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ATENOLOL AND CHLORTHALIDONE IN COMBINATION FOR HYPERTENSION

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1 The hypotensive effect of single daily dosing with atenolol 100 mg and chlorthalidone 25 mg given alone or in combination has been assessed in a double-blind, crossover, placebo controlled trial in fifteen hypertensive patients.

2 Average lying blood pressures were:
Placebo 155.4/103.9 mm Hg, atenolol 134.6/85.8 mm Hg, chlorthalidone 139.5/90.1 mm Hg, combination 127.7/82.5 mm Hg.

3 The effect of the combination therapy in reducing lying diastolic pressure compared with placebo (a fall of 21.4 mm Hg) was significantly less than the 31.9 mm Hg fall predicted from the sum of the individual effects ($P=0.01$).

4 Observations on blood pressure at rest and under mental, isometric and bicycle ergometer stress were made pre-dose and post-dose for a 12 h period at the end of the last treatment period.

5 Lying blood pressure declined from the zero hour (pre-dose) reading on all treatments to a low at 15.00–18.00 h and then rose again.

6 The rise in systolic blood pressure after isometric exercise and mental stress was of a similar magnitude with all four treatment regimes.

7 Atenolol, alone and in combination with chlorthalidone, reduced the blood pressure and the pulse rate increase on exercise 2 h post-dose when compared with readings 24 h post-dose.

8 Once daily dosing with a combination of atenolol and chlorthalidone produced a fall in supine blood pressure over a 24 h period but the effect on exercise induced changes was not uniform over this period.

Introduction

The successful treatment of the hypertensive patient depends on two main factors. Firstly the doctor must prescribe medication that is appropriate both in terms of effectiveness in reducing blood pressure and lack of side effects, and secondly the patient must take the medication prescribed regularly.

Failure of patients to comply with prescribed drug therapy appears to be an important factor in failure to obtain satisfactory blood pressure control (Haynes, Sackett, Gibson, Taylor, Hackett, Roberts & Johnson, 1976). One approach to the problem of compliance is to give therapy in the form of a single daily drug dosage (Gatley, Dunne, Handley & Hazleman, 1968).

We report here a study of a single daily dose regimen comprising atenolol, a cardioselective β-adrenergic receptor blocking agent (Barrett, Carter, Fitzgerald, Hull & Le Court, 1973) and the diuretic chlorthalidone. The trial was designed to assess the interaction between these agents and to examine 24 h control of blood pressure.

Methods

Treated hypertensive patients were recruited for the study from a hypertension clinic. They were invited to participate if they were males aged 18 to 64 years or post-menopausal females less than 65 years old and had no history of obstructive airways disease, gout, diabetes or ischaemic heart disease. In addition, a normal chest X-ray, ECG, haemoglobin, random blood sugar and serum biochemical profile was

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obtained, together with a creatinine clearance estimated at above 60 ml/min. Formal ethical consent was obtained from each patient and the study was approved by the Ethics Committee of the Royal Postgraduate Medical School.

The patients first entered a period of 1 month placebo therapy during which time they were seen every 2 weeks. They were excluded from the study at this stage if they had lying diastolic pressure after 10 min rest below 95 mm Hg or above 115 mm Hg.

Criteria for exclusion from the formal trial were lying diastolic blood pressure above 115 mm Hg, development of hypertensive or drug related complications, unacceptable side effects, or significant intercurrent illness.

Design of trial

The formal trial was of double-blind randomised cross-over design. Four treatment phases of 4 weeks each were used and these consisted of (a) atenolol 100 mg, (b) chlorthalidone 25 mg, (c) atenolol 100 mg + chlorthalidone 25 mg and (d) placebo. The treatment orders were randomly allocated so that each treatment was given with approximately equal frequency at each period. Patients were asked to take two tablets each day, one from each of two bottles, i.e. an active or placebo atenolol and an active or placebo chlorthalidone at between 07.00 h and 08.00 h. Throughout the study they received tablets which were identical in appearance and taste. The patients visited the out-patient laboratory every 2 weeks and were seen approximately 8 h after their drug dose. Recordings of blood pressure and pulse were taken in duplicate using a Roche Arteriosonde 1217 sphygmomanometer after 10 min supine rest and 3 min standing. Pulse rate was measured by a 1 min radial pulse count.

At the end of every treatment phase blood was taken for electrolytes and serum biochemical profile. In addition a self administered side effects questionnaire was completed (Bulpitt, Dollery & Carne, 1974). Pill counts were performed at every visit to check on compliance.

24 h blood pressure control

At the end of the last treatment phase each patient attended the clinical laboratory for a day study. They attended fasting at 07.00 h–08.00 h without having taken their therapy for that day. Observations were made before dosing and every 2 h after dosing for 12 h.

The observations consisted of measurements of blood pressure and pulse rate after lying 10 min and standing 3 min as above. The effects of three types of stress on blood pressure were also measured. These were isometric handgrip, mental stress and exercise on a bicycle ergometer.

Isometric handgrip was maintained for 3 min at a contraction of 30% of maximal using a mercury sphygmomanometer cuff as a dynometer held in the left hand. Blood pressure was measured during the last half minute of handgrip in the right arm with the Arteriosonde. Mental stress was achieved using a mental arithmetic test, subjects were asked to take a 2 digit number from a 4 digit number as rapidly as possible calling each number out. Blood pressure was recorded during the last 30 s of a 2 min period with the Arteriosonde. Exercise was performed on a bicycle ergometer at 450 or 650 kpm for 5 min, the load depending on the individual patients exercise ability. Blood pressure readings were taken in triplicate with a Hawksley random zero sphygmomanometer during the last 2 min of this exercise.

An ECG was recorded continuously throughout the stress tests via a Grass Polygraph Recorder. Pulse rates were counted directly from the ECG during the last half minute of each stress test.

A light breakfast was given after drug dosing and patients had lunch and evening meal in the laboratory. They were allowed to walk about between test periods if they so desired.

Open study

At the end of the double-blind trial fourteen of the patients entered an open study during which they took a single combination tablet of atenolol 100 mg and chlorthalidone 25 mg (Tenoretic). Blood pressures and pulse recordings were taken fornightly for two visits as above, with electrolyte and biochemical profile values at 1 month.

Analysis

The data from the trial was analysed for a factorial experiment to show main effects and interactions using analysis of variance techniques (Armitage, 1971). The 'main effects' were calculated by comparing the two phases in which a particular agent 'A' was included in the treatment regimen with the two in which it was not included. This is simply represented as:-

(pressure when drug 'A' given alone) + (pressure when drug 'A' given in combination) − (pressure when placebo given alone) − (pressure when drug 'B' given alone) ÷ 2.

The equation is divided by two as each treatment agent was administered twice in the trial. The effects of the combination of the drugs were compared with the observed changes caused by the individual treatment regimens. The analysis assessed whether the combined effect of the addition of the two active therapies was significantly greater or less than would be predicted, i.e. whether the two drugs are simply additive, or significantly greater or less than additive when taken together.

Results

Patients

Seventeen patients entered the study. Two withdrew, one because of a move in job to another town and one because of inability to keep his regular appointments; fifteen patients completed the study: eleven males and four females. The age range was 31 to 64 years.

Compliance as assessed by tablet counts in these subjects was satisfactory. Eight patients took all tablets prescribed and the remaining seven patients took more than 95% of prescribed tablets.

Results of randomised trial

The blood pressure and pulse results refer to the last recordings of each of the treatment phases. This was to minimise carry-over effects and the mean values are shown in Table 1. All three active treatments produced significant falls in systolic and diastolic blood pressure ($P<0.001$) compared to placebo (lying blood pressure (mm Hg) placebo 155.4/103.9, atenolol 134.6/85.8, chlorthalidone 139.5/90.1, combination 127.7/82.5). The combination therapy was significantly more effective than chlorthalidone for all blood pressure measurements, ($P<0.01$) but only significantly more effective than atenolol in reducing lying systolic pressure ($P<0.05$). There was a significant decrease in pulse rate with atenolol treatment ($P<0.001$), alone or in combination.

The results of the analysis of variance are shown in Table 2. There was a significant interaction for lying diastolic pressure, the effect of the two drug combination being significantly less than the predicted additive effect which was -31.9, the observed effect being -21.4 ($P=0.01$).

The effect of the treatment regimens on the biochemical indices of potassium, creatinine, uric acid and calcium is shown in Table 3. There was a significant ($P<0.001$) decrease in potassium with chlorthalidine treatment (placebo 3.83 mmol/l, chlorthalidone 3.48 mmol/l, atenolol 3.94 mmol/l, combination 3.58 mmol/l). Elevation of uric acid and calcium with chlorthalidone failed to reach conventional statistically significant levels ($P=0.09$). Atenolol, when added to chlorthalidone or placebo, caused an increase in potassium of 0.1 mmol/l ($P=0.29$) and in uric acid of 0.027 mmol/l ($P=0.18$).

The data on side effects are shown in Table 4 and six of the symptoms are recorded. In no instance did an excess of symptoms with any one therapy reach statistical significance, though the significance value of the effect of atenolol in producing cold extremeties was $P<0.1$.

Substitution of the combination tablet at the end of the trial in fourteen patients produced blood pressure readings similar to those during the combination treatment phase, being 126.9/80.4 lying and 123.3/89.4 standing, as compared with 129.6/82.9 and 129/89.2 on the individual components taken as two tablets.

12 h study results

Blood pressure and pulse recordings during the 12 h study were made in five patients on atenolol alone, four patients on chlorthalidone alone, three patients on atenolol and chlorthalidone and three patients on placebo. The mean blood pressures and pulse rates for the groups over the day are shown for lying value in Figure 1 and for ergometer exercise in Figure 2. There was little difference in the pattern of lying blood pressure control between the groups. Blood pressure fell on all treatments over the first half of the day to a low at 15.00–17.00 h. At 6 h post-dose falls in mean arterial pressure from 24 h values averaged for placebo 10.2 mm Hg to 113.7 mm Hg, atenolol 9.9 mm Hg to 99.7 mm Hg, chlorthalidone 8.6 mm Hg to 103.8 mm Hg, and combination 6.1 mm Hg to 93 mm Hg. A decrease in pulse rate and systolic blood pressure on exercise in the subjects who received atenolol as part of their therapy was observed during the period 2 to 4 h (Figure 2). The magnitude of increase in systolic blood

Table 1 Mean ± s.e. mean blood pressure (mm Hg) and pulse rate (beats/min) for each treatment phase, lying and standing

	Placebo	*Atenolol*	*Chlorthalidone*	*Atenolol and chlorthalidone*
Lying				
Systolic	155.4 ± 3.6	134.6 ± 3.5	139.5 ± 4.4	127.7 ± 3.7
Diastolic	103.9 ± 2.3	85.8 ± 2.2	90.1 ± 1.3	82.5 ± 2.0
Pulse	80.7 ± 3.5	60.0 ± 1.9	83.2 ± 3.1	59.7 ± 2.5
Standing				
Systolic	161.0 ± 3.6	133.5 ± 4.1	141.5 ± 3.6	127.5 ± 4.3
Diastolic	112.9 ± 2.0	93.7 ± 2.9	100.8 ± 2.0	88.3 ± 2.6
Pulse	89.9 ± 4.0	61.3 ± 2.1	93.9 ± 3.5	63.9 ± 2.6

Table 2 Changes of blood pressure (mm Hg) and pulse rate (beats/min): Observed drug effects (drug less placebo differences) and main effects calculated as the pressure when the drug was given less the pressure when not given. Also shown is the significance of the main effects (***$P<0.001$, **$P<0.01$) and of any drug interaction i.e. the comparison of the observed effect of the combination (Column 3) with the theoretical sum of the observed individual effects (Column 6)

	Observed drug effects			*Calculated main effects*		*Theoretical sum of individual effects (Columns 1 and 2)*	*Significance level of interaction*
	Atenolol	*Chlorthalidone*	*Combination*	*Atenolol*	*Clorthalidone*		
Lying							
Systolic	−20.8	−15.9	−27.7	−16.3***	−11.4**	−36.7	0.25
Diastolic	−18.1	−13.8	−21.4	−12.7***	−8.6***	−31.9	0.01
Pulse	−20.7	+ 2.5	−21.0	−22.2***	+1.2	−18.2	0.63
Standing							
Systolic	−27.5	−19.2	−33.5	−20.8***	−12.7**	−46.7	0.11
Diastolic	−19.2	−12.1	−24.6	−15.9***	−8.7**	−31.3	0.12
Pulse	−28.6	+4	−25.9	−29.3***	+3.4	−24.6	0.82

Table 3 Biochemical indices during treatment phases: Observed changes and main effects (see text)

	Observed				*Main effects*	
	Placebo	*Atenolol*	*Chlorthalidone*	*Combination*	*Atenolol*	*Chlorthalidone*
Potassium (mmol/l)	3.83	3.94	3.48	3.58	+0.104	−0.356**
Creatinine (μmol/l)	89.1	93.9	93.9	96.1	+3.5	+3.5
Uric acid (mmol/l)	0.351	0.390	0.397	0.411	+0.027	+0.034†
Calcium (mmol/l)	2.47	2.45	2.50	2.49	−0.014	0.036†

**$P<0.01$, †$P<0.1$

Table 4 Recorded side effects as percentage of patients complaining on different therapies

Symptom	*Placebo*	*Atenolol*	*Chlorthalidone*	*Atenolol and chlorthalidone*
Sleepyness	7%	20%	20%	27%
Dry mouth	0%	7%	13%	20%
Blocked nose	7%	7%	20%	20%
Dreams	13%	13%	20%	7%
Cold hands and feet	13%	33%	13%	33%
Short of breath	27%	13%	27%	27%

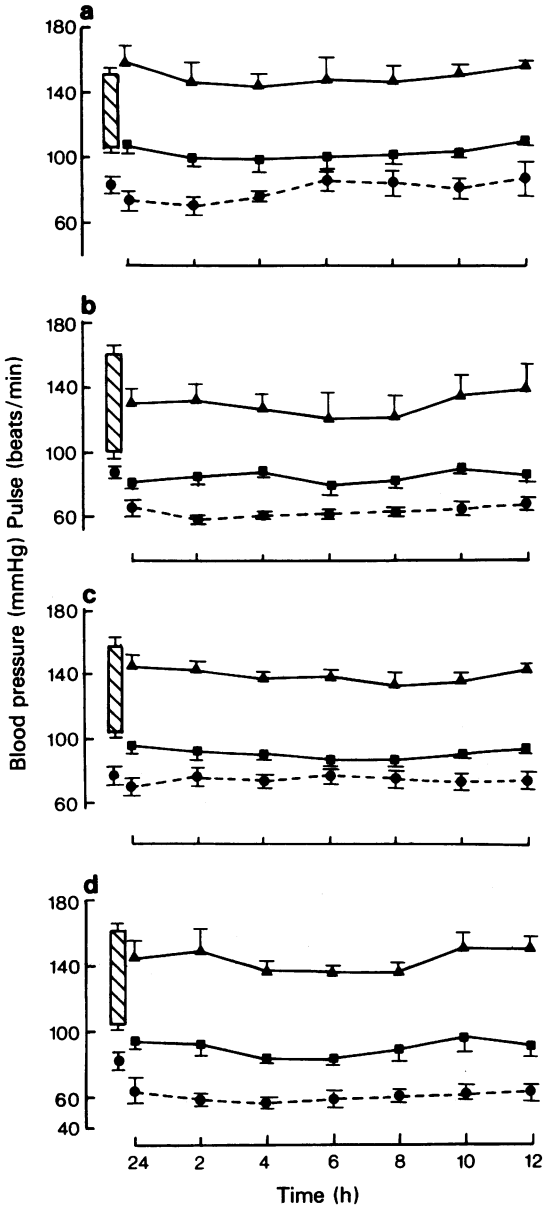

Figure 1 Day study: Lying blood pressure (systolic ▲, diastolic ■) and pulse (●) in each treatment group, mean ± s.e. mean (a placebo $n=3$; b atenolol and chlorthalidone $n=3$; c chlorthalidone $n=4$; d atenolol $n=5$). Hatched bars represent mean placebo values during trial run-in and placebo phases. 24 h = pre-dose.

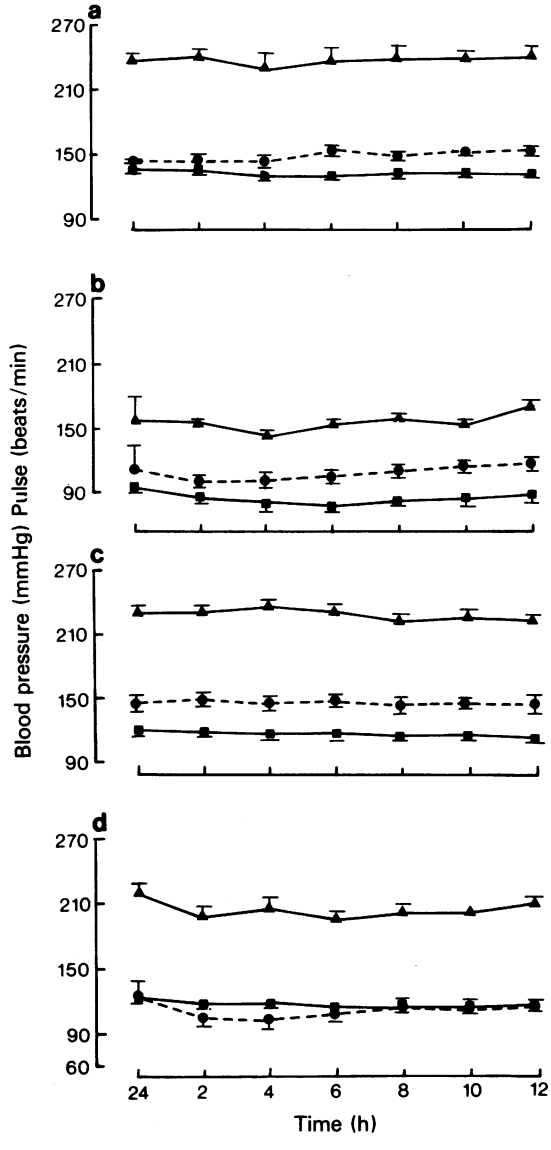

Figure 2 Day study: Exercise blood pressure (systolic ▲, diastolic ■) and pulse (●) in each treatment group, mean ± s.e. mean. (a placebo $n=3$; b atenolol and chlorthalidone $n=3$; c chlorthalidone $n=4$; d atenolol $n=5$). 24 h = pre-dose.

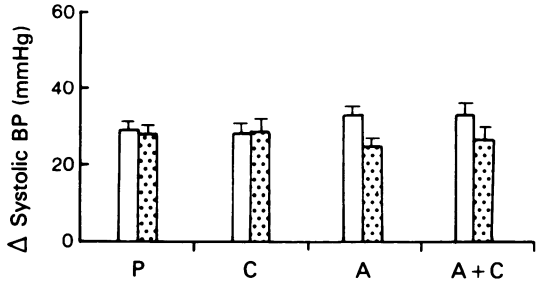

Figure 3 Day study: Increase in systolic blood pressure after mental stress (□) and isometric exercise (▨) shown as mean ± variance for all studies performed in each treatment group.
P = placebo;
C = chlorthalidone;
A = atenolol;
A + C = combination

pressure in the different treatment groups induced by isometric and mental arithmetic stress was not significantly different (Figure 3).

Six of the subjects were restudied when they had received 1 months' therapy with atenolol and chlorthalidone in the single combination tablet (Tenoretic). They had been taking either placebo or chlorthalidone for their previous day study performed during the course of the double-blind trial. The protocol was the same as for the original 12 h study and exercise loads were identical but the duration of study was reduced to 6 h. The changes in systolic blood pressure during the stress tests are shown in Figure 4. The increases in systolic blood pressure during the stress tests 24 h after dosing with the atenolol-chlorthalidone combination tablet were not significantly different to those which had been obtained 24 h after placebo or chlorthalidone alone. There was no significant effect of β-adrenoceptor blockade on the rise in pressure with isometric handgrip or mental stress at 2 and 4 h post-dose. There was, however, a highly significant ($P < 0.001$) decrease in the bicycle exercise induced rise of systolic blood pressure at 2 and 4 h after β-adrenoceptor blocker administration. This coincided with a significant reduction in exercise tachycardia (115.3 ± 6.5 beats/min at 24 h, 102.3 ± 4.6 at 2 h, 101.7 ± 4.5 at 4 h, $P < 0.005$).

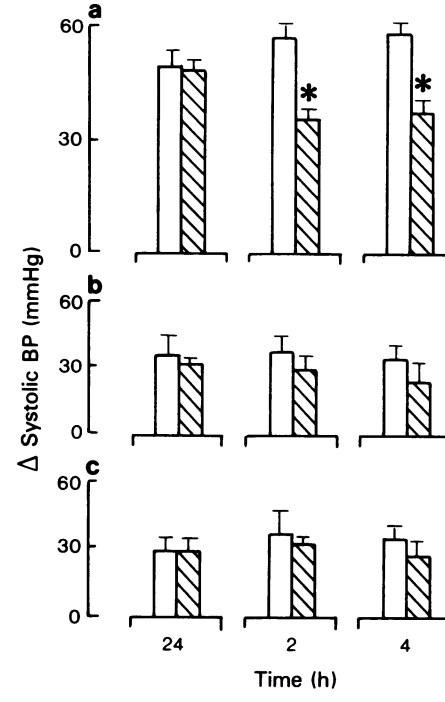

Figure 4 Increase in systolic blood pressure after stress (a ergometer exercise; b isometric exercise; c mental stress). □ placebo or chlorthalidone. ▨ atenolol and chlorthalidone combination tablet (Tenoretic). $n = 6$, mean ± s.e. mean. 24 h = pre-dose. *$P < 0.05$ when compared to 24 h reading.

Discussion

The use of a fixed ratio drug regime in therapeutics has the advantage of being simple, but has the disadvantage of limiting the ability to titrate an individual patient's dosage.

The dose response curves of atenolol (Myers, Lewis, Steiner & Dollery, 1976; Jeffers, Webster, Petrie & Barker, 1977) and chlorthalidone (Cranston, Juel-Jensen, Semmence, Handfield-Jones, Forbes & Mutch, 1963; Tweeddale, Ogilvie & Ruedy, 1977), are known to be relatively flat, and a single dose of 100 mg atenolol or 25 mg chlorthalidone would be expected to produce a near maximal effect on blood pressure. The objective of this study was to study the effect of single daily dosing with this drug combination and see whether this would give blood pressure control over 24 h.

The flat dose-response curve means in practice that there is a limit to additional fall in blood pressure that can be achieved by increasing the dose of a single agent. We have shown that there was a greater effect on blood pressure with the combination of drugs than with one alone. This has also been shown for other fixed drug combinations (Pearson, Bending, Bulpitt, George, Hole, Williams & Breckenridge, 1976; Chalmers, Horvath, Tiller & Bune, 1976) in studies using a similar protocol. The present study demonstrates, however, that the effect on blood pressure of the addition of atenolol and chlorthalidone

is significantly less than the sum of the individual effects.

One potential advantage of a β-adrenoceptor blocking agent-diuretic combination is a sparing effect on diuretic induced hypokalaemia (Hettiarachchi, Ramsay, Davies, Fraser & Watson, 1977). We were unable to demonstrate a significant interaction of atenolol on potassium, the mean level on chlorthalidone being 3.48 mmol/l against 3.58 mmol/l on the combination ($P=0.29$).

Atenolol has been shown to control supine blood pressure when given once daily when readings are taken at 24 h post-dose (Douglas-Jones & Cruikshank 1976). In this study the pattern of control of supine blood pressure during the day was the same on the active treatment regimens as on placebo, but was set at a lower level (Figure 1).

Three stimuli were used to cause elevation of blood pressure, bicycle exercise, mental arithmetic and isometric exercise. At the peak of drug action, approximately 2 h after dosing, there was a greater inhibition of exercise induced rise in blood pressure with atenolol than at 24 h after dosing.

There was no significant effect of the drugs on the rise of blood pressure resulting from mental arithmetic and isometric muscle contraction, which is in common with the findings of other groups (Martin, Shaver, Leon, Thompson, Reddy & Leonard, 1974; Nyberg, Graham & Stokes, 1977). In contrast to control of recumbent pressure, inhibition of exercise rise with atenolol was not uniform, the rise in systolic pressure being 22 mm Hg less 2 h post-dose than at 24 h. Exercise induced rise in blood pressure was not significantly reduced 24 h after atenolol.

None of the symptom complaints reached statistical significance but there was an increase in patients complaining of cold extremeties ($P<0.1$) with atenolol which is of interest with a cardioselective β-adrenoceptor blocking agent.

The symptom of blocked nose was prominent with the diuretic. Atenolol had no demonstrable effect on dream production or shortness of breath in this small number of patients.

In conclusion, once daily dosing with atenolol and chlorthalidone produced a satisfactory fall in recumbent blood pressure but had no effect on the magnitude of increase in blood pressure on isometric and mental arithmetic stresses. The effect on exercise induced changes in blood pressure was not uniform through the day.

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