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A comparison of once and twice daily atenolol in hypertension

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Summary

The hypotensive action of atenolol has been studied in a randomized double-blind crossover comparison. Twelve patients showed a highly significant reduction in average supine systolic and diastolic blood pressures from pre-treatment values of 196·3/115·9 to 159·1/89·2 mmHg (26·1/15·4 kPa to 22·2/11·9 kPa) after 2 weeks on once daily atenolol. No dose-related reduction in blood pressure was seen and the single 100 mg daily dose was as effective as 100 mg twice daily or 50 mg twice daily. Blood pressures recorded after 2 weeks' atenolol were lower than those obtained at 7 days irrespective of dose.

Introduction

β-adrenoceptor antagonists are widely used in the treatment of arterial hypertension, but owing to the relatively short half-life of alprenolol, oxprenolol and propranolol most physicians use them in divided doses. A further addition to this series, atenolol or 4-(2-hydroxy-3-isopropylaminopropoxy)phenylacetamide‡ shows relative cardioselectivity (Barrett *et al.*, 1973) and has a half-life of 6–9 hr (Conway *et al.*, 1976). In view of the latter the authors have investigated the possibility of using this drug on a once daily basis in hypertension.

Materials and methods

Fourteen patients aged 22–64 years took part in a double-blind crossover comparison of atenolol and an identical placebo. Clinical details relating to the patients are given in Table 1. None had evidence of other serious disease or significant complications of hypertension, including uraemia or grades III and IV retinopathy. None of the patients gave a history of airways obstruction or heart failure. The study was approved by the local Ethical Sub-Committee and all patients freely gave their informed consent.

The duration of the trial was 12 weeks during which the patients were seen at weekly intervals. In the first 2 weeks all received placebo tablets twice daily. Thereafter, they were given 'identical' tablets

TABLE 1. Individual patient data

Patient	Sex	Age	Wt. (kg)	Relevant history	Previous therapy
HC	F	22	66	Hypertension (5 years)	Nil
HJ	M	64	64	Longstanding hypertension	Clonidine, methyldopa
SW	M	53	87	Nil	Nil
AB	M	50	76	Longstanding hypertension	Methyldopa
LP	F	64	60	Nil	Methyldopa
BS	F	36	79	Nil	Hydrochlorothiazide
ET*	F	59	59	Nil	Nil
RP	M	52	65	Hypertension (5 years)	Propranolol
BR†	F	44	74	Nil	Nil
AD	F	32	70	Sustained hypertension following oral contraception	Bendrofluazide, propranolol
IF	M	51	70	Nil	Nil
JE	M	58	60	Renal calculus removed 1 year previously	Nil
GR	F	60	65	Hypertension (5 years)	Bendrofluazide, diazepam
AG	M	49	71	Nil	Nil

* Mild heart failure 4 weeks after starting trial. Hypertension subsequently controlled with bendrofluazide 10 mg daily; † admitted to hospital for hysterectomy 2 weeks after starting trial.

‡ ICI 66082, Tenormin.

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containing either atenolol 50 mg b.d. (a), atenolol 100 mg b.d. (b), or atenolol 100 mg once daily and placebo tablet once daily (c) for a period of 2 weeks. Each 2-week period of active therapy was followed by a fortnight's 'washout' period in which placebo tablets were taken twice daily (Table 2). The order of the 3 active treatments a, b and c was randomized. A symptomatic enquiry was made by JRED or CMC at each visit and an independent observer (CFG) took duplicate readings of blood pressure, supine (after 5 min) and standing (2 min) with a Hawksley random-zero sphygmomanometer and measured heart rate.

The first six patients were seen before noon on each occasion and were instructed not to take their morning dose until after their clinic visit: this ensured that when on schedule c they had not received atenolol for about 28 hours. However owing to re-scheduling of the hypertension clinic the remaining patients were seen in the afternoon: during schedule c these patients received atenolol (100 mg) 18–19 hr before having their blood pressure recorded. Average values of systolic and diastolic blood pressure taken during the various treatment schedules were compared using Student's *t*-test for paired data.

Results

Twelve of the fourteen patients completed the study: one patient was withdrawn following admission for abdominal hysterectomy: a second, aged 59 years, developed mild heart failure whilst receiving atenolol. She made an uneventful recovery following withdrawal of atenolol, and her hypertension was subsequently controlled on bendrofluazide 10 mg daily. In the twelve remaining patients, blood pressure before atenolol therapy averaged 196·3/115·7 mmHg (26·1/15·4 kPa) in recumbency and heart rate 77·8 beats/min. Atenolol produced a highly significant reduction in blood pressure, in both supine and standing positions as well as in heart rate (Tables 3 and 4). Blood pressures were, however, lower during the second week of each active treatment than during the first. In contrast, blood pressures recorded between 18 and 28 hr after a single 100 mg daily dose c did not differ significantly from those obtained when the same patients received atenolol in a twice-daily dosage. Although there was a small, but statistically insignificant, dose-related reduction in heart rate, pressure control was similar at total daily doses of 100 and 200 mg.

Side effects

The occurrence of heart failure in the patient who was withdrawn was the only drug-related side effect identified in the present study. One other patient experienced mild Raynaud's phenomenon but this was present in the run-in phase on placebo as well as on atenolol. Average weights remained constant, except during week 2 on treatment b ($P<0·05$) (Table 4) and routine haematologic and biochemical screens showed no evidence of toxicity.

Discussion

The present findings confirm that atenolol, like other β-adrenoceptor antagonists, will produce a satisfactory reduction in arterial blood pressure when given chronically by mouth. Unlike propranolol, however, no dose-related reduction in blood pressure was identified. This confirms the findings of Myers *et al.* (1976) and Amery *et al.* (1976). A further advantage of atenolol is that blood pressure control appears to be adequate on a single daily dose confirming claims made by Douglas-Jones and Cruickshank (1976). Since compliance is one of the major problems in the management of hypertensive patients, a single 100 mg daily dose may confer significant advantages in clinical practice. It appears, however, that the full hypotensive action of atenolol takes at least 2 weeks to develop even though the majority of this is seen within 1 week of starting the treatment. However, like other β-adrenoceptor antagonists, atenolol has predictable adverse effects which include Raynaud's phenomenon (Marshall, Roberts and Barritt, 1976) and heart failure.

TABLE 2. Sequence of treatments administered during the trial

	Weeks					
	1–2	3–4	5–6	7–8	9–10	11–12
Treatment	Placebo Run-in 1 tablet b.d.	Atenolol* 50 mg b.d.	Placebo washout 1 tablet b.d.	Atenolol* 100 mg o.d. + placebo 1 tablet daily	Placebo washout 1 tablet b.d.	Atenolol* 100 mg b.d.

* Treatment randomized.

TABLE 3. Mean +(s.e.) of blood pressure, heart rate and weight recorded during the trial (12 patients)

	Initial	Run-in		Washout 1		Washout 2		Atenolol 50 mg b.d.		Atenolol 100 mg b.d.		Atenolol 100 mg o.d. +placebo	
	0	1	2	5	6	9	10	Wk 1	Wk 2	Wk 1	Wk 2	Wk 1	Wk 2
Systolic BP (mmHg) Lying	196·30 (7·28)	188·08 (6·54)	194·08 (4·84)	173·67 (5·93)	172·42 (5·91)	172·75 (5·80)	177·17 (5·92)	163·90 (7·20)	160·50 (7·96)	161·92 (5·67)	157·54 (7·07)	163·58 (7·43)	159·08 (6·61)
Diastolic BP (mmHg) Lying	115·90 (2·39)	108·17 (3·55)	111·58 (3·29)	103·75 (4·46)	101·58 (4·34)	100·33 (3·59)	101·92 (2·48)	98·20 (1·45)	95·40 (2·67)	93·33 (4·12)	92·45 (3·30)	94·42 (2·80)	89·17 (3·37)
Systolic BP (mmHg) Standing	185·89 (5·69)	185·83 (3·84)	182·50 (5·41)	167·25 (5·97)	166·08 (7·29)	166·58 (6·53)	170·42 (6·31)	159·20 (6·65)	148·80 (6·59)	161·33 (5·52)	150·91 (7·70)	165·08 (7·65)	152·08 (5·45)
Diastolic BP (mmHg) Standing	114·33 (2·86)	115·08 (3·13)	112·33 (3·07)	108·17 (3·24)	105·67 (3·93)	103·08 (3·56)	106·42 (4·10)	100·60 (2·45)	95·00 (3·23)	98·17 (3·10)	95·36 (3·89)	99·00 (2·23)	93·67 (3·42)
Pulse (rate/min) Lying	77·75 (5·67)	82·67 (5·28)	80·33 (4·65)	82·50 (5·46)	82·83 (3·43)	75·83 (3·71)	78·17 (5·04)	66·40 (3·52)	65·80 (3·14)	63·00 (2·85)	64·00 (2·03)	63·33 (2·87)	63·58 (2·47)
Weight (kg)	69·42 (2·32)	69·80 (2·44)	69·75 (2·36)	69·71 (2·46)	69·30 (2·43)	70·08 (2·55)	69·09 (2·60)	69·59 (2·81)	69·64 (2·72)	69·59 (2·47)	70·35 (2·60)	69·15 (2·45)	69·48 (2·42)

TABLE 4. Levels of statistical significance for between-treatment means

	Run-in v. atenolol 50 mg		Run-in v. atenolol 100 mg		Run-in v. atenolol 100 mg + placebo	
	Week 1	Week 2	Week 1	Week 2	Week 1	Week 2
Systolic blood pressure lying	$P<0.01$	$P<0.001$	$P<0.001$	$P<0.01$	$P<0.001$	$P<0.001$
Diastolic blood pressure lying	$P<0.001$	$P<0.001$	$P<0.01$	$P<0.001$	$P<0.001$	$P<0.001$
Systolic blood pressure standing	$P<0.01$	$P<0.001$	$P<0.01$	$P<0.001$	$P<0.05$	$P<0.01$
Diastolic blood pressure standing	$P<0.01$	$P<0.001$	$P<0.001$	$P<0.01$	$P<0.01$	$P<0.001$
Pulse lying	$P<0.01$	$P<0.02$	$P<0.007$	$P<0.001$	$P<0.01$	$P<0.01$
Weight	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.

There were no statistically significant differences found between the mean values recorded during the three active treatments, except for weights on atenolol 50 mg b.d. and atenolol 100 mg b.d., week 2 ($P<0.05$).

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