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Difficulties in Evaluating the Efficacy of an Anticonvulsant in the Presence of Other Anticonvulsants

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The evaluation of new anticonvulsants in the United States requires add-on studies that may be open studies as part of phase II testing or double-blind as part of phase III testing (Cereghino and Penry, 1972; Food and Drug Administration, 1977). When a new anticonvulsant is added to an existing drug regimen there are major problems in measuring the efficacy and safety of the new drug because the interactions between the drugs are complex and difficult to evaluate. Because of these interactions, it is frequently difficult to distinguish effects, therapeutic and/or toxic, of the drug being studied from those of the drugs not being studied. At the University of Washington Epilepsy Center, we are currently engaged in a large double-blind study comparing the efficacy and toxicity of clorazepate with that of phenobarbital in patients already taking phenytoin who have persistent focal seizures. This chapter describes the problems we have identified in the course of this study and strategies we have developed to overcome these problems.

PROBLEMS

In order to evaluate the usefulness of a new anticonvulsant, the only factor that should change in the patient's environment is the new medication. Because of drug interactions, however, the addition of a second drug or a change in its dose will frequently affect the first drug. Thus in add-on studies a stable background for evaluating the new anticonvulsant is rarely if ever achieved.

Serum Level Changes

The most common change that investigators must deal with is an alteration in the serum level of the background anticonvulsant. Investigators are then faced with a dilemma. First, in any study of finite length only a limited number of changes can be made in the dose of medications. In general, the dose of only one drug should be changed at any one time so that the effect of that change can be observed independently of any other changes in medication. If investigators attempt to maintain a constant serum level of the non-study drug they may expend so much time and effort changing its dose that they do not adequately test the study drug at different dose levels. Effectiveness or toxicity of the new drug at high doses may be missed because there is no opportunity to raise the dose sufficiently.

On the other hand, if changes are made only in the dose of the study drug, the levels of the non-study drug will change because of drug interactions. Serum levels of the baseline drug may increase just as phenobarbital levels increase in the presence of valproic acid (Pinder et al., 1977). Serum levels may decrease as phenytoin levels do in the presence of carbamazepine (Hansen et al., 1971). Even when the probable interaction is known before the study the effect of the interaction in an individual patient may be different. Thus, although phenytoin levels are generally lower in the presence of phenobarbital than in its absence, in any individual they may increase, decrease, or remain the same when phenobarbital is added (Kutt et al., 1969; Morselli et al., 1971). Investigators are then faced with a problem of analysis. Whenever such drug interactions occur, changes in seizure frequency may be due either to the study drug or to changes in the serum level of the other drug. Similarly, toxicity may be secondary to either medication.

Free Fraction Changes

Even if the total serum level of the baseline medication does remain constant the investigators must be aware of other less obvious changes in distribution of the drug in the body. Anticonvulsant activity of a drug is thought to be related to its brain concentration. Although brain concentrations cannot be directly measured they are thought to be proportional to free serum levels and these in turn are supposed to be a constant fraction of total serum levels. The chain of assumptions that efficacy is related to brain levels and these in turn are related to free serum levels cannot, for practical purposes, be tested in a clinical study and thus has to be accepted. However, the assumption that the free level is always a constant fraction of the total serum level may not be valid. The free fraction of a drug can change because of a disease state or because of changes in other medications (Lunde et al., 1970; Hooper et al., 1974). A change in the free fraction can produce a small absolute change

in the free level, which may be large in a relative sense. This change may not be reflected by significant changes in total drug level. Thus, phenytoin is usually 10% free and 90% bound with a free level of approximately 2.0 $\mu\text{g/ml}$ when the total level is 20 $\mu\text{g/ml}$. A small absolute change of only 1 $\mu\text{g/ml}$ in free level to 3.0 $\mu\text{g/ml}$ because of a shift in binding so that 15% is free will leave the total phenytoin serum level unchanged. However, the amount of drug proportional to the brain concentration is increased by 50%. An alteration such as this in the non-study drug may produce major changes in clinical state that could be assigned to the study drug if the investigators are not alert.

Synergism

A final problem involving interactions can occur at the brain level. Two drugs may have a synergistic or antagonistic interaction on the brain. Thus, in the presence of one drug a new medication may work well, whereas it may be ineffective in the presence of some other anticonvulsant. This type of interaction is impossible to predict or detect without serially testing a new drug in combination with several other drugs. Therefore, even if a new medication produces good results in one combination, and even if these results can be shown not to be due to changes in the non-study drug, the results cannot automatically be extrapolated so as to assume the efficacy of the new medication when it is alone or when it is combined with some other drug.

STRATEGIES

When it is necessary to do an add-on study, the problems can be simplified by adding the new medication to only a single non-study drug. Even in a two-drug system, there are numerous interactions that make analysis difficult. This difficulty is much greater in a three-drug system. Only if the new drug produces spectacular results in a large percentage of cases, such as valproic acid, will the results be unequivocal in the presence of many different anticonvulsants; and even in the case of valproic acid the data have been questioned (Van Belle, 1978). The single non-study drug should be the same for all patients. If it is not, in reality, you are carrying out as many studies as you have different non-study drugs because the study drug will interact in a different way with each of the non-study drugs. Thus, in an add-on study, the experimental medication should be added to a single standard anticonvulsant and, where possible, its effect should be measured against the subject's status while he or she is on only the standard anticonvulsant, using a placebo in a double-blind manner.

Serum Level Changes

Once the proper basic study design is established, the investigators must avoid the temptation of trying to keep the non-study drug serum level constant. Even if they try, they will rarely succeed. Except when absolutely necessary, as when toxicity occurs because of increasing non-study drug levels, changes should be made in study drug dose rather than in the dose of the baseline drug. Some fluctuation in the level of the baseline drug must be accepted in order to allow for assessment of the study drug effects at various doses. At the end of the study, these fluctuations must be acknowledged in the analysis.

To make analysis practical under these circumstances, careful attention must be paid to clinical detail. Detailed, preplanned, clinical assessments are made at regular intervals. These should include seizure counts, objective measurements of toxicity, and subjective assessments by the patient of toxicity and seizure control. Changes in seizure type or quality should be noted. If a large blinded study is being contemplated, a small open pilot study should be done first to acquaint the investigators with at least some of the problems, primarily those of toxicity, which may arise during the blind study. The investigators will then be able to make management decisions that are more likely to solve the clinical problems.

Anticonvulsant serum levels must also be obtained. Because levels of medications vary with the time after each dose, they should be measured at a set time in relationship to dosing. In general, the best time is just prior to a dose, usually the first dose of the day when levels are at their lowest. Other times may be chosen depending on the information desired, i.e., peak levels versus lowest levels, convenience of the subjects, and the pharmacokinetics of the drugs being studied. Where possible, serum levels should be known before the end of the clinic visit so that drug dosage can be adjusted, if necessary, in the light of the levels. In blinded situations, the level of the drug not under study should be available at the clinic visit. Provided there is no known obvious drug interaction such that a change in standard drug level indicates the presence or absence of a blinded drug, this will not interfere with the blind nature of the study. Whenever drug changes must be made between regular visits because of toxicity or increased seizures, serum levels should be obtained if possible, so that information as to the cause of the problem is available when the data are analyzed.

Free Fraction Changes

Although accurate measurement of unbound anticonvulsant requires time-consuming procedures such as ultracentrifugation or equilibrium dialysis, for some anticonvulsants an estimate of free levels can be obtained relatively simply. Salivary anticonvulsant levels are good estimates of unbound

serum drug levels for anticonvulsants such as phenytoin (Troupin and Friel, 1975). When free levels can be estimated easily in this manner, they should be measured. If there is a change in free levels that is not reflected by a change in total serum anticonvulsant level, it can then be detected. Changes in clinical status secondary to free drug level changes can then be accounted for in the final analysis.

Other Strategies

Because anticonvulsants affect neuropsychological functions, comprehensive neuropsychological evaluation of the subjects should be undertaken on and off the study drug. Each anticonvulsant tends to alter a particular set of tests (Dodrill and Troupin, 1977). Clinical changes that coincide with non-study drug level changes may be accompanied by changes in neuropsychological test results which are attributed to either the study drug or the non-study drug. Thus, the neuropsychological tests may assist the investigators in assigning clinical changes to either the study or non-study drug. The investigators then do not have to be as concerned about keeping the standard drug level constant but can concentrate on changes in the study drug.

Once the study has been completed there is no single method of analysis that can separate out the effects of the study drug from the effects of the non-study drug. This does not mean, however, that nothing can be done. A biostatistician familiar with the study should assist in the careful evaluation of the data. If, for example, the effects of blood level changes of the non-study drug are understood, the biostatistician may be able to adjust for these changes in the analysis. Thus, although extra caution in the interpretation is warranted, add-on studies can provide valuable information about the efficacy of new anticonvulsants.

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