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THE PHARMACODYNAMICS AND PHARMACOKINETICS OF CONVENTIONAL AND LONG-ACTING PROPRANOLOL IN PATIENTS WITH MODERATE HYPERTENSION

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1 The effects on heart rate and blood pressure after single and multiple dosing (1 month) of a long acting formulation of propranolol 160 mg daily, and conventional propranolol, 80 mg twice daily, or 160 mg daily were compared in 11 moderately hypertensive subjects previously shown to respond to propranolol.

2 After acute dosing all three treatments produced significant reduction in blood pressure. After multiple dosing all three treatments maintained significant reductions in lying, standing and exercise heart rate and blood pressure throughout the 24 h. At 24 h, after multiple dosing, the fall in resting and standing systolic BP was significantly greater with LA propranolol than with conventional propranolol 80 mg twice daily or conventional propranolol 160 mg once daily (P at least < 0.05).

3 The plasma propranolol concentration time curve after LA propranolol showed slowed absorption, and the area under the curve was significantly lower than after conventional propranolol (acute dosing; LA propranolol 160 mg 560 mg ml^{-1} h, conventional propranolol 80 mg twice daily 1135 mg ml^{-1} h, conventional propranolol 160 mg daily 1414 mg ml^{-1} h).

Introduction

Compliance with drug therapy may be improved by reducing the frequency of medication, preferably to a once daily regime (Gatley, 1968; Marshall & Barritt, 1977). Long acting propranolol (Inderal LA (Inderal LA is a trade mark, the property of Imperial Chemical Industries PLC)) is a sustained release formulation of propranolol whose administration has been shown to result in sustained blood levels throughout the 24 h, following a single dose (McAinsh *et al.*, 1978; Leahey *et al.*, 1980). The plasma elimination half life of conventional propranolol is short (3–5 h) (Shand *et al.*, 1970) and a clear relationship has been demonstrated between plasma concentration and β-adrenoceptor blockade, as measured by a reduction in exercise induced tachycardia (George *et al.*, 1974; Serlin *et al.*, 1980). However, there is a poor relationship between the plasma concentration of propranolol and its antihypertensive effect, and thus the comparative efficacy of conventional and LA propranolol in lowering blood pressure is a matter of conjecture and considerable therapeutic importance.

The purpose of this present study was to investigate the antihypertensive effect and pharmacokinetics of LA propranolol in patients with moderate hypertension, and compare these effects with conventional propranolol, given once daily or in two divided doses. These measurements were made in hypertensive patients over a 24 h period, both after a single dose and following 28 days therapy.

Methods

Patients studied

Twelve patients with moderate hypertension, nine male and three female, were selected for this study. One male patient proved to be an unreliable attender, and was withdrawn during the placebo run-in period. The study concerns the remaining 11 patients, aged 24–58 years. From previous therapy, they were all known to respond to propranolol, and were accepted for randomization at the end of a therapy free, placebo run-in period of 4 weeks during which a resting blood pressure of 160/100 mm Hg or more had been recorded.

Patients were excluded from entry to the study by virtue of age (below 20 or above 65 years), previous history of myocardial ischaemia, cerebrovascular accident, heart failure, heart block, airways obstruction, diabetes mellitus, malignant or accelerated hypertension. No patients taking drugs known to

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affect blood pressure control, e.g. contraceptive steroids, were included. All patients were considered to have essential hypertension by the criteria of normal urinalysis and intravenous pyelography, normal vanillylmandelic acid excretion and normal serum electrolytes. No patients with biochemical evidence of hepatic or renal disease or diabetes mellitus were included.

All the patients gave informed written consent for the study, which had the approval of the Ethics Committee of the Mersey Regional Health Authority.

Plan of study

The study was a within-patient, double-blind, placebo-controlled, cross-over design, using a double dummy tablet and capsule technique. All medication was stopped at least 4 weeks prior to the study. After a 4 week placebo run-in period (Figure 1), the following regimes were studied, each being given to each patient for 4 weeks in random sequence; conventional propranolol 80 mg twice daily, conventional propranolol 160 mg once daily, and long acting propranolol 160 mg once daily. There was a 2 week placebo washout period between each of the active treatment periods. Long acting propranolol was taken as a capsule at 09.00 h, conventional propranolol 160 mg was taken as a tablet at 09.00 h and conventional propranolol 80 mg as a tablet at 09.00 h and 18.00 h. Matching placebo capsules and tablets were prepared so that each patient took a capsule and a tablet at 09.00 h and a further tablet at 18.00 h, irrespective of treatment period.

Patients were seen at 2 weekly intervals for measurement of blood pressure and heart rate, and reporting of side effects. On the first and last day of each 4 week active treatment period, patients were admitted to the investigation unit for a more detailed study of blood pressure response after acute and multiple dosing with propranolol. Pre-dose and at 1, 3, 5, 7, 9, 12 and 24 h after the morning dose of propranolol, blood pressures and heart rate were recorded after 5 min recumbency, standing after 1 min in the erect position, and after a Master's two step exercise test. The duration of this test was determined for each patient at the end of the placebo run-in period, so that the heart rate would increase to at least 150 beats/min. The same exercise was then performed on each occasion. Blood pressure measurements were made, using a Hawksley randomized zero sphygmomanometer; diastolic blood pressure was taken as muffling of the heart sounds (phase 4). Blood samples were taken at each time point for measurement of plasma propranolol concentration (McAinsh *et al.*, 1978).

Statistical methods

Analysis of variance was used to look for any differences between non-active treatment periods. Paired *t*-tests comparing the immediately preceding non-active period with each active treatment period have been performed to show efficacy. Because of the large amount of data, these results were only analysed at 3, 12 and 24 h after dosing. Relationships between log plasma propranolol concentrations and effect were determined, using linear regression correlation coefficients.

Results

All 11 patients completed the study. Side effects volunteered during the study on all treatment regimes were minimal (Table 1). All haematological and biochemical tests remained within the normal range.

Table 2 shows the mean systolic and diastolic blood pressures and heart rates, at the end of the 4 week placebo run-in period, and at the end of each 2 week placebo washout period. No statistically significant differences were found between the run-in and washout periods.

Acute dosing

Figure 2 shows the mean standing blood pressure and heart rate during the first 24 h of treatment with each regime. Three hours after dosing, all three treatments had produced highly significant ($P < 0.001$) reductions in both systolic and diastolic blood pressure. At 24 h after dosing with LA propranolol, and 15 h after the second dose of 80 mg propranolol (i.e. 24 h after first dose), resting, standing and exercise blood pressures and heart rates were significantly reduced (P at least

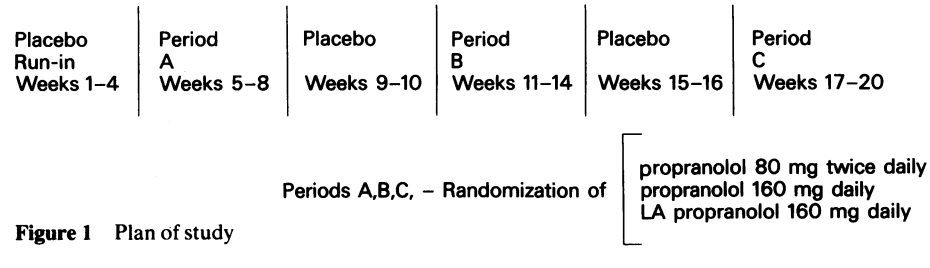

Figure 1 Plan of study

Table 1 Side effects—volunteered by 11 patients during the study

	Placebo	*Propranolol 160 mg*	*Propranolol 80 mg twice daily*	*Propranolol LA*
Tiredness	1	0	1	0
Dizziness	1	1	0	0
Cold extremities	0	0	0	0
Sweating	0	0	2	1
Loss of libido	0	0	1	0
Depression	0	0	0	1
Headache	3	0	0	0
Wheeze	0	0	0	0
Nocturnal frequency	0	0	0	0
Change in bowel habit	0	0	3	1
Others	2	2	2	4

< 0.05) compared with the immediately preceding placebo period. For conventional propranolol 160 mg, significant reductions are seen for the same variables, (P at least < 0.05) with the exception of standing systolic and diastolic pressures (NS) and exercise diastolic pressure ($P < 0.099$) (see Table 3). All three regimes produced significant reductions in standing heart rate throughout the 24 h period (Table 3, Figure 2). Similar reductions in blood pressure and heart rate in the lying position and after exercise are produced by all three regimes compared with preceding placebo values. Relevant significances are shown in Table 3.

Multiple dosing

Figure 3 shows the mean standing blood pressure and heart rate for the patients over the 24 h period at the end of 4 weeks treatment with the three different propranolol regimes, compared with the pressures during the preceding placebo period. All three treatments produced significant reductions in resting blood pressure at 3, 12 and 24 h (P at least < 0.05). Similar significant reductions in blood pressure are seen in the supine position and after exercise (Table 4). Table 5 shows the significances between treatments at 24 h for blood pressures and heart rates. There are no significant differences between the conventional formulations. Propranolol LA produced significantly lower values in standing and resting systolic blood pressure compared with conventional 80 mg twice daily ($P < 0.05$), and significantly lower values in resting and standing systolic ($P < 0.01$) and exercise systolic ($P < 0.05$) blood pressure compared with conventional 160 mg propranolol.

At 12 h exercise systolic blood pressures are signific-

Table 2 Mean ± s.e. mean blood pressures and pulse rates in the three positions at the end of the 4 week placebo run-in period, and at the end of each placebo washout period for the 11 patients studied.

		Run-in	*Washout 1*	*Washout 2*
Resting				
	BP	160.1 + 4.1	156.9 + 5.5	158.9 + 4.2
	(mm Hg)	98.6 ± 2.0	98.4 ± 2.0	99.9 ± 1.4
	Pulse (beats/min)	78.2 ± 3.0	77.6 ± 3.5	78.7 ± 3.1
Standing				
	BP	157.0 + 4.9	146.4 + 3.7	148.5 ± 5.2
	(mm Hg)	105.9 ± 2.0	99.5 ± 2.2	104.1 ± 2.1
	Pulse (beats/min)	88.0 ± 2.6	86.9 ± 3.4	89.8 ± 2.7
Exercise				
	BP	197.0 + 10.4	185.7 + 9.2	188.0 + 5.8
	(mm Hg)	103.9 ± 4.00	97.2 ± 4.3	100.5 ± 2.5
	Pulse (beats/min)	154.3 ± 2.4	157.3 ± 5.4	151.8 ± 4.2

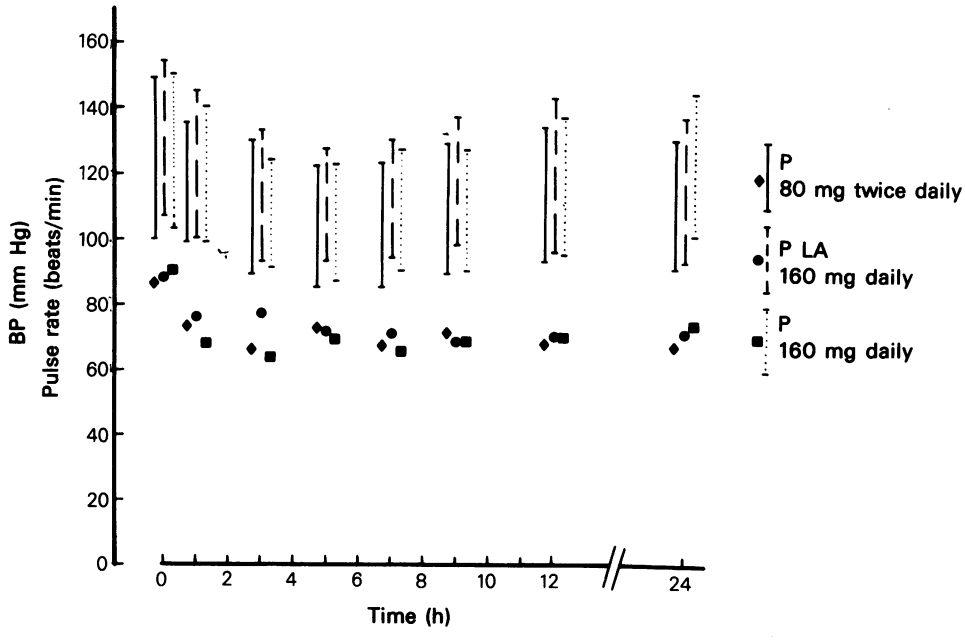

Figure 2 Mean standing blood pressures and pulse rates after acute dosing with the three propranolol (P) regimes.

antly lower with conventional 160 propranolol ($P < 0.01$) and conventional 80 mg twice daily propranolol ($P < 0.001$) compared with propranolol LA. The exercise diastolic pressure, is also significantly lower on 160 mg conventional ($P < 0.05$) and 80 mg twice daily conventional ($P < 0.05$) compared with LA propranolol.

All three propranolol regimes produced significant reductions in heart rate at 3, 12 and 24 h (P at least < 0.05) in all three positions, compared with preceding placebo periods. The reductions in heart rate produced by the three treatments were not significantly different from each other, except for exercise heart rate at 12 h for 80 mg twice daily compared with propranolol LA ($P < 0.05$).

Plasma propranolol concentrations

Figure 4a shows the mean plasma propranolol concentrations with the three regimes after acute dosing. Peak concentrations were reached within 3 hours of dosing. The highest concentrations occurred after conventional propranolol 160 mg with a 30 fold interpatient variability (range 10–296 ng/ml). At 24 h after dosing the mean plasma concentration with conventional propranolol 160 mg daily (5 ± 2 ng/ml) was significantly lower ($P < 0.001$) than after conventional propranolol 80 mg twice daily (20 ± ng/ml). Plasma propranolol concentrations after long acting propranolol varied little between 3 and 24 h. Similar plasma propranolol concentration-time curves were obtained after multiple dosing with the three treatment regimens (Figure 4b).

The area under the plasma concentration time curves (AUC) between 0 and 24 h for each treatment after acute or multiple dosing is shown in Table 6. There was no significant difference in the area under the curves after dosing with conventional propranolol 80 mg twice daily or 160 mg daily, either after acute or multiple dosing; but both regimes with conventional propranolol gave significantly greater AUC than long acting propranolol 160 mg daily. After multiple dosing there were no significant differences in AUC for any treatment compared to that seen after acute dosing. There were significant ($P < 0.01$) negative correlations between exercise heart rate and plasma propranolol concentration after both acute and multiple dosing with conventional propranolol 160 mg daily or 80 mg twice daily, but there was no such correlation after long acting propranolol (Table 7).

Discussion

A therapeutically useful sustained release drug formulation should fulfil two objectives. Firstly to achieve an effective plasma concentration throughout the dosing interval, while avoiding potentially toxic peak concentrations or ineffective plasma concentrations that might occur with conventional formulations, and secondly to produce a pharmacological effect as effective, at least, as the con-

Table 3 Table of means and s.d. ($n = 11$) for the three treatments at times 3, 12 and 24 h with their preceding placebo levels (acute dosing).

		Conventional propranolol 80 mg twice daily				*LA propranolol 160 mg*				*Conventional propranolol 160 mg daily*			
		Placebo	*3*	*12*	*24 h*	*Placebo*	*3*	*12*	*24 h*	*Placebo*	*3*	*12*	*24 h*
			***	**	***		**		***		***		**
Systolic BP Resting (mm Hg)	Mean	156.91	137.00	132.82	132.91	161.54	145.18	150.64	139.73	157.45	131.36	144.09	143.18
	s.d.	17.91	17.04	18.81	16.52	12.61	11.44	19.01	13.08	14.93	15.34	27.73	18.68
			**	**	***		*	*	**		**	*	**
Diastolic BP Resting (mm Hg)	Mean	98.09	88.18	81.91	85.82	100.91	92.54	92.73	88.27	97.91	84.73	88.64	89.00
	s.d.	5.79	11.77	12.25	8.12	4.11	11.00	10.09	9.14	7.35	10.84	13.72	8.91
			***	**	***		**	*	***		***	***	***
Pulse rate Resting (beats/min)	Mean	76.36	62.73	60.00	61.27	78.18	69.09	65.64	64.18	80.00	64.73	64.36	66.91
	s.d.	10.65	7.23	9.51	8.11	10.45	12.69	12.19	11.54	10.28	7.76	10.27	11.08
			***	**	***		***		**		***		
Systolic BP Standing (mm Hg)	Mean	148.00	128.82	130.27	129.45	153.91	132.73	145.73	136.00	150.00	126.00	137.45	144.45
	s.d.	16.67	13.67	16.41	13.11	11.85	15.74	23.27	14.05	18.44	12.78	24.34	20.34
			***		*		***	*	***		***		
Diastolic BP Standing (mm Hg)	Mean	100.09	88.36	90.82	91.91	106.82	94.54	97.91	92.73	102.64	90.73	94.09	99.09
	s.d.	6.52	10.94	11.08	7.94	5.86	11.20	12.45	8.75	8.26	7.72	13.13	13.76
			***	**	***		***	**	***		***	***	***
Pulse rate Standing (beats/min)	Mean	86.18	66.18	67.09	68.60	87.82	74.36	71.45	70.00	90.73	64.91	69.45	73.45
	s.d.	10.97	10.93	13.22	10.33	8.27	11.76	13.89	11.21	9.22	6.47	12.30	11.10
			***	***	***		***	**	***		***	**	**
Systolic BP Post-exercise (mm Hg)	Mean	189.00	149.82	152.45	152.82	193.91	157.54	167.18	157.18	187.82	138.36	162.54	171.64
	s.d.	30.52	18.69	14.82	20.55	23.78	24.44	20.60	10.61	32.24	15.52	26.51	26.78
			*	*	*		*		**		**		
Diastolic BP Post-exercise (mm Hg)	Mean	98.64	88.64	87.09	86.73	104.73	92.64	96.27	87.82	98.27	86.18	91.36	91.91
	s.d.	13.40	8.12	6.25	9.75	9.56	11.23	13.43	13.72	13.12	7.18	19.73	14.72
			***	***	***		***	***	***		***	***	***
Pulse rate Post-exercise (beats/min)	Mean	154.91	102.36	108.73	110.36	150.36	117.45	119.64	116.73	158.09	96.36	114.00	118.91
	s.d.	9.44	10.87	17.62	12.16	13.23	18.98	17.54	20.81	17.48	13.82	18.42	13.54

Significance of difference from preceding placebo values $*P < 0.05$, $**P < 0.01$, $***P < 0.001$

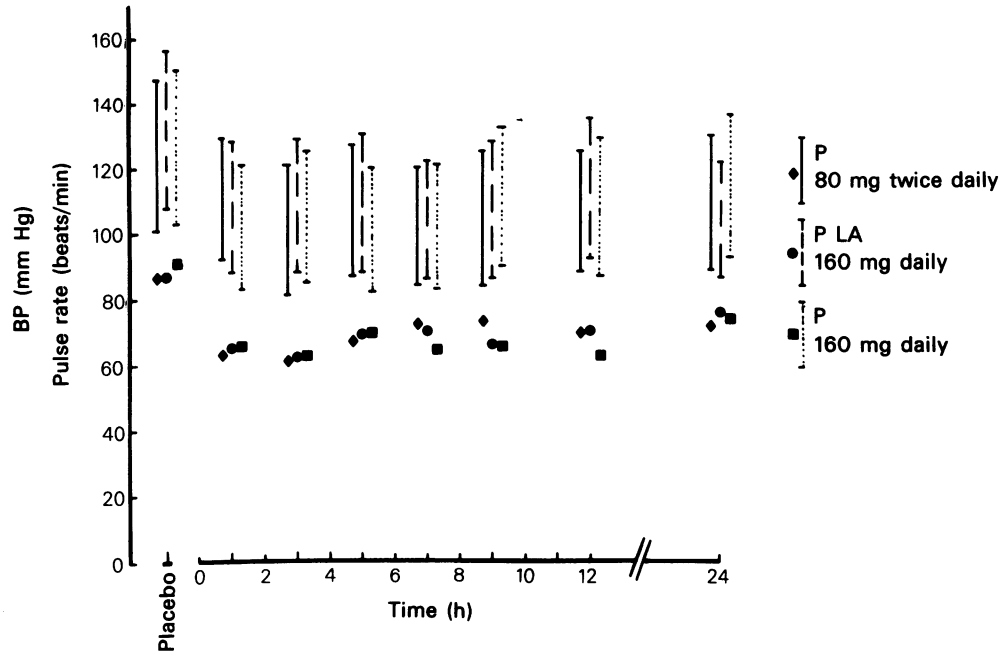

Figure 3 Mean standing blood pressures and heart rates after 28 days treatment with the three propranolol (P) regimes (with preceding placebo values).

ventional drug given at more frequent dosing intervals. The aim of this study was to examine whether the slow release formulation of propranolol (LA propranolol) achieved these objectives in hypertensive patients. Since it was not our intention to prove the efficacy of propranolol as an antihypertensive agent, only patients known to respond to β-adrenoceptor blockade were studied.

Peak plasma propranolol concentrations were reached within 3 h of dosing with all three regimens. As would be expected conventional propranolol 160 mg produced the highest concentration, while LA propranolol produced the lowest concentrations. After dosing with conventional propranolol (either 160 mg or 80 mg twice daily) plasma concentrations fell exponentially from 3 h after dosing with a half-life of approximately 5 h. With LA propranolol this was not the case; the plasma concentration fell relatively slowly between 3 and 24 h after dosing, presumably the result of continued slow absorption.

At 24 h, after acute dosing, plasma propranolol concentrations were significantly lower with conventional propranolol 160 mg, than either LA propranolol 160 mg or conventional propranolol 80 mg twice daily. The area under the plasma propranolol concentration time curve after LA propranolol 160 was significantly smaller than after conventional propranolol (either 160 mg daily or 80 mg twice daily) after acute and multiple dosing. These results obtained in hypertensive patients are in agreement with those of other workers studying LA propranolol kinetics in healthy volunteers (McAinsh *et al.*, 1978; Leahey *et al.*, 1980). The smaller area observed with the slow release propranolol formulation is probably a result of increased hepatic extraction due to slower absorption of the drug. However, in this study we completed blood sampling at 24 h after dosing, by which time plasma propranolol concentrations after LA propranolol had declined little from the peak concentrations at 3 h. Since the area under the curve could only be calculated to 24 h it is possible that the differences in bioavailability between conventional and LA propranolol may be less marked than suggested by these results.

In pharmacodynamic terms LA propranolol once daily was as effective as conventional propranolol given twice daily. After 4 weeks treatment all three regimens produced significant reductions in blood pressure (systolic and diastolic) resting, standing and after exercise, throughout the 24 h. At 24 h (following 4 weeks treatment) LA propranolol produced equal falls in exercise blood pressure, but greater falls in resting and standing blood pressures, as compared with results after conventional propranolol 80 mg twice daily. All three blood pressure measurements at 24 h were significantly lower after LA propranolol

Table 4 Table of means and s.d. for the three treatments at times 3, 12 and 24 h with their preceding placebo levels. (Multiple dosing).

		Conventional propranolol 80 mg twice daily				*LA propranolol 160 mg*				*Conventional propranolol 160 mg daily*			
		Placebo	*3*	*12*	*24 h*	*Placebo*	*3*	*12*	*24 h*	*Placebo*	*3*	*12*	*24 h*
			***	*	**		***	***	***		***	***	***
Systolic BP	Mean	155.89	124.22	130.78	132.33	158.78	137.22	136.44	129.22	157.45	135.09	131.45	138.27
Resting	s.d.	19.15	6.68	21.56	13.42	11.01	12.63	13.97	16.03	14.93	12.60	19.90	11.96
(mm Hg)	*n*	9	9	9	9	9	9	9	9	11	11	11	11
			***	**	***		**	**	***		**	***	**
Diastolic BP	Mean	99.44	80.44	83.89	82.44	100.33	85.67	84.00	80.33	97.91	85.64	82.27	87.00
Resting	s.d.	4.93	4.39	9.97	6.67	4.18	9.11	10.12	9.70	7.35	10.42	9.95	11.76
(mm Hg)	*n*	9	9	9	9	9	9	9	9	11	11	11	11
			***	*	*		***	**	**		***	***	***
Pulse rate	Mean	76.89	60.67	63.33	66.67	78.22	56.67	63.33	65.33	80.00	57.00	60.18	64.54
Resting	s.d.	11.54	10.39	11.87	9.75	8.51	4.47	7.35	7.55	10.28	8.18	11.33	5.52
(beats/min)	*n*	9	9	9	9	9	9	9	9	11	11	11	11
			***	**	**		***	**	***		**	**	*
Systolic BP	Mean	147.33	121.56	126.33	130.44	156.00	131.89	135.44	128.67	150.00	124.09	128.09	135.64
Standing	s.d.	16.98	8.76	13.74	14.52	12.19	14.72	20.83	15.49	18.44	11.01	15.36	13.37
(mm Hg)	*n*	9	9	9	9	9	9	9	9	11	11	11	11
			***	*	***		***	**	***		***	***	**
Diastolic BP	Mean	101.33	82.87	90.44	88.56	107.67	89.56	93.22	87.33	102.64	84.54	87.18	94.27
Standing	s.d.	5.43	7.31	9.64	5.98	5.68	8.41	12.17	8.77	8.26	12.66	11.36	7.11
(mm Hg)	*n*	9	9	9	9	9	9	9	9	11	11	11	11
			***	**	*		***	**	*		***	**	***
Pulse rate	Mean	86.67	64.67	71.11	72.67	86.89	64.22	71.11	72.67	90.73	62.70	64.91	73.45
Standing	s.d.	11.83	9.38	12.77	12.00	6.64	7.64	14.53	12.37	9.22	13.50	21.93	8.99
(beats/min)	*n*	9	9	9	9	9	9	9	9	11	10	11	11
			**	**	**		**	**	***		***	***	***
Systolic BP	Mean	191.22	142.00	148.00	156.78	197.00	157.44	165.56	154.89	187.82	145.00	152.27	167.36
Post-exercise	s.d.	33.22	16.66	19.15	17.10	25.46	24.17	16.48	23.96	32.24	18.83	15.86	26.01
(mm Hg)	*n*	9	9	9	9	9	9	9	9	11	11	11	11
			***	*	***		**	*	***		**	***	**
Diastolic BP	Mean	101.67	83.56	84.78	82.11	104.00	85.89	90.78	81.22	98.27	85.82	81.54	88.54
Post-exercise	s.d.	9.77	8.86	12.80	8.19	8.66	7.20	9.35	9.44	13.12	10.32	12.86	12.08
(mm Hg)	*n*	9	9	9	9	9	9	9	9	11	11	11	11
			***	***	***		***	***	**		***	***	***
Pulse rate	Mean	155.11	100.62	107.56	117.89	152.67	106.00	114.89	121.33	158.09	97.27	108.18	126.54
Post-exercise	s.d.	7.88	17.18	16.90	18.35	9.27	17.66	15.27	27.28	17.48	22.61	21.59	19.64
(beats/min)	*n*	9	8	9	9	9	9	9	9	11	11	11	11

Significance of difference from preceding placebo values * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$

Table 5 Comparison of 24 h blood pressure and heart rates after multiple dosing with the three treatments (Refer to Table 4 for actual values)

	LA propranolol vs *conventional propranolol 80 mg twice daily*	*Conventional 80 mg once daily* vs *conventional 160 mg once daily*	*LA propranolol* vs *conventional 160 mg once daily*
Resting systolic BP	$P < 0.05$	NS	$P < 0.01$
Resting diastolic BP	NS	NS	NS
Resting heart rate	NS	NS	NS
Standing systolic BP	$P < 0.05$	NS	$P < 0.01$
Standing diastolic BP	NS	NS	NS
Standing heart rate	NS	NS	NS
Exercise systolic BP	NS	NS	$P < 0.05$
Exercise diastolic BP	NS	NS	NS
Exercise heart rate	NS	NS	NS

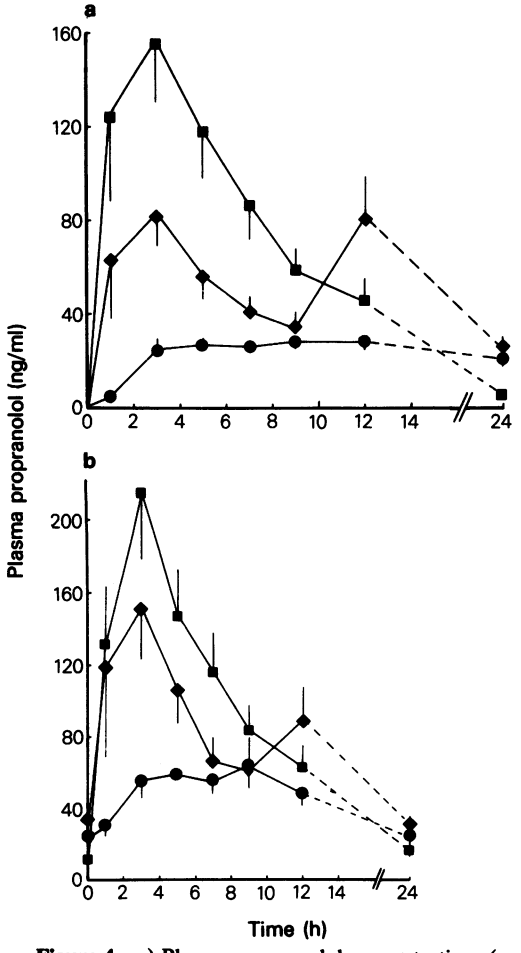

Figure 4 a) Plasma propranolol concentrations (mean of 11 subjects ± s.e. mean) after acute dosing.
b) Plasma propranolol concentrations (mean of 11 subjects ± s.e. mean) after 28 days treatment. ◆propranolol 80 mg twice daily, ■ propranolol 160 mg once daily, ● propranolol LA 160 mg once daily

than conventional propranolol 160 mg daily. However, at 12 h, after dosing, the converse was true, for exercise systolic and diastolic pressures with conventional propranolol, when 160 mg and 80 mg twice daily produced a greater hypotensive effect than LA propranolol. Our results confirm the findings of other workers (Van den Brink *et al.*, 1980; England, 1981) that conventional propranolol, given as a single daily dose may be effective in the treatment of hypertension.

It was notable that within 3 h of acute dosing, significant reductions in blood pressure were produced by all three regimes. At 24 h, after dosing, this effect was still apparent. Although the rate of fall of blood pressure with a β-adrenoceptor blocking drug, such as propranolol, has in the past been said to be slow (Prichard & Gillam, 1969) with the maximal effect occurring weeks after the onset of treatment, we found a significant, but submaximal fall in blood pressure during the first 24 h of therapy, with little further fall by 4 weeks.

All three regimes produced significant reductions in heart rate throughout the 24 h. Predictably, the greatest reduction in exercise heart rate at 3 h, was produced by conventional propranolol 160 mg, but there was no difference amongst the treatments at 24 h. Multiple dosing produced no greater reduction in heart rate at 24 h, with any of the three regimes.

The results of this study suggest that LA propranolol is an effective antihypertensive agent (at least in patients known to respond to propranolol), but is no more effective than conventional propranolol twice daily. At 24 h after administration, however, it has a more marked antihypertensive effect than an equal dose of conventional propranolol, given as a single daily dose.

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Table 6 Area under the plasma propranolol—time curve (0–24 h) (ng ml^{-1} h). Mean of 11 patients ± s.e. mean

	Propranolol 80 mg twice daily	*Propranolol LA 160 mg daily*	*Propranolol 160 mg daily*
Acute dosing	1135 ± 224*	560 ± 76**	1414 ± 238
Chronic dosing	2090 ± 530*	934 ± 151*	1852 ± 321

*$P < 0.05$, **$P < 0.01$

Table 7 Relationships between exercise heart rate and log plasma propranolol concentrations

	Correlation coefficient	P(*significance*)
Acute dosing		
Conventional propranolol 160 mg daily	− 0.713	< 0.001
Conventional propranolol 80 mg twice daily	−0.362	< 0.01
Long acting propranolol 160 mg daily	−0.253	NS
Multiple dosing		
Conventional propranolol 160 mg daily	−0.660	< 0.001
Conventional propranolol 80 mg twice daily	−0.567	< 0.001
Long acting propranolol 160 mg daily	−0.052	NS

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