Clinical Evaluation of Antihypertensive Drugs

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The evaluation of antihypertensive drugs has become a big business. Hundreds of people who work in some aspect of clinical investigation spend at least part of their time in this process. Their observations determine the expenditure, first by the drug companies and then by the public, of some millions of dollars a year. Even the law recognizes the fact that no accumulation of pharmacology, however sound, and no amount of promotion can do anything for a drug which has not had a reasonably adequate clinical trial. Everyone acknowledges that it is the crucial aspect determining drug sale. But so far no one has paid much attention to the definition of the term, "adequate" or the characterization of the proper means of study of an antihypertensive drug.

This is partly because it is a new field of effort. Less than 10 years ago we used to plead with manufacturers to turn their attention to the field of antihypertensive medication. But, in a world in which the industrial emphasis was on antibacterials and vitamins, and with the medical profession apparently satisfied with garlic and phenobarbital, we got very little response. At long last, the commercial possibilities of a chronic and very common disease have been abundantly recognized and the dam has broken. The ensuing flood of drugs has taken most investigators by surprise, finding them without real agreement on technics and procedures. As a result, there is a great deal of repetition and of waste effort, and the investigator too often deserts his legitimate field of basic scientific study to spend his time in a process in which he may eventually become enmeshed.

The definition of what is a proper study of an antihypertensive drug or procedure is by no means easy. Those of us who attempt this process look with real envy on our colleagues who deal with the clinical trial of antibacterial drugs. They are concerned, for the most part, with diseases of brief duration and well-defined course and, above all, with such unexceptionable measurements as those of fever and leukocytosis. We, on the other hand, deal with a process usually of long and, very often, of unpredictable duration and with, as one of our basic measurements, arterial pressure, a notoriously labile function. The field is, therefore, very naturally vexed and confused. Claims and counterclaims are continually made. There is even some competition among investigators for the latest drug, some natural tendency to puff it at a scientific meeting. As a result, the literature abounds with unimaginative research and shows occasional lapses into flagrant lauding of the latest product at hand.

Our own studies in the treatment of hypertension have nearly always been concerned with patients who have severe or "malignant" hypertensive disease. There are two reasons for this choice. One is that the procedures we have had available, first anterior nerve-root section, then lumbar sympathectomy and, later, kidney extracts and pyrogens, were admittedly somewhat heroic. Like the Mikado, we wished to let the punishment fit the crime. Next, the problem extends beyond the blood pressure; people die, not of hypertension, but of hypertensive disease. In this selected group of patients we had to deal with hypertensive disease as well as with hypertension, with a
serious indication for treatment, with a reasonably certain prognosis, and with consistently and severely increased blood pressure.

Most such patients are glad enough to enter the hospital, so that this selection has directed us to technics of clinical trial in hospital. We believe that this has been a fortunate, if involuntary, choice; we have no intention of decrying the efforts of those whom circumstances force into clinical study of milder hypertensive disease in offices or out-patient departments. In fact we do this ourselves, since we quite agree that the value of a drug can only be assessed finally in terms of its activity under the normal circumstances of daily life. On the other hand, the concentration on severe hypertensive disease in the hospital has the real advantage of a potentially well-controlled experiment, and one that can yield reasonably accurate information from a small number of patients.

What Blood Pressure?

If we dismiss as premature the speculations that some of the available antihypertensive drugs, with the specific exception of sympatholytic agents in pheochromocytoma, have definable points of attack on the basic mechanisms responsible for hypertension, then the basic rationale of antihypertensive therapy depends on our recognition of the fact that severe and persistent high blood pressure is bad for the vessels. In this light, anything that is reasonably safe and tolerable and that produces by almost any means a persistent decrease of blood pressure is a potentially useful antihypertensive drug. Hence, much as we would like to deal only with the basic problem of hypertensive disease as such, we are forced to depend on measurements of blood pressure. The question is what pressure?

The measurement we would like to have is one that would be representative of the patient's blood pressure as it is most of the time. The basal blood pressure, which is rather tediously secured, probably does not meet this requirement. Certainly the casual "resting" blood pressure does not, even when it is indefinitely multiplied. Casual readings are usually high. A minority of patients show waking, p

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sumably basal pressure readings, consistently higher than their casual, resting pressures as measured in the afternoon. Reliance on uncontrolled, casual readings accounts for most of the vexatious claims in this field.

We have arbitrarily resolved this difficulty by dealing with weekly averages of supine, resting pressures. And, with the advent of drugs that cause orthostatic drops in pressure, we have added averages of standing pressures. Others, using these drugs, have measured sitting pressures and, since most people with severe hypertension sit a good deal of the time, this is probably also a representative datum. Our usual procedure is to average the pressures weekly of the readings made twice daily. The average obliterates most of the peaks and the valleys and provides only a single datum for a week's effort. But our experience indicates that this is a valid and representative datum.

The Control Period

Most of the difficulty with the assessment of drugs depends on the wide variety of opinions on what is a "reasonable" control period. We have reported our own experience elsewhere. Briefly we have found that, in patients with severe or malignant hypertensive disease, the average from the first week in hospital tends to be higher by 8/5 mm. Hg for malignant hypertension and 10/5 mm. Hg for severe essential hypertension than the average of the second week. The averages of the second and third weeks usually correspond closely, although a minority of patients, usually those with milder disease, continue to show some decrease in pressure averages over three or more weeks. These decreases represent adaptation to the ordered hospital routine, protection from the onslights of the world outside, the psychotherapeutic effects of close and sympathetic observation, and to these we often add the effects, if any, of placebo medication.

An extensive analysis of the effects of prolonged hospitalization on means of basal blood pressures of patients with essential hypertension yields data similar to our own, in that the latter weeks of hospitalization usually demonstrate considerable stability of the means, while the mean of the first week's pressures and the
sequence of changes in pressure individually tends to be somewhat variable. Undoubtedly, there is no substitute for prolonged control observations. On the other hand, particularly in patients with demonstrably severe and advancing hypertensive disease, the means of the second and third weeks of pressures form representative indices of pressure level during hospitalization and, as such, adequate baselines for therapeutic study.

There is no doubt that this is a tedious and expensive process. But it has two large advantages. First, it provided us with a blood pressure datum that is truly significant. Secondly, time is made available for detailed clinical study and for the investigation of dubious points in the physical or laboratory examination. As a result, treatment begins only after the patient’s status in terms of hypertensive disease is reasonably characterized.

The Estimate of Hypertensive Disease

This is made in terms of four panels, of which the diastolic blood pressure average is one. The others concern the cerebral and renal circulations and the heart. A large amount of data has accumulated to suggest that it might also be desirable to evaluate other data, such as serum β-globulin.

The estimate of cerebral vascular disease is either presumptive or objective; the presumptive evidence, still very unsatisfactory, is gathered from history of headaches, encephalopathy, mild seizures and, probably best of all, from a pooled estimate by several observers of the status of the fundi and retinal arterioles. The latter is made numerically in terms of constriction, sclerosis, exudate, hemorrhage, and papilledema, and this series of examinations is continued weekly.1

Fortunately, the renal panel, so important in these patients, is much more accessible than the cerebral. This circulation is assessed in terms of approximate filtration rate (from urea clearance) or plasma creatinine, often by measurements of plasma para-aminohippurate (PAH) and mannitol clearances for better definition, by measurements of maximum concentrating power (Addis test) and by quanti-

tative determinations of urine protein and sediment.

Cardiac status is assessed in terms of functional capacity and, objectively, in terms of cardiac enlargement as determined by the telerentgenogram and the electrocardiogram. When, as commonly happens, there is evidence of congestive heart failure, this is appropriately treated and brought to some optimum status before the control period ends.

The results of this study are plotted graphically in a “long chart” that has two large advantages: It permits rapid visualization of the trends of these significant functions during control and treatment periods and it is also a perpetual reminder to the investigator of examinations that may be inadvertently omitted. This chart (fig. 1), derived from one used by Dr. D. D. Van Slyke in his study of Bright’s disease, has saved untold time in record-searching, and is freely and wholeheartedly recom-

![Fig. 1. A “long chart” showing how the data are graphically ordered. The chart is used along with the clinical notes as a continuous record of the course of the patient’s illness.](http://circ.ahajournals.org/content/3/4/870/F1)

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mended as a tool in any prolonged therapeutic trial.

The results of this study can also be lumped together into a single numerical "severity index,"\(^4\) in which a maximum score of 4 is assigned to each of the four panels.

A maximum of four points each is assigned to estimates of average supine diastolic pressure and of the extent of hypertensive vascular disease in the heart, kidneys and brain. For example, a patient with diastolic pressure averaging more than 140 mm. Hg, grade IV, heart failure, uremia and grade IV retinopathy, plus encephalopathy, would be graded 16; improvement in any category reduces the grade below 16.

Comparisons of pre- and post-treatment severity index in patients with like pretreatment indices is a useful way of summarizing the experience with a drug. We are well aware that the index we suggest is highly subjective in its scoring and that a vast amount of study might well be devoted to the compilation of one more objectively based on the solid datum of mortality in untreated patients. Such patients are now rare. Still, if there could be some agreement on this, or a like system of scoring, there would be less controversy about the value of this or that experimental drug or procedure in any large group of patients. The history of sympathectomy is a case in point and Dr. Smithwick’s scoring is an attempt like ours, at securing comparability in the data.

**Placebos and Blind Tests**

We noted above that placebos are commonly given during the second and third weeks of the "control" period. Theoretically, there might be an advantage in starting the test period as a blind or double-blind experiment. But this procedure has serious disadvantages and is, in fact, impractical. We deal with highly vasoactive drugs. Quite apart from their effects on blood pressure, which most patients soon learn in one way or another, these all have side-effects that are definite and unmistakable. As a result, a blind test loses its point because the patient and the doctor very quickly recognize when a placebo is substituted for an active drug. We still attempt such substitution whenever it seems practical, which is usually when the dosage of active drug has been reduced to a point at which side-effects are not easily discerned. As a routine procedure, however, we doubt its value, and use the placebo during the pretreatment period.

It may seem heresy in some eyes that we believe it advantageous for the investigator to be specifically interested in, and enthusiastic about, the drug he is studying, and that there is a real scientific disadvantage in a dispassionate attitude. Two examples come to mind. One concerns hexamethonium, which was used and studied by Dr. F. H. Smirk with real devotion. As a result, his scrutiny was closer and his therapeutic results were better than ours or those of most other workers. His estimate of the status of this agent was more accurate than the appraisals of those who desultorily gave it to a few people and, troubled by side-effects, more or less sneeringly gave it up. The other concerns hydralazine; this has been widely despised of as a useful medication; on the other hand, because our colleague, Dr. Robert Taylor, and we were fascinated by its properties, we used it in such a way that we have come to regard it as a very useful and often a lifesaving drug. This experience depended largely on our having enough enthusiasm for it to persuade ourselves and our patients that it was to their advantage to accept and control its common, initial, disagreeable side-effects.

**The Out-Patient Study: Home Pressures**

When the time comes for discharge from the hospital, there is no need to give up the experiment. As long as we relied on out-patient casual pressures we had few data from our out-patients that we would regard as convincing. Partly, this is because of the "break-through" of pressures under the emotional stimulus of a critical examination. Patients whose pressure averages at home or in the hospital were reasonably normal, frequently showed high casual resting pressures as out-patients. In fact, some of the best responders to hydralazine would not have been recognized as such had only the casual pressures been available (fig. 2). Rather, they would have been categorized as showing improvement in their hypertensive disease.
FIG. 2. Open bars are means respectively of 4 and 24 casual measurements of pressure; solid bars are weekly means of hospital pressures and cross-hatched bars are weekly means of home pressures. Hydralazine treatment was started on discharge from hospital and showed no effect as judged from casual pressures. Readmission to hospital established, by comparison of hospital means, that pressure had actually decreased, and this was confirmed by the subsequent means of home pressures. (Reproduced, with permission, from the Annals of Internal Medicine.1)

without corresponding changes in pressure, as in the past, were so many sympathectomized patients. From such data as these, the erroneous conclusion has been drawn that, with this or that agent or procedure, hypertension and hypertensive disease are dissociated phenomena. As far as we know this is a very rare occurrence.

With the advent of the ganglion blocking agents, we embarked on a much wider program of home-pressure readings than before. Data have since accumulated to show that, in most patients, the home-pressure averages correspond fairly well to hospital averages and that a lack of such correspondence usually has a clearly definable connotation that bears on the patient’s problem. We have also become impressed with the value of the datum provided by most of these patients as a basis for therapeutic trial and, in many of them, with the personal therapeutic advantage of knowing their blood pressure and knowing that it is under control. We would not recommend this procedure to everyone. Those who use it are a selected group. Only one out of some hundreds has demonstrated what might be interpreted as significant psychologic stress from the procedure; this was a young man who manifested the same psychologic stress to any procedure related to his hypertensive disease, which he was quite unwilling to accept.

The Cocktails

Each of the presently available, antipressor drugs has a limited field of usefulness. Some patients respond to one, some to another and not to the first. The dosage at which a response is obtained varies from person to person and, in the same person, from time to time. As a result, each drug has to be individually adjusted or, to adhere to the current jargon, “titrated.” Many drugs, notably the sympatholytic and ganglion-blocking agents, elicit a state of tolerance more or less rapidly. This is perhaps a good thing. We have a sardonic suspicion that there would be a vast new field of significant illness if most of the ganglion-blocking agents, in the dosages administered, were not almost inert in most of the people who take them.

These considerations weigh heavily against the dispensing of mixtures of hypotensive drugs. They do not bear on the possibility that some patients may gain an advantage from combinations of such agents. Of course they may. But they gain only when the dosage of each can be appropriately selected, which is not the case when these agents are all packaged together in one pill. The use of these mixtures seems to us scientifically and professionally indefensible unless it can be shown that there does exist some very unusual patient who has no problems of tolerance or specific responsiveness.

The Cost

Hospitalization is costly; the investigator’s time and energy are costly; technicians are costly; thus, the whole process of clinical trial is enormously expensive. Probably the greatest expense is the time spent away from fundamental investigation and contemplation of
basic mechanisms, with all its attendant risks of ultimate intellectual sterilization of a potentially productive person. Very little of this cost is defrayed by those who receive the largest financial advantage. Perhaps this is as it should be. It may be that the psychologic boost of being “first” and of reading a paper each year on the merits of some new drug is reward enough. To our minds, this is not enough. Certainly there are many who would look with a jaundiced eye on a clinical trial that was wholly and effectively supported by the interested drug company. But the same critics would not hesitate to accept a report from the same investigator on an animal or chemical study, wholly subsidized and of potential commercial value. There must be some middle way between the present system, which inequitably distributes a large commercial cost on investigators, hospitals and patients, and an equitable method, which would not be open to the suspicion of commercial prejudice. The solution of this problem might well be a specific aspect of the function of the newly created Committee on the Investigation of Antihypertensive Agents, recently formed by the American Medical Association’s Council on Pharmacy.

REFERENCES


Disease in man is never exactly the same as disease in an experimental animal, for in man the disease at once affects and is affected by what we call the emotional life. The physician who attempts to take care of a patient while he neglects this factor is as unscientific as the investigator who neglects to control all the conditions that may affect his experiment. The good physician knows his patients through and through, and his knowledge is bought dearly. Time, sympathy, and understanding must be lavishly dispensed, but the reward is to be found in that personal bond which forms the greatest satisfaction of the practice of medicine. One of the essential qualities of the clinician is interest in humanity, for the secret of the care of the patient is in caring for the patient.—Francis Weld Peabody. The Care of the Patient. Harvard University Press, 1927.
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