New Drugs

Angiotensin converting enzyme inhibitors

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The development of angiotensin converting enzyme inhibitors is often cited as a prime example of task oriented research. The truth is far from this, and, as so often, chance played a large part in the development of this group of drugs. Some 25 years ago a group of Brazilian pharmacologists was searching for substances that would block the inactivation of bradykinin, a process subsequently shown to take place in man in the pulmonary vascular bed. It was shown that this was also the site for the conversion of angiotensin I to the potent vasoconstrictor angiotensin II, and the two processes were controlled by enzymes that, if not the same, were very similar.

It has been appreciated for many years that the renin-angiotensin-aldosterone system is important in the control of blood pressure. Most early stratagems to lower blood pressure clinically, however, were based on manipulating the sympathetic nervous system, and attempts to perturb the renin-angiotensin-aldosterone system came much later. The use of effective orally active angiotensin converting enzyme inhibitors depended on translating the experiences of pharmacologists, who were interested primarily in the breakdown of bradykinin, to physiologists, who were interested in the mechanisms of controlling blood pressure, and then using the skills of medicinal chemists and clinical pharmacologists to design and test suitable compounds. A recent review by Ferreira, an important figure in the early development of this subject, details this interesting story.[1]

There are currently two orally active angiotensin converting enzyme inhibitors available in the United Kingdom, captopril and enalapril. Some 20 compounds that have a similar pharmacological activity are in various stages of development, several of them having been already given to volunteers and patients. This review will concentrate on the two marketed products because, as will be seen below, a risk-benefit analysis for angiotensin converting enzyme inhibitors can be made only after extensive exposure of patients, and any assessment of new members of the group is difficult. I will therefore compare captopril and enalapril with respect to their pharmacology, relative efficacy, and relative toxicity.

Pharmacology

Angiotensin converting enzyme is responsible for converting angiotensin I to angiotensin II and for inactivating bradykinin. Other enzymes will also break down bradykinin but will not convert angiotensin I. Angiotensin II increases blood pressure by direct vasoconstriction and by causing the release of aldosterone and thus the retention of sodium. It is now known that angiotensin converting enzyme is a widespread enzyme, but it is mainly active in the vascular endothelium of the lungs. Angiotensin converting enzyme inhibitors have several possible modes of action[2]; current evidence favours the hypothesis that inhibiting the conversion of angiotensin in the periphery is more important for their therapeutic action than inhibiting the inactivation of bradykinin, which may, however, have a role in producing some of the adverse effects seen with this group of drugs. The evidence for angiotensin converting enzyme inhibitors having a central role in opioid pharmacology is not strong, but they do show important interactions with the sympathetic nervous system.[2]

Captopril is a derivative of the amino acid proline and contains a sulphydryl (SH) group. About three quarters of an oral dose is absorbed in healthy fasting volunteers, but ingestion with food reduces absorption by some 30%. Maximum plasma concentrations of captopril are reached between 0·5 and 1·5 hours after administration, when the peak angiotensin converting enzyme inhibitory and haemodynamic effects are also seen. After a 25 mg oral dose these effects return to baseline after four to six hours. Its elimination half life from plasma is between one and two hours, and it is excreted by the kidney partly unchanged and partly oxidised to form mixed disulphides (which are inactive). The elimination of captopril correlates closely with renal function, and a considerable increase in its half life is seen in patients who have creatinine clearances of less than 20 ml/min.[3]

Enalapril is also a derivative of proline but unlike captopril does not contain a sulphydryl group. Some three fifths of a dose is absorbed, irrespective of food. Enalapril, however, is a prodrug that needs to be converted by esterase activity in the liver to the active moiety enalaprilat. Enalapril itself achieves peak plasma concentrations one hour after dosing and disappears from the plasma by four hours. Enalaprilat on the other hand reaches its peak concentration in plasma about four hours after dosing with enalapril and has a half life of some 35 hours; it is still detectable in the plasma after 96 hours. The maximum inhibition of angiotensin converting enzyme activity occurs with peak plasma concentrations of enalaprilat but, unlike with captopril, is sustained for 10 hours and reverses gradually. Enalaprilat is excreted by glomerular filtration and, like captopril, will accumulate in patients who have advanced renal failure.[4]

The differences in kinetics and dynamics between captopril and enalapril mean that captopril must be given two or three times daily while enalapril can be given once daily.

Clinical efficacy

HYPERTENSION

Both captopril and enalapril decrease blood pressure in patients who have different degrees of hypertension, irrespective of the underlying basis of the disease. Patients who have higher plasma renin activity (and thus higher angiotensin I concentrations) probably show greater decreases in blood pressure than those with low plasma renin activity, but hypotensive activity can be shown even in anephric patients.

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The addition of a diuretic (thiazide or loop) to both angiotensin converting enzyme inhibitors will increase the hypotensive activity. This may be due to the increase in plasma renin activity that is produced by diuretics and that will therefore augment the efficacy of the angiotensin converting enzyme inhibitor as well as to the additive hypotensive action of the two groups of drugs. The addition of β blockers (which suppress plasma renin activity) to angiotensin converting enzyme inhibitors is of less value than the addition of diuretics; calcium antagonists such as nifedipine have been shown to have an additive effect.[4]

The hypotensive efficacy of both captopril and enalapril has been compared with that of diuretics, β blockers, and calcium antagonists. Individual studies may have claimed to show superiority of one or other angiotensin converting enzyme inhibitor over the other drugs, but overall this is difficult to sustain.

The main differences in clinical efficacy between captopril and enalapril relate to doses and dosing intervals. There have been problems with both drugs in establishing initial dosing regimens and the optimal dose that should be given in both hypertension and heart failure. For captopril it is now recommended that in patients who have mild to moderate hypertension the initial dose should be 12·5 mg twice daily and the maximum dose 50 mg twice daily. For patients taking diuretics the initial dose should be 6·25 mg twice daily. In patients who have severe hypertension a daily dose of 150 mg/day should not be exceeded. In the elderly and patients who have renal failure the dose should be kept as low as possible. For enalapril the initial dose in uncomplicated hypertension should be 5 mg/day, but if the patient is also taking diuretics a starting dose of 2·5 mg/day is recommended. The usual maintenance dose is 10-20 mg/day, and the maximum daily dose is 40 mg. The elderly and patients who have renal failure should initially receive no more than 2·5 mg/day.

It should be noted that neither captopril nor enalapril is recommended as first line treatment for patients who have hypertension. Captopril should be given to patients who have severe hypertension only when standard treatment has failed and to patients who have mild to moderate hypertension as an adjunct to thiazide treatment where the response is inadequate. Similar constraints are placed on the use of enalapril, which can be used in all grades of hypertension but only when standard treatment is ineffective or inappropriate because of adverse effects.

One point should be emphasised with respect to the use of angiotensin converting enzyme inhibitors. Patients usually feel well when taking them; whether this is a positive attribute of the drugs or because of a lack of the adverse effects that bedevil many other antihypertensive agents is an interesting debate. The phrase "quality of life" has been widely used in this discussion.[5]

HEART FAILURE

Among the main haemodynamic disturbances found in heart failure are an increase in the systemic vascular resistance mediated by angiotensin II, causing an increase in the left ventricular afterload, and an increase in the left ventricular filling pressure (preload), caused by retention of fluids mediated by excess aldosterone. By decreasing angiotensin II concentrations both the afterload and the preload can be reduced, both in the short and long term.[6]

Comparison with other forms of vasodilator treatment for heart failure[7] suggests that angiotensin converting enzyme inhibition is superior to both hydralazine and prazosin as judged by exercise performance and haemodynamic measurements in patients who have already been dosed with digitalis and diuretics. Packer suggests that the administration of either captopril or enalapril in heart failure may take several weeks to show an optimal effect, and that this may be due to the reversal of a slow pressor effect of angiotensin II leading to an improvement in the peripheral use of oxygen rather than to the more immediate diuresis mediated by the suppression of aldosterone and the subsequent reduction in the left ventricular filling pressure.[7]

Most studies of the effects of angiotensin converting enzyme inhibitors have had an open design because of the nature of the condition, but sustained benefit and haemodynamic improvement for up to a year have been reported.

In short term haemodynamic studies, the administration of captopril in doses ranging from 12·5 mg to 150 mg/day have shown increases in cardiac output and a reduction in peripheral and pulmonary vascular resistance. In some studies a sustained improvement in renal function has been shown, but in others the initial decrease in blood pressure has produced a decrease in renal function. Usually this returns to pretreatment levels or even improves with long term treatment.

Most trials have been carried out in patients who have severe heart failure, in whom digitalis and diuretics have been co-administered. These long term studies have confirmed the observations seen after short term drug administration. The few double blind studies carried out in patients who had less severe heart failure have shown an improvement in cardiac haemodynamics.

As with captopril, short term studies have shown that enalapril reduces left ventricular filling pressure in patients who have heart failure that is resistant to standard treatment with digitalis and diuretics. The addition of enalapril to conventional treatment in patients who have severe congestive heart failure can reduce mortality and improve symptoms.[8]

A study was designed to evaluate the importance of the duration of angiotensin converting enzyme inhibition in heart failure in which enalapril 40 mg once a day was compared with captopril 50 mg three times a day, both treatments aiming to produce a similar inhibition of angiotensin converting enzyme activity.[9] Forty two patients who had severe heart failure and required digitalis and diuretic treatment were studied over one to three months. Decreases in systemic blood pressure were similar with both drugs, but the hypotensive effects of enalapril were more prolonged and persistent than those seen with captopril. Thus though both groups improved clinically and haemodynamically, serious symptomatic hypotension was seen primarily among the patients treated with enalapril. The authors suggest that sustained hypotension also probably accounted for the decline in creatinine clearance and retention of potassium seen in the enalapril group. The conclusion reached was that in heart failure shorter acting angiotensin converting enzyme inhibitors may be more advantageous.

As with hypertension, there are differences in the dosing regimens in heart failure between captopril and enalapril. Both drugs must be started under close hospital supervision and as an adjunct to diuretics and digitalis. The starting dose of captopril should be 6·25 mg or 12·5 mg to minimise any hypotensive effect, and the usual maintenance dose is 25 mg three times a day, with a maximum dose of 150 mg/day. The initial dose of enalapril should be 2·5 mg/day and the usual maintenance dose 10 mg or 20 mg/day with a maximum of 40 mg/day.

Adverse effects

There has been considerable debate over whether the sulphydryl group of captopril confers on it a pattern of adverse effects not seen with enalapril. Any analysis of relative toxicity is rendered more difficult by the trend towards smaller doses with both agents in both hypertension and heart failure. At the high doses previously used there seems to be little doubt that disturbances in taste, neutropenia, and skin rashes were commoner in patients treated with captopril, but at the lower doses now recommended only the first of these effects is convincingly commoner in such patients.[10]

The most important adverse effects seen with angiotensin converting enzyme inhibition are:

Large and unexpected decreases in blood pressure—These are seen with both angiotensin converting enzyme inhibitors in both heart failure and hypertension. They are seen usually in patients who previously received large doses of diuretics with fluid depletion, in whom plasma concentrations of angiotensin I are high. Further, the larger the initial dose of angiotensin converting enzyme inhibitor the more frequent the effect. It is seen earlier in the course of captopril treatment than enalapril treatment because of the need to

convert enalapril to the active drug in the liver, but as described above, it seems to be more prolonged with enalapril than captopril.[9]

Renal impairment—This may occur as a result of the decrease in blood pressure described above, when it is usually attributed to the withdrawal of angiotensin II, which increases efferent arteriolar tone within the kidney and helps to maintain filtration pressure. It is commoner in patients whose renal function is already compromised, and though it is usually reversible, cases have been reported with both angiotensin converting enzyme inhibitors where this is not so. A question remains whether there is a cohort of patients in whom treatment with either long term angiotensin converting enzyme inhibitor may result in an irreversible deterioration of renal function. From a regulatory standpoint this is a great concern and places a question mark over the use of this group of agents for mild hypertension that is not immediately life threatening. Monitoring renal function throughout treatment with these agents is thus mandatory.

Neutropenia—Captopril in high doses (150 mg/day or greater) has been associated with a prevalence of neutropenia (white blood cells $<1000/mm^3$) of 0·02% in patients who have normal renal function, 0·4% in patients who have impaired renal function, and 7·2% in patients who have renal impairment and collagen disease.[11] At lower doses of captopril (50 mg/day and less) there are few reported cases of neutropenia. The combination of captopril and allopurinol has been reported to cause a decrease in white cell count in some patients. Enalapril has rarely been reported to cause neutropenia.

Angioneurotic oedema—Both agents have been reported to cause angioneurotic oedema. The basis of this effect may be the inhibition of bradykinin breakdown by inhibiting angiotensin converting enzyme (for kininase II); this has resulted in the death of some patients.

Rash—At higher doses (≥150 mg/day) captopril caused rashes in some 12% of patients, but at the lower doses now recommended the incidence is less than 1% with both angiotensin converting enzyme inhibitors.

Taste disturbance—Loss of taste is seen exclusively with captopril and again is related to dose. Probably 0·5% of patients who have normal renal function and receive the lower recommended doses now suffer from loss of taste.[11] The loss may take several weeks to return.

Cough—Persistent cough is seen in a very small number of patients given either angiotensin converting enzyme inhibitor. Again, its basis is poorly understood, and speculation abounds as to the role of bradykinin.

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Letter from . . . Fiji

School of medicine's uncertain future

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The hand delivered invitation arrived just after 9 40 am on the rather dull morning of 14 May 1987. It was to lunch on the following day with Dr Timoci Bavadra, Prime Minister of Fiji and leader of the Labour-National Federation Party coalition, which had been democratically elected to govern Fiji for five years on 11 April 1987. The opportunity for which so many had worked and waited for so long had arrived. At last there was a chance to sit with the top political figures in the land and begin to discuss in earnest the realities of the future for the Fiji School of Medicine, of medical education in the vast reaches of the south west Pacific, and other urgent matters relating to the health of Fiji.

At 10 04 am, just 20 minutes later, Lieutenant Colonel Sitiveni Rabuka, third in command of the Royal Fiji Military Forces, entered the Fiji parliament with 10 armed soldiers and placed Dr Bavadra—a former graduate of the Fiji School of Medicine—and his 14 cabinet colleagues under house arrest. A military coup had taken place and the future of the school, and indeed of this beautiful multiracial island is now in limbo.

Probably no medical school in the world has a prouder past, but today none has a less certain future. Founded in 1885, its history is interminably bound in the story of nineteenth century white incursion into the vast south west Pacific Ocean and of the introduction of foreign communicable disease into immunologically virgin island populations.

Fiji is a group of over 320 volcanic islands and coral atolls almost two thirds of the way between Hawaii and Australasia. The country was never annexed by Great Britain, but was ceded to it in 1874 by its paramount chief, Ratu Seru Cakobau (King Thakombau) and a group of 13 associated chieftains. They did so in an effort to repay their debts to marauding European, Australasian, and Yankee invaders, and to bring peace and stability to the area.

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