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Some Problems With Antihypertensive Drug Studies in the Context of the New Guidelines

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A dose-response analysis establishes the efficacy of most drugs. The medical literature is replete with so-called "Dose-Responses" to antihypertensive agents. The majority of these have failed. The use of a placebo helps minimize bias, though most studies here simply compared a test drug with the old drug. Short-acting drugs can have their duration of effect prolonged by giving larger doses than necessary.

In order to produce more meaningful data, the Food and Drug Administration gathered together a group of experts who collectively proposed a set of Guidelines for studying these drugs. Though the final version has not yet been issued, investigators and clinicians working with this class of drugs are vitally interested in these guidelines, and have already encountered several problems. We identify some of these problems and propose some solutions. Am J Hypertens 1990;3:151-155

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There are aspects of hypertension which suggest that the clinical development of antihypertensive drugs should be straightforward. Hypertension is widely prevalent, making study patients comparatively easy to find. Most IRB will permit placebo-controlled studies as long as they are not too lengthy and the severity not excessive. The usual study endpoint, blood pressure, is easily, reliably and relatively cheaply obtained. Most new antihypertensive agents have effects on blood pressure that are easily detectable in studies of moderate or even small size. Given all this, one might assume that developing the data necessary to obtain approval of an antihypertensive drug in the US would be a rather uncomplicated affair. However, evaluating an antihypertensive drug is more difficult than it might appear.

We wish to describe some of the more common problems which might lead to nonapproval or delayed approval of antihypertensive agents. These problems are viewed in the light of the draft antihypertensive guidelines of the Food and Drug Administration's (FDA) Division of Cardio-Renal Drug Products, which has the responsibility for reviewing antihypertensive drugs.[1] In addition to discussing common current problems in hypertension trials, we will describe some problems that may arise in the future as a result of new data requirements contained in the latest version of the guidelines. The guidelines were written in the last year by FDA staff, working together with a small group of experts in hypertension organized by the American Society for Clinical Pharmacology and Therapeutics. The guidelines were reviewed and approved by FDA's Cardiac and Renal Drugs Advisory Committee at an open meeting in June, 1988, resulting in several changes in the

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The opinions expressed here are those of the authors only. Martin Rose was a major participant in writing the draft guidelines at FDA. He spent three years in FDA's Division of Cardio-Renal Drug Products. Gilbert McMahon was a member of the American Society for Clinical Pharmacology and Therapeutics committee which met with FDA personnel during 1988 on the development of these guidelines. He has also spent most of his professional life involved in hypertension—publishing, reviewing articles and conducting clinical trials.

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document. In the near future, FDA expects to publish the guidelines in the *Federal Register* to elicit comments from interested parties. They will then be released by FDA in final form. However, the guidelines have been presented already at several well-attended academic meetings, and we expect that few further changes will result.

DOSE RESPONSE STUDIES

Failure to Have a Concurrent Placebo Group A placebo helps minimize observer bias. In a blood pressure study that compares only active drugs, everyone expects blood pressure to fall so this bias can be highly significant. Placebo groups add critical information to most dose-response studies. Without them, it is usually impossible to know the true antihypertensive effect at any particular dose level, and it is possible to conclude that a less than maximal effect dose is effective when indeed it is not.

Failure to Employ a Wide Enough Range of Doses The hypertension literature is replete with flawed attempts to obtain dose-response data. One of the reasons that a zero slope dose response curve is obtained is that the lowest and highest doses used may only differ by a factor of 2 or 3. Indeed, some very large multiclinic studies have been done using a range of doses less than two-fold with the three or four doses employed.

In drug development, the purpose of a dose response study is to define the useful dosing range of the drug. The guidelines state that at a minimum, the study should define the lowest dose that produces a maximal antihypertensive effect. Usually, this will require showing that a dose at least twice as large has no greater effect. However, sometimes the development of side effects makes this impossible, and an alternative to defining the lowest dose with a maximal effect is to determine a less than maximally effective dose beyond which side effects are intolerable. The study should also define at least one dose that is well down on the dose-response curve, perhaps producing about one-half the maximal effect (the ED_{50}). This will help determine the usual starting dose for the drug, which in most cases will not be a fully effective dose. It is also helpful, but usually not essential, to determine the smallest dose that has a net mean effect, or the minimally effective dose, which may help define a starting dose in certain sensitive individuals. The study should be placebo controlled. The doses employed should usually be separated from each other by a factor of 2 to 4. There is no need to show statistically significant differences in response between doses.

Figure 1 displays a hypothetical dose-response curve which includes all the above points and one dose that was found to be ineffective. Point 1 is the ineffective dose, Point 2 is the minimally effective dose, Point 3 is the ED_{50}, Point 4 the lowest fully effective dose, and Point 5 a higher dose without a greater effect. Figure 1 includes placebo plus five doses of the drug, with doses separated by a factor of 2. The study spans a 16-fold range of doses. In our experience, this span is near the practical minimum. Studies which span a smaller dosage range run an appreciable risk of failure. Studies using four active doses may succeed if the dosage span is wide enough. If a minimally effective dose is not sought and perfect guesses about dosage are made, one might get by with three doses plus placebo, but the chances for failure with this approach are great.

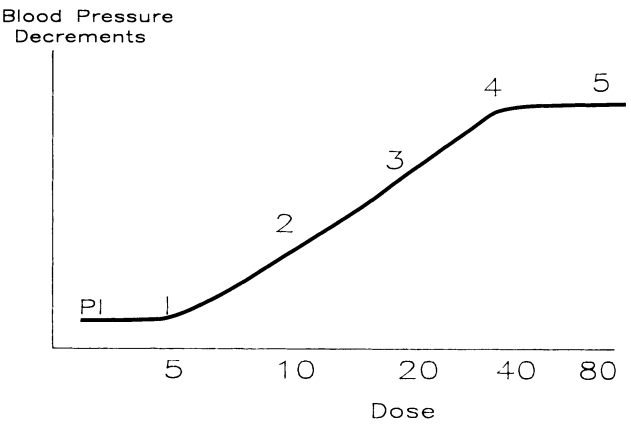

FIGURE 1. *Sample dose-response curve.*

Too Few Patients Per Dose Regardless of the nature of the study design, a dose response study ought to have a large population (n) per dose in parallel studies so that demographic variables such as race, diet, weight, age, and plasma renin levels are mitigated, and sample means are likely to be near the true population means. About 30 to 40 patients per cell are usually sufficient.

There is another important reason to use fairly large group sizes. The guidelines state that the statistical demonstration of a nonzero slope for a dose response curve is evidence of efficacy, meaning that a successful dose-response study can be one of the two well-controlled studies that are necessary to establish effectiveness.

Design Problems and Other Issues Most sponsors are now performing randomized, parallel dose-response trials, a design which is easily evaluated by FDA. Titration and crossover designs are also acceptable.

Any dose response trial should account for placebo effects. Other issues to keep in mind in designing and analyzing a dose-response trial include carry-over effects and insufficient duration of treatment at any given dosage level. This last issue is of particular interest in analyzing titration trials, but is applicable to any trial. Treatment periods of 4 weeks or more are almost always adequate. Shorter intervals may suffice, but should be supported convincingly by data showing that changes

in blood pressure after the chosen treatment duration are unimportant.

Another important issue of special relevance to titration trials relates to the target value selected to stop dose escalation. In order to maximize the likelihood of success in a dose-response trial, the target value should be well down into the normal range, ie, a diastolic blood pressure of 80 to 85 mm Hg.

In addition, the guidelines now state that a new nondiuretic antihypertensive drug proposed as monotherapy should be dose-ranged in the presence of a diuretic. This is because most physicians include a diuretic whenever two antihypertensive agents are given. It is unclear whether this new requirement will appear in the final version of the guidelines, and if so, how much weight FDA will place on it.

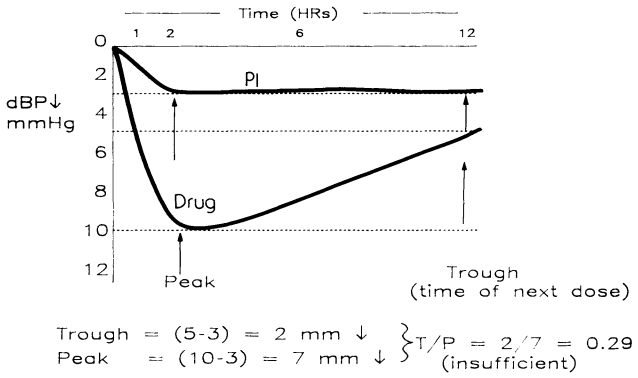

FIGURE 2. *Blood pressure reduction following drug and following placebo, showing both the points of peak effect and trough effect.*

Dosing Regimen Issues The choice of an inappropriately long dosing interval may now be the most frequent cause for the nonapproval of antihypertensive agents. Generally, this has occurred when sponsors have forced up the dose of a relatively short-acting drug to produce some net effect (ie, superiority over placebo) at the interdosing interval (the trough), usually at 12 or 24 h after dosing. In such cases, the peak effects usually will be substantially larger than the trough effects, risking hypotension, or at minimum, producing wide variation in the extent of blood pressure control during the day. However, FDA has made the assumption that hypertensive patients are likely to achieve the greatest benefits from therapy when the antihypertensive effects of therapy do not vary excessively during the day, and now requires sponsors to demonstrate that antihypertensive agents meet specific arithmetic standards with respect to the time course of their effects.

Specifically, usually after obtaining preliminary information on the time course of the effect from studies in confined subjects, the sponsor should conduct a placebo controlled study of substantial size using the proposed dosing regimen, measuring blood pressure at the time of peak effect and at the time of least effect, which is usually assumed to be at the day's longest interdosing interval. After subtracting the placebo effect, the net drug effect at trough (diastolic pressure) should be at least one-half of the net peak effect. If the net effect of the drug appears particularly small, perhaps 5 mm Hg at peak, a larger relative trough effect, up to two-thirds of the peak effect, may be required.

In calculating the trough to peak (T/P) ratio, it is critical to subtract the placebo effect first (Figure 2). Some investigators have failed to do this properly[2] and have miscalculated ratios (Table 1). Here the actual T/P ratio for 5 mg of controlled release felodipine (F-CT) is $5 - 1/10 - 1 = 4/9 = 44\%$ and not 58%. Likewise, the T/P for 10 mg is $5 - 1/11 - 1 = 4/10 = 40\%$.

Table 2 gives an example of a hypothetical drug that does not quite meet the required ratio for twice daily dosing, but is satisfactory for thrice daily dosing. Surveying row three of this table reveals the true peak effect of the drug to occur at 3 h, about the expected time for this hypothetical agent. The 12 h trough is then 4.3 and the peak is 11.5 and the T/P ratio is 4.3/11.5 or 37% (an insufficient residual to permit twice daily dosing). However, at 8 hours, the T/P is 6.4/11.5 or 56%, permitting a three times daily dose.

It seems prudent to use a dose-response study to obtain the required peak and trough data, as FDA suggests. Not obtaining both in a dose-response trial may result in inappropriate dose selection in a subsequent single dose trial where the T/P ratio is obtained.

However, FDA appears to be backing away from strict imposition of the T/P ratio requirements. At an advisory committee meeting held on November 3, 1988, FDA officials agreed with the committee that nicardipine was approvable for hypertension when given three times daily. Notably, the drug produced dramatic peak to trough swings in blood pressure control in a placebo controlled study, with a net trough effect of 6 to 7 mm Hg and a T/P ratio about 40%. Dr. Robert Temple, who has final authority to approve or reject an NDA for a cardiovascular agent, stated that he did not see how FDA could reject nicardipine when the data showed a trough effect on diastolic pressure that appeared as large as several other recently-approved agents, and a peak effect that was larger. His point seemed to be that the agent should not be kept off the market because it was *more* effective at peak. He emphasized the importance of the magnitude of the effect on blood pressure at trough (see below). In a related vein, it was also noted at the meeting that the area under the curve for blood pressure effect *v* time appeared to be relatively large with nicardipine. Also, the effect on systolic blood pressure appeared slightly larger than the effect on diastolic pressure, with less peak to trough variation. Finally, the fact that hypotensive symptoms at peak were not prom-

TABLE 1. TROUGH/PEAK RATIO CALCULATIONS

Study	Drug	Daily Dose	N	BP Reduction (mm Hg) Trough SBP/DBP	Peak	Trough/Peak (%) SBP/DBP
A	Placebo		23	−5/−1	−8/−1	75%/0
	F-CT	5 mg	31	−9/−5	−16/−10	59%/58%
		10 mg	29	−14/−5	−22/−11	62%/44%
		20 mg	14	−12/−9	−22/−16	47%/58%
B	Placebo		49	−8/−4	−11/−7	70%/57%
	F-ER	10 mg	45	−10/−7	−17/−15	56%/44%
		20 mg	38	−14/−8	−23/−18	61%/48%

These trough/peak ratios are incorrectly calculated. Shapiro et al pioneered the presentation of T/P data, and explain the disparity in that they used unrounded blood pressures to calculate T/P while their table showed only rounded values. They feel T/P ratios should be calculated with and without placebo being subtracted (Authors note). From Shapiro et al, with permission.[2]

inent for nicardipine was clearly important in reaching the conclusion that the drug could be approved. However, Dr. Temple did indicate that the labeling for nicardipine might contain a statement regarding the likelihood of peak to trough swings in blood pressure control.

EFFICACY ISSUES

Too Little Effect on Blood Pressure In recent speeches, FDA representatives have stressed that for a few agents, the net effect on trough diastolic blood pressure has been small, in the range of 2-3 mm Hg, although statistical significance over placebo was achieved. FDA has stated that such effects are of little clinical relevance, and that in such cases the drug will not be approved, or at best, will be approved with labeling indicating the magnitude of the effect. Such labeling is probably a great marketing liability. Indeed, oxprenolol, approved in the US with such labeling, has never been marketed here. One way to possibly avoid this consequence is to include an established drug in the same class as a third arm in a placebo controlled study and demonstrate that it has a similar effect as the new agent.

Failure to Establish Long-Term Efficacy The draft guidelines state that the sponsor should demonstrate that a new antihypertensive agent is effective after 12 weeks of therapy. This may be done most directly by performing a 12 week placebo controlled study. However, FDA has stated that it will accept data from a randomized placebo controlled withdrawal from open therapy, or from both arms of an active controlled trial. Another acceptable method is to run a three way study with the new agent, placebo, and an established agent. After 4 weeks, the placebo patients can be dropped or blindly switched to active therapy, which is continued for 12 weeks. If efficacy at 12 weeks is demonstrated in one of these three types of studies, then only one other study, generally of 4 weeks duration, need be conducted to satisfy FDA's basic requirement of two well-controlled studies which demonstrate efficacy.

However, it should be recognized that the 12 week efficacy requirement is new. Like the new requirement of a dose-ranging study in the presence of a diuretic, it is unclear whether this will become a pivotal standard.

OTHER ISSUES

A variety of other errors in performing or analyzing studies can complicate the consideration of a New Drug Application for an antihypertensive agent. These issues include:

Failure to Include Data on Effects on Systolic Blood Pressure FDA has stated that a new antihypertensive drug should have effects in systolic as well as diastolic blood pressure; both should be analyzed and reported. If blood pressure is measured in more than one position

TABLE 2. BLOOD PRESSURE DECREMENTS (mm Hg) AFTER HYPOTHETICAL DRUG

	1 h	2 h	3 h	4 h	6 h	8 h	10 h	12 h
After Placebo	3.7 / 0.8	4.7 / 1.8	3.6 / −0.5	1.2 / 1.1	5.7 / 7.1	−1.0 / 3.7	−2.7 / 2.3	3.8 / 5.5
After Therapeutic Dose	13.8 / 11.7	16.9 / 12.3	19.4 / 11.0	17.0 / 10.6	17.5 / 13	9.4 / 10.1	7.8 / 7.8	5.9 / 9.8
Adjusted Effect on Diastolic BP	10.9	10.5	11.5	9.5	5.9	6.4	5.5	4.3

(as it should be), systolic and diastolic pressure for each position should be analyzed and reported.

Reliance on "Percent Responders" FDA has repeatedly emphasized that blood pressure should be analyzed as a continuous variable. Responder analyses cannot substitute for failure to demonstrate efficacy using a continuous variable analysis.

Failure to Include Data on Postural Hypotension For most new antihypertensive agents, sponsors should include a study of the postural effects of the agent. This study should include data on changes in blood pressure when patients change from the lying to the standing position.

CONCLUSION

We have attempted to describe some of the more common problems that impede the approval of new agents to treat hypertension. When they are finally issued, FDA's antihypertensive guidelines should greatly simplify the drug development process by providing clear information to sponsors regarding what is necessary to obtain the approval of an antihypertensive drug. The widespread availability of this information should further reduce the number of New Drug Applications whose approval is rejected or delayed by FDA, thereby increasing physicians' options in treating this important disorder and improving the health of millions of Americans.

REFERENCES

1. Draft of the Proposed Guidelines for the Clinical Evaluation of Antihypertensive Drugs. Food and Drug Administration, Division of Cardio-Renal Drug Products, 5600 Fishers Lane, HFD-110, Room 16B45, Rockville, Maryland 20857.
2. Shapiro DA, Elmfeldt D, Sjogren E, et al: The trough-to-peak ratio of felodipine, a novel approach to the evaluation of antihypertensive efficacy throughout the dosing interval (abst). Am J Hypertens 1988;1:23A.