A comparison of bisoprolol and atenolol in the treatment of mild to moderate hypertension

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1 Fourteen patients (mean age 56.0, range 37–61 years; eight females) with mild essential hypertension (DBP >90 mm Hg on placebo) completed a randomised, double-blind placebo controlled crossover study comparing the hypotensive effects of bisoprolol (10–20 mg) and atenolol (50–100 mg) each taken once daily.

2 Bisoprolol had a significantly greater antihypertensive effect than atenolol, reducing sitting blood pressures by 15.9 mm Hg (diastolic) and 21.9 mm Hg (systolic) compared with placebo. Corresponding figures for atenolol were 10.7 and 5.7 mm Hg respectively. Bisoprolol reduced standing blood pressures by 15.9 mm Hg (diastolic) and 22.8 mm Hg (systolic) compared with 7.3 and 8.6 mm Hg respectively for atenolol.

3 Examination of the pharmacokinetic data showed that bisoprolol had a median elimination half-life of 11.2 h during chronic dosing, compared with 6.4 h for atenolol. For bisoprolol, the median clearance fell from 264 ml min⁻¹ after a single dose to 212 ml min⁻¹ during chronic dosing, although clinically significant accumulation would not be expected during chronic administration.

4 Overall, the results suggest that bisoprolol may be a more effective antihypertensive agent than atenolol but larger studies are necessary to confirm these findings.

Keywords bisoprolol atenolol hypertension

Introduction

Bisoprolol fumarate is a new β -adrenoceptor antagonist which may have certain advantages over existing members of this class of drugs. In particular, it is thought to be one of the most β_1 -selective adrenoceptor blocking drugs available at the present time (Klockow *et al.*, 1986). It may, therefore, be of particular value in patients with co-existing medical disorders such as insulin dependent diabetes mellitus, in whom β_2 -adrenoceptor blockade is particularly undesirable (Deacon & Barnett, 1976). It has several favourable pharmacokinetic properties including a long plasma half-life (Leopold *et al.*, 1986b) and high oral bioavailability (Leopold *et al.*, 1986a). It is cleared from the plasma by a combination of renal excretion and hepatic metabolism (Leopold, 1986). Studies in healthy

volunteers have suggested that, on a molar basis, bisoprolol is about 5, 7 and 10 times more potent than propranolol, atenolol and metoprolol, respectively (Leopold *et al.*, 1986b). The aim of the present study was to investigate the efficacy, the safety and the pharmacokinetic profile of single daily doses of bisoprolol in the treatment of patients with mild to moderate essential hypertension.

Methods

Twenty patients (9 males; 11 females) aged between 26 and 61 years (mean $\pm$ s.e. mean; 47.4 ± 2.3) were recruited into the study (Table 1). All had mild to moderate essential hyper-

Table 1 Demographic data for the 20 patients who entered the study

	Males Females	9 11
Mean age $\pm$ s.e. mean (Range) years		47.4 $\pm$ 2.3 (26–61)
Mean weight $\pm$ s.e. mean (Range) kg		80.1 $\pm$ 3.0 (53.1–99.8)
Mean height $\pm$ s.e. mean (Range) cm		167.6 $\pm$ 2.5 (150–188)
Mean duration of hypertension $\pm$ s.e. mean (Range) years		5.9 $\pm$ 1.7 (1 month–32 years)
Mean cardiothoracic ratio $\pm$ s.e. mean (Range)		44.3 $\pm$ 0.7 (40–50) NS–4 patients

tension with diastolic blood pressures within the range 90–120 mm Hg. Women of child bearing age who were not using effective contraception were excluded, as was any individual with renal impairment (serum creatinine $> 250 \mu\text{mol l}^{-1}$), hepatic impairment, obstructive airways disease, insulin dependent diabetes mellitus, peripheral vascular disease or secondary hypertension.

Patients who fulfilled these criteria entered the first part of the study, a run-in period during which placebo tablets were taken once daily after breakfast. This run-in period was of 4 weeks duration for newly diagnosed hypertensives and those who had previously been taking β -adrenoceptor blockers, and of 6 weeks duration for patients who had previously been taking diuretics. At the end of this period 17 patients had sitting diastolic blood pressures of between 90 and 120 mm Hg, and which were within 5 mm Hg of the pressures recorded 2 weeks earlier. These individuals then entered the double-blind phase of the study. The first active medication phase comprised 6 weeks treatment with either one 10 mg bisoprolol tablet and one atenolol placebo, or one bisoprolol placebo and one 50 mg atenolol tablet each taken once daily. Active and placebo formulations of each drug were identical in taste and appearance and were taken at the same time as during the placebo phase. If, however, after 2 weeks on this medication regime the sitting diastolic blood pressure had not fallen below 90 mm Hg, or by 10 mm Hg from the end of the run-in period (whichever the greater) the dose was doubled for the remaining 4 weeks (bisoprolol 20 mg or atenolol 100 mg).

At the end of this first 6 week period, patients entered a second placebo phase of at least 2 weeks duration. During this period, one bisoprolol placebo and one atenolol placebo

were taken at the same time as before until the sitting diastolic blood pressure had increased to within 5 mm Hg of that obtained at the end of the first placebo phase. Patients then entered the second active phase during which they received the alternate medication to that of the first phase, with the same capacity to increase the dose if necessary.

Patients were seen at the ends of the second and sixth weeks of each active treatment period and at 2 weekly intervals throughout the placebo periods. All clinical measurements were made between 23 and 25 h after the last dose of study drug. At each visit blood pressures were recorded in triplicate, at intervals of 1 min, using a Hawksley random zero sphygmomanometer. Pressures were measured sitting and after standing for 2 min. Diastolic blood pressures were recorded at Korotkoff phase 5. Fundoscopy, electrocardiography and full biochemical and haematological screening tests were carried out at the ends of the first placebo and each active treatment phase.

Pharmacokinetic studies were carried out in each subject after the first and last doses of bisoprolol and atenolol in each active treatment phase. Venous blood was taken immediately before dosing and at the following intervals thereafter: 30, 60, 90 min and 2, 3, 4, 6, 8 and 24 h. The plasma was separated and stored at -20°C pending analysis of plasma drug concentrations using h.p.l.c. techniques (Buhring & Garbe, 1986; Ioannides, personal communication; Yee *et al.*, 1979).

Changes in blood pressure, measured from the end of the preceding placebo period, were examined using analysis of variance. Because of withdrawals, more patients received bisoprolol rather than atenolol as their first treatment and all treatment effects were therefore adjusted for period effect before significance was tested. The pharmacokinetic parameters for each plasma screen were derived using the computer program STRIPE (Johnston & Woollard, 1983). The data were fitted to either a one or a two compartment model, the choice of model being made using Akaike's Information Criterion (Yamaoka *et al.*, 1978). Comparison of the parameters on single dose and during chronic administration were made using the Wilcoxon signed ranks test.

Results

Patients

Fourteen patients (mean age 56.0, range 37–61 years, eight females) completed the study. Of the remainder, two were withdrawn during the

second placebo period as their blood pressures failed to rise to within 5 mm Hg of the baseline recordings after a period of 6 weeks. One patient was found to be non-compliant and data from this subject were excluded from the analysis. No patient had to be withdrawn because of side effects or any adverse reaction.

Duration of hypertension ranged between 1 month and 32 years. Ten patients had previously received treatment with a β -adrenoceptor blocker, either alone or in combination with a diuretic. Five of the patients were cigarette smokers. The mean serum creatinine concentration was 91 (range 64–117) $\mu\text{mol l}^{-1}$.

Pharmacodynamic results (Tables 2 and 3)

Both atenolol and bisoprolol reduced sitting and standing blood pressures compared with the preceding placebo period. During each treatment period, blood pressures failed to fall below 90 mm Hg in four patients, and drug dosages were therefore doubled in these individuals.

Bisoprolol had a consistently greater anti-hypertensive effect than atenolol. Compared with placebo, bisoprolol reduced mean sitting blood pressures by 15.9 mm Hg (diastolic) and 21.9 mm Hg (systolic). The corresponding reductions seen with atenolol were 10.7 and 5.7 mm Hg respectively. The differences in hypotensive effect between atenolol and bisoprolol were statistically significant for systolic ($P < 0.01$) but not diastolic ($< 0.1 P > 0.05$) blood pressures.

Similarly, bisoprolol achieved significantly greater reductions in standing blood pressure, reducing diastolic pressures by 15.9 mm Hg and systolic pressures by 22.8 mm Hg. Corresponding figures for atenolol were 7.3 and 8.6 mm Hg respectively. The differences in hypotensive effect between atenolol and bisoprolol were statistically significant at the 1% (diastolic) and 5% (systolic) levels.

Mean resting heart rates were reduced by both atenolol ($-18.0 \text{ beats min}^{-1}$) and bisoprolol ($-17.4 \text{ beats min}^{-1}$). The differences between the two drugs were not statistically significant.

Pharmacokinetic data

Details of the pharmacokinetic profiles for bisoprolol and atenolol are shown in Table 4. Bisoprolol was found to have a median half-life of 11.2 h during chronic dosing, compared with 6.4 h for atenolol. For bisoprolol, there were significant differences between single dosing and chronic administration in the maximum plasma concentration (C_{max}), AUC and clearance. The median C_{max} rose from $42 \mu\text{g l}^{-1}$ after the single

Table 2 Mean blood pressures (and range) seen in 14 patients with mild hypertension during treatment with bisoprolol and atenolol

	Placebo		Bisoprolol		Placebo 2		Atenolol	
	Week 2	Week 6	Week 2	Week 6	Week 2	Week 6	Week 2	Week 6
Sitting diastolic (mm Hg)	103.3 (90.0–125.7)	87.0	87.9 (70.0–110.0)	103.3 (91.3–121.3)	91.6	93.6 (71.3–119.3)	91.6	93.6 (71.3–119.3)
Standing diastolic (mm Hg)	108.8 (93.3–129.3)	92.7	93.2 (69.3–114.0)	104.8 (94.7–118.7)	94.9	100.1 (77.0–123.3)	94.9	100.1 (77.0–123.3)
Sitting systolic (mm Hg)	167.5 (131.3–224.7)	144.8	146.3 (96.0–200.3)	156.6 (128.7–190.0)	151.9	150 (105.3–216.0)	151.9	150 (105.3–216.0)
Standing systolic (mm Hg)	167.3 (120.7–212.7)	145.6	143.4 (100.0–203.3)	159.0 (134.0–189.3)	145.3	155.4 (109.0–211.7)	145.3	155.4 (109.0–211.7)

Table 3 Reductions in blood pressure (compared with placebo) seen during treatment with atenolol and bisoprolol in 14 patients with mild hypertension

	<i>Sitting diastolic (mm Hg)</i>	<i>Standing diastolic (mm Hg)</i>	<i>Sitting systolic (mm Hg)</i>	<i>Standing systolic (mm Hg)</i>
Bisoprolol	-15.9	-15.9	-21.9	-22.8
Atenolol	-10.7	-7.3	-5.7	-8.6
Difference between means	5.2*	8.6**	16.2***	14.2**
95% C.I. for difference	-2.6 to 13.0	3.2 to 13.8	6.6 to 25.8	3.4 to 24.9

* $P < 0.1 > 0.05$
 ** $P < 0.05$ for differences between atenolol and bisoprolol
 *** $P < 0.01$

dose to $60 \mu\text{g l}^{-1}$ at steady state. The median AUC rose from 633 ($\text{AUC}_{0-\infty}$) to $787 \mu\text{g l}^{-1} \text{h}$ (AUC_{0-24}). This was accompanied by a fall in the median clearance from 264 after the single dose to 212 ml min^{-1} during chronic dosing. For atenolol there was also a fall in median clearance

from 333 after the single dose to 289 ml min^{-1} during chronic administration but this did not reach statistical significance. There were no other significant changes in the pharmacokinetic parameters recorded between single dose administration and the steady state for atenolol.

Figure 1 Changes in a) systolic and b) diastolic blood pressures seen during treatment with bisoprolol (----) and atenolol (—) in 14 patients with essential hypertension.

Adverse effects

Both treatments were well tolerated and none of the patients suffered serious adverse effects during either of the two active treatment periods. However, one patient did show an increase in glutamyl transferase activity from 39 to 114 IU l⁻¹ after treatment with bisoprolol. No other significant biochemical or haematological changes were noted during the course of the study.

Discussion

The results of this study suggest that bisoprolol is an effective and a well tolerated antihypertensive agent.

In the present study, 10–20 mg of bisoprolol had a significantly greater antihypertensive effect than 50–100 mg of atenolol. It is, however, important to note that treatment with 10 mg bisoprolol failed to reduce blood pressures to target levels in four of the 14 patients and in this respect it was no more effective than atenolol. Both drugs produced a similar reduction in the resting heart rate but this, in itself, is not indicative of similar degrees of β -adrenoceptor blockade. Reduction of exercise induced tachycardia is a better index of β -adrenoceptor blockade and, on this basis, there is evidence to suggest that 10 mg of bisoprolol might achieve a greater degree of β -adrenoceptor-blockade than 50 mg of atenolol (Leopold *et al.*, 1986b). Nevertheless, there is generally only a weak relationship between the extent of β -adrenoceptor blockade and hypotensive effect and it has been shown that increasing the dose of atenolol from 50 mg to 100 mg does not significantly increase its antihypertensive effect (Jeffers *et al.*, 1977). Differences in the extent of β -adrenoceptor blockade may not, therefore, explain the greater antihypertensive effect seen with bisoprolol. Furthermore, there is evidence from other studies to suggest that bisoprolol does appear to have a greater antihypertensive action than atenolol (Buhler *et al.*, 1986), although these have shown smaller differences than those which were found in the present study.

Nevertheless, the results are surprising as the various β -adrenoceptor antagonists are generally thought to have similar antihypertensive effects, and these appear to be unrelated to ancillary properties such as β_1 -selectivity and partial agonist activity (Davidson *et al.*, 1976). Interestingly, it has been shown that most β -adrenoceptor blockers lower blood pressures by approximately 20 mm Hg systolic and 12 mm Hg

Table 4 Comparison of the pharmacokinetic properties of atenolol and bisoprolol after single doses and during chronic administration: median (and range) results for 14 patients

	Atenolol		Bisoprolol	
	Single dose	Chronic administration	Single dose	Chronic administration
Elimination half-life (h)	6.5 (3.4–19.4)	6.4 (4.0–11.1)	10.5 (5.0–16.3)	11.2 (8.5–19.0)
Clearance (ml min ⁻¹)	333 (210–444)	289 (187–423)	264 (175–454)	212 (162–321)
Volume of distribution (l)	194 (117–367)	168 (80–406)	221 (170–345)	224 (140–312)
AUC (μ g l ⁻¹ h) (AUC _{0–24} : AUC _{0–∞})	2502 (1876–3965)	2883 (1971–4463)	633 (367–951)	787 (520–1028)
Maximum plasma concentration (μ g l ⁻¹)	228 (131–383)	282 (159–377)	42 (30–67)	60 (37–86)
Time to reach maximum plasma concentration (h)	3.0 (1.0–5.9)	2.0 (1.5–6.0)	3.9 (1.5–4.0)	2.0 (520–1028)

diastolic (Davidson *et al.*, 1976). Thus, the large differences in hypotensive effects between atenolol and bisoprolol found in the present study may be due, in part, to smaller than expected decreases in blood pressure during treatment with atenolol. If bisoprolol does, in fact, have a greater hypotensive effect than the other β -adrenoceptor blockers, this may be attributable to properties other than β -adrenoceptor blockade alone. For example, one particular β -adrenoceptor blocker (bevantolol) also appears to act as a partial α -adrenoceptor agonist and this may increase its antihypertensive action by reducing peripheral vascular resistance (Cooke *et al.*, 1987). It is not known whether bisoprolol does exhibit a significant degree of α -adrenoceptor agonism but this might be one possible explanation for the results obtained in the present study. On theoretical grounds, one might expect that exceptionally high degrees of β_1 -selectivity may increase the hypotensive effects of the β -adrenoceptor blockers as inhibition of β_2 mediated vasodilatation would tend to increase peripheral vascular resistance. However, there is no evidence to suggest that atenolol has a greater antihypertensive effect than propranolol (Davidson *et al.*, 1976), despite the fact that the former exhibits relatively little β_2 -adrenoceptor blockade at normal doses.

Examination of the pharmacokinetic data confirms that bisoprolol has a long half-life. This indicates that once-daily dosing is likely to maintain adequate plasma drug concentrations

throughout the 24 h period. This property would be of particular value in the treatment of angina pectoris, where therapeutic effect is more closely related to the extent of β -adrenoceptor blockade. Despite the changes seen in various pharmacokinetic parameters during chronic dosing, clinically significant accumulation would not be expected in clinical practice. The predicted percentage accumulation for bisoprolol would be a 31% increase in $C_{\max}$ and, as the β -adrenoceptor blockers generally have wide therapeutic ratios, such an increase is unlikely to be of importance in practice. It is possible, however, that such an accumulation may lead to some loss of β_1 -adrenoceptor selectivity. Our results for the pharmacokinetic data of atenolol generally correlate well with those reported by others. Brown *et al.* (1976), Fitzgerald *et al.* (1978) and Kirch *et al.* (1981) reported elimination half-lives of between 5.9 and 6.7 h.

There is currently a wide range of effective antihypertensive drugs, including a relatively large number of β -adrenoceptor antagonists. Safety, tolerability and once-daily dosing are all important considerations in the choice of agent. Bisoprolol appears to have a greater antihypertensive effect than atenolol, but further studies using larger numbers of patients are necessary to confirm our results. Further work is necessary to elucidate mechanisms other than β -adrenoceptor antagonism which may contribute to the antihypertensive actions of bisoprolol.

References

- Brown, H. C., Carruthers, S. G., Johnston, G. D., Kelly, J. G., McAinsh, J., McDevitt, D. G. & Shanks, R. G. (1976). Clinical pharmacologic observations on atenolol, a β -adrenoceptor blocker. *Clin. Pharmac. Ther.*, **20**, 524–534.
- Buhler, F. R., Berglund, G., Anderson, O. K. (1986). Double-blind comparison of the cardioselective β -blockers bisoprolol and atenolol in hypertension: The bisoprolol international multicenter study. *J. cardiovasc. Pharmac.* **8** (Suppl. 11) 122–127.
- Buhring, K. U. & Garbe, A. (1986) Determination of the new β -blocker bisoprolol and of metoprolol, atenolol and propranolol in plasma and urine by high-performance liquid chromatography. *J. Chromatogr.*, **382**, 215–224.
- Cooke, E. D., Maltz, M. B., Smith, R. L., Bowcock, S. A., Watkins, C. J. & Carim, A. J. (1987). Peripheral vascular effects of β -adrenoceptor blockade: comparison of two agents. *Br. J. clin. Pharmac.*, **24**, 359–366.
- Davidson, C., Thadani, U., Singleton, W. & Taylor, S. H. (1976). Comparison of antihypertensive activity of beta-blocking drugs during chronic treatment. *Br. med. J.*, **2**, 7–9.
- Deacon, S. P. & Barnett, D. (1976). Comparison of atenolol and propranolol during insulin induced hypoglycaemia. *Br. med. J.*, **2**, 272.
- Fitzgerald, J. D., Ruffin, R., Smedstad, K. G., Roberts, R. & McAinsh, J. (1978). Studies on the pharmacokinetics and pharmacodynamics of atenolol in man. *Eur. J. clin. Pharmac.*, **13**, 81–89.
- Jeffers, T. A., Webster, J., Petrie, J. C. & Barker, N. (1977) Atenolol once daily in hypertension. *Br. J. clin. Pharmac.*, **4**, 523–527.
- Johnston, A. & Woollard, R. C. (1983). STRIPE: an interactive computer program for the analysis of drug pharmacokinetics. *J. Pharmac. Methods*, **9**, 193–199.
- Kirch, W., Kohler, H., Mutschler, E. & Schäfer, M. (1981). Pharmacokinetics of atenolol in relation to renal function. *Eur. J. clin. Pharmac.* **19**, 65–71.
- Klockow, M., Greiner H. E., Haase, A., Schmitges, C. J. & Seyfried, C. (1986). Studies on the receptor profile of bisoprolol. *Drug Res.*, **36**, 197–200.
- Leopold, G. (1986). Balanced pharmacokinetics and metabolism of bisoprolol. *J. cardiovasc. Pharmac.*, **8**, (Supp. II) 5–16.
- Leopold, G., Pabst, J., Ungethum, W. & Buhring, K.

- U. (1986a). Basic pharmacokinetics of bisoprolol, a new highly selective beta-1 selective adrenoceptor antagonist. *J. clin. Pharmac.*, **26**, 616–621.
- Leopold, G., Ungethum, W., Pabst, J., Simane, Z., Buhning, K. U. & Wiemann, H. (1986b). Pharmacodynamic profile of bisoprolol, a new β_1 -selective adrenoceptor antagonist. *Br. J. clin. Pharmac.*, **22**, 293–300.
- Yamaoka, K., Nakagawa, T. & Uno, T. (1978) Application of Akaike's information criterion (AIC) in the evaluation of linear pharmacokinetic equations. *J. Pharmacokin. Biopharm.*, **6**, 165–175.
- Yee, Y. G., Ruben, P. C. & Blashke, T. F. (1979) Atenolol determination by HPLC and fluorescence detection. *J. Chromatogr.*, **171**, 357–362.

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