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Pharmacokinetics and dynamics of a new formulation of slow release oxprenolol combined with triamterene and hydrochlorothiazide in healthy man

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Summary

A new slow release formulation of the β-adrenoceptor antagonist, oxprenolol, and the diuretics triamterene and hydrochlorothiazide, were investigated alone and in combination in 2 groups of healthy volunteers. In the first study the new slow release oxprenolol alone gave lower ($P < 0.05$) peak plasma levels following single dose administration than the standard release formulation, although the AUC_{0-24} values were comparable. In the second study, chronic administration of the new sustained release formulation in combination with triamterene and hydrochlorothiazide reduced ($P < 0.05$) heart rate and blood pressure. Heart rate was reduced ($P < 0.05$) on day 8 at zero time compared to day 1, but it was not significantly different from placebo 24 h after the last dose. Triamterene plasma levels were 2–3 times higher in the presence of oxprenolol compared to placebo.

Introduction

β-Adrenoceptor antagonists and diuretics are widely used in the treatment of hypertension either alone or in combination. The fall in blood pressure attainable from a combination of these drugs, especially in patients who do not respond to the drugs given singly, is greater than that which occurs with either drug alone (Agrawal et al., 1979; Bateman et al., 1979; Jaattela, 1979). However, multiple dosage regimens involving drugs with short plasma elimination half-lives being administered more than once a day, lead to a poor patient compliance. This has resulted in procedures to prolong the plasma elimination half-life by using slow release formulations to allow once daily administration, especially of the β-adrenoceptor antagonists, and to fixed dose combinations as a method of reducing the number of tablets a patient must take. However, whilst long-acting propranolol gives β-adrenoceptor blockade over 24 h on once daily administration (Leahey et

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al., 1980a), previous long acting formulations of oxprenolol did not (Kerr et al., 1981). The present study investigated the pharmacokinetics and pharmacodynamics of a new formulation of slow release oxprenolol plus triamterene and hydrochlorothiazide in healthy volunteers.

Materials and Methods

Observations were made in 2 groups of healthy male volunteers, who gave written consent to the procedures which were explained to them. The protocol of the study had been approved by the Research Ethical Committee of The Queen's University of Belfast.

Study 1: oxprenolol in a new sustained release formulation

Ten healthy male subjects mean age 23.8 ± 2.0 years, mean wt. 68.7 ± 2.6 kg, entered a 2 way cross-over comparison of a new sustained release oxprenolol formulation (SK&F UK 52) tablet and a standard release oxprenolol formulation 'Trasicor' tablet (Ciba). Both preparations contained 160 mg oxprenolol hydrochloride and were administered once daily for 8 days, with a 7 day washout period in between. Volunteers reported to the clinic at 08.00–09.00 h, following an overnight fast and a standard light breakfast at least 30 min before arrival. A 10 ml blood sample was collected before drug administration on days 1–5; on day 8 of each study period samples were taken before and 30 min, 1 h, 1 h 30 min and at 2, 3, 4, 5, 6, 8, 12 and 24 h after drug administration for estimation of plasma concentration of oxprenolol. Plasma from the samples was separated and stored at $-20\,^{\circ}C$ until assayed for oxprenolol concentration (Leahey et al., 1980b).

Statistical analysis involved a 2-period cross-over analysis on (a) oxprenolol plasma concentrations before dosing on each of the days prior to day 8, except day 1 when all concentrations were 0 mg/l and days 6 and 7 (Saturday and Sunday) when no samples were taken, (b) on day 8, $\log_{10}$ AUC (logarithm of the area under the concentration vs time curve (calculated using the trapezoidal role from 0 to 1440 min, i.e. 24 h)), (c) Cp_{max} (peak concentration reached (mg/l)) and (d) T_{max} (time taken to reach peak concentration (min)).

Study 2: oxprenolol in a new sustained release formulation combined with triamterene / hydrochlorothiazide vs standard and conventional sustained release oxprenolol plus triamterene / hydrochlorothiazide (dyazide)

Eight healthy male subjects mean age 22.3 ± 1.2 years, mean wt. 69.2 ± 2.1 kg, participated for 4 separate 8 day periods each separated by a 7 day wash-out period. During each study period they attended the clinic on day 1 and day 8 at 08.00–09.00 h having fasted overnight and eaten a standard light breakfast 30 min before arrival. On arrival, a 15 ml blood sample was taken for the assays of oxprenolol, triamterene (Sved et al., 1979) and hydrochlorothiazide (Vandenheuvel et al., 1975). Heart rate and blood pressure were measured after 15 min supine and 3 min standing; and heart rate within 15 s of completing a 3 min period of exercise, performed by stepping on and off a box 46 cm high at the rate of 32 steps/min. The preparations (randomized double blind) for each study period were (a) slow release oxprenolol 160 mg (Slow-Trasicor, Ciba) plus triamterene 50 mg and hydrochlorothiazide 25 mg (Dyazide, SK&F), (b) the new formulation of sustained release oxprenolol 160 mg, triamterene 50 mg and hydrochlorothiazide 25 mg (SK&F formulation UK D100/4) + an extra dyazide tablet, (c) standard release oxprenolol 160 mg ('Trasicor' Ciba) plus triamterene 50 mg and hydrochlorothiazide 25 mg ('Dyazide', SK&F), (d) triamterene 50 mg and hydrochlorothiazide 25 mg ('Dyazide', SK&F) plus a placebo capsule to match UK D100/4.

Supine and standing blood pressure (4th Korotkoff sound-Hawksley Random Zero Sphygmomanometer) and heart rates (Lead I standard ECG) were recorded on day 1 and day 8 of each study period at 2, 4, 8 and 24 h after administration of the treatment; 20 ml blood samples were taken at 30 min, 1 h, 1 h 30 min, and at 2, 3, 4, 5, 6, 8, 12 and 24 h after administration for estimation of concentration of oxprenolol (days 1 and 8) and triamterene and hydrochlorothiazide (day 8).

Statistical analysis involved a 4 period cross-over analysis of variance and was performed on

supine/standing heart rate and blood pressure, exercise heart rate and pharmacokinetic parameters for oxprenolol, triamterene and hydrochlorothiazide.

Results

Study 1: sustained release oxprenolol preparations vs standard-release oxprenolol

Oxprenolol plasma concentrations (Table 1) following the standard formulation, were less ($P < 0.01$) than those of the new sustained release formulation prior to dosing on days 2, 3, 4 and 5 (Table 1). However, the bioavailability (area under the plasma concentration time curve) for day 8 was not significantly different for the two preparations (Table 2). The maximum plasma concentration (Cp_{max}) achieved and the time to Cp_{max} were different ($P < 0.01$); standard release 1.32 mg/l at

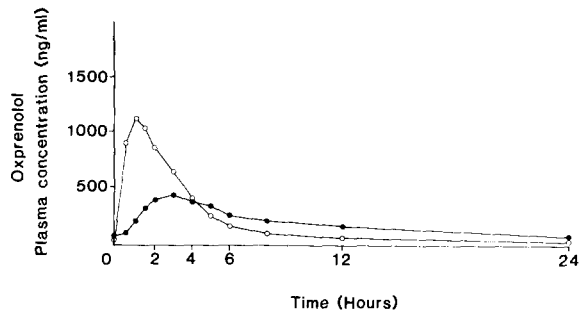

Fig. 1. Mean plasma concentrations of oxprenolol on day 8 following a single oral dose of standard release oxprenolol 160 mg (○) and a new sustained release formulation of oxprenolol 160 mg (●) in 10 healthy volunteers for 8 days.

TABLE 1

Analysis of mean trough oxprenolol plasma concentration (mg/l) following standard release oxprenolol 160 mg and a new sustained release formulation of oxprenolol 160 mg

Oxprenolol plasma concentration prior to dosing (mg/l)	Standard release	No. of volunteers	New sustained release	No. of volunteers	Difference between means	S.E. for difference between means	95% C.I. for difference between means	SIG
Day 2	0.002	9	0.039	9	0.037	0.0086	(0.016, 0.057)	$P < 0.01$
Day 3	0.006	9	0.034	9	0.028	0.0107	(0.003, 0.053)	$P < 0.01$
Day 4	0.003	9	0.039	9	0.036	0.0075	(0.018, 0.053)	$P < 0.01$
Day 5	0.003	9	0.031	9	0.028	0.0058	(0.015, 0.042)	$P < 0.01$

TABLE 2

Analysis of mean log_{10} AUC, Cp_{max} and T_{max} following 8 days administration of standard release oxprenolol 160 mg and a new sustained release formulation of oxprenolol 160 mg

	Log_{10} AUC (antilog) ($mg \cdot l^{-1} \cdot min^{-1}$)	Cp_{max} (mg/l)	T_{max} (min)
Standard release	246.43	1.32	63
No. of patients	9	9	9
Sustained release	234.09	0.44	153
No. of patients	9	9	9
Ratio of means	94.99%	–	–
95% C.I. for ratio of means SYMMETRIC	(81.39%, 118.61%)	–	–
Difference between means	–	−0.88	90
S.E. for difference between means	–	0.095	23.4
95% C.I. for difference between means CONVENTIONAL	–	(−1.10, −0.65)	(35, 145)
SIG	n.s.	$P < 0.01$	$P < 0.01$

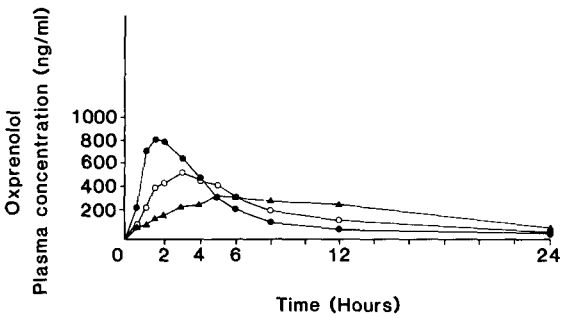

Fig. 2. Mean plasma concentration of oxprenolol following 8 days treatment with standard release oxprenolol 160 mg (●), conventional slow release oxprenolol 160 mg (○) and a new sustained release formulation of oxprenolol 160 mg (▲) in 8 healthy volunteers.

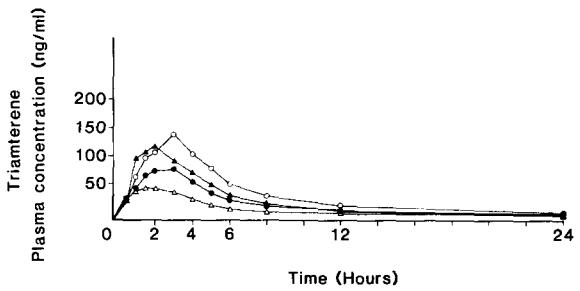

Fig. 3. Mean plasma concentrations of triamterene following 8 days administration of triamterene and hydrochlorothiazide in combination with standard release oxprenolol 160 mg (▲), conventional slow release oxprenolol 160 mg (●), a new sustained release formulation of oxprenolol 160 mg (plus dyazide) (○) and placebo (△) in 8 healthy volunteers (an extra tablet of triamterene and hydrochlorothiazide was added to the new sustained release formulation).

63 min vs new sustained release 0.44 mg/l at 153 min, (Fig. 1).

Study 2: sustained release oxprenolol combined with triamterene / hydrochlorothiazide vs standard and conventional sustained release oxprenolol plus triamterene and hydrochlorothiazide (dyazide)

On day 1 the mean maximum plasma concentration (Cp_{max}) of oxprenolol for standard release oxprenolol and dyazide was greater ($P < 0.01$) than either the conventional or the new sustained release preparation combined with dyazide (985.3, 472.9 and 444.78 ng/ml respectively). On day 8 the new sustained release formulation had a lower Cp_{max} (Fig. 2) than either the conventional sustained release formulation or the standard release formulation (349.4, 545.3 and 942.2 ng/ml respectively); the time to Cp_{max} was 5.1, 3.01 and 1.61 h respectively. At 24 h on day 8 the plasma concentrations of oxprenolol for the new formulation (48.4 ng/ml) were greater ($P < 0.05$) than for conventional sustained release (15.1 ng/ml) or standard release formulation (0 ng/ml). Mean maximum (Cp_{max}) plasma triamterene levels on day 8 (Fig. 3) were 62.2 ng/ml for dyazide administered in combination with placebo; in combination with the oxprenolol formulations, triamterene concentrations increased ($P < 0.05$) to 99.02 ng/ml for the conventional sustained release preparation, 129.1 ng/ml for the standard release and 154.7 ng/ml for the new sustained release preparation with extra dyazide added (i.e. double the amount of triamterene and hydrochlorothiazide); T_{max} values were not significantly different (1.52–2.78 h).

Hydrochlorothiazide Cp_{max} for the combination of placebo and dyazide (Fig. 4) was 197 ng/ml. This was not significantly different from the combination with the conventional sustained release and standard release formulations (195.1, 177.0 ng/ml). However the new sustained release formulation with the extra dyazide present gave approximately twice the plasma concentration of hydrochlorothiazide (355.1 ng/ml); T_{max}'s were not significantly different (2.71 to 3.52 h).

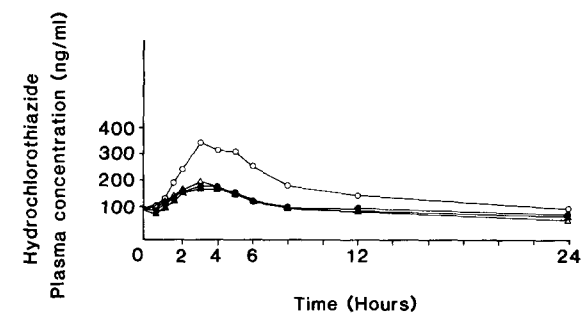

Fig. 4. Mean plasma concentration of hydrochlorothiazide following 8 days administration of triamterene and hydrochlorothiazide in combination with standard release oxprenolol 160 mg (▲), conventional slow release oxprenolol 160 mg (●), a new sustained release formulation of oxprenolol 160 mg (plus dyazide) (○) and placebo (△) in 8 healthy volunteers. (An extra tablet of triamterene and hydrochlorothiazide was added to the new sustained release formulation).

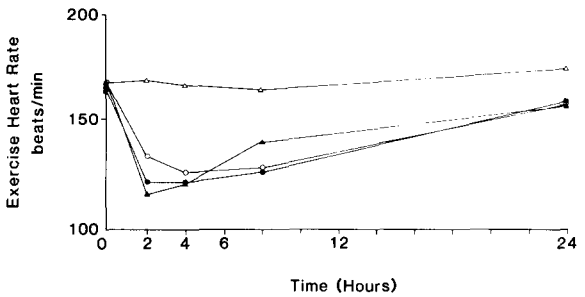

Fig. 5. Mean exercise heart rate following a single oral dose of standard release oxprenolol 160 mg (▲), conventional slow release oxprenolol 160 mg (●), a new sustained release formulation of oxprenolol 160 mg (plus dyazide) (○) and placebo (△) each combined with triamterene and hydrochlorothiazide in 8 healthy volunteers. (An extra tablet of triamterene and hydrochlorothiazide was added to the new sustained release formulation).

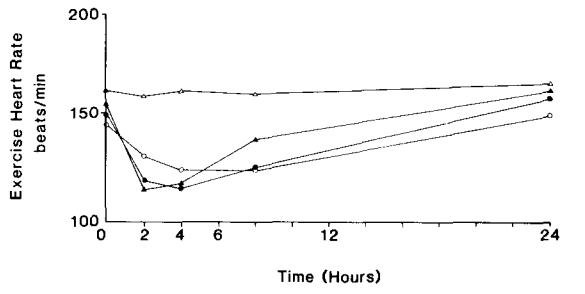

Fig. 6. Mean exercise heart rate following 8 days treatment with standard release oxprenolol 160 mg (△), conventional slow release oxprenolol 160 mg (●), a new sustained release formulation of oxprenolol 160 mg (plus dyazide) (○) and placebo (△) each combined with triamterene and hydrochlorothiazide in 8 healthy volunteers. (An extra tablet of triamterene and hydrochlorothiazide was added to the new sustained release formulation).

Exercise heart rate following placebo in combination with dyazide at zero time on day 1 was 167.3 ± 4.8 (mean $\pm$ S.E.M.) beats/min and did not change significantly during day 1 (Fig. 5) or day 8 (Fig. 6). Maximum reductions in exercise heart rate on day 1 occurred at 2 h with the standard release formulation (114.0 ± 2.8 beats/min (31.5% reduction)) and at 4 h with the conventional sustained release and new sustained release formulation (120.4 ± 2.1 (26.3% reduction), 125.6 ± 2.6 beats/min (20.7% reduction)). At 24 h on day 1 exercise heart rates for the 3 formulations were not significantly different from placebo. On day 8 the initial pretreatment exercise heart rate was reduced ($P < 0.05$) for the new sustained release formulation to 145.6 ± 2.9 beats/min compared with 162.5 ± 3.6 beats/min for placebo and 150.4 ± 3.1, and 156.6 ± 3.9 beats/min for the standard and conventional sustained release formulation respectively. Twenty-four h after the last dose on day 8 the exercise heart rate following placebo was 167.4 ± 4.3 beats/min and 158.1 ± 5.5, 149.8 ± 3.7 and 163.3 ± 4.0 beats/min for conventional sustained release, new sustained release and standard release formulations respectively. In the supine and standing positions at 24 h

TABLE 3

Heart rate (beats/min) in the supine and standing position following 8 days treatment

Treatment	0 h	2 h	4 h	8 h	24 h
Supine					
A	62.25 ± 3.702	54.63 ± 1.945	53.00 ± 1.500	54.75 ± 2.042	65.00 ± 4.106
B	62.13 ± 2.831	55.75 ± 2.381	55.00 ± 2.493	54.13 ± 2.489	59.50 ± 4.110
C	62.75 ± 2.914	57.50 ± 2.625	57.50 ± 2.632	58.25 ± 2.789	64.13 ± 3.548
D	64.75 ± 1.989	58.38 ± 1.963	55.88 ± 1.931	58.13 ± 2.735	64.63 ± 2.859
Standing					
A	82.75 ± 3.529	76.25 ± 3.326	73.25 ± 2.033	73.63 ± 2.500	85.00 ± 4.822
B	83.25 ± 3.972	78.63 ± 2.283	70.75 ± 2.305	75.13 ± 2.057	84.38 ± 2.291
C	87.25 ± 2.789	73.88 ± 2.748	74.63 ± 3.428	77.38 ± 3.484	91.13 ± 4.569
D	87.63 ± 3.891	82.88 ± 3.796	82.38 ± 6.041	84.25 ± 3.421	88.13 ± 4.068

Eight healthy volunteers were treated with conventional sustained release oxprenolol 160 mg (A), a new sustained release formulation of oxprenolol 160 mg (B), standard release oxprenolol 160 mg (C) and placebo (D) each combined with triamterene and hydrochlorothiazide. (An extra tablet of triamterene and hydrochlorothiazide was added to the new sustained release formulation). Results are expressed as the mean $\pm$ S.E.M.

TABLE 4

Systolic blood pressure (mmHg) in the supine and standing position following 8 days treatment

Treatment	0 h	2 h	4 h	8 h	24 h
Supine					
A	119.00 ± 4.629	110.50 ± 2.797	108.75 ± 4.208	115.25 ± 3.069	113.50 ± 4.031
B	118.25 ± 2.403	111.25 ± 3.315	111.75 ± 2.963	114.75 ± 2.801	115.25 ± 1.998
C	116.00 ± 2.903	103.25 ± 2.776	105.25 ± 2.644	111.75 ± 4.165	116.25 ± 3.104
D	117.50 ± 2.528	111.25 ± 1.998	109.75 ± 2.343	114.50 ± 2.557	115.00 ± 1.927
Standing					
A	120.25 ± 3.807	106.25 ± 3.172	102.50 ± 3.813	107.00 ± 2.299	113.25 ± 2.033
B	109.75 ± 4.463	107.75 ± 4.479	106.50 ± 3.775	104.00 ± 3.423	115.00 ± 3.423
C	114.25 ± 4.113	99.00 ± 6.118	102.25 ± 4.300	111.25 ± 3.835	111.75 ± 2.938
D	114.75 ± 4.157	110.50 ± 3.887	106.25 ± 4.283	111.00 ± 4.424	116.75 ± 2.852

Eight healthy volunteers were treated with conventional sustained release oxprenolol 160 mg (A), a new sustained release formulation of oxprenolol 160 mg (B), standard release oxprenolol 160 mg (C) and placebo (D) each combined with triamterene and hydrochlorothiazide. (An extra tablet of triamterene and hydrochlorothiazide was added to the new sustained release formulation). Results are expressed as the mean ± S.E.M.

TABLE 5

Diastolic blood pressure (mmHg) in the supine and standing position following 8 days treatment

Treatment	0 h	2 h	4 h	8 h	24 h
Supine					
A	65.75 ± 2.603	65.75 ± 3.239	72.75 ± 2.102	70.50 ± 1.918	66.75 ± 3.421
B	65.50 ± 2.130	68.25 ± 3.057	72.50 ± 2.163	70.75 ± 2.534	67.25 ± 2.698
C	69.00 ± 2.952	65.75 ± 3.473	72.25 ± 2.313	68.00 ± 2.619	73.00 ± 1.464
D	69.75 ± 2.119	72.50 ± 1.637	75.25 ± 2.068	74.75 ± 2.776	71.75 ± 1.709
Standing					
A	82.25 ± 3.390	74.50 ± 3.018	79.25 ± 3.250	81.75 ± 2.576	82.25 ± 2.865
B	77.25 ± 3.161	80.50 ± 2.612	81.25 ± 2.877	78.00 ± 2.360	79.50 ± 3.333
C	82.75 ± 4.157	70.75 ± 5.502	75.75 ± 4.651	80.75 ± 3.294	80.50 ± 3.354
D	80.25 ± 1.436	84.25 ± 2.763	82.25 ± 2.433	81.25 ± 3.400	82.00 ± 2.673

Eight healthy volunteers were treated with conventional sustained release oxprenolol 160 mg (A), a new sustained release formulation of oxprenolol 160 mg (B), standard release oxprenolol 160 mg (C) and placebo (D) each combined with triamterene and hydrochlorothiazide. (An extra tablet of triamterene and hydrochlorothiazide was added to the new sustained release formulation). Results are expressed as the mean ± S.E.M.

the reductions in heart rate on day 8 with the new sustained release formulation were slightly greater than with the other treatments (Table 3). Small reductions with all treatments were observed in supine and standing systolic or diastolic blood pressure (Tables 4, 5) during the course of the study period.

Discussion

The results of the first study indicate that with the new sustained release preparation of oxprenolol the trough plasma levels 24 h after dosing were greater ($P < 0.01$) than those of the standard release formulation (Table 1). Peak plasma levels were also reduced ($P < 0.01$) after chronic dosing; the bioavailability was not different over 24 h for both formulations. In the second study similar results occurred for the comparison between the standard release and new sustained release formulation. The comparison between the conventional sustained release and new sustained release formulation indicated no difference in bioavailability, Cp_{max} or T_{max}, although the mean Cp_{max} tended to

be slightly lower 444.8 vs 472.9 ng/ml and T_{max} slightly later 3.6 vs 3.1 h. The plasma levels of triamterene (Fig. 3) demonstrated 2–3 fold increases in the presence of oxprenolol for the standard and conventional sustained release formulation compared to placebo; in the presence of the new sustained release formulation the plasma levels of triamterene elevated in keeping with the extra dose of hydrochlorothiazide and triamterene during this treatment period. This variation in plasma levels is thought to be due to the large interindividual differences previously reported in the absorption, binding and elimination of triamterene (Pruitt et al., 1977) which may be influenced by β-adrenoceptor blockade. The evaluation of the haemodynamic effects of the new sustained release formulation indicated that the increased trough levels of oxprenolol 24 h after chronic dosing were associated with significant β-adrenoceptor blockade; day 8 pretreatment exercise heart rate was reduced ($P < 0.05$) with the new sustained release formulation to 145.6 ± 2.9 beats/min compared with 162.5 ± 3.6 (placebo), 180.4 ± 3.1 (standard release) and 156.6 ± 3.9 beats/min (conventional sustained release formulation). However, in keeping with previous single dose studies (Bobik et al., 1979; Leahey et al., 1980b; Kerr et al., 1981) no effect could be demonstrated on an exercise tachycardia 24 h after a single dose.

The mechanism of reduction of arterial blood pressure with β-adrenoceptor antagonists is multifactorial and does not appear to bear a relationship to blockade of β-receptors (Reybrouck et al., 1978). Hydrochlorothiazide, a thiazide diuretic, has an important antihypertensive effect which appears to depend upon both a reduction in blood volume and a direct vasodilator effect (associated with this is potassium loss). The duration of action of hydrochlorothiazide is approximately 10 h. Triamterene has only weak natriuretic properties, but it can be used to potentiate the diuretic effect of thiazide and to prevent hypokalaemic alkalosis; its plasma elimination half-life is 1.5–2 h although the duration of action is similar to hydrochlorothiazide. In the present study the hypotensive effect of all 4 treatments was apparent during the study period on day 8 (Tables 4 and 5).

In conclusion, the pharmacokinetic profile of the new sustained release formulation of oxprenolol 160 mg given chronically in combination with hydrochlorothiazide and triamterene makes it acceptable for once daily administration.

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