Does Pharmacological Profiling of a New Drug in Normotensive Volunteers Provide a Useful Guideline to Antihypertensive Therapy?

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SUMMARY Similar pressor mechanisms should be active in hypertensive and normotensive subjects since hypertension is a quantitative rather than qualitative disorder. Consequently, if an antihypertensive drug is designed to specifically block a well-defined mechanism involved in blood pressure regulation, it should be possible to evaluate its efficacy rather precisely in normotensive volunteers before even administering the compound to a hypertensive patient. That this is indeed the case is illustrated by the example of angiotensin-converting-enzyme inhibitors. The magnitude of blockade that can be obtained in humans, the minimal dose needed for maximal efficacy, and the onset and duration of action of the agents have all been precisely determined in normotensive volunteers. Subsequent administration to hypertensive patients merely confirmed these findings. Moreover, if the antihypertensive effect of converting-enzyme inhibitors could not be predicted in an individual hypertensive patient, this is not related to some unknown action of the drug that cannot be assessed in normal volunteers but rather to our lack of understanding of the precise mixture of pathogenetic mechanisms prevailing in any particular patient. Only the safety evaluation and the search for side-effects still has to be carried out in nonspecific fashion, thus requiring long-term observations in large numbers of patients. If the tolerance of new converting-enzyme inhibitors were more predictable, the number of studies in hypertensive patients could be drastically reduced since the antihypertensive profile of any new converting-enzyme inhibitor can probably be precisely determined in normotensive volunteers. (Hypertension 5 (supp III): III-101-III-107, 1983)

KEY WORDS • hypertension • antihypertensive therapy • angiotensin converting-enzyme inhibition • captopril • anopril

TRADITIONALLY, drugs used to treat various diseases have been developed empirically through vast screening programs. The most spectacular results were often obtained in areas where they were least expected. Mechanisms of action were usually not well understood, and there was also a lack of knowledge of the pathogenetic mechanisms involved in the disease. Except for acute tolerance studies, drug administration in normal volunteers was of limited usefulness for the development of guidelines for the therapeutic use of such compounds. Nevertheless, new drug assay techniques in plasma, urine, and feces made pharmacokinetic studies more widely available. However, considerable discrepancies between such pharmacokinetic observations and therapeutic profiles of some drugs have become apparent.

For instance, with diuretics or propranolol, therapeutic efficacy and plasma drug levels have not always been found to be strictly related.

A progressively better understanding of pathogenetic mechanisms involved in various diseases has markedly influenced the development of new therapeutic agents. Thus, in recent years, new drugs have been more and more based on prospective design, with a very specific mechanistic aim in mind rather than on mass screening. As a result, these agents interfere specifically with well-defined mechanisms. This great specificity probably enhances efficacy and may in addition improve the safety profile by avoiding nonspecific side-effects.

As pointed out many years ago by Sir George Pickering, hypertension is a quantitative rather than a qualitative disorder. The mechanisms involved in the disease, even if all are not yet completely understood, probably also exist in normotensive subjects, albeit in a quantitatively different mixture. Accordingly, if the mechanism of action of an antihypertensive agent is well understood and directed specifically to one factor...
involved in blood pressure regulation, studies of its
effect in normotensive volunteers will provide useful
information to develop guidelines for the treatment of
hypertensive patients.

Agents that inhibit angiotensin-converting enzyme
and thereby the generation of angiotensin II (All) cer-
tainly are representatives of this new generation of drugs
based on perspective design and directed at well-de-
defined mechanisms.3-7 This has become increasingly
clear as it is now more and more evident that their
effect on bradykinin metabolism probably has only a
limited influence on blood pressure regulation.9 These
compounds have the additional and specific advantage
that methods are available not only to measure plasma
levels of the administered drug but also to quantitate
the various components of the pressor system on which
they exert their effect. In the following analysis, we
shall evaluate retrospectively how much information
can be gained from the study of converting-enzyme inhibitors in normotensive volunteers that might be
useful for the subsequent treatment of hypertensive
patients.

Useful Information Obtained from Studies
in Normotensive Volunteers

Blockade of the Renin System

In assessing a new drug designed specifically to
inhibit the renin angiotensin system by blocking the
conversion of angiotensin I (AI) to All, the first task
would seem to be to demonstrate in humans that the
drug produces this effect. Several techniques have
been used to evaluate this action. The most direct but
also most invasive approach is intraarterial pressure
intravenous monitoring during bolus injections of AI
in normotensive volunteers after administration of the
drug. In this way, it was shown for the first time that
teprotide or SQ 20,881 blocks the pressor effect of
exogenous AI in normal humans.9 In later studies, this
was also demonstrated with the first orally active con-
verting-enzyme inhibitor SQ 14,225 or captopril10 (fig.
1) and then with MK 421 or enalapril,11 MK 521,11
RHC 3569,12 and CGS 13945.13

While the administration of exogenous AI and
blockade of its pressor effect may be considered the
absolute test for converting-enzyme inhibition, several
other methods of evaluation have been compared over
the years to this 'gold standard.'14 If less All is gener-
ated following blockade of the conversion, plasma All
levels should fall. Reduction of circulating All levels
has indeed been observed with several converting-enzyme inhibitors in normotensive volunteers.12-14 How-
ever, the quantitation of plasma All is still hampered
by methodological problems such as assay blanks,
cross-reaction of the All antibody with high All lev-
els,13 and possibly also with some All metabolites. As
a consequence, many investigators still regard plasma
All determinations with a certain suspicion. One puz-

Since, in addition to other factors such as potassium,
ACTH, and possibly unidentified mechanisms, All stimulates the secretion of aldosterone from the adren-
al cortex, reduction of All by converting-enzyme inhibi-
tors should result in reduction of plasma aldoste-
one levels. This expected additional effect has actually
been observed following the administration of MK
421,14 MK 521,14 RHC 3459,12 and CGS 13945.13 Of
course, this observation in turn provides more strength
to the changes in plasma All levels measured in the
same volunteers.

Another way of assessing blockade of converting-
enzyme activity is to measure plasma converting-en-
zyme activity in the normal volunteers before and after
administration of a converting enzyme inhibitor. Plas-
ma converting-enzyme activity in normal volunteers
was indeed reduced following administration of the
converting-enzyme inhibitors studied so far.12-14 How-
ever, since it is known that in vivo the bulk of conver-
sion of AI to All does not occur in plasma but rather in
the pulmonary capillary bed10 and possibly in other
organs, it could be argued that plasma converting-
enzyme activity is not necessarily a good indicator of
total angiotensin conversion. That plasma converting-
enzyme activity does indeed reflect very well the total
conversion of AI to All was suggested by findings in
normal volunteers receiving MK 421 or MK 521.11
Figure 2 depicts the relationship between plasma con-

\begin{figure}
\centering
\includegraphics[width=\textwidth]{fig1.png}
\caption{Systolic pressor responses to angiotensin I (AI) before (•) and after (○) 5 or 20 mg of oral captopril in two
normal volunteers. At both doses, captopril markedly attenuated pressor responses to exogenous AI. (From Ferguson et al.,
see ref 10.)}
\end{figure}
FIGURE 2. Relationship between plasma converting-enzyme activity and systolic blood pressure response to angiotensin I before and after oral administration of the converting enzyme inhibitors MK 421 (enalapril), MK 422, or MK 521. (Results are adapted from Biollaz et al., see ref. 11.)

VERTING-ENZYME ACTIVITY AND THE SYSTOLIC BLOOD PRESSURE RESPONSE TO ANGIOTENSIN I BEFORE AND AFTER ORAL ADMINISTRATION OF THE CONVERTING ENZYMIE INHIBITOR MK 421 (ENALAPRIL), MK 422, OR MK 521. (RESULTS ARE ADAPTED FROM BIOLLAZ ET AL., SEE REF. 11.)

CONVERTING-ENZYME ACTIVITY AND THE SYSTOLIC BLOOD PRESSURE RESPONSE TO EXOGENOUS AI BEFORE AND AFTER ADMINISTRATION OF THESE CONVERTING-ENZYME INHIBITORS TO NORMAL VOLUNTEERS. IT CAN BE SEEN THAT THE PLASMA CONVERTING-ENZYME INHIBITOR ACTIVITY CLOSELY CORRELATES WITH THE SYSTOLIC BP RESPONSE TO AI, WHICH MUST BE AN INDEX OF TOTAL CONVERSION OF AI TO AI1.

THERE IS ONLY ONE PRECAUTION THAT MUST BE OBSERVED WITH THE MEASUREMENT OF PLASMA CONVERTING-ENZYME ACTIVITY FOLLOWING ADMINISTRATION OF CONVERTING ENZYME INHIBITORS: WITH CAPTOPRIL17 AND RHC 3569,12 DETERMINATIONS OF CONVERTING ENZYME-ACTIVITY WERE NOT REPRODUCIBLE AFTER STORAGE OF THE PLASMA SAMPLES, SUGGESTING THAT SOME DISSOCIATION OF THE CONVERTING ENZYME FROM THE ANTAGONIST OCCURS DURING STORAGE. ACCORDINGLY, WHEN USING THESE DRUGS, SAMPLES MUST BE PROCESSED IMMEDIATELY. THIS PROBLEM DOES NOT EXIST WITH MK 421 (ENALAPRIL), MK 521, AND CGS 13945.

THUS, THERE EXIST SEVERAL METHODS TO ASSESS BLOCKADE OF CONVERTING-ENZYME INHIBITION IN NORMAL VOLUNTEERS. THE MOST DIRECT METHOD IS BLOCKADE OF THE PRESSOR EFFECT OF EXOGENOUS AI. SINCE THE ALTERNATE METHODS ARE WELL ESTABLISHED, ONE MIGHT EVEN ARGUE THAT THIS INVASIVE METHOD WILL NOT BE NECESSARY IN THE DEVELOPMENT OF ANY FUTURE CONVERTING-ENZYME INHIBITORS. ONCE CONVERTING-ENZYME INHIBITION BY A CERTAIN AGENT IS ESTABLISHED IN NORMAL VOLUNTEERS, THIS POINT NEED NOT BE STUDIED ANY FURTHER IN HYPERTENSIVE PATIENTS.

DOSE

THE MINIMAL DOSE OF THE CONVERTING-ENZYME INHIBITOR NEEDED TO OBTAIN NEARLY COMPLETE BLOCKADE OF THE SYSTEM IS ALSO EASILY ESTABLISHED BY ADMINISTERING EXOGENOUS AI TO NORMAL VOLUNTEERS. IN THE CASE OF CAPTOPRIL, OUR INITIAL STUDY10 CARRIED OUT IN 1976 IN 14 NORMAL VOLUNTEERS CLEARLY ESTABLISHED THAT 20 MG OF ORAL CAPTOPRIL WERE SUFFICIENT TO ALMOST COMPLETELY PREVENT 320 NG/KG OF AI FROM EXERTING ANY MAJOR PRESSOR EFFECT. SINCE CONVERTING-ENZYME INHIBITORS ARE DESIGNED AS COMPETITIVE ANTAGONISTS, THE DOSE NECESSARY TO OBTAIN Consistent blockade of the system should depend on the circulating AI levels, at least in theory. ONE COULD THEREFORE ARGUE THAT THE DOSE ESTABLISHED IN NORMAL VOLUNTEERS MAY NOT BE RELEVANT TO HYPERTENSIVE PATIENTS WHO MAY EXHIBIT EXTREMELY HIGH AI LEVELS. HOWEVER, THE AMOUNT OF AI ADMINISTERED ACUTELY TO THE NORMAL VOLUNTEERS IS PROBABLY SUCH THAT COMPARABLE PLASMA LEVELS ARE RARELY IF EVER REACHED IN HYPERTENSIVE PATIENTS. IT IS MORE LIKELY THAT THE MINIMAL DOSE DETERMINED TO BE NECESSARY TO BLOCK THE PRESSOR EFFECT OF EXOGENOUS AI IN NORMAL VOLUNTEERS IF ANYTHING IS OVERESTIMATED RATHER THAN UNDERESTIMATED. IN THE CASE OF CAPTOPRIL, THIS WAS SUGGESTED BY OUR INITIAL STUDIES18 IN HYPERTENSIVE PATIENTS WHEN WE FOUND THAT AN INCREASE IN THE DOSE BEYOND 25 MG P.O. DID NOT ENHANCE THE AMPLITUDE OF THE ANTIHYPERTENSIVE EFFECT (FIG. 3). AFTER A PROLONGED AND UNFORTUNATE EXPERIENCE WITH OVERDOSING CAPTOPRIL, WHICH HAS LED TO UNNECESSARY SIDE-EFFECTS OF THE MEDICATION, WELL-CONTROLLED STUDIES IN LARGE NUMBERS OF PATIENTS HAVE FINALLY CONFIRMED THAT Doses SUFFICIENT TO BLOCK THE PRESSOR EFFECT OF AI IN NORMAL VOLUNTEERS WERE IDENTICAL TO THOSE NEEDED TO TREAT HYPERTENSIVE PATIENTS.19

A SIMILAR OBSERVATION WAS MADE WITH ENALAPRIL WHERE 10 MG WAS FOUND TO BE SUFFICIENT TO BLOCK THE PRESSOR RESPONSE TO EXOGENOUS AI IN NORMAL VOLUNTEERS (FIG. 4).11 WHILE HIGHER DOSES HAVE BEEN USED IN HYPERTENSIVE PATIENTS,20 IT APPEARS NOW THAT CONTROLLED STU-
ies in patients also confirm that the 10 mg dose is adequate for the treatment of hypertension (Merck Sharp and Dohme, unpublished data).

The measurement of plasma converting-enzyme activity in normal volunteers is also very useful in establishing the minimal dose of a blocking agent that is necessary to inhibit the renin-angiotensin system. Plasma converting-enzyme activity must be reduced to less than 10% of its initial value to consistently abolish the pressor response to exogenous AI. Therefore, the minimal inhibiting dose should induce a more than 90% inhibition of converting-enzyme activity. In the case of enalapril, this again has been shown in normal volunteers to correspond to the 10 mg dose. Moreover, a close correlation between plasma converting-enzyme inhibition and plasma enalapril levels has been demonstrated. Thus, in normal volunteers, it was actually possible to establish the minimal blood concentration of the antagonist that is necessary to inhibit the renin-angiotensin system adequately (fig. 5). Furthermore, by using these minimal doses in normal volunteers, it was also confirmed that they were adequate to induce significant reductions in plasma in AlI and aldosterone.

Onset and Duration of Action

Onset of the action of captopril occurs in less than 15 minutes. This was clearly established in the initial study of 1976, which assessed captopril's effect on the pressor response to exogenous AI in normal volunteers. This rapid onset was confirmed in patients with hypertension or congestive heart failure. In the early volunteer studies with enalapril, a delayed onset of action of close to 2 hours was found, and the initial studies in hypertensive patients immediately confirmed this slower action of this new type of converting-enzyme inhibitor. Measurement of plasma converting-enzyme activity confirmed that 1½ to 2 hours were necessary to obtain a greater than 90% inhibition of plasma enzyme activity following enalapril administration. Based on the pressor response to exogenous AI in normal volunteers, the action of captopril was found to last for less than 4 hours. In the case of enalapril, this method could not be used in normal volunteers to assess the duration of action for ethical reasons, since we could not leave intraarterial catheters for a long enough period. However, the measurement of plasma converting-enzyme activity demonstrated that inhibition was still excellent 10 hours after drug administration, but after 24 hours, enzyme activity had already reassumed about 20% of its control activity. Not surprisingly then, after 10 hours plasma AlI and aldosterone levels were still significantly reduced in these normotensive subjects, but after 24 hours, they were both back to initial values (fig. 6). Again, these observations were confirmed in hypertensive patients following acute administration of enalapril.

Thus, it appears that the minimal doses needed to block the renin system in normal volunteers, as as-
FIGURE 5. Relationship in normal volunteers between the active metabolite (MK 422) of enalapril and the percent inhibition of plasma converting enzyme activity following a single oral dose of 10 mg enalapril. (From Biollaz et al., see ref. 21.)

Information that Cannot Be Obtained from Studies in Normotensive Volunteers

Safety and Tolerance

Unlike mechanisms of action of new drugs, which are more and more based on prospective design and therefore more and more specific with predictable efficacy, side-effects are still totally unpredictable and can only be assessed by evaluating large numbers of subjects. However, only relatively small numbers of normal volunteers are studied and usually only a single or a few repeated doses of the investigational agent are administered. Thus, even if the drug is well tolerated in normal volunteers, major side-effects may develop in hypertensive patients treated chronically.

Antihypertensive Efficacy in Individual Hypertensive Patients

Human hypertensive disease, though probably a quantitative disorder, has nevertheless a very heterogeneous appearance. Most relevant to the present discussion, this heterogeneity has been best demonstrated by the broad spectrum of plasma renin activity in patients with essential hypertension. Moreover, since most hypertensive patients have in common an increased peripheral arteriolar resistance, relatively non-specific drugs such as vasodilators, which induce peripheral vasodilation by a direct effect on vascular smooth muscle, exert rather regularly an antihypertensive effect. The price paid for this relatively predictable antihypertensive effect is a host of side-effects, a majority of which are probably related to the lack of specificity of the approach. On the other hand, when a very specific approach to the treatment of hypertension is used, such as blocking the renin-angiotensin system, the result may vary tremendously from one patient to another. Although the response to such a therapy is related to the pretreatment activity of the renin-angiotensin system, measurements of plasma renin activity are usually not available before initiating treatment and, therefore, the antihypertensive effect of convert-
ing enzyme inhibitors can usually not be predicted at the outset.

In the context of the present discussion, it is however important to recognize that treatment failures with new converting enzyme inhibitors have nothing to do with the drugs per se but are solely related to our lack of understanding of the pathogenetic mechanisms involved in every individual hypertensive patient. If we had a precise knowledge of the contribution of the renin-angiotensin system to the hypertension of each individual patient, it is likely that, based exclusively on the results obtained in normotensive volunteers, the antihypertensive effect of the drug could be precisely predicted in each patient. Our present procedure of evaluating antihypertensive drugs in large numbers of hypertensive patients may, in the case of converting-enzyme inhibitors, reveal more about the prevalence of the renin factor in the hypertensive population than any new findings not obtained in normal humans concerning the efficacy of the agent in question.

Duration of Action with Chronic Therapy

Although it was recognized very early that increasing the dose of captopril beyond 25 mg did not enhance the magnitude of the blood pressure reduction in hypertensive patients, most investigators have used considerably higher doses. Knowledge of the drug’s short half-life in normal volunteers prompted a desire to prolong the duration of action by administering large doses. While this has created the well-known problems of side-effects, it has in addition turned out to be totally unnecessary. Thus, even with large doses of captopril given twice daily, converting enzyme could not be blocked around the clock. Nevertheless, blood pressure remained controlled.

Similar observations were made in hypertensive rats treated for long periods of time with captopril; discontinuation of this therapy led only to a slow and gradual increase in blood pressure, clearly in no way related to the half-life of the drug. It is now recognized that chronic treatment with enalapril also lowers blood pressure for a time that exceeds its duration of efficient blockade of the renin-angiotensin system (Merck Sharp and Dohme, unpublished data). One possible explanation is that converting-enzyme inhibitors are less specific than thought hitherto. Possibly some metabolites with nonspecific effects have a much longer half-life. Much more likely is the hypothesis that prolonged treatment of hypertension leads to important adaptive changes including structural modifications in the arterial wall, which reduce the responsiveness of the arterioles to All and other pressor mechanisms. It is of note that in animals, much smaller doses of All are needed to achieve a given blood pressure increase if it is administered chronically rather than acutely.

Similarly, the intermittent increases in plasma All occurring with chronic administration of converting-enzyme inhibitors do not seem to have the same pressor effect as similarly elevated plasma All concentrations which are continuously present.

Conclusions

Several methods are available for establishing in normal volunteers the efficacy of converting-enzyme blockade with a considerable degree of precision. In addition, studies in volunteers permit precise determination of the minimal dose needed to obtain close to maximal blockade of the renin system and also the onset and duration of action, at least for acute administration. These findings have subsequently been confirmed in hypertensive patients at least in the case of captopril and enalapril. Studies in hypertensive patients are unlikely to provide any new surprising information, since the unpredictability of an individual hypertensive patient’s response to a converting-enzyme inhibitor is in no way related to some unknown feature of the drug but rather to the absence of a precise knowledge of the pathogenesis of the hypertension of this individual subject. Similarly, the prolonged duration of action of converting-enzyme inhibitors observed in patients treated chronically is more likely related to structural adaptations of the treated organisms than to some unforeseen new effect of the drug.

Thus, now that it is well established how converting-enzyme inhibitors act, any new drugs in this class could at least theoretically be largely evaluated in a few normal volunteers. Efficacy, minimal effective dose, and onset of action could certainly be determined before the drug has been given to any hypertensive patient. It would be extremely surprising if any major change in these predicted values would have to be made after the drug reaches hypertensive patients. It is even unlikely that new converting-enzyme inhibitors with substantially greater efficacy will be discovered since the presently available drugs seem to block conversion almost completely. The main and almost sole reason for testing new drugs in a large number of patients is to evaluate safety and tolerance, since there is no substitute at present for this elaborate and rather unsatisfactory approach.

References

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