Dose response relationships in clinical pharmacology
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DOSE-RESPONSE AND REGISTRATION OF NEW DRUGS

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INTRODUCTION

Careful characterization of the dose-response relationship of a drug would seem to be an essential feature of drug development, yet surprisingly often this characterization has been found incomplete, at times almost totally absent, when an application to market the drug is submitted to the Food and Drug Administration. Early clinical pharmacology studies certainly provide a clue to the correct dose but they have rarely, until recently, been followed up with studies designed to explore dose-response relationships in the clinical setting. Indeed, some clinical trial practices common in the past had the effect of guaranteeing that no dose-response data could be obtained and, for reasons explained below, assuring that the recommended dose would be excessive. FDA began to appreciate this situation in the late 1970's and, through public statements, guidelines, and meetings with sponsors, has succeeded in altering it.

I will first review the history of our interest in this matter and some of the practices that led to the obscuring of dose-response relationships. Next I will show some recent examples of better evaluations and illustrate the potential and real gain to sponsors and users of the agents that have emerged. Finally, I will describe the current regulatory status of dose-response information and consider some current trends and remaining questions.

In the late 1970's we become aware of two publications, one by Tweeddale, et al (1) in 1977, the other by Materson, et al (2) in 1978, that compared several fixed doses (i.e., patients were randomly assigned to a specific dose and then kept on it) of chlorthalidone. Chlorthalidone had been traditionally given at a dose of 100 mg per day and even more, but these studies showed that 50 mg, or even 25 mg, was a fully effective dose, as effective as 100-200 mg, and that 12.5 mg was active. Table 1 shows the results of Materson's comparison of placebo and 12.5, 25, 50, and 75 mg of chlorthalidone. It is apparent that a 3-fold increase in dose from 25 mg gave no further blood pressure response. Tweeddale showed that 200 mg gave no greater response than 50 mg. There were, however, clear dose-related decreases in serum potassium.

TABLE 1

DATA OF MATERSON

Fall in blood pressure (systolic/diastolic) from baseline in erect and supine position with each of four dose levels of chlorthalidone and placebo.

Dose	Fall in Blood Pressure (mmHg) Supine	Standing
Placebo	0/2	0/0
12.5 mg	5/4	6/4
25 mg	11/5	15/7
50 mg	10/6	14/5
75 mg	11/6	14/6

Use of the lowest effective dose of thiazides and related drugs is clinically important. Reports from NIH of the Multiple Risk Factor Intervention Trial (MRFIT) have suggested (3) that high doses (100 mg) of diuretics may be associated with an increased mortality in certain subsets of patients. While this cannot be rigorously proved, even the possibility is

a concern, as the high doses appear to confer no benefit over as little as 25 mg of chlorthalidone or hydrochlorothiazide. Moreover, apart from the MRFIT findings, high doses of diuretics cause other problems, including elevations in uric acid, blood glucose, and cholesterol, the first a rare, but real, cause of clinical gout, the last two undoubted risk factors for coronary artery disease. Hypokalemia is also plainly dose-related. While the importance of hypokalemia in causing arrhythmias can be debated, there is no doubt that, together with bradycardia and a prolonged QT interval, hypokalemia is a risk factor for Torsade de pointes type arrhythmias. Given the prevalence of drugs that can prolong the QT and decrease heart rate, serious adverse consequences of hypokalemia in some patients are inevitable. Finally, the excessive doses of diuretics must, at a minimum, lead to efforts to correct hypokalemia through wide use of potassium supplements or potassium-retaining diuretics. Apart from potential adverse effects of these agents, their cost is very substantial.

Impediments to Good Dose-Finding

Impressed by the chlorthalidone case, and by how excessive the usual dose had been, we began to examine then-current cardiovascular NDAs, most for antihypertensive drugs, for dose-response information. Let me describe, first in general, then more specifically, what we found:

1. Most studies that used more than one dose, including otherwise well-designed randomized, placebo-controlled trials, used some kind of titration scheme, usually titration to some tolerance or effectiveness end-point, that obscured dose-response relationships.

   Many conditions studied in drug trials, such as angina, hypertension, anxiety, and depression, tend to improve spontaneously over time, often markedly. If dose is increased with time it is impossible to distinguish such spontaneous improvement from

improvement due to the increased dose, except by comparison to a concurrent placebo control. In a study where dose is fixed, the treatment and control group can be compared over time; the difference between them, whatever the size of the spontaneous change from baseline in the placebo group constitutes a valid measure of drug effect. If the dose is allowed to change, however, the comparison may become complicated. In theory, if titration occurred at specified intervals and was not dependent on response, and the entire treated group had the dose changed at the same time, and enough time was allowed between dosage changes for the full effect of the drug to be exerted, the drug-placebo difference could be compared for each dose level and a dose-response relationship derived, even in the face of a changing placebo value. Usually, however, studies are not designed that way. Instead, titration is discretionary, with titration occurring only in patients who do not respond adequately to the lower dose, so that titration does not take place in every patient, or does not occur at the same time in every patient. The patient subgroups that receive any given dose thus become non-comparable to the placebo group and to each other, and dose-response relationships are obscured. In fact, a common result is that the patients on larger doses are found to have smaller effects than patients on low doses. This occurs when the lowest dose in the study is an active dose and the dose-response curve is relatively flat. Then patients who respond especially well to the drug receive only the lowest dose, while the more resistant patients, who may not respond well to any dose, receive the highest doses.

The situation is much worse if there is no control group or if there is an active control, as there is then no placebo group to show whether there has been a

spontaneous change over time. Such spontaneous changes, which are often large compared to the drug effect, will be indistinguishable from an increased response to the increased dose.

2. The flawed study designs lead not only to an inaccurate impression of dose response but to a consistent tendency to overestimate the needed dose when the condition studied tends to improve spontaneously.

   As noted, in titration trials, especially active control or uncontrolled trials, spontaneous improvement over time, which is common for many kinds of drug studies, cannot be distinguished from an increased effect due to increased dose. But if this uncertainty is not appreciated, and it usually is not, and if an increased response to dose is anticipated, which it usually is, the changes seen over time will be attributed to the increased dose.

   Selective recall may also contribute to the impression that larger doses yield greater effects. Even a few patients who seem to respond favorably to a higher dose where a lower one failed are likely to be recalled and interpreted as showing that at least some patients benefit from higher doses. Patients who do worse on the higher dose are forgotten, or are merely recognized as showing the expected spontaneous variability of measurement. Doses are almost never back-titrated unless toxicity is seen.

3. There are strong reasons for preferring the titration type of study.

   While titration studies as usually conducted are poor designs for assessing dose-response, they have some very attractive characteristics. Large scale clinical

trials are time-consuming and costly, and there is a powerful desire to initiate them rapidly and in a "fail safe" manner. Because the optimum dose is generally unknown, because titration to a defined endpoint seems a reasonable way to give a drug its best chance at being effective, (i.e., whatever you do, don't use too little), and because titration is a usual means of dose-selection in clinical practice and seems a very safe way to proceed, a titration procedure appears to be a very desirable method.

Some specific examples will illustrate these general conclusions:

1. Nadolol

Nadolol is a long half-life non-selective beta-blocker approved in 1979 for treatment of hypertension and angina. The recommended starting dose was 40 mg once daily with increases up to 240 mg in angina and 320 mg in hypertension. The design of all placebo-controlled studies in angina or hypertension was to initiate treatment at 80 mg per day, then titrate, by the end of the first week, to 240 or 320 unless the drug was poorly tolerated. Everyone thus was expected to get the highest dose and no attempt was made to find the lowest dose that might be effective. The basis for initial dosing was the impression in short-term studies that nadolol was less potent than propranolol.

In the clinical studies it became apparent that even the lowest doses used (80 mg) had a sustained effect and in other studies even 40 mg seemed to be active. The recommended initial dose was therefore 40 mg. In retrospect, this was still not low enough, as it has been reported that the ED 50 for nadolol is actually 0.3 mg (4), so that even the reduced starting dose was more than an order of magnitude too high. We do not know exactly what the fully effective dose of nadolol

is, but it is almost surely not more than 3 mg, making the top recommended dose about two orders of magnitude too high. In part the error here was failure to appreciate that whatever the potency relation in acute studies of nadolol and propranolol, the roughly 10 times greater half-life of nadolol would lead to a much smaller needed daily dose. Despite the large dosing error, it must be acknowledged that use of excessive doses of non-selective beta-blockers like nadolol seems to have little consequence. Once the beta-receptor is blocked more or less fully, larger doses do little more. Note, though, that this would not be the case for a cardioselective agent, where a difference in receptor responsiveness is critical to the drug's effect. If the drug is cardioselective by a factor of 10, for example (pulmonary receptors require 10 times the dose to be blocked), use of a ten-fold excess of the dose needed to block cardiac receptors would block pulmonary receptors as well, obliterating the benefits of cardioselectivity. Dose-selection could also be important for drugs with intrinsic sympathomimetic activity.

2. Captopril

Captopril was the exciting first member of a new kind of anti-hypertensive agent, the ACE (Angiotensin-Converting Enzyme) inhibitors. It was in many respects very carefully evaluated but was not, until quite late, fully evaluated with respect to dose-response. Captopril was most commonly used in clinical trials at doses of 150 mg or even 200 mg t.i.d. There seemed to be little toxicity from these doses and it was thought that some patients needed such doses for control. This impression was based on positive control studies and open studies, as described above, and was, in retrospect, clearly wrong. Doses of 75-150 mg per day of captopril, often even less, give the full effect of the drug.

There was, in fact, evidence of this in one trial, a parallel, placebo-controlled study that used the kind of titration-to-an-endpoint design described earlier. In this case the titration was complete enough at each week (i.e., most patients were titrated to the next step at the same time) to give a series of placebo comparisons involving essentially the whole population. The results (Table 2) clearly show that the captopril-placebo difference in diastolic pressure did not change materially between 150 mg and 450 mg.

TABLE 2

PLACEBO-CONTROLLED STUDY OF CAPTOPRIL IN MILD TO MODERATE HYPERTENSION

Group mean diastolic pressure at baseline and at weeks one through four, the captopril-placebo difference in change from baseline; the captopril dose at each week.

	Week				
	0	1	2	3	4
Captopril DBP (mmHg) 110	100	99	96	94	
Placebo DBP (mmHg)	110	104	104	103	101
C-P difference (mmHg)	4	5	7	6	
Titrated t.i.d. dose (mg)	0	25	50	100 (70%*)	150 (50%*)

*Not all patients reached the 100 or 150 mg dose. Figures in parentheses show the percent of patients at the 100 mg and 150 mg doses.

By the time the drug was marketed, the effectiveness of the 75-150 mg daily dose was recognized, but this was only after thousands of patients had been studied

at higher doses. It is possible that the severe hematologic toxicity of the drug found in these trials, which limited its initial use to very resistant hypertensives, resulted from use of these needlessly large doses, especially in patients with renal impairment, whose blood levels are substantially increased compared to patients with normal renal function.

3. Guanabenz

Guanabenz is a central alpha-agonist approved in 1982 for treatment of hypertension. In virtually every study the initial dose was 8 mg twice daily and patients were then titrated, if the desired response was not seen, to 16 or 32 mg twice daily. While effectiveness compared to placebo was shown, the adverse reaction profile compared to other agents was highly unfavorable and the somnolence and dry mouth typically seen with this class of drugs led to a high drop-out rate. Late in development, this situation was improved merely by starting with a 4 mg twice daily dose, and this starting dose led to an acceptable rate of side effects. A proper assessment of dose-response has never been carried out, however, and the rates of adverse reactions cited in labeling would not seem to encourage use of the drug: 28% dry mouth, 39% drowsiness or sedation, 17% dizziness, and 10% weakness, all much greater than the placebo rates. This example is of particular interest because of its contrast with guanfacine, a pharmacologically similar drug whose evaluation will be described below.

Studies That Can Assess Dose Response

There are straightforward ways to evaluate dose-response relationships. The simplest conceptually is the parallel group fixed dose study. After preliminary estimates of dose-response (open studies, single dose studies) and perhaps a small

well-controlled study at a relatively high dose to establish a drug's activity with certainty, the presumed correct or optimal dose should be compared with at least one larger and one smaller dose, and to placebo, in a parallel-design study, with patients randomly assigned to each of the treatments. Patients need not be placed on a high dose immediately, but can be brought up to it in steps to satisfy safety concerns. The final dose in each group is fixed, however, and is the dose on which group comparisons are made. If many patients do not tolerate the larger dose, that is a good reason for concluding that the initially selected dose cannot be exceeded. How large a dose range to study is a matter of judgment, but it should be noted that many of these studies fail to show a dose response, probably because the lowest dose selected was too large.

There are now many examples of such trials, especially in the cardiovascular area, where we have been asking for them since the late 1970's, and more recently in other areas. Not all such trials are fully successful in defining dose-response, usually because the lowest dose studied is still too large (but even this outcome allows the larger doses to be discarded) or because the size of the effect in the study is so small that distinctions between doses are impossible to detect.

1. Atenolol

Atenolol, a cardioselective beta-blocker approved in 1981, was ahead of its time in being subjected to relatively vigorous attempts to identify the correct dose. As noted earlier, this is quite important for a selective agent. Table 3 shows the extensive range of attempts to compare various doses and regimens. While results are not perfectly consistent, it appeared that 25 mg once daily was not fully effective but that 50 to 200 mg were indistinguishable in most studies. The recommended initial dose, one that would usually have the full effect but give maximum cardioselectivity, was therefore 50 mg, and increases to 100 mg were allowed. The labeling stated strongly that larger doses would yield no greater effect.

TABLE 3

DOSE-RESPONSE STUDIES OF ATENOLOL

Design	Dose	n	Baseline BP (S/D)	BP Decrease at End-Rx (S/D)
1. Double-blind, parallel,	placebo	12	147/96	5/4
placebo-controlled	A 25 mg od	11	144/97	8/8*
Dose response	A 50 mg od	11	154/97	13*/10*
	A 100 mg od	10	146/95	15*/11*
	A 200 mg od	15	154/96	17*/12*
2. Double-blind, x-over,	placebo	21	161/106	1/1
placebo-controlled,	A 50 mg od	21	164/107	20*/14*
Dose-response	A 100 mg od	21	160/105	16*/13*
	A 200 mg od	21	161/104	16*/11*
3. Double-blind, parallel	A 50 mg od	10	154/101	12+/12+
Dose-response	A 100 mg od	10	162/102	17+/14+
	A 200 mg od	10	158/101	16+/14+
4. Double-blind, x-over,	A 50 mg bid	10	173/105	9+/11+
Dose-response	A 100 mg bid	12	184/104	24+/12+
	A 100 mg od	12	178/105	19+/16+
5. Double-blind, x-over,	1 50 mg bid	25	153/98	16+/15+
od vs bid	1 50 mg od	25	153/98	14+/14+

2. Indapamide

The only thiazide-type diuretic developed in recent years, indapamide, was approved in 1983. Almost all of the major studies were parallel fixed dose studies that compared various doses of indapamide from 1.0 to

5 mg (Table 4). It was possible to show clearly that 1 mg had some, but not full activity, while 2.0-2.5 and 5.0 mg were usually indistinguishable and equivalent to 50-100 mg of hydrochlorothiazide. Hypokalemia was greater at the higher indapamide doses.

TABLE 4

PARALLEL DOSE-RESPONSE STUDIES OF INDAPAMIDE

	Dose (mg)	n	Baseline BP (S/D)	BP Decrease at End-Rx (S/D) Standing	Supine
1. Dose-response	placebo	17	146/102	3/3	1/1
	1.0	14	143/103	7/5	6/6
	1.5	13	141/101	5/4	5/3
	2.0	15	150/102	21/9*	18/7
	2.5	14	151/104	20/9	17/7
2. Dose-response	placebo	19	153/103	1/2	1/2
	1.0	21	155/104	12/5	10/5
	2.5	21	148/102	14/7	15/6
	5.0	20	153/102	14/6	13/6
3. Dose-response	placebo	8	163/103	+6/3	+0/6
	1.0	9	174/106	10/4	10/8
	2.5	9	164/104	29/12	22/6
	5.0	8	171/105	37/15	28/15
4. Dose-response vs HCTZ	2.0	30	141/101	12/8	11/7
	2.5	25	147/103	12/7	11/7
	HCTZ 100	28	150/101	12/8	11/6
5. Long-Term (40wk)	2.5	62	148/100	13/8	12/9
	5.0	71	145/101	14/10	13/9
	HCTZ 50	54	145/101	12/10	11/9

*Underlined values significantly different from placebo

3. Penbutolol

Penbutolol is a non-selective, long-acting beta-blocker approved in 1987. In most of the clinical studies dose was simply titrated from 40-80 mg or 40-120 mg. One trial, however, randomized non-responders at 40 mg to either 80 mg or 40 mg and showed no increased response at 80 mg; suggesting that the doses above 40 mg were not of use. To explore lower doses the sponsor carried out a placebo-controlled, parallel, fixed dose, dose-response study comparing 10, 20 and 40 mg. Table 5 shows that the final visit effect of 20 and 40 mg were indistinguishable and were not very different from 10 mg. For patients completing 6 weeks of treatment, the 3 doses gave almost identical responses. There were interesting time effects, however, as shown in figure 1. The 10 mg dose was not distinguishable from the 20 and 40 mg doses at 6 weeks of treatment but was clearly less effective at 2 weeks. The 20 mg dose was equivalent to 40 mg at all times and became the recommended dose. Figure 2 shows the same results as dose-response curves over time. It is worth noting that even a stepped forced titration study, i.e., with all patients moved to the next dose at intervals, would have given misleading results in this case if the steps were not at 4 week or greater intervals, a difficult design to carry out. If the time course of the drug's effect is not well established, the parallel design is probably safer.

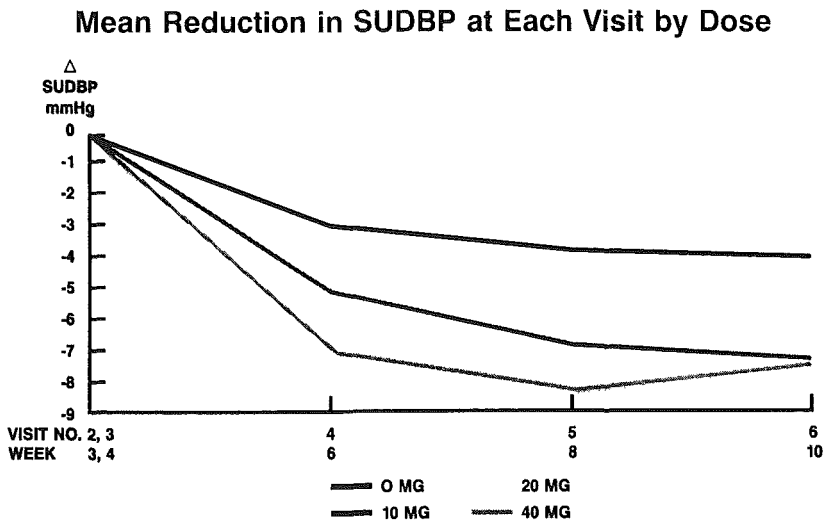

Figure 1 Blood pressure (supine diastolic) response to penbutolol.

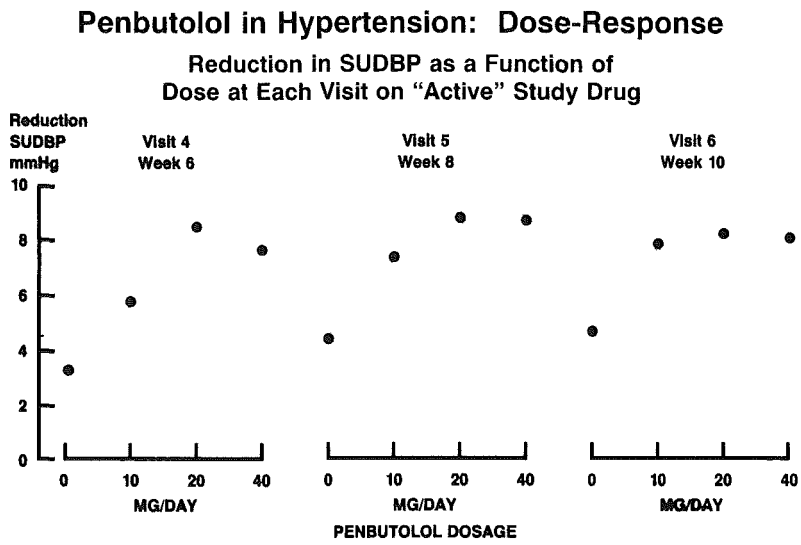

Figure 2 Dose-response curves for penbutolol over time.

TABLE 5

PENBUTOLOL DOSE-RESPONSE

Differences from placebo in systolic and diastolic pressure at final visit for the 10, 20, and 40 mg dose groups.

	Difference in BP, Placebo-penbutolol (mmHg)		
	10 mg	20 mg	40 mg
Standing	6.6/3.5	8.0/5.3	7.1/4.8
Supine	2.4/2.9	6.5/3.7	4.5/3.4

4. Fluoxetine - a non-cardiovascular example

Fluoxetine is a non-tricyclic antidepressant approved in 1987. It was the first psychotropic drug I can recall for which there was a study in the application randomizing patients to more than one dose. In the past, if different fixed doses were studied at all, they were studied in separate trials, a virtually useless approach, given the trial-to-trial variability to antidepressant studies. The very delayed response to antidepressants makes it seems particularly apparent that a titration design using clinical endpoints to guide titration cannot give useful dose-response data. In early studies of fluoxetine patients were titrated up to 60 mg by one week, then kept at 40-80 mg, according to how the drug was tolerated. The usual dose was 80 mg. The sponsor, however, was quite properly not satisfied with available dosing information and carried out a placebo-controlled comparison of 20, 40, and 60 mg in a total of 365 patients.

Drop-out rates were high, especially in the high-dose group, probably because the full assigned dose was given on day one, without a slower step-up as had been used earlier, and the study did not give an entirely definitive answer on dose-response. It did, however, show unequivocally that the 20 mg daily dose was effective and that 40 mg gave no suggestion of being better. Further evidence from trials at still lower doses appears to show that they are effective.

Anti-depressants, as a class, have not been well-tolerated, and fluoxetine has a high rate of side effects, some of which are not acceptable to some patients. It seems very likely that the reduction of the starting and usual dose by 75% will make the drug better tolerated and ultimately more useful.

5. Guanfacine

Guanfacine is a long half-life central alpha agonist drug approved in 1986, with pharmacologic properties generally similar to clonidine and guanabenz. While not every parallel dose-response study gives the hoped for result, the dose-response study of guanfacine carried out by A. H. Robins was surely a gratifying experience for the sponsor and for the FDA staff who conferred with the sponsor about its design. The results described below make a striking contrast with those of guanabenz, a drug developed more than 4 years earlier.

Guanfacine had been marketed in Europe, generally at a dose of 3 mg per day. Robins designed a study to explore doses of 3 mg per day and below.

The dose-response study was straightforward in design (Figure 3). Following a 5-week single blind placebo period, 361 patients with a sitting diastolic pressure of at least 95 mmHg despite a daily diuretic were randomized to placebo or to single daily doses of 0.5, 1, 2, 3 mg of active drug. The doses above 0.5 mg were reached in steps by titrating upward at 2 week intervals. The total treatment period with active drug was 12 weeks, with at least 6 weeks at the final dose.

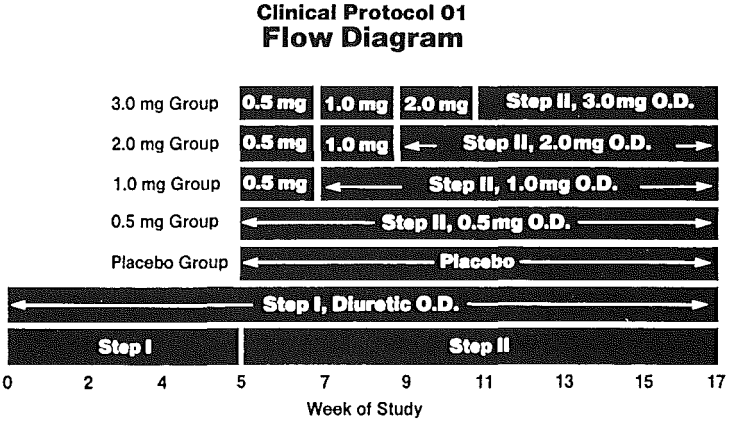

Figure 3 Guanfacine Trial: treatment flow diagram. All patients received diuretic for a 5 week single-blind placebo period (Step 1), then were randomized (Step II) into one of the five treatment groups while continuing to receive the diuretic.

The effects at the end of treatment are shown in Figure 4. There was a good-sized placebo response of about 5-7 mmHg for systolic, diastolic, and mean sitting pressures, and the 0.5 mg dose showed a response similar to placebo. The 1 mg, 2 mg, and 3 mg treatment groups, however, showed an additional change of about 8-10/6-7 mmHg with no real suggestion of an increasing response to doses greater than 1 mg. Standing values showed a similar result (Figure 5), with some evidence of an increase in effect, especially systolic, at the highest dose.

Endpoint Means by Treatment Group

Response Criteria	Statistic	Treatment Group				
		Placebo	0.5	1.0	2.0	3.0
	N	63	63	64	58	59
Diastolic Blood Pressure	Mean Change	−7.1	−5.6	−12.7	−13.3	−13.1
Systolic Blood Pressure	Mean Change	−4.7	−4.7	−14.0	−11.6	−15.6
Mean Arterial Pressure	Mean Change	−6.3	−5.3	−13.1	−12.8	−13.9
Heart Rate	Mean Change	+1.2	+2.1	−4.4	−4.7	−4.5

Figure 4 Guanfacine trial: changes from baseline in sitting diastolic, systolic, and mean blood pressure, and heart rate at 12 weeks.

Endpoint Means by Treatment Group

Response Criteria	Statistic	Treatment Group				
		Placebo	0.5	1.0	2.0	3.0
	N	63	63	64	58	59
Diastolic Blood Pressure	Mean Change	−5.5	−3.7	−8.9	−10.0	−11.7
Systolic Blood Pressure	Mean Change	−3.3	−4.9	−10.7	−9.5	−15.0
Mean Arterial Pressure	Mean Change	−4.8	−4.1	−9.5	−9.8	−12.8
Heart Rate	Mean Change	+2.1	+1.3	−3.9	−4.6	−3.7

Figure 5 Guanfacine trial: changes from baseline in standing diastolic, systolic, and mean blood pressure, and heart rate at 12 weeks.

The time course of diastolic pressure response is shown in Figure 6. For each group given 1 mg or more the full response was reached by week 4, reflecting 2 weeks on 1 mg of drug per day.

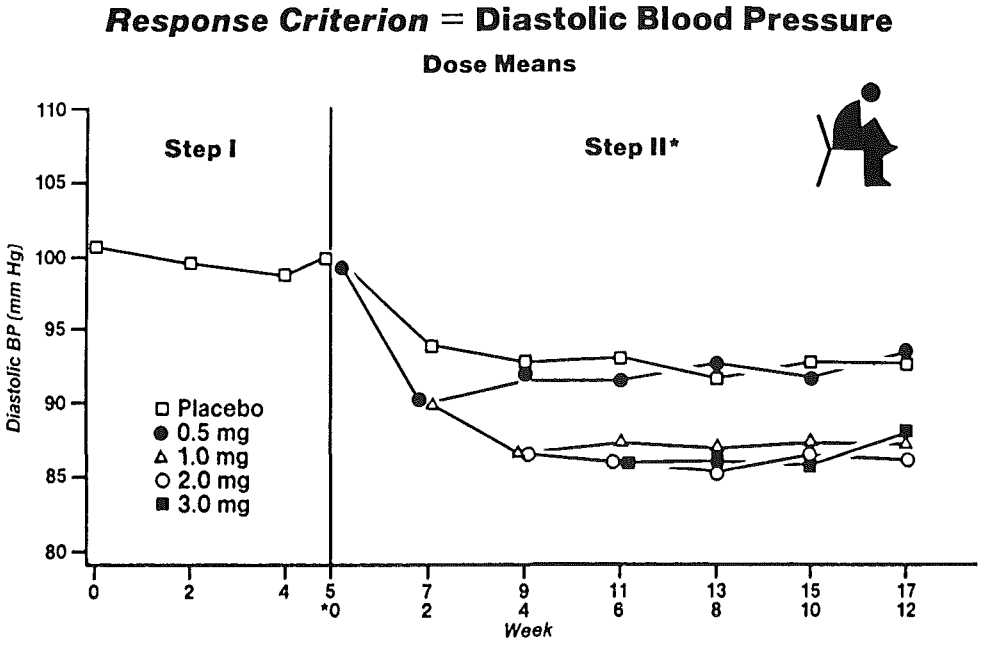

Figure 6 Guanfacine trial: diastolic pressure in all dosage groups in relation to time.

Side effects, unlike the blood pressure effect, showed a marked increase with increased dose (Figure 7). The major side effects of this drug class, dry mouth, somnolence and aesthenia, were no more common in the 1 mg dosage group than in the placebo group. The 2 and 3 mg groups, in contrast, had a higher frequency of each effect, much higher in the case of the 3 mg group, and perhaps more impotence as well. These effects influenced patient participation in the trial. During active treatment there were a total of 43 patients (of the 361 who started guanfacine or randomized placebo therapy) who did not complete the trial because of adverse effects: 6, 7, 4, 12, and 14 in the placebo, 0.5 mg, 1 mg, 2 mg, and 3 mg groups, respectively.

Frequency Distribution of Patients with Most Common Adverse Experiences (Possibly or Probably Related Only)

Adverse Experience	Assigned Treatment Group				
	Placebo	0.5mg	1.0mg	2.0mg	3.0mg
N =	73	72	72	72	72
Dry Mouth	5	4	6	8	20
Somnolence	1	3	0	1	10
Asthenia	1	3	2	6	8
Dizziness	2	1	3	6	3
Headache	3	4	4	1	2
Impotence	1	1	0	2	3

Figure 7 Guanfacine trial: frequency of specific adverse experiences in relation to dose.

The dose-response study provided data that seem of considerable medical and commercial significance. Central alpha-agonists have had their use limited by frequent and severe side effects. The guanfacine study seems to show that a nearly complete separation of the blood pressure and side effect dose response curves can be obtained.

Current Status of Dose Response Information; Trends and Questions

Current regulations [21 CFR 314.50(d)(5)(v)] call for an Integrated Summary of effectiveness including "evidence . . . to support the dosage and administration section of the labeling." The recently published Guideline for the Format and Content of the Clinical and Statistical Section of New Drug Applications explains in more detail the kind of information wanted. Increased awareness of the dose-response question has led in recent years to great improvements in the quality of dose-response information submitted in many new drug applications, but major changes do not occur overnight and the best intentions do not always yield complete success. Applications are generally not denied approval if studies were

planned in good faith, show acceptable toxicity at the doses used and give some reasonable idea of the dose range that is appropriate. Post-marketing studies to refine dosing instructions are requested fairly frequently.

The future, however, should bring much more early attention to dose-response relationships, as new agents are developed initially with this in mind and as older agents are studied after marketing. Further, much more attention needs to be paid to blood level-response relationships, especially for drugs with variable metabolism or absorption and narrow toxic/therapeutic ratios. With such data, it may become easier to learn to adjust doses more precisely in special populations, such as the elderly or patients with renal disease, than it is now using relatively crude clinical measurements.

The parallel dose-response study, which I have emphasized here, and which is clearly useful, can be a very substantial undertaking, and is not the only possible way to obtain dose-response information. It has, apart from its size, one important limitation, namely, it provides only group information, and a group dose-response curve. While this can describe definitively the lowest dose worth trying (the dose at which any detectable effect is seen) and the largest dose worth trying (the dose beyond which no further effect is seen) it does not reveal the shape of individual's dose-response curves. Studies in which patients are given more than one dose, i.e., crossover studies, can show individual dose-response curves, so long as it is possible to account for spontaneous change and separate it from the response to increased dose. A way to do this was described earlier, with forced titration of the entire patient group to a series of rising doses while maintaining a parallel placebo group. It is also possible to randomize patients to various doses and to placebo in a classical randomized crossover design. Sheiner and his associates have been exploring the use of dose-escalation designs in which individuals may not receive all doses. Comparisons of these methodologies have been made in a few cases and more will occur.

A difficulty in many dose-response studies is a maximal effect that is too small to allow discrimination between doses with reasonable numbers of patients. One possibility is to carry out dose-response studies in patients identified in advance as responders. A second study, exploring larger doses, could be carried out in non-responders.

It has become apparent that one must look at both peak and trough effects, for both beneficial and adverse effects where these are accessible, to get a true picture of the clinically relevant dose response, especially where the dose interval is long compared to the half life. No doubt a variety of innovative approaches as well as new questions will emerge in the next few years.

We at FDA feel quite good about the changes we are seeing and the world-wide increased attention to dose selection. While in some pharmacologic areas, e.g., analgesics, clinical dose-response studies have long been the norm, for most therapeutic classes the issue lay ignored. For some drugs, such as antihypertensives, overestimates of the dose needed were almost routine and even for relatively toxic drugs, where such overestimates are not so usual, it has been uncommon to have well-defined estimates of the relation of dose to useful and adverse effects.

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Discussion - Dose-response relationships and the registration of new drugs

F. García Alonso

From a regulatory point of view, what are your feelings about the range of doses that can be approved?

R.J. Temple

In general, if one can find a dose at which a few people respond, and if there is any side effect problem, one probably wants to stop there. I think you can argue for betablockers that you don't have to be too compulsive about that because there doesn't seem to be a great deal of dose-related toxicity. So in the atenolol case, for example, one could easily argue that 25 mg should have been a starting dose because at least some people respond to it. We didn't, we thought it was reasonable to use a dose that captured almost everybody. But not 5 times that dose, or 100 times that dose, which was the case with nadolol. That seems imprudent. So, in general, we would like to see the dose that has a reasonable effect in a fair fraction of people, quite judgemental and arguable, be the starting dose.

T.R. Weihrauch

What are your recommendations about measuring peak and trough effects? What about the case of sustained release preparations?

R.J. Temple

To do proper dose finding studies, especially when the half life is short compared to the interval between doses, it is important to look for both peak and trough effects. In some cases, as in hypertension, you can find them easily but when effect is delayed, as in depression, (i.e., it is not measured hour by hour) you can't look for peak and throughs, because response is an all or none phenomenon that follows treatment by. Typically, in an effort to increase the dosing interval, rather large doses are given less often, so you tend to see less dose-response at peak and more at the end, when the drug is starting to disappear. For sustained release products, where the peak is broad and flattened, it doesn't really matter that much.

D.S. Davies

I was interested in your comments on guanfacine. We studied about a dozen of these clonidine-like compounds, and if you go for equi-hypotensive effects, in single or multiple dose studies, you see no difference between any of them in terms of sedation versus hypotensive effect. But what happens during chronic dosing is that is there a tolerance or maybe an acceptance of the sedation, and I think that is slightly different. Undoubtedly, if you come back on the dose and don't go for maximal hypotensive effect, which I think is what happened in the case of guanfacine, then you do reduce the sedation.

R.J. Temple

That seems completely plausible to me, but it is a fact that these drugs have been used very little in the U.S. because of the poor toleance. I suspect it is because people didn't realise there is a dose they could find that would be well tolerated. It seems possible also to me that the long half life of this drug, with the result of lesser peak to trough differences, may give it some advantage. I don't know if you could dose clonidine, with its relatively short half life, in such a way that you do not get side effects at peak and too little effect at trough. What is important, though, is that it seems to me that guanabenz could have been studied the same way, and not have that awful labeling.

L. Lasagna

Is there a tendency in the patient populations in the field of hypertension to include patients that are trivially hypertensive?

R.J. Temple

No, but for some reason the size of the response to therapy seems to be decreasing. As near as we can tell the patients entered are more or less the same as they have always been. Patients put into placebo-controlled trials on the average are not very sick. Doctors don't want to put up anybody with a diastolic pressure above 105 mm into such a trial, so patients tend to be in the 95-105 range, not trivial but certainly not very hypertensive. The average response seems to be falling, even

though the baseline pressure is today about the same. One thought we have had is that dose-response studies might be done in people identified before the study as responders. One could still do another trial of non-responders to see if very large doses would have an effect. But why not look at the people who can show some response to get some idea of what their dose-response curve is? We have been suggesting that for a year or two, but nobody has done it yet.