

ANGIOTENSIN CONVERTING ENZYME INHIBITORS

**A Position Statement of the NSW Therapeutic Assessment Group Inc.
1994**

Professor L Howes
Department of Clinical Pharmacology
St George Hospital, Kogarah

Dr Ian Whyte
Department of Clinical Pharmacology
Mater Misericordiae Hospital, Newcastle
Newcastle

This review was prepared by the authors in consultation with members of the NSW Therapeutic Assessment Group Inc.

This work is copyright of the NSW Therapeutic Assessment group Inc and NSW Health department. Apart from any use as permitted under *The Copyright Act 1968*, no part of this information may be reproduced by any process without written permission.

Whilst the information contained in this document has been presented with all due care, and the information is considered to be true and correct at the date of publication, changes in circumstances after publication may impact on the accuracy of the information.

This document represents expert consensus opinion and should not be relied upon as professional advice other than in this context. The information provided should not be regarded as a substitute for detailed expert advice in individual cases. NSW Therapeutic Assessment Group Inc will accept no responsibility for any loss, claim or damage suffered or caused by any person acting or refraining from action as a result of any material in this document.

NOT CURRENT

EXECUTIVE SUMMARY

Angiotensin converting enzyme (ACE)-inhibitors are accepted as first-line therapy for the treatment of hypertension and heart failure in appropriately selected patients.

In recent years there has been a rapid growth in the number of ACE-inhibitors entering the market. Most have claimed some sort of an advantage based on differences in pharmacokinetics, metabolism or tissue ACE-binding. These differences do not, however, translate into significant clinical differences in the majority of patients.

Captopril remains the drug of choice for initiating therapy in patients with severe heart failure who are at risk of first dose hypotension because of rapid onset of action and relatively short duration of action. Longer acting ACE-inhibitors may be preferable, however, for chronic therapy of heart failure.

The duration of action of ACE-inhibitors is determined by two properties, the plasma half-life and the affinity of binding to tissue ACE. All of the ACE-inhibitors (with the possible exception of captopril) can provide satisfactory 24-hour blood pressure control in the majority of patients with mild to moderate hypertension when given once daily. Lisinopril provides consistently better 24-hour control of blood pressure than either captopril or enalapril. Evidence for a superior duration of action over enalapril for the other newer ACE-inhibitors is either inadequate or unconvincing. Furthermore, data relating the duration of blood pressure control over the course of the day with a reduced incidence of cardiovascular events or complications are lacking.

All of the ACE-inhibitors have a low incidence of withdrawal of therapy due to adverse events and in general are well tolerated in both young and elderly patients. The recent demonstration that captopril therapy was associated with a better quality of life than enalapril therapy, requires further confirmation. However, it is likely to stimulate further interest in the central nervous system effect of these drugs.

Improvements in glucose tolerance, improved arterial compliance and regression of cardiac and vascular hypertrophy are class effects which occur with all ACE-inhibitors.

We recommend that practitioners become familiar with one or two ACE- inhibitors of their choice and become confident with adapting the dose and dosage interval of these drugs to suit their individual patient needs.

1 INTRODUCTION

Angiotensin converting enzyme inhibitors were first introduced for the treatment of hypertension in the early 1980's. Captopril was the first drug to be developed. Concerns about the potential toxic effects of the sulphhydryl group in captopril and the fact that it needed to be given twice or three times a day, led to the development of enalapril, a non-sulphydryl derivative. Since that time, a number of newer ACE inhibitors have been developed and granted general marketing approval in Australia.

Lisinopril, perindopril, quinapril, ramipril, fosinopril and trandolapril all now have general marketing approval for hypertension. Captopril, enalapril, lisinopril and perindopril have marketing approval for heart failure. Captopril also has approval for use in diabetic nephropathy.

ACE-inhibitors have been shown to improve survival in patients with both symptomatic and asymptomatic left ventricular dysfunction and to reverse the abnormal modelling of the left ventricle that occurs during chronic left ventricular failure. The pharmacological effects of ACE-inhibitors are the result of their ability to inhibit angiotensin converting enzyme, a non-specific dipeptidase, which is involved in the conversion of angiotensin I, to the more active angiotensin II. This enzyme is also involved in the activation and inactivation of other peptides such as bradykinin and Substance P. A reduction in plasma and tissue angiotensin II generation results in a wide range of pharmacological effects, including the relaxation of blood vessels, a reduction in cardiac inotropic responses, reduced release of aldosterone with a consequent reduction in sodium retention and a removal of the trophic effects of angiotensin II on cardiovascular tissues. There is also some evidence that the enhanced formation of bradykinin which results from angiotensin converting enzyme inhibition may be responsible for at least part of the reduction in blood pressure that accompanies ACE-inhibitor therapy.

ACE-inhibitors are in general well tolerated, the major side-effects being cough and dizziness with occasional cases of angioneurotic oedema and skin rashes. Cough and angioneurotic oedema are believed to be a consequence of the inhibition of bradykinin metabolism. Occasional cases of renal failure attributed to ACE-inhibitor therapy are usually due to their inadvertent use in patients with bilateral renal artery stenosis.

The intention of this position statement is to concentrate on the differences in metabolism, pharmacokinetics and pharmacodynamics of the various ACE inhibitors and to place into perspective the clinically relevant differences between them.

2 DIFFERENCES IN METABOLISM, PHARMACOKINETICS AND PHARMACODYNAMICS OF ACE-INHIBITORS

The pharmacological profiles of the ACE-inhibitors currently available in Australia are summarised in Table 1.

All of the ACE-inhibitors, with the exception of captopril and lisinopril, are prodrugs which require de-esterification by the liver to form the active moiety. It has been proposed that drugs that do not require de-esterification by the liver may have an advantage in patients with liver disease. In practice, this does not represent a clinically important difference as the proportion of patients requiring ACE-inhibitor therapy who have advanced liver disease is relatively small. Furthermore, the severity of liver disease does not reliably predict whether a significant impairment of the ability to de-esterify ACE-inhibitors exists and even in circumstances where de-esterification is impaired, dosage adjustments titrated against the clinical response will allow adequate compensation.

The short duration of action and rapid onset of ACE-inhibition by captopril makes it particularly useful for initiating therapy for heart failure in patients who are at risk of first dose hypotension. If hypotension occurs, it will become apparent about 20 minutes after the administration of captopril and is likely to be less persistent than would occur with a longer acting ACE-inhibitor. Once therapy has been successfully initiated, it may be preferable to use a longer acting ACE-inhibitor for chronic therapy 1,2.

Food can influence the absorption of a number of the ACE-inhibitors. The amount of drug absorbed is reduced by up to 35% in the case of captopril, perindopril and quinapril. Some delay in the rate of absorption with no effect on the total amount absorbed is seen with fosinopril. These effects of food on absorption can be avoided by asking the patient to take their medication one hour before meals.

All of the ACE-inhibitors, with the possible exception of captopril, can provide 24-hour blood pressure control in most patients with mild to moderate hypertension when given once daily. Some studies have also demonstrated 24 hour antihypertensive activity for captopril when given once daily. However, some of the drugs may produce a greater and more predictable fall in blood pressure 24 hours after dosing than others.

The duration of action of an ACE-inhibitor is determined mainly by two properties. For example, some drugs with a short plasma half life but high tissue ACE binding such as quinapril are active for 24 hours. Other drugs such as lisinopril have weaker tissue-ACE binding but a much longer plasma half-life. In contrast captopril, which has a relatively short duration of action has weak tissue-ACE binding and a short plasma half-life. The property of clinical relevance is whether or not an ACE-inhibitor has a sufficiently long duration of action to enable once daily dosing. It is of little clinical relevance whether this is achieved by a long plasma half-life, a high level of tissue ACE-binding or both.

All of the ACE-inhibitors are predominantly excreted by the kidneys with the exception of fosinopril for which 50% or more of the drug is excreted by non-renal mechanisms. This gives fosinopril the potential advantage of not requiring dosage adjustments in patients with significant renal impairment. However, the number of patients requiring significant dosage adjustments because of marked renal impairment is likely to be small, and it is relatively easy to adjust the dose of other ACE-inhibitors with predominately renal excretion to compensate for impaired renal function.

3 COMPARISONS OF EFFICACY BETWEEN ACE-INHIBITORS

The only way of establishing whether significant differences in efficacy exist between ACE-inhibitors is by well designed prospective comparative studies. While most of the new generation ACE-inhibitors have been compared with captopril and enalapril, there are relatively few studies comparing the newer ACE-inhibitors with each other. Furthermore, the results of studies comparing the efficacy of different ACE-inhibitors depend very much upon the design of the study. Most comparative studies show little differences in efficacy provided the dose was optimised. Generally where one agent has been proven superior to another there are generally other studies which show either the opposite effect or an equality between the two drugs.

4 DURATION OF ACTION OF ACE-INHIBITORS : ONCE DAILY THERAPY

The once daily administration of ACE inhibitors has been studied most extensively in the treatment of hypertension. It should be emphasised however, that the evidence supporting once daily administration for the management of hypertension depends on the definition of 24 hour efficacy. The most common method of defining this is that blood pressure is significantly lower or controlled (e.g. a diastolic blood pressure <95mm Hg) 24 hours post dose following once daily administration of the tablet for a period of several weeks. The duration of action of ACE-inhibitors is to a large extent dependent upon the dose administered. Drugs with a relatively short duration of action may control blood pressure adequately 24 hours after dosing if the dose is large enough. Another way of assessing duration of action of an ACE-inhibitor is to measure the ratio of the peak blood pressure fall (which is usually around two to three hours after the peak plasma concentration) to the trough blood pressure fall (which is immediately prior to the next once daily dose). A method of assessing the suitability of an ACE-inhibitor for once daily therapy which has clinical relevance is to compare the efficacy of a single daily dose with the same dose given in equal divided doses twice daily. This has been performed for quinapril, and no difference was found between once daily and twice daily administration. All of the newer ACE-inhibitors have been compared with enalapril and been shown to be at least as effective as enalapril at controlling blood pressure 24 hours post dose when given once daily. There are few direct comparisons between the newer ACE-inhibitors.

Probably the best evidence supporting once daily dosing is careful documentation of the 24 hour duration of effect of a single daily dose using 24 hour ambulatory blood pressure monitoring. Data of this type has been recorded in a number of studies for lisinopril, which clearly has a better 24 hour duration of effect than enalapril⁵. Ramipril has been shown to lower blood pressure to an equivalent or greater extent than lisinopril 24 hours post dose, but there has not been a comparison between these two long-acting ACE-inhibitors using 24 hour blood pressure monitoring.

It should be emphasised, that 24 hour duration of antihypertensive activity is a relative measure. Thus the majority of patients may be readily controlled with a once daily dosing of a drug with a relatively shorter duration of action such as enalapril, and the remaining patients who do not achieve ideal 24 hour control may be better controlled with the same dose divided into two equal doses given twice daily. Alternately the relatively small number of patients who do not achieve

optimal control with once daily enalapril could conceivably be controlled better with once daily dosing with a longer acting agent such as lisinopril or ramipril. It should also be emphasised that the duration of blood pressure control over a 24 hour period has not yet been shown to influence the incidence of cardiovascular events or complications for any antihypertensive drug. Thus the potential benefits of differences in 24 hour blood pressure control of one drug over another are largely theoretical.

5 DIFFERENCE IN TOLERABILITY

There have been few studies of adequate size comparing different ACE-inhibitors to establish differences in the incidence of side effects and the withdrawal of therapy because of adverse drug reactions. Where comparisons have been made most have been between the relatively newer ACE-inhibitors and the two older drugs captopril and enalapril. In general, these comparisons have not shown a significant difference in the incidence or nature of side effects between any of the ACE-inhibitors.

In a pooled analysis of comparisons between quinapril and captopril or enalapril the adverse event rate leading to withdrawal of therapy was lower for quinapril than for enalapril or captopril⁶. The withdrawal rate because of adverse events was low for all three drugs. Furthermore, statistical analysis was not provided to support the apparent superiority of quinapril.

A recent publication in the New England Journal of Medicine⁷ reported a better quality of life for hypertensive patients treated with captopril compared to enalapril. In patients who had a good quality of life to begin with, enalapril reduced the quality of life while captopril had no effect. In patients with a poor quality of life, captopril improved the quality of life while enalapril had no effect. This was a very interesting observation which requires further confirmation. One theory that has been proposed to explain this apparent difference is that the effect of captopril may have been mediated via the central nervous system. As captopril is more liposoluble than enalapril, it is possible that the amount of drug reaching the central nervous system in man following chronic administration is greater for captopril than for enalapril. This clearly requires further research; in particular, it needs to be established whether other highly liposoluble ACE-inhibitors such as ramipril and quinapril produce substantially better improvements in quality of life in hypertensive patients than other less liposoluble ACE-inhibitors.

6 ADDITIONAL PHARMACODYNAMIC BENEFITS

A number of pharmacodynamic effects of ACE-inhibitors have been described and largely promoted by the manufacturers of the drugs for which the property was first extensively investigated. These include improvements in glucose tolerance, improvements in large arterial vessel compliance and regression of vascular and cardiac hypertrophy. It is almost certain now that these effects are class effects of ACE inhibitors and are not restricted to individual agents.⁸

7 USE IN CHILDREN AND DURING PREGNANCY

There is relatively little experience with the use of ACE inhibitors in children, with the exception of captopril. Because this is a highly specialised area, ACE-inhibitor therapy in children should be restricted to an appropriately experienced paediatric specialist. While ACE-inhibitors are not classically teratogenic (ie. they do not produce dysmorphic effects by interfering with organogenesis), they have considerable fetal toxicity, principally during the second and third trimesters. These effects probably result from foetal and uterine hypotension, and include oligohydramnios, neonatal anuria, pulmonary hypoplasia, mild to severe intrauterine growth retardation, persistent patent ductus arteriosus, skull hypoplasia and foetal death. ACE-inhibitors are not contraindicated in women of child bearing potential, but women who become pregnant while receiving ACE inhibitors should have their therapy changed to an alternative drug as soon as possible after pregnancy is confirmed.

8 CONCLUSIONS

There is little to choose between the various ACE-inhibitors for the vast majority of patients encountered in general practice. All of the ACE-inhibitors currently available (with the possible exception of captopril) can be confidently used to initiate mono-therapy using once daily dosing in mild to moderate hypertension. If adequate blood pressure control is not obtained with once daily dosing, it may be preferable to try dividing the dose rather than increasing the once daily dose, except for the longest acting ACE-inhibitors (e.g. lisinopril, ramipril). Some practitioners may find it easier to use fosinopril in patients with substantial renal impairment, while others may feel more comfortable with adjusting the dose of another ACE-inhibitor with which they have the most experience. It is possible that there are some differences between the ACE-inhibitors, such as the apparent lower incidence of withdrawals due to adverse events with quinapril compared to captopril and enalapril. Such differences are likely to be small and not of major clinical importance. The newer ACE-inhibitors have the economical advantage of being a little cheaper than equivalent doses of captopril or enalapril.

A practical recommendation is for prescribers to become familiar and confident with the use of one or two of the ACE-inhibitors and to be comfortable with adjusting the dose and dosage interval of these drugs to suit their individual patients' needs.

REFERENCES

1. Giles TD, Katz R, Sullivan JM, Wolfson P, Haugland M, et al. Short and long acting angiotensin converting enzyme inhibitors : a randomised trial of lisinopril versus captopril in the treatment of congestive heart failure. *AMJ Cardiol* 1989; 13: 1240-7.
2. Pouleur H, Rousseau M F, Oakley C, Ruden L. Difference in mortality between patients treated with captopril or enalapril in the Xamoterol in severe heart failure study. *AMJ Cardiol* 1991; 68: 71.
3. Todd PA, Goa KC. Enalapril. A reappraisal of its' pharmacology and therapeutic use in hypertension. *Drugs* 1992; 43: 346.
4. Taylor SH. The treatment of mild to moderate hypertension with ACE-inhibitors. *J Cardiovasc Pharmacol* 1990; (Suppl 2) 15: S24. 1990.
5. Conway J, Coats AJS, Bird R. Lisinopril and enalapril in hypertension : a comparative study using ambulatory monitoring. *J Human Hypert* 1990; 4: 235.
6. Knapp LE Frank GJ, McLain R, Rieger MM, Posuar E, Singer R. The safety and tolerability of quinapril. *J Cardiovasc Pharmacol* 1990;25: (Supp.2) S47.
7. Testa MA Anderson RB, Nackley JF, Hollenberg NK and the Quality-of-Life Study Group. Quality of life and antihypertensive therapy in men. A comparison of captopril with enalapril. *New Engl J Med* 1993; 328: 907-13
8. Paolisso G Gambardella A, Verza M, D'Amore A, Sgambato S, Varricchio M. ACE-inhibition improves insulin sensitivity in aged insulin resistant hypertensive patients. *J Human Hypertension* 1992; 6(3): 175-9

TABLE 1 Comparative Properties of ACE-Inhibitors

| | Captopril | Enalapril | Lisinopril | Perindopril | Fosinopril | Ramipril | Quinapril | Trandolapril |
|-----------------------------------|-----------|-----------|------------|--------------|----------------|--------------|-----------|--------------|
| Prodrug | No | Yes | No | Yes | Yes | Yes | Yes | Yes |
| Effect of food on absorption | Up to 35% | Nil | Nil | Up to 35% | Little | Nil | Up to 35% | Delay |
| Initial plasma half life (approx) | 2 hours | 11 hours | 13 hours | 9 hours | 4 hours | 17 hours | 3 hours | 22 hours |
| Tissue ACE binding (relative) | + | ++ | ++ | +++ | ++ | ++++ | ++++ | ++++ |
| Dosage regimen for hypertension | bd - tds | od - bd | od | od | od | od | od | od |
| Indicated in heart failure | Yes | Yes | Yes | Yes | No | No | No | No |
| Elimination | Renal | Renal | Renal | Mainly Renal | >50% Non Renal | Mainly Renal | Renal | Mainly Renal |