Dose-response relationships in clinical pharmacology
L Lasagna, S Erill, C A Naranjo, editors

THE DOSE-RESPONSE CURVES IN ESSENTIAL HYPERTENSION

PIERRE LAROCHELLE

Laboratory of Clinical Pharmacology and Cardiovascular Physiology,
IRCM, 110 Pine Avenue West, Montreal, Quebec, CANADA H2W 1R7.

INTRODUCTION

In a previous presentation, Dr. Robert Temple evaluated the relevance of dose-response curves available for most of the currently used antihypertensive drugs. From that presentation, it is very clear that studies of dose-response curves reported prior to 1980, at least in essential hypertension, had some deficiences. As mentioned in this presentation and because of the study designs used, most drugs were not evaluated properly and did not evaluate the effect of time or spontaneous improvement in a disease such as essential hypertension. The study design used at the time overestimated the needed dose and somehow underestimated the adverse effects. The use of a standard titration with a gradual increase in the dose was favoured in that time because it seemed to be a reasonable way to administer a drug.

Considering these flawed designs, various regulatory bodies such as the FDA or its Canadian counterpart, the Health Protection Branch, revised their recommendations and guidelines, and succeeded in obtaining more adequate dose-response studies.

A review of the dose-response curves for most recently marketed antihypertensive drugs, as well as for some of our older drugs such as thiazide and captopril, is included in the previous presentation by Dr. Robert Temple. An attempt will be made in this manuscript to look at some of the points which could further improve the evaluation of dose-response curves for antihypertensive drugs in patients with essential hypertension. These improvements could be obtained from a better definition of the measurement of the blood pressure itself, a better description of the patient and a better clarification of the

objective of the studies.

Measurement of blood pressure

The apparent advantage of drug trials in hypertension is the measurement itself of the blood pressure. Measuring blood pressure is the most common medical act being done today, and the tools to measure blood pressure are easily affordable and usable. However, this measurement coulb be one of the major handicaps of drug trials in hypertension. Objectives of trials have been set at lowering blood pressure to levels lower that 90 mmHg diastolic or to lower the blood pressure by more than 10 mmHg. These measurements are usually obtained in an office setting or in a hospital clinic. Standards have been described on how to measure blood pressure using a cuff and a mercury sphygmomanometer [1], and large epidemiological studies, as well as the large intervention trials, have been based on correlations with these measurements obtained at a fixed time, in a fixed position, and in a precise setting. As it is well known today, intervention trials have been unable to demonstrate a correlation between the lowering of blood pressure and the reduction in coronary mortality. Among the various explanations being given for these lack of correlations, has been the method by which the measurement itself was obtained. It has been assumed that this once-a-day-measurement, since it has given us some correlations with morbidity and mortality will also give us the same usefulness when used in intervention trials. Very well designed double-blind randomized parallel trials were therefore based on this one measurement although it is also well known that blood pressure varies constantly throughout the day and that other measurements may be more accurate than this once-a-day-measurement. These large trials have therefore included because of these once-a-day measurements, a large number of their population which were not hypertensives. Of this 20% of patients which were called "placebo responders", most in fact were probably falsely diagnosed hypertensives rather than placebo responders. There was also a significant population (10%) which was more severely hypertensive than expected. The quality of this method to measure blood pressure could be

interpreted as being deficient.

Although there are no methods which have been tested as thoroughly as the once-a-day blood pressure measurement, more sophisticated methods are now available to more accurately define the level of blood pressure during a 24-hour period. Ambulatory 24-hour monitoring can certainly give a more accurate and precise description of the blood pressure of a patient during a full 24 hours [3]. These ambulatory blood pressure monitoring devices have been found to be more precisely correlated with the degree of left ventricular hypertrophy [4] than either home blood pressure or once-a-day blood pressure. Problems will have evidently to be solved before the measurement can become a routine method of evaluation. For example, there is no definition of what numbers should be used to obtain in a large population these correlations: the peak, the through, average of daily blood pressures, average of the 24-hour blood pressures or average of night blood pressures. On the other hand, these methods can give us a much better evaluation of the effect of drugs over a 24-hour period, including night blood pressures, exclude the patients who are falsely diagnosed hypertensives, as well as the patients described as "white coat hypertensives", and at the same time, evaluate the effect of the various drugs on the blood pressures. Obtaining dose-response curves using averages of blood pressure during the day would or could establish much better dose-response curves and should be looked at more specifically.

Definition of hypertension

The second problem which has arisen in these studies of dose-response curves in hypertension has been the choice of subjects. In most studies evaluating antihypertensive drugs, normal subjects are of minimal use. Normal control subjects can still be included in protocols in some very specific studies such as the evaluation of the degree of beta-blockade using isoproterenol curves to determine beta-blocking potency although this potency does not seem to translate in blood pressure lowering effects. The information obtained is still useful to help choose the doses in phase 2 studies. Similarly, normal subjects

can be used in the studies of ACE inhibition looking at the inhibition of angiotensin I blockade to determine the dose which will block the effect of angiotensin I. Normal volunteers can be used for pharmacokinetic studies although there are very few examples of direct correlations between plasma concentrations of antihypertensive drugs and their effect. There is a number of counter regulatory mechanism in blood pressure homeostasis such as the renin-angiotensin system, catecholamines, prostaglandins, AVP, and potentially other factors such as ANF and endothelin. All these factors will respond to a lowering of blood pressure and will make the correlations between plasma concentrations of these drugs, and their effect on blood pressure difficult to evaluate.

On the other hand, the choice of hypertensive subjects is also an important factor. Hypertensive patients have been dealt with as a group and on the basis of blood pressure alone. There are some attempts made to match subjects for age, sex, race and weight, at least in the larger trials, and there have been attempts to more specifically define and categorize our hypertensive patients according to other humoral factors such as hemodynamic factors, biochemical factors and etiological factors. The general conclusion, in most small studies, will be that drugs give a positive response in a percentage of patients and there are a certain number of non responders. The average dose reported will be the average of the dose in these two groups (responders-non responders) while in fact the non responders should be completely excluded from these studies and doses should be given only for a responder. Non responders will be the patients receiving the highest doses with limited benefit and with most of the adverse effects either biochemical or symptomatic, because of the higher doses needed to obtain these minimal effects. Historically, we have the examples of the diuretics, the beta-blockers as well as of the captopril, all of whom were used at too high doses and are plagued with their complications. Hypertension is not a single entity and has been known from many years to be a multifactorial disease. Dose-response curves should reflect this knowledge

although it would make protocols more difficult to design. A more specific definition of the hypertensives would make dose-response curves more useful and certainly give them a meaning even in relationship to ordinary medical practice. It would be certainly more difficult for the drug industry, as well as the various investigators to obtain this more accurate definition of their population, but when we consider the duration of the therapy, as well as the cost of therapy and the adverse effects, more precise information would be very useful.

Objectives of the trials

Finally, the objective of the dose-response curve has been up to now to lower blood pressure to a certain degree either below 90 mmHg diastolic or more than 10 mmHg from the initial diastolic blood pressure. Sir George Pickering [2] wrote a number of years ago that hypertension was a quantitative disease, not a qualitative disease. By this, it was meant that the cardiovascular complications of essential hypertension are based on the level of the blood pressure itself: the higher blood pressure, the higher the risk of developing one of the cardiovascular complications: cerebrovascular accident, heart failure, ruptured aortic aneurysm and coronary artery disease. Looking at the actuarial data, as well as the epidemiological data, we can also get the impression that the lower the blood pressure, the longer the chance of a survival free of cardiovascular complications. The objective therefore of the treatment of hypertension has been to lower the blood pressure and in most cases, using antihypertensive drugs, to the lowest obtainable and symptom free level of pressure. Dose-response curves in essential hypertension are based in this assumption. Blood pressure should be measured appropriately and this number should be reduced accordingly in all patients with essential hypertension. We realize now that this may be a very near sighted objective since the objective of antihypertensive therapy is in fact to reduce morbidity and mortality not to lower only pressure considering that hypertension is a cardiovascular risk factor among other risk factors such as cholesterol levels, lipid profile,

cigarette smoking, a presence of left ventricular hypertrophy, glucose intolerance, obesity, exercise, etc. It is also now common knowledge that some of our drugs have an effect on some risk factors such as the lipid profile, glucose levels, uric acid level, and there is a potential interaction between some of our drugs and smoking (beta-blockers and cigarettes). On the other hand, we do not know the effect as using the more recent drugs such as the ACE inhibitors and the calcium antagonist on long term mortality and morbidity in various populations either the young or the old hypertensives. The informations we obtain now from the dose-response curves are on blood pressure (mmHg), while the informations we would like to obtain should be on morbidity and mortality. These trials are long and costly, but there are still the objective of reducing blood pressure since hypertension is a chronic disease and not a short term disease. The statement by Sir George Pickering on blood pressure being a quantitative disease certainly can be challenged. In fact, hypertension becomes a qualitative disease depending on the associated risk factors to this disease. The risk associated with a diastolic pressure of 105 mmHg is not the same in a 55 years old male, smoker and hyperlipidemic than it is in a young white woman (age: 40) whose a non smoker with a low cholesterol, has normal electrocardiogram and no family history of hypertension. In these particular situations, hypertension becomes a qualitative disease where aggressiveness of treatment is based, not only on the level of the blood pressure, but also on the associated risk factors. The dose-response curves which we obtain should reflect these various differences, and qualitative studies should be done involving not only hypertensive patients as a group, but high risk of patients, as well as low risk patients. The objective of antihypertensive therapy being to reduce morbidity and mortality, the long term trials of possibly various doses could be started prior to the marketing of the drug and continued into the marketing phase. Responders and non responders should not be included in the same protocols since they are not identical patients even etiologically.

In summary, the protocol involving dose-response curves in patients with essential hypertension has improved markedly over the last decade. Although there has been a significant improvement, further improvements could be obtained from a more adequate definition of the measurement of blood pressure, the type of patients to be used and the goal of the dose-response curve in these trials.

REFERENCES

1. Perloff D, Sokolow M, Cowan R (1983) The prognostic value of ambulatory blood pressure. JAMA 249: 2792-2798

2. Pickering G (1961) The nature of essential hypertension, Grune and Stratton Inc., New York, pp 1-151

3. Devereux RB, Pickering TG, Alderman MH, Chien S, Borer JS, Laragh JH (1987) Hypertension 9 (Suppl II): 11-53-11-60

4. Kirkendall WM, Feinleib M, Freis Ed, Mark AL. Recommendations for human blood pressure determination by sphygmomanometers: Subcommittee of the AHA Postgraduate Education Committee. American Heart Association No. 70-019-B, 1980-1981

Discussion - Dose-response curves in cardiovascular pharmacology

L. Lasagna

We obviously know from these all day long and all night long monitors that funny things happen to blood pressure during the day. Do we have any ideas as to whether wild swings are more or less important than sustained high blood pressure during much of the day, with regard to stroke, heart attack, heart failure and so forth? And secondly, in constructing dose-response curves for any anti-hypertensive, how different would the curve look if one used just once a day blood pressure, as opposed to some other end point -however you defined it- on a 24 hour basis?

P. Larochelle

We do not know what these swings mean, and it is awfully difficult to agree on what values are worth considering. It may be that averages, or peaks or low levels or a certain number of measurements per day are particularly important with regard to mortality or morbidity, but we have to wait for the results of studies now under way to have sensible answers. We do not have dose-response curves for antihypertensives using this kind of technology but it is time to start working on them. Continous monitoring of blood pressure may exclude from the studies many subjects who are not truly hypertensive and may provide different response profiles for different categories of durgs. For instance, it may well be that peaks of high blood pressure during the day are better reduced by beta-blockers than by ACE inhibitors or diuretics.

M. Orme

Can I slightly disagree with the suggestion that measuring blood pressure on a 24 hour basis, particularly with the machines that are coming in, will necessarily give us better data. We won't get rid of the white-coat responders. There are studies with these machines that show that people will actually respond to having their blood pressure taken whether it be done automatically or done by themselves. The other thing is that some of these machines actually may give the wrong result.

P. Larochelle

I agree entirely. These machines are not perfect and we will still be left with some of these high reactors, but maybe these are the patients that should be treated. My point is that getting this data throughout the day will give us much more information that the customary once a day measurement of blood pressure and that this may be relevant from a therapeutic point of view.

R.J. Temple

It seems to me before the 24 hour measurement and things like that will become useful, we need a whole new set of epidemiologic data. All we really know is based on, as you said, single measurements, and all we really know about improving survival and decreasing morbidity is that it can be done with drugs that are extremely long acting. Because of that, we generally take the position that we want to be sure that any drug that is approved for hypertension has a long acting effect, i.e. that it acts throughout the dosing interval. It seems very treacherous to move on to a new set of standards and leave behind the only information we really have, which is that long acting drugs lowering casual measurement of blood pressure to values near 120 over 80 are what seems to be beneficial. It's hard to take the next steps, because it requires huge studies to do this.

P. Larochelle

I agree, but we shall be aware that the notion entertained by some that the lower the blood pressure the better off we are is probably not true. I mean there is some data showing that in general population when you reduce diastolic blood pressure below 85 the mortality curve starts increasing again.