HYPERTENSION

Role of ACE inhibitors in uncomplicated essential hypertension

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The design and early development of drugs which inhibited angiotensin converting enzyme (ACE inhibitors) was conducted with the expectation that the principal applications of such agents would lie in clinical syndromes in which the activity of the renin-angiotensin system was enhanced—for example, renovascular hypertension and certain varieties of cardiac failure. With the introduction of the first orally active ACE inhibitor, captopril, it quickly became apparent, however, that such treatment was applicable to essential (primary) hypertension, in which both the antihypertensive efficacy and the acceptability of ACE inhibitors were found to be at least comparable with those of other drug classes. The use of ACE inhibitors, either given alone or in combination with other drugs, in uncomplicated essential hypertension now constitutes a major indication and has appreciably increased therapeutic freedom. Even so, there remains a remarkable reluctance on the part of some authorities to endorse the use of ACE inhibitors as initial (so-called “first line”) treatment in essential hypertension.^{1,2} I consider this seemingly strange anomaly later in this article.

ACE inhibitors given alone (“monotherapy”)

Even in uncomplicated essential hypertension, circulating plasma concentrations of angiotensin II are within a range in which they exert an immediate, direct effect on arterial pressure.³ Thus acute blockade of the renin-angiotensin system, as by infusing an angiotensin II antagonist such as saralasin or by inhibiting ACE, causes an immediate reduction of both arterial pressure and plasma aldosterone, in proportion to the previously prevailing plasma angiotensin II concentration.⁴ In essential hypertension, however, circulating concentrations of renin and angiotensin II are usually modest or low⁵ and decline further with age. Thus the progressive and often eventually distinct antihypertensive effect seen with long term oral administration of an ACE inhibitor was unexpectedly gratifying, not least because it occurred also in elderly subjects.

Given alone, ACE inhibitors are broadly similar in antihypertensive efficacy to a range of other drug classes.⁶ This has been apparent in direct prospective comparisons, including double blind studies.

Table 1 summarises the outcomes of 21 parallel group trials comparing six different ACE inhibitors with placebo, one another, or other antihypertensive agents in essential hypertension.^{7–28}

Individual reports have found ACE inhibitors to be as effective as diuretics,²² β blockers,²⁴ calcium antagonists,²⁹ and methyldopa.³⁰

In a double blind trial Herrick *et al* showed enalapril to have a significantly greater antihypertensive effect than atenolol.³¹

Probably because of their effect in slowing heart rate, β blockers are liable to have a modest capacity to lower systolic pressure.^{32,33} Systolic blood pressure reduction has, perhaps not surprisingly therefore, been found to be greater with lisinopril than metoprolol²⁴ or atenolol.¹⁹ Even so, enalapril was seen also to lower systolic pressure more than did hydrochlorothiazide.¹⁸ Conversely, both isradipine³⁴ and labetalol³⁵ were slightly more effective than enalapril in other studies.

The antihypertensive effect of ACE inhibitors is sustained with long term treatment.⁶ There is little to suggest that their effectiveness is altered with age.³³

Comparative antihypertensive effect of different ACE inhibitors

The time of onset and the duration of antihypertensive effect vary considerably between different ACE inhibitors. Table 2 compares data obtained with a range of such agents.³⁶

Although the long term antihypertensive potency of different ACE inhibitors is, at currently recommended doses, broadly similar,^{6,7} some differences may exist. Using ambulatory blood pressure measurement, Conway *et al* saw a significantly greater reduction in systolic pressure over 24 hours with lisinopril than with enalapril; a similar trend with diastolic pressure was not significant.³⁷ But, as Hansson *et al* have rightly emphasised,⁶ more extensive comparative studies, with a wide range of doses, are needed to clarify this issue.

ACE inhibitors combined with other forms of treatment

DIURETICS

Predictably, the combination of ACE inhibitor with diuretic is particularly effective in

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Table 1 Some parallel group studies comparing ACE inhibitors with other antihypertensive agents in mild to moderate hypertension[†]

Reference No	Authors (year)	No of patients	Duration (weeks)	Drug dosage (mg/day)	Decrease in blood pressure (systolic/diastolic) (mm Hg)*	Response rate (%)†	Comments
8	Andrén <i>et al</i> (1985)	50	8	Captopril { C 75-300 A 50-200 }	31/20 24/18 }		HCT added in 30 cases; open study 2 years
9	Captopril Research Group of Japan (1985)	270	12	{ C 37.5-75 Pr 60-120 }	26/15 23/12 }		TCM added in all cases; less adverse effects with C
10	Garinin (1986)	135	16	{ C 50-100 E 10-20 }	17/14 19/16 }		HCT added in 26 cases
11	Rumboldt <i>et al</i> (1988)	69	9	{ C 100-200 E 40-80 }	28/21 35/25 }	97 100	HCT added in 53 cases
12	Witte and Walter (1987)	222	16	{ C 200 R 10 }	20/19; 26/18‡ 22/20; 28/18‡	83 77	HCT added in 76 cases
13	Chrysant <i>et al</i> (1983)	31	18	Enalapril { E 5-40 Placebo }			Well tolerated, effective
14	Goodwin (1984)	367	12	{ E 20-40 Pr 160-240 }	13/13% 11/12%	77 59	
15	Helgeland <i>et al</i> (1986)	436§	16	{ E 20-40 A 50-100 HCT 25-50 }	18/12 14/13 16/9 }		10 Week extension
16	Sassano <i>et al</i> (1984)	100	26	{ E+ T+ }	20/19% 17/17% }		Hypokalemia with E
17	Thind <i>et al</i> (1985)	32	16	{ E 10-40 C 75-300 }	28/18 29/17 }	75 75	HCT 50 added to all
18	Vidt (1984)	455	8	{ E 20-40 HCT 50-100 E + HCT }	15/11% 20/13% 33/21% }	22 42 80	
19	Bolzano <i>et al</i> (1987)	490	24	Lisinopril { L 20-80 A 50-100 }	89 87		
20	Gomez <i>et al</i> (1985)	102	6	{ L 1.25-80 Placebo }	16/10		
21	Merrill <i>et al</i> (1987)	207	8	{ L 20 HCT 12.5 L + HCT }	9.2% 6.4% 15.7% }		8.2% Stopped by adverse effects
22	Pool <i>et al</i> (1987)	394	24	{ L 20-80 HCT 12.5-50 L + HCT }		82 67 84	
23	Morlin <i>et al</i> (1987)	136	12	{ L 20-80 N 48-80 }		82 79	
24	Zachariah <i>et al</i> (1987)	175	8	{ L 40-80 M 100-200 }		63 65	
25	Karlberg <i>et al</i> (1987)	34	4	Ramipril { R 5-10 Placebo }	22/9		
26	Villamil <i>et al</i> (1987)	86	4	{ R 2.5-5 Placebo }	15/18		19 Patients dropped out
27	Morgan <i>et al</i> (1987)	32	4	Perindopril { Pe 2-8 Placebo }	22/11 3/2		Effects of Pe were independent of sodium intake
28	Gavras (1984)	8	1	Quinapril Q 0.625-10	27/26		

* Compared with baseline or placebo values; † responders were patients in whom diastolic blood pressure was reduced to ≤ 90 mm Hg or by $\geq 5-10$ mm Hg; ‡ blood pressure reduction with addition of hydrochlorothiazide; § single blind study. A, atenolol; HCT, hydrochlorothiazide; E+, E + HCT + oxprenolol + dihydralazine; M, metoprolol; N, nifedipine; Pr, propranolol; T+, HCT + oxprenolol + dihydralazine; TCM, trichlormethiazide.

Table 2 Relation between time and effect for some ACE inhibitors.³⁶ Time is in hours

	Captopril	Enalapril	Lisinopril	Ramipril	Cilazapril
Time to peak blood concentration	1	3	7	2.5	2
Hypotensive response to single dose:					
Onset	0.5	1-1.5	2	2	1
Time to maximal effect	1	4	6	4	6
Duration of effect	4-6	8-12	18	18	10

lowering arterial pressure. Diuretics increase circulating concentrations of angiotensin II, and this limits their antihypertensive effect.⁶ Thus giving an ACE inhibitor with a diuretic prevents the rise in angiotensin II concentration and clearly enhances efficacy. Indeed, hypertension is adequately controlled in more than 80% of patients when these two classes of drug are given together.³⁸ Alternatively, the introduction of an ACE inhibitor can allow the dose of thiazide to be lowered.³⁹

The combination of ACE inhibitor with a loop acting diuretic is valuable in controlling previously unresponsive hypertension.^{40 41} ACE inhibitors, by lowering plasma angiotensin II concentration, diminish aldosterone secretion and so minimise⁶ the potassium depletion and hypokalaemia which otherwise accompany the use of thiazides or loop acting diuretics.⁴² An important corollary is that potassium sparing diuretics such as amiloride, triamterene, and spironolactone are usually

unnecessary in this combination; indeed, in patients with renal impairment, which may be occult in elderly subjects, dangerous hyperkalaemia might be provoked by their use. A further theoretical gain with the addition of ACE inhibitor to thiazide or loop acting diuretic is that raised plasma potassium concentrations could enhance the antihypertensive effect.⁴³ Additional bonuses are that the potentially adverse effects of thiazides on plasma lipids, uric acid, and glucose are lessened.^{6 44}

DIETARY SALT RESTRICTION

Dietary salt restriction, like diuretic use, raises plasma angiotensin II concentration,⁴⁵ which thus, for similar reasons, inhibits the antihypertensive effect. Again and predictably, the addition of ACE inhibitor enhances the reduction in blood pressure.⁴⁶

β ADRENERGIC BLOCKADE

One of the actions of β blocking drugs is inhibition of renin secretion and hence the lowering of plasma angiotensin II concentration.⁴⁷ Although the importance of this action as a contributor to the blood pressure reduction seen with β adrenergic blockade has been disputed,⁴⁷ it will be apparent that ACE inhibitors and β blockers share this mode of action. Thus it might be that the combination of these two classes of agent would be relatively ineffective. The clinical evidence is, however, conflicting.

Wing *et al* found the combination of enalapril with atenolol to be largely ineffective.⁴⁸ Similarly, although MacGregor *et al* found that the addition of either nifedipine or hydrochlorothiazide to captopril was useful, no further fall in blood pressure occurred with the addition of propranolol to captopril.⁴⁹

By contrast, Staessen *et al* found a similar additional antihypertensive effect with either propranolol or thiazide given with pre-existing captopril.⁵⁰ Similarly, Belz *et al* observed a worthwhile further reduction in blood pressure when cilazapril and propranolol were combined.⁵¹

The age of the patients studied might partially explain some of these seemingly discrepant reports.^{6 52} Plasma renin declines with age,⁵ hence differing effects might be seen according to age. The addition of lisinopril to atenolol caused a 56% greater fall in diastolic pressure in patients under 50 compared with those of 50 and over.⁵²

DIURETIC PLUS β BLOCKER PLUS ACE INHIBITOR

Examining a range of drugs added to the treatment of patients whose blood pressure was inadequately controlled by thiazide plus β blocker, Bevan *et al* found captopril to be more effective than nifedipine or hydralazine.⁵³ When these results were combined with those from an earlier trial of identical design from the same centre,⁵⁴ captopril was the most effective third drug in comparison with methyl dopa, prazosin, hydralazine, and nifedipine. All the third drugs did better than

placebo. In this context, considering acceptability as well as efficacy, captopril was evidently the most suitable third drug.

α ADRENERGIC BLOCKADE

The combination of either captopril or enalapril with doxazosin has been reported to be both effective and well tolerated.⁵⁵

KETANSERIN

Studies combining either captopril⁵⁶ or enalapril⁵⁷ with ketanserin, an antagonist of serotonin type 2 receptors and α_1 adrenergic receptors, have shown particularly good antihypertensive efficacy. When ketanserin and captopril were given together the combined blood pressure lowering was more than twice that of either drug given alone.⁵⁶

TYPE 2 CALCIUM ANTAGONISTS

The combination of a type 2 calcium antagonist (dihydropyridine) with ACE inhibition is especially effective.⁵⁸⁻⁶⁰ Moreover, because ACE inhibition can reduce the tachycardia, headache, and pedal oedema induced by calcium antagonists, tolerance of calcium antagonists is improved.⁶⁰

Mechanism of antihypertensive effect of ACE inhibitors

The necessarily appropriate acknowledgement that the mechanism or mechanisms of the antihypertensive action of ACE inhibitors is imperfectly understood is to recognise a similarity with other widely used drug classes such as thiazides and β blockers, for which, likewise, the mode of action remains partly obscure.

The immediate effect of the administration of ACE inhibitor is a reduction in peripheral plasma angiotensin II concentration, with a proportionate acute fall in blood pressure. With continued administration of an ACE inhibitor, however, a further substantial fall in arterial pressure usually occurs in essential hypertension. Several mechanisms have been proposed to explain this progressive antihypertensive effect. These are not mutually exclusive; all are currently speculative.

The existence of numerous local tissue renin-angiotensin systems is well established. Inhibition of these might, in several ways, contribute to lowering of arterial pressure. Among these, an especially attractive theory is that ACE inhibition reverses the broadly "trophic" action of angiotensin II on the medial smooth muscle of resistance arteries; reversal of this trophic effect causes regression of the medial thickening, and hence enhancement of blood pressure reduction.⁶¹ Recent evidence suggests that medial thickening in resistance arteries in hypertension is achieved by rearrangement of smooth muscle cells and not by either their hypertrophy or hyperplasia. This newer knowledge requires some readjustment of concepts.⁶¹

The effects achieved via modification of endothelial function are considered in this supplement by Drexler.⁶²

Inhibition of the formation of angiotensin II, both within the circulation and locally in the brain, will diminish sympathetic nervous discharge.⁶³ Such an effect has been clearly shown in certain clinical circumstances, notably cardiac failure.^{64 65} A similar action should contribute to blood pressure reduction in essential hypertension.

Diminution of circulating concentrations of angiotensin II lowers the rate of aldosterone secretion. Among the consequences of this is raised plasma potassium concentration, which is likely to contribute, albeit modestly, to the antihypertensive effect.⁴³

Another consequence of a reduction in aldosterone secretion is promotion of natriuresis. Long term use of ACE inhibitors alone lowers exchangeable body sodium in patients with renal artery stenosis.⁶⁶ Whether a similar effect obtains in essential hypertension is unknown, although the noticeable additional antihypertensive effect when ACE inhibitors are combined with diuretics or salt restriction (see above) indicates that in these circumstances it is at most modest.

Angiotensin converting enzyme is identical with kininase II, the enzyme responsible for degradation of kinins. Thus ACE inhibition should lead to the accumulation of vasodilator kinins in the circulation or various other tissues, or both.³⁶ To what extent any such effects contribute to the blood pressure reduction remains uncertain.

Possible ancillary benefits

In recent years increasing attention has been directed at the possible benefits of some classes of antihypertensive drug in addition to their capacity to lower arterial pressure. These approaches might enhance the so far limited (albeit distinct) achievements of antihypertensive treatment in reducing morbidity related to hypertension.⁶⁷ Especially promising approaches have been directed towards the limitation of myocardial ischaemia and to minimising the development of atheroma.

One avenue is to use antihypertensive drugs that can also reverse left ventricular hypertrophy. The limitations of retrospective analyses in the evaluation of the comparative efficacy of different drug classes in correcting left ventricular hypertrophy are illustrated by the different results obtained in three such major surveys.⁶⁸⁻⁷⁰ Specifically designed prospective trials are likely to be more revealing. These matters are discussed in detail in this supplement by Richards *et al.*⁷¹

A second approach is to improve the compliance of large arteries in hypertension. Diminished compliance is accompanied by a disproportionate increase in systolic pressure, increased turbulence of blood flow, and predisposition to the formation of atheroma.⁶⁷ Several clinical trials have indicated that ACE inhibitors are effective—and more effective than some other classes of drug—in improving the compliance and distensibility of large arteries in hypertension.⁷²

A third approach is to use antihypertensive

drugs that could limit endothelial damage and preserve the beneficial biochemical, biophysical, and physiological properties of vascular endothelium. These aspects are discussed further by Drexler in this supplement.⁶²

The vexed question of whether modestly raised plasma renin, and hence raised angiotensin II concentrations, carries a specific adverse prognosis in essential hypertension remains unresolved. (Undoubtedly, markedly raised plasma concentrations of angiotensin II can cause myocardial necrotic lesions, arterial damage, and renal tubular necrosis.⁷³) The original proposal, that modestly raised plasma renin activity in essential hypertension predisposes to stroke and myocardial infarction, has been abandoned. In a later prospective study, Alderman *et al* found that hypertensive subjects with raised plasma renin activity were more likely than those with lower renin activities to suffer myocardial infarction, but not stroke.⁷⁴ The analysis was, however, based on few events and was not confirmed by the large study of Meade *et al.*⁷⁵ Most relevant is that the results were insufficiently impressive to deter Alderman from subsequently advocating thiazide diuretics, which raise plasma renin and angiotensin II values, as first treatment in hypertension.⁷⁶ Thus these aspects cannot at present be convincingly invoked in favour of the early use of ACE inhibitors in essential hypertension.

Quality of life

Early open studies, in which ACE inhibitors were given to patients with poorly controlled hypertension, raised the possibility, not wholly welcome, that these drugs might possess a euphoriant effect,⁷⁷ perhaps because of central inhibition of enkephalinase. Closer critical evaluation suggested, however, that a more likely explanation was that the ACE inhibitor was giving relief from the unpleasant symptoms associated with other drugs.

RESULTS OF STUDIES

In a double blind study Callender *et al* found a slight but significant depression of mood when captopril was substituted for placebo.⁷⁸ Dahlöf *et al* observed that in patients with essential hypertension measures of wellbeing increased when placebo was substituted for previous diuretic and β blocker treatment and remained significantly better when enalapril was introduced.⁷⁹ Olajide and Lader found neither enalapril nor placebo to have measurable effect on mood in normal volunteers.⁸⁰ Lichter *et al* observed a slight but significant impairment of memory on treatment with atenolol but not with enalapril in essential hypertension.⁸¹ In a large trial in men with essential hypertension captopril was more acceptable than either methyldopa or propranolol in several measures of quality of life.³⁰ Lisinopril was compared with nifedipine over 10 weeks in 828 patients with essential hypertension. Only at the highest dose (80 mg) of nifedipine was wellbeing impaired.⁸²

The superiority of ACE inhibitors was not

confirmed in a range of studies comparing them with more modern drugs. No major differences were found when atenolol was evaluated against enalapril,^{31 83} captopril,^{83 84} and delapril hydrochloride.⁶ In a controversial report by Testa *et al* captopril was more acceptable than enalapril.⁸⁵ This study has been both severely criticised⁸⁶⁻⁸⁸ and defended.⁸⁹

CONCLUSION

ACE inhibitors do not usually have major adverse effects on the quality of life. They seem to be distinctly superior to methyldopa and propranolol and probably also nifedipine. There is no good evidence of long term superiority over atenolol. A suggestion that captopril is more acceptable than enalapril has been questioned. ACE inhibitors do not have a euphoriant effect. There is no good evidence that ACE inhibitors cause sexual problems.

Side effects

As Fletcher and Dollery have emphasised,⁷⁷ side effects associated with ACE inhibitors can be placed into four principal groups: effects related to the main pharmacological action (hypotension, bradycardia, renal impairment); effects connected with subsidiary actions (enhancement of kinins, inhibition of enkephalinase); idiosyncratic class effects (cough, angioneurotic oedema, Raynaud's phenomenon); and compound specific (mainly captopril) effects (proteinuria, the nephrotic syndrome, taste disturbance, rash, and perhaps Guillain-Barré neuropathy).

FIRST DOSE HYPOTENSION

ACE inhibition will cause an initial acute fall in arterial pressure, in proportion to the prevailing peripheral plasma concentration of angiotensin II. This is unlikely to cause problems with the introduction of an ACE inhibitor in previously untreated essential hypertension, when plasma renin and hence angiotensin II concentration are likely to be normal or low. Caution is needed if previous treatment, such as diuretics, has raised angiotensin II concentrations. Severe first dose hypotension, endangering cerebral and renal blood flow, can readily occur in these circumstances.⁹⁰ Whenever possible, such antecedent treatment should be withdrawn for a few days before starting ACE inhibition. Otherwise, the ACE inhibitor should be introduced under strict supervision, with facilities (such as angiotensin II for infusion) available for resuscitation as necessary.

First dose hypotension is not necessarily a sole consequence of acute loss of the arterial constrictor effect of angiotensin II. Contributions may also come from loss of angiotensin mediated sympathetic enhancement and vagal inhibition, when bradycardia can be an added hazard. However, these additional problems (which may call for the administration of atropine) are more likely in heart failure treated by diuretics and digoxin than in essential hypertension.⁹¹

First dose hypotension has also been asserted to occur independently of the prevailing angiotensin II concentration in elderly subjects with essential hypertension, although this is not well substantiated. Elderly subjects are, nevertheless, likely to tolerate hypotension poorly.

RENAL IMPAIRMENT

Renal functional deterioration is not likely with the use of ACE inhibitors in uncomplicated essential hypertension. More usually it stems from loss of angiotensin II mediated sustenance of renal function in circumstances of impaired renal blood flow—for example, cardiac failure or renal artery stenosis.⁹² Occult renal artery stenosis in patients with apparent essential hypertension can cause problems; it is more prevalent in elderly subjects and in those with evident arterial disease at other sites.

HYPERKALAEMIA

Hyperkalaemia occurs with ACE inhibitors only if they are given incorrectly, with potassium conserving agents, or to patients with renal impairment.

SINUS TACHYCARDIA

Sinus tachycardia, which can persist, is an unusual, but real, problem, most often occurring with concomitant diuretic and ACE inhibition.⁹³

COUGH

That ACE inhibitors can provoke dry cough has been known since the paper of Havelka *et al* in 1982.⁹⁴ The reported prevalence of this side effect varies widely, from less than 1% up to 22%.⁷⁷ The problem seems common to all currently used clinical ACE inhibitors.

The cough is associated with increased sensitivity of the cough reflex. Some, but not all, asthmatic subjects seem to be especially susceptible. Although the mechanism is not known, an increase in tissue kinin may be contributory.

ANGIONEUROTIC OEDEMA

Angioneurotic oedema, which can affect the lips, tongue, glottis, mouth, or larynx, can be life threatening. It affects some 0.2% of patients and seems to be independent of the individual ACE inhibitor used. Most cases occur in the first week of treatment, and these are potentially the most serious.⁷⁷

With angioneurotic oedema ACE inhibition should be stopped. Most instances resolve spontaneously; there has been a suggestion that addition of antihistamines can be helpful.

If the tongue, glottis, or larynx are affected to an extent that the airways are obstructed subcutaneous adrenaline solution (1:1000 (3-5 ml)) should be given at once.

RAYNAUD'S PHENOMENON

Raynaud's phenomenon is an unusual complication of both captopril and enalapril treatment.⁹⁵ In one double blind trial

comparing enalapril with atenolol, enalapril induced Raynaud's phenomenon was sufficiently severe in one patient to cause the drug to be withdrawn³¹; no patient taking atenolol encountered this problem.

It is probable that because of the supposed unlikelihood of this side effect (ACE inhibitors have been tried as treatment for Raynaud's phenomenon) it has been misattributed and hence under-reported.⁹⁵

GUILLAIN-BARRÉ NEUROPATHY

Rare cases have been described of Guillain-Barré neuropathy as a complication of captopril treatment.⁷⁷ In one instance it was seen at a dose of only 75 mg daily. There is one report of peripheral neuropathy in association with enalapril.⁹⁶

RASH

Rash, usually maculopapular and with accompanying pruritis, was common with captopril treatment when high doses were used; it is much less common with the lower doses currently given.⁷⁷ ACE inhibitors other than captopril do not seem to be associated with rash more often than are other antihypertensive agents.⁷⁷

TASTE DISTURBANCE

Taste disturbance, like rash, was commonly reported in the early days of captopril treatment, when large doses were used. The problem was attributed to the zinc binding properties of the sulphhydryl group in the captopril molecule.

The side effect has receded with the use of more modest doses of captopril and now occurs no more frequently than with other ACE inhibitors such as enalapril.⁷⁷

PROTEINURIA: THE NEPHROTIC SYNDROME

Another problem attributable to former large doses of captopril, and seemingly due to the sulphhydryl group, was proteinuria, with occasional frank cases of the nephrotic syndrome.⁹⁷ In one patient the nephrotic syndrome occurred with high doses of captopril and resolved when enalapril was substituted.⁹⁸

Such severe proteinuria is no longer encountered with the lower doses of captopril now used.

NEUTROPENIA

Neutropenia was associated with high doses of captopril and was thought to be a consequence of the sulphhydryl moiety. It is no longer a problem with current lower doses.⁷⁷

Hypertension in pregnancy

ACE inhibition in pregnant animals has been associated with fetal loss. Although controlled data are elusive for human pregnancy, intra-uterine growth retardation, fetal abnormalities, oligohydramnios, and anuria and hypotension in the newborn have been reported.⁶⁻⁹⁹ ACE inhibitors are therefore not recommended for pregnant women with essential hypertension.

Hypertension in children and adolescents

ACE inhibitors are useful in treating essential hypertension in children and adolescents.⁶ Because of the previously mentioned hazards of ACE inhibition in pregnant women, especial caution is needed when treating girls of reproductive age.

Antihypertensive doses of ACE inhibitors

As I have already said, doses of ACE inhibitors used in treating essential hypertension were formerly unnecessarily large. In the case of captopril in particular these high doses were accompanied by various unwanted effects, some of which were serious. With the lower doses now used the side effect burden has lightened substantially. The recommended oral doses of some currently available ACE inhibitors in the treatment of essential hypertension are as follows.¹⁰⁰

Captopril—The usual starting dose is 12.5 mg twice or thrice daily. This is lowered to an initial dose of 6.25 mg in subjects likely to suffer first dose hypotension. The maximum recommended total daily dose is 150 mg—that is, 75 mg twice daily or 50 mg thrice daily. Doses are lower in renal impairment.

Cilazapril—The initial dose is 1 mg once daily, increasing to a maximum of 5 mg once daily. Dosage should be reduced in renal impairment.

Enalapril—The initial dose is 2.5 mg or 5 mg once daily, increasing to a usual maintenance dose of 10–20 mg once daily. The maximum recommended dose is 40 mg once daily. Lower doses are needed in renal impairment.

Lisinopril—The initial dose is 2.5 mg once daily, increasing to a usual maintenance dose of 10–20 mg once daily. The maximum recommended dose is 40 mg once daily. Lower doses are recommended with renal impairment.

Perindopril—The initial dose of 2 mg once daily can be increased to a maximum of 8 mg once daily. Doses are lower in renal impairment.

Quinapril—An initial dose of 10 mg once daily can be titrated by doubling to a maximum of 80 mg daily. The usual maintenance dose is 20–40 mg once daily. Lower doses are given in renal impairment.

Ramipril—The initial dose is 1.25 mg once daily, increasing to a usual maintenance dose of 2.5–5 mg once daily. The maximum dose is 10 mg once daily. Doses are lower in renal impairment.

Place of ACE inhibitors in the antihypertensive repertoire

The data I have summarised indicate that ACE inhibitors are a valuable addition to the therapeutic repertoire in essential hypertension. Though some of their properties may confer benefits additional to those stemming from blood pressure reduction alone, this

remains to be assessed, and substantiated or denied, in future trials.⁶

The most recent treatment guidelines issued by the World Health Organisation and International Society of Hypertension recommend that ACE inhibitors are used as initial treatment in essential hypertension.¹⁰¹ The 1993 USA Joint Committee,¹ reversing an earlier view, does not, while the British Hypertension Society was unable to reach consensus on this point.² The arguments advanced against accepting ACE inhibitors as initial treatment are not models of lucid rational thought: in several respects they exemplify well the problems of attempting to propagate science by committee, a procedure previously much derided.^{102 103}

For example, the American and British committees erroneously state that only diuretics and β blockers have been adequately tested in major trials of antihypertensive treatment.^{1 2} Whereas debate may be centred on what constitutes a major trial, a very wide range of other drugs has been included in studies showing benefit from antihypertensive treatment. This range includes guanethidine, reserpine, methyldopa (extensively), clonidine, hydralazine (extensively), and nifedipine.¹⁰⁴ The available evidence suggests that blood pressure reduction in itself is accompanied by benefit; thus if ACE inhibitors lower blood pressure safely—and I have reviewed the substantial information in this article—they merit appropriate use. These concepts do not of course exclude the possibility of important additional benefits deriving from drug properties ancillary to blood pressure reduction.^{67 104} Any such benefits nevertheless require critical evaluation.

Even more remarkable is that all three committees^{1 2 101} recommend non-pharmaceutical measures both to precede and to accompany drug treatment. This is even though it is also conceded, correctly, that no therapeutic benefit has been shown for such non-pharmaceutical measures.

Non-pharmaceutical approaches are, unlike ACE inhibitors, apparently regarded by the committees as safe. Some others are more wary. For example, the safety of dietary salt restriction has been seriously questioned.¹⁰⁵⁻¹⁰⁷ Although disputed,¹⁰⁸ this issue, like others concerning non-pharmacological measures, remains untested. Moreover, all three committees recommend, without qualification, dietary attempts to lower serum cholesterol concentration despite the fact that two large trials have shown that hypertensive subjects over the age of 60 have a better prognosis the higher their serum cholesterol concentration.^{109 110}

I am unimpressed by the inconsistent, sometimes contrary, and often unsubstantiated arguments advanced by these committees.¹⁰⁴ A more reasonable conclusion is that ACE inhibitors are a valuable, if still imperfect, addition to the therapeutic repertoire in essential hypertension. There are no evident reasons for undue reluctance about their early introduction.

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