Feature Article

Raised blood pressure in the aged — to treat or not to treat*

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Curriculum vitae

Prof Brocklehurst is Professor of Geriatric Medicine at the University of Manchester. He obtained his MBChB at the University of Glasgow in 1947, his MD with Honours in 1950 and has been awarded FRCP Edinburgh and Glasgow and an Honorary MSc from the University of Manchester in 1974. He has been very involved in the geriatric field for the last two decades, and his present appointment (since 1970) is Professor of Geriatric Medicine of the University of Manchester and a Director of the Unit for Biological Ageing Research, University of Manchester, since 1974. In January 1988 he was knighted by Queen Elizabeth. He has published nine text books on Geriatrics and has contributed chapters to twenty text books written by others. He also has over 50 scientific papers, mainly in relation to the ageing bladder and incontinence, vitamins and nutrition in the elderly, the structure of geriatric care, stroke, and the geriatric day hospital.

KEYWORDS: Blood Pressure; Hypertension; Age Factors

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Summary

There is still doubt in the over 65s as to what constitutes hypertension and whether or not it should be treated. With advancing age there is a gradual increase in systolic blood pressure in both sexes. The first difficulty is to decide what is normal; if only modest improvements in morbidity and mortality can be shown from normalising high blood pressure, the benefits cannot be regarded as certain unless side effects of the therapeutic agents are less hazardous than the anticipated risks of the untreated state. The reaction to hypotensive drugs may vary because of age effects on the regulation of blood pressure through the baroreceptor reflex. Ageing also affects pharmacokinetics and pharmacodynamics. A few studies of the treatment of hypertension in the elderly are discussed.

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While it is well established that hypertension in the under 65s should almost always be treated, there is less agreement as to its management in patients above this age and particularly those over 75. This is because blood pressure, as measured in normal populations, shows an increase with age. This has been recorded in many studies with a considerable range of difference, but in general there is a rise in systolic pressure but little change in diastolic pressure (Fig 1). There is also some difference between the sexes. Figure 2 gives an illustration of one such

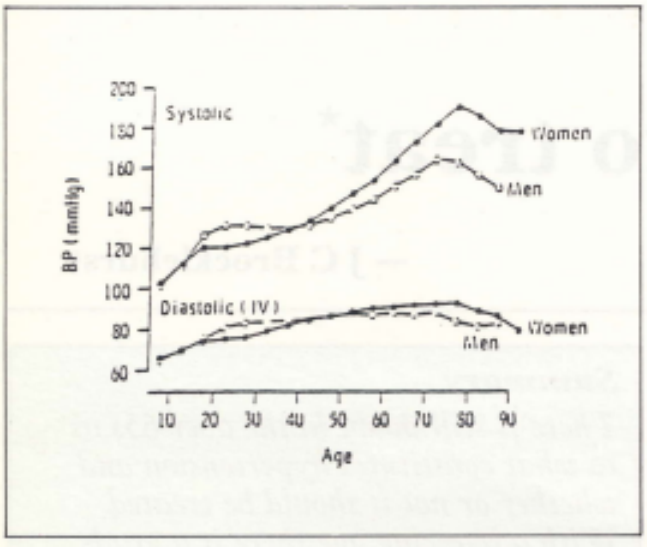

Figure 1
Mean arterial pressures by age and sex. Rhondda Fach and Vale of Glamorgan. Pooled data from four surveys. (Miall WE & Brennan PJ.)[13]

study and since it indicates that 33% of men aged 75 have a systolic blood pressure of 190 mm Hg, which in younger people would be regarded as abnormal, the question of treating one third of the population of this age group raises real problems. This is particularly so when the side effects of the drugs involved are borne in mind. In women the case is even more striking since the mean systolic blood pressure at age 75 is about 190 mm Hg. Any effective

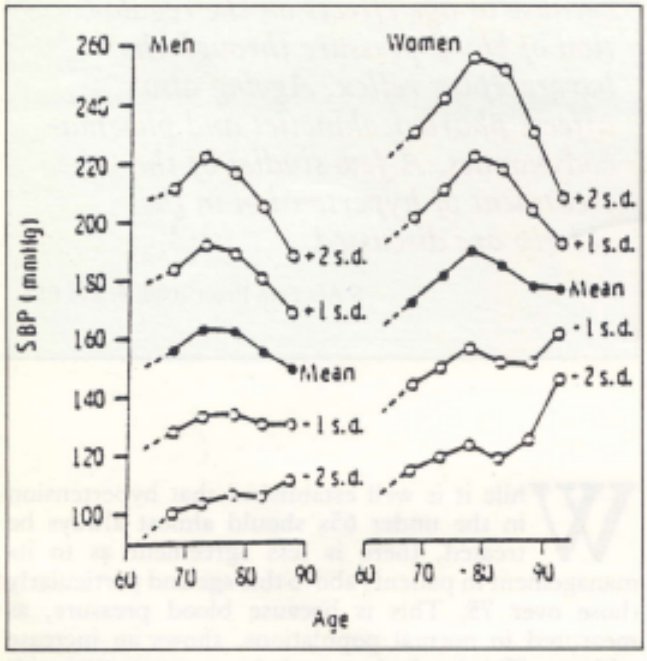

Figure 2
Mean systolic pressures and pressures 1 s.d. and 2 s.d. above and below the mean age and sex. Men and women aged 65 years and over. Rhondda Fach and Vale of Glamorgan. (Miall WE & Brennan PJ.)[13]

treatment of hypertension may produce postural hypotension leading to falls and fractures in the very old. The most benign form of treatment with thiazides may produce secondary gout and elevations of serum creatinine and glucose. The drugs required for more advanced treatment have additional hazards. Therefore the case has to be strongly made in favour of hypotensive therapy in old people before it may be generally recommended.

Malignant hypertension is rare in old age and it is the complications which commonly arise from benign hypertension that are important. These include stroke, congestive heart failure and myocardial infarction.

Before proceeding to analyse the trials that have been carried out, a word or two on the measurement of blood pressure is appropriate. Everyone recognises that blood pressure is relatively labile and, indeed, that there may be some diurnal variation[1]. The actual measurement is not always easy and it is important to distinguish which level is regarded as the diastolic blood pressure — Korotkov 4 (that is when muffling appears) or Korotkov 5 (disappearance of all sound). The latter is usually accepted as the diastolic blood pressure but difficulties may arise in patients with atrial

The first difficulty in hypertension in the elderly, is to decide what is normal.

fibrillation and in occasional others. The normal indirect method of measurement under-estimates systolic and over-estimates diastolic blood pressure when compared with direct readings from the radial artery[2]. However, this difference is the same in the old as in the young and thus the conventional method of measurement is acceptable at all ages.

The work of the Framingham Study[3] has shown beyond doubt that the reduction of high blood pressure in the under 65s diminishes the incidence of strokes and heart disease. Unfortunately this study has not dealt extensively with the over 65s although the most recent information does extend to those aged up to 74 and similar conclusions are reached that not only should high systolic and diastolic pressure be normalised, but that high systolic pressure alone is a risk factor in older as in younger subjects.

Rajala[4] and colleagues from Tampere in Finland fired off a lively correspondence in the Lancet in 1983 when they published findings of hypertension in subjects aged 85 and over, based on a population study of 83% of the population of that age in Tampere. They indicated that systolic and diastolic hypertension was negatively associated with mortality in the following two years and those most at risk had a systolic blood pressure less than 110 and a diastolic blood pressure less than 70. Lindholm[5] from Dalby in Sweden had evidence from a cohort of 174 people aged 70 and

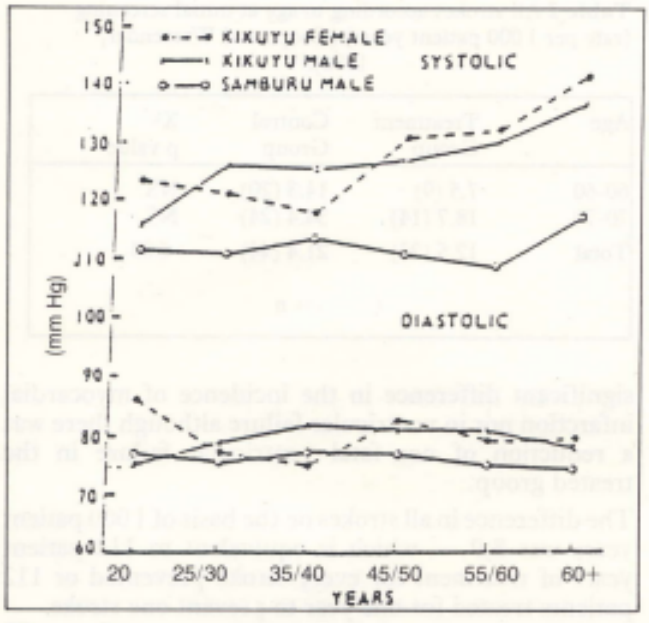

Figure 3
Age changes in systolic blood pressure among two African tribes with contrasting ecologies: the Kikuyu, sedentary agriculturalists, and the Samburu, nomadic cattle herders. (Bourliere F & Vallery-Masson J.)[9]

over living in the community in which they found no difference in mortality or in cardiovascular morbidity in those with hypertension in a ten-year prospective study (Fig 3). Fry[6] also reported no difference in mortality in 70-year-old hypertensives. Mitchell[7] reported on elderly residents in old people's homes in whom hypertensives treated with methyldopa did worse than controls. They divided their series of 549 individuals into tertiles according to diastolic blood pressure and found that in men aged 75 to 94 and women aged 85 to 94, those in the top tertile (highest diastolic blood pressure) had the best prognosis. This study was criticised by Langford and Abernethy[8] who indicated that for significant conclusions to be drawn, a sample ten times greater than that used (that is a sample of 5 000) would be needed. They suggested that the fact of admission to

Ageing has an important affect on pharmacokinetics and pharmacodynamics.

a residential home was itself a marker for impending death (although this would not explain the difference between the hypertensive and the non-hypertensive subjects).

Levels of blood pressure in older people may also relate to their ethnic and ecological backgrounds. For instance, a difference between two African tribes has been illustrated by Bourliere and Vallery-Masson[9] (Fig 4) who show a lifelong difference in systolic blood pressure levels between the Kikuyu and Samburu. In the former, systolic blood pressure rose from the age of 35 to 40 whereas in the latter it only began to rise at the age of 60. There was no difference in diastolic blood pressure. It showed no increase with age in either tribe. The Kikuyu are sedentary agriculturalists and the Samburu nomadic cattle-herders.

Complications which commonly arise from benign hypertension, especially in the aged, are important.

An attempt to dissociate the cardiovascular adaptations to high blood pressure from those simply due to ageing was made by Messerli et al[10] who compared a group of matched older patients with hypertension and a group of younger hypertensive patients. The mean ages were 73 and 32 years respectively, the mean systolic and diastolic blood pressures were 182/81 and 153/93. These differences gave an identical mean arterial pressure of 114 ± 16,7 for the old and 113 ± 16,2 for the young. They found significant differences between the two age groups in relation to many indices of haemodynamic and endocrine effects (eg cardiac output, stroke volume, renal blood flow, plasma renin

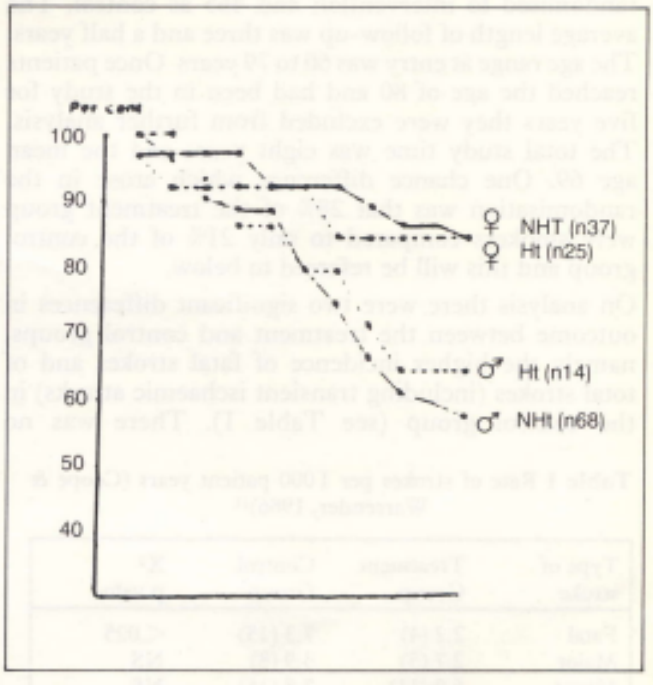

Figure 4
Survival rate of male and female pensioners who reached the age of 70 and had the diagnosis of hypertension (Ht) in comparison with pensioners without hypertension at that age (NHt). (Lindholm L, et al[5]*)*

activity) and on this basis they concluded that "essential hypertension is a pathophysiological process that accelerates the physiological haemodynamic fluid volume and endocrine processes of ageing . . .".

The ultimate answer to the question as to when to treat lies in a study of the beneficial effects, if any, of hypotensive treatment in comparative trials in old people. A number of these have been published and I should like to consider two in some detail. The first study by Coope and Warrender[11] is a trial within a large number of general practices of the treatment of hypertension identified on a community screening programme. The trial compared treated and untreated groups on the basis of random assignment after a

Blood pressure is labile and even diurnal variation occurs.

number of exclusion criteria were applied. It was not, however, a placebo nor a double-blind trial for practical reasons. The blood pressure levels chosen for treatment were either a systolic of 170 or a diastolic of 105, or both. The first line of treatment was atenolol 100 mg in the morning. If necessary, bendrofluazide 5 mg daily was added and if further treatment was needed methyl-dopa 500 mg was added. In cases where such treatment was inappropriate, atenolol was diminished to 50 mg or withdrawn altogether.

A total of 884 subjects entered the trial, 419 being randomised to intervention and 465 as control. The average length of follow-up was three and a half years. The age range at entry was 60 to 79 years. Once patients reached the age of 80 and had been in the study for five years they were excluded from further analysis. The total study time was eight years and the mean age 69. One chance difference which arose in the randomisation was that 28% of the treatment group were smokers compared to only 21% of the control group and this will be referred to below.

On analysis there were two significant differences in outcome between the treatment and control groups, namely the higher incidence of fatal strokes and of total strokes (including transient ischaemic attacks) in the control group (see Table 1). There was no

Table 1 Rate of strokes per 1 000 patient years (Coope & Warrender, 1986)[11]

Type of stroke	Treatment Group	Control Group	X^2 p value
Fatal	2.2 (4)	7.3 (15)	<.025
Major	2.7 (5)	3.9 (8)	NS
Minor	6.0 (11)	7.8 (16)	NS
TIA	1.6 (3)	2.4 (5)	NS
Total	12.5 (23)	21.4 (44)	<.030

( ) = n

Table 2 All strokes according to age at initial screening (rate per 1 000 patient years) (Coope and Warrender, 1986).[11]

Age	Treatment Group	Control Group	X^2 p value
60-60	7.5 (9)	14.3 (20)	NS
70-79	18.7 (14)	34.4 (24)	NS
Total	12.5 (23)	21.4 (44)	<.03

( ) = n

significant difference in the incidence of myocardial infarction nor in ventricular failure although there was a reduction of non-fatal ventricular failure in the treated group.

The difference in all strokes on the basis of 1 000 patient years was 8,9 — which is equivalent to 112 patient years of treatment for every stroke prevented or 112 patients treated for one year to prevent one stroke.

There were no important side effects in the treatment compared to the control group although there were significant biochemical changes with elevation of blood urea, serum creatinine, blood sugar and serum uric acid at both one and two years of treatment. The total death rate for the two groups was the same and there was no difference in all causes of mortality except stroke. When the subjects were divided by age into 60-69 and 70-79 (at entry) there was no significant difference between treatment and control groups in either of these two age cohorts although in the 60-69 group there were more than twice as many strokes per 1 000 patient years (see Table 2).

When the smokers and non-smokers were considered separately (Table 3) there was no statistical difference

Table 3 All strokes according to smoking at initial screening — rate per 1 000 patient years (Coope & Warrender, 1986)[11]

	Treatment Group	Control Group	X^2 p value
Smokers	17.4 (9)	23.1 (10)	NS
Non-smokers	10.5 (14)	20.9 (34)	<.03
Total	12.5 (23)	21.4 (44)	<.03

( ) = n

in the incidence of stroke between the treatment and control group among the smokers and the difference lay, therefore, among the non-smokers.

The second important study is that of the "European Working Party Trial on high blood pressure" in which physicians from nine European countries collaborated. Results were published in 1985 and 1986[12]. This trial differed from the general practice trial of Coope and Warrender, inasmuch as the patients treated were those referred to hospital clinics and discovered to be

hypertensive. The general practice trial was carried out on a random screening of a population which was not reporting illness. The minimum blood pressure measurements at entry were different inasmuch as blood pressure had to be equal to or greater than both systolic of 160 and diastolic of 90. The minimum age at entry was 60 years. The initial treatment was by hydrochlorothiazide 25 mg and triamterene 50 mg daily increasing this to twice daily if necessary and thereafter adding 500 mg of methyl-dopa, again if necessary. A total of 840 patients were entered, 416 in the treatment group and 424 in the control group, with an average period of treatment of just over four and a half years.

The ultimate answer to the question when to treat, lies in the beneficial effects, if any, of hypotensive treatment.

The findings were analysed in three ways — fatal events, non-fatal events requiring termination of the trial and non-fatal events not requiring termination of the trial. These are shown in Tables 4, 5 and 6. It will be seen that in contrast to the previous trial, there was no significant difference in fatal strokes between the two groups and although there was a significant difference in the total number of cardiovascular events this significance lay in the number of myocardial infarcts and in the total number of cardiac events including sudden death.

In non-fatal terminating events, severe congestive heart failure occurred more than twice as often in the control group and again there was a significant difference in the total number of cardiovascular events. In the number of non-fatal, non-terminating events, there was a significant difference in the incidence of cerebral thrombosis.

The side effects, apart from biochemical changes, were not important.

. . . another study gave evidence that there was little or no benefit in treatment beyond 80.

The second paper (European Working Party, 1986) made a separate analysis by age and blood pressure level of the data and gave some evidence that treatment benefit decreased with advancing age and that there was little or no benefit in treatment beyond the age of 80. In addition, the cardiovascular mortality and terminating events were significantly related to systolic but not to diastolic blood pressure at the time of entry.

Table 4 Fatal events per 1000 patient years (European Working Party, 1985)[12]

	Treatment Group	Control Group	X^2 p value
Stroke	9 (12)	15 (19)	NS
Myocardial infarct.	5 (7)	13 (16)	.043
Total cardiac	12 (17)	23 (29)	.048
Total cardio-vascular	30 (42)	48 (61)	.023

( ) = n

Table 5 Non-fatal terminating events per 1000 patient years (European Working Party, 1985)

	Treatment Group	Control Group	X^2 p value
Severe CCF	5 (7)	13 (17)	.014
Cerebral haemorrhage	3 (4)	2 (3)	NS
Papilloedema, retinal haemorrhage or exudates	5 (0)	4 (5)	
Total cardiovascular	8 (11)	20 (25)	.0064

( ) = n

Table 6 Non-fatal non-terminating events per 1000 patient years (European Working Party, 1985)

	Treatment Group	Control Group	X^2 p value
Cerebral thrombosis	4 (5)	10 (12)	.026
Total cerebro-vascular	9 (13)	20 (24)	.053
Total cardiac	32 (42)	31 (37)	NS

( ) = n

It is concluded from this trial that the treatment of 1 000 patients each for one year, would lead to 18 fewer cardiovascular deaths, including six fewer deaths from stroke, and 25 fewer non-fatal cardiovascular events including 12 fewer strokes and eight fewer cases of severe congestive heart failure.

A comparison between these two trials indicates that while 112 patient treatment years are required to

prevent one stroke in the general practice series, only 56 patient treatment years are required to prevent one stroke on the hospital series. The difference between these two figures must reflect the essential difference of patients recruited to the two trials — many of the former having asymptomatic hypertension at entry whereas many of the latter were symptomatic. A further difference is the absence of a significant difference in cardiac mortality and morbidity in the first group compared to the second.

The final conclusions to be drawn from all the evidence presented above is still uncertain in relation to the treatment of hypertension in the over 70s. It seems clear that treatment is not indicated in patients over 80 and in patients with diastolic blood pressure levels below 95. Systolic blood pressure, on the other hand, seems to be the important index for treatment as suggested from the Framingham study, and treatment should be seriously considered in asymptomatic patients with a systolic blood pressure over 190 or symptomatic patients with a systolic blood pressure over 170.

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SCHEDULING STATUS: S4
PROPRIETARY NAME:

RENITEC* 5 Tablet

RENITEC* 20 Tablet

COMPOSITION

Each RENITEC 5 tablet contains 5 mg enalapril maleate, MSD.
Each RENITEC 20 tablet contains 20 mg enalapril maleate, MSD.

PHARMACOLOGICAL CLASSIFICATION

A.7.1.3 Vascular medicines - other hypotensives

PHARMACOLOGICAL ACTION

RENITEC (enalapril maleate, MSD) is the maleate salt of enalapril, a derivative of two amino acids, L-alanine and L-proline. Following oral absorption, RENITEC is hydrolysed to enalaprilat, which is a specific, long-acting, non-sulphhydryl angiotensin converting enzyme inhibitor.

INDICATIONS

RENITEC is indicated in:
all grades of essential hypertension
renovascular hypertension
congestive heart failure

CONTRA-INDICATIONS

Pregnancy and lactating mothers.
Hypersensitivity to the product or its components.

DOSAGE AND DIRECTIONS FOR USE

ORAL: Since its absorption is not affected by food, RENITEC tablets may be administered before, during or after meals.

The usual daily dosage ranges from 10 to 40 mg in all indications. RENITEC may be administered once or twice a day. The maximum dose studied in man is 80 mg daily.

In the presence of renal insufficiency and cardiac failure, lower doses and/or less frequent administration of RENITEC may be required (see **SIDE EFFECTS AND SPECIAL PRECAUTIONS**).

Essential Hypertension

The initial dose is 10 to 20 mg depending on the degree of hypertension and is given once daily. In mild hypertension the recommended initial dose is 10 mg daily. For other degrees of hypertension the initial dose is 20 mg daily. The usual maintenance dose is one 20 mg tablet taken once daily. The dosage should be adjusted according to the needs of the patient.

Concomitant Diuretic Therapy in Hypertension

Symptomatic hypotension may occur following the initial dose of RENITEC; this is more likely in patients who are being treated currently with diuretics.

Caution is recommended, therefore, since these patients may be volume or salt depleted. The diuretic therapy should be discontinued for 2-3 days prior to initiation of therapy with RENITEC. If this is not possible, the initial dose of RENITEC should be low (5 mg or less) to determine the initial effect on the blood pressure. Dosage should then be adjusted according to the needs of the patient.

Renovascular Hypertension

Since blood pressure and renal function in such patients may be particularly sensitive to ACE inhibition, therapy should be initiated with a lower starting dose (e.g. 5 mg or less). The dosage should then be adjusted according to the needs of the patient. Most patients may be expected to respond to one 20 mg tablet, taken once daily. For patients with hypertension who have been treated recently with diuretics, caution is recommended. (See paragraph above.)

Dosage in Renal Insufficiency

Generally, the intervals between the administration of enalapril should be prolonged and/or the dosage reduced.

Renal Status	Creatinine-Clearance ml/min	Initial Dose mg/day
Mild impairment	<80 >30	5
Moderate impairment	≤30 >10	2,5
Severe impairment. Normally, these patients will be on dialysis	≤10	2,5 mg on dialysis days†

†Enalapril is dialysable. Dosage on non-dialysis days should be adjusted depending on the blood pressure response.

Congestive Heart Failure

Blood pressure and renal function should be monitored closely before and after starting treatment with RENITEC (see **Precautions**) because hypotension and consequent renal failure have been reported. In patients with CHF, the usual maintenance dose is 10-20 mg daily, given in single or divided doses. The initial dose of RENITEC in patients with CHF (especially renally impaired or sodium- and/or volume-depleted patients) should be lower (5 mg or less), and it should be administered under close medical supervision to determine the initial effect on the blood pressure. If possible, the dose of diuretic should be reduced before beginning treatment. The appearance of hypotension after the initial dose of RENITEC does not imply that hypotension will recur during chronic therapy with RENITEC and does not preclude continued use of the drug.

In the absence of, or after effective management of symptomatic hypotension following initiation of therapy with RENITEC in CHF, the dose should be gradually increased, depending on the patient's response, to the usual maintenance dose (10-20 mg) given in a single or divided dose. This dose titration may be performed over a 2-4 week period, or more rapidly if indicated by the presence of residual signs and symptoms of heart failure.

SIDE EFFECTS AND SPECIAL PRECAUTIONS

Dizziness and headache were the more commonly reported side effects. Other side effects occurred and included fatigue, asthenia and hypotension, orthostatic hypotension, syncope, nausea, diarrhoea, muscle cramps, rash, cough and angioneurotic oedema.

Hypersensitivity/Angioneurotic Oedema

Angio-oedema has been reported in patients treated with RENITEC. Hypersensitivity reactions such as angioneurotic oedema with swelling of the face, the tongue, and the glottis together with serious shortness of breath have been reported in individual cases. In such instances RENITEC should be discontinued and appropriate medical measures should be initiated immediately.

Clinical Laboratory Test Findings

Increases in blood urea and serum creatinine, usually reversible upon discontinuation of RENITEC, have been seen. These are most likely to occur in the presence of bilateral renal artery stenosis, especially in patients with renal insufficiency.

Transient increase in blood urea and serum creatinine may occur in patients without evidence of pre-existing renal impairment, especially in patients taking diuretics. Slight decreases in haemoglobin, haematocrit and white cell count, as well as elevation of liver enzymes, have been reported.

Symptomatic Hypotension

This has occurred following the initial dose of RENITEC. It is more likely to occur if the patient has been volume-depleted, e.g. by prior diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting. In patients with heart failure, symptomatic hypotension is most likely to occur in those patients with more severe degrees of heart failure, as reflected by the use of high doses of loop diuretics, hyponatraemia or functional renal impairment. Should hypotension develop, the patient should be placed in a supine position. Volume repletion with oral fluids or intravenous normal saline solution may be required. Treatment with RENITEC may usually be continued following restoration of effective blood volume and pressure.

In some patients with congestive heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with RENITEC. This effect is anticipated, and usually is not a reason to discontinue treatment. If hypotension becomes symptomatic, a reduction of dose or discontinuation of RENITEC may be necessary.

Impaired Renal Function

Patients with renal insufficiency may require reduced and/or less frequent doses of RENITEC. (See **DOSAGE AND DIRECTIONS FOR USE**.) In some patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, increases of blood urea and serum creatinine, reversible upon discontinuation of therapy, have been seen. This is especially likely in patients with renal insufficiency.

Some hypertensive patients with no apparent pre-existing renal disease have developed minor and usually transient increases in blood urea and serum creatinine when RENITEC has been given concomitantly with a diuretic. Dosage reduction of RENITEC and/or discontinuation of the diuretic may be required.

Surgery/Anaesthesia

In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, enalapril blocks angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Paediatric Use

RENITEC has not been studied in children.

Drug Interactions

The combination of RENITEC with other antihypertensive drugs may increase the antihypertensive effect, especially in combination with diuretics.

The combination of RENITEC with beta-adrenergic blocking agents and methyldopa improves the efficacy of lowering the blood pressure.

Ganglionic blocking agents or adrenergic blocking agents, combined with RENITEC, should only be administered with careful observation of the patient.

Because of lack of experience, concomitant treatment of RENITEC with calcium antagonists is not recommended.

The lithium elimination may be reduced. Therefore the lithium levels of serum should be carefully compared if lithium salts are to be administered.

Serum Potassium

In patients with renal failure, the administration of RENITEC may lead to elevation of serum potassium. Potassium supplements, or potassium sparing diuretics such as spironolactone, triamterene or amiloride are usually not recommended, particularly in patients with impaired renal function, since they may lead to significant increases in serum potassium. If concomitant use of the above-mentioned drugs is deemed appropriate, they should be used with caution and with frequent monitoring of serum potassium.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Limited data are available with regard to overdosage in humans. The most likely manifestation of overdosage would be hypotension, which can be treated, if necessary, by intravenous infusion of normal saline solution.

Several hypertensive patients in clinical studies have received as much as 80 mg of enalaprilat intravenously over a fifteen minute period. No adverse effects, other than those associated with recommended dosages, were observed.

Enalaprilat may be removed from the general circulation by haemodialysis.

CONDITIONS OF REGISTRATION

Advertising to the professions only.

IDENTIFICATION

RENITEC 5 is a white, barrel-shaped, biconvex, 7 x 3 mm tablet, one side engraved "RENITEC", other side scored.

RENITEC 20 is a peach coloured, barrel-shaped, biconvex, 7 x 8 mm tablet, one side engraved "RENITEC", other side scored.

PRESENTATION

RENITEC tablets are available in packs of 30 (with desiccant).

STORAGE INSTRUCTIONS

Store the tablets with desiccant in a dry place below 25 °C. Protect from light.
KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS

RENITEC 5: T/7.1.3/164
RENITEC 20: T/7.1.3/166

NAME AND BUSINESS ADDRESS OF THE APPLICANT

LOGOS PHARMACEUTICALS (PTY) LTD†, Old Pretoria Main Road, Halfway House 1685, Republic of South Africa.

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