health Organization Group determines and assigns the average maintenance dose of a drug for its main indication—the defined daily dose—for each individual drug by analysis of literature and drug registration data. The defined daily dose values of antiepileptic drugs are listed in Table I. The prescribed daily dose is the average prescribed dose in a particular population.

The prescribed daily dose/defined daily dose ratio can be used to calculate the drug load in treatment groups when the prescribed daily dose is used as the average dose of a drug taken in a certain treatment group. The method assumes that, thus normalized, the loads of several drugs in one regimen may be added.

For example, the defined daily dose of valproate sodium is 1500 mg and patients in group A taking 900 mg valproate would have a drug load of 900/1500, that is, 0.6 prescribed daily dose/defined daily dose. The defined daily dose of carbamazepine is 1000 mg and patients in group B taking 600 mg carbamazepine would have a drug load of 600/1000, which is also 0.6 prescribed daily dose/defined daily dose. Patients in group C taking 450 mg valproate and 300 mg carbamazepine would have an equal total drug load of 0.6 prescribed daily dose/defined daily dose, which makes them eligible for comparison with patients of groups A and B.

*For information on assigned defined daily dose values, contact the World Health Organization Collaborating Centre for Drug Statistics Methodology, c/o Norsk Medisinaklepot AS, PO Box 100, Veitvet, N-0158 Oslo, Norway (phone: 47-22169810; fax: 47-22169818).
Results in epilepsy research

We have applied the described method of measuring drug loads in a retrospective analysis of antiepileptic drug trials in which multiple drug regimens were used. In this review, toxicity was weakly but significantly correlated with drug load and not with the number of antiepileptic drugs. In one of the trials we analyzed, the authors assessed the neuropsychologic effects of a fixed dose of the antiepileptic drug vigabatrin in an add-on placebo-controlled paradigm. No differences in neuropsychologic effects were found, and it was concluded that vigabatrin did not have a large effect on cognitive functioning. However, analysis of the total drug loads of the two treatment groups revealed that, notwithstanding the addition of vigabatrin to one group, drug loads in both treatment groups differed only slightly. This greatly decreases the likelihood of finding any difference in effect, if mechanisms are similar.

We have also used the prescribed daily dose/defined daily dose ratio to start patients off with equal drug loads in both treatment groups of a clinical trial. In a recently initiated trial, we are comparing carbamazepine monotherapy to a combination of carbamazepine and valproate sodium and all patients start with a drug load of 0.4 prescribed daily dose/defined daily dose, whether receiving monotherapy or duotherapy. This prevents bias; for example, when one treatment group starts with a lower drug load it may take longer to get these patients into remission, although the drugs may be equally effective. Alternatively, in a treatment group that starts off with a higher drug load, more patients may drop out fast because of adverse effects, while in fact the two regimens may be equally toxic. Accordingly, in a treatment group that starts off with a higher drug load, more patients may drop out fast because of adverse effects, while in fact the two regimens may be equally toxic when equal drug loads are used. Furthermore, the prescribed daily dose/defined daily dose ratio allows physicians participating in this trial to adjust the dose in terms of prescribed daily dose/defined daily dose, thus keeping physicians, patients, and investigators blinded.

In addition, prediction of the outcome of drug withdrawal after a reasonable symptom-free period may benefit from the concept of drug load. Until now, the number of antiepileptic drugs has been deemed to be an important factor in determining the risk of seizure recurrence. The total drug load of the antiepileptic drug regimen may very well prove to be of more relevance in this respect.

Discussion

Failure to evaluate drug load may complicate the evaluation of drug efficacy and toxicity, especially where combination therapy or fixed dosages are concerned. Equal drug loads should be verified at the start of treatment, as well as determined in the retrospective analysis of clinical trials. In our field—antiepileptic drug treatment—neglecting drug load obscures the evaluation of new antiepileptic drugs and has also unjustly caused polytherapy to be blamed for increased toxicity.

With use of the prescribed daily dose/defined daily dose ratio, it is possible to evaluate whether an equal load of polytherapy may offer advantages compared with conventional monotherapy. Obviously, the inherent assumption when using this method is that the combination will exhibit additive activity. Deviations then will provide information about infraadditive or supraadditive activity. Another assumption is that the defined daily doses published by the World Health Organization are equipotent.

Conclusion

Drug load is a neglected factor in many trials in which drug combinations or fixed dosages are used. Taking drug load into account will clarify the interpretation of the results of these trials. As a crude indicator the prescribed daily dose/defined daily dose ratio has already been useful to us in the assessment and planning of antiepileptic drug trials.

References

5. Ferrendelli JA. Relating pharmacology to clinical


