COMPARISON OF TWO LONG-ACTING PREPARATIONS OF METOPROLOL WITH CONVENTIONAL METOPROLOL AND ATENOLOL IN HEALTHY MEN DURING CHRONIC DOSING

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- 1 Eight healthy men received two long-acting formulations of metoprolol 200 mg (SA Astra, SR Geigy), conventional metoprolol 200 mg and atenolol 100 mg once daily for 1 week each in balanced, crossover fashion. There was a washout period of at least a week between each phase.
- 2 On the last day of each phase, post-exercise heart rate was recorded at intervals and compared to pretreatment values. Plasma metoprolol concentrations were measured.
- 3 The mean AUC was similar after each of the three formulations of metoprolol (relative bioavailability of SA and SR v conventional was 97%) but with SA and SR metoprolol the time to peak was significantly delayed by about 2 h.
- 4 In comparison to conventional metoprolol only metoprolol SA was associated with significantly higher plasma metoprolol concentrations at the end of a dosing interval (mean values: conventional, 25 ng/ml, SR 37 ng/ml, SA 51 ng/ml).
- 5 Mean ($\pm$ s.d.) reduction in exercise tachycardia at the end of a dosing interval was significantly greater with atenolol ($14.8 \pm 4.5\%$) and metoprolol SA ($13.7 \pm 10.3\%$) than with metoprolol SR ($10 \pm 8.4\%$) and conventional metoprolol ($8.2 \pm 7.1\%$).
- 6 The variability in β -adrenoceptor blockade at 24 h was much greater with each of the three metoprolol formulations than that with atenolol. This was explained by the variability in metoprolol metabolism.
- 7 Oxidation phenotype testing with debrisoquine showed there were six extensive metabolisers and two poor metabolisers. The AUC, half-life and response to metoprolol at 24 h were much greater in poor metabolisers. Response to atenolol was not influenced by phenotype.

Introduction

Metoprolol is used for the treatment of hypertension and for the prevention of angina. The duration of action in hypertension is known to be at least 24 h and therefore the drug may be taken once daily (Reybrouck *et al.*, 1978). The control of angina, however, depends on effective β -adrenoceptor blockade throughout a dosing interval. This may entail dosing at least twice daily (Reybrouck *et al.*, 1978) as the half-life is usually short (3 h) (Johnsson *et al.*, 1975). In contrast, once daily atenolol (half-life 7 h) provides significant reduction in exercise tachycardia for 24 h (Petrie *et al.*, 1980). Two new long-acting preparations of metoprolol have just been marketed employing film coated tablets (Geigy) and durules (Astra) respectively. They will be welcome additions to therapeutics providing that the duration of effective β -adrenoceptor blockade extends throughout 24 h following once daily administration. However, pre-

vious experience has shown that the formulation is important in determining the duration of effect of a β -adrenoceptor blocker. Studies with sustained-release oxprenolol have shown that, at 24 h β -adrenoceptor blockade is negligible or no different from conventional oxprenolol (Petrie *et al.*, 1980; Bobik *et al.*, 1979; Leahey *et al.*, 1980). In contrast, the slow release formulation of propranolol prolongs the duration of β -adrenoceptor blockade with this compound (Petrie *et al.*, 1980; Leahey *et al.*, 1980).

We have compared the pharmacokinetic and β -adrenoceptor blocking profiles of the two sustained release formulations of metoprolol with those of conventional metoprolol and atenolol, after chronic once daily dosing with each preparation. In two subjects we observed an unusually high AUC and half-life which led us to investigate the kinetics of metoprolol in relation to the metabolism of debrisoquine. The latter is known to be a useful marker of a genetic defect in drug oxidation (Mahgoub *et al.*, 1977). These data are published in detail elsewhere (Lennard *et al.*, 1982).

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Methods

Subjects and protocol

Eight healthy men aged 28–35 years were allocated to four treatments each administered for 1 week in balanced crossover fashion with 1 week washout between treatments. The following were taken once daily in the morning:

- conventional metoprolol 200 mg;
- film-coated sustained release metoprolol 200 mg (metoprolol SR, Geigy);
- sustained action metoprolol durules 200 mg (metoprolol SA, Astra);
- atenolol 100 mg.

On day 7 of each treatment phase dosing was performed at least 1.5 h after a light breakfast and approximately 24 h after the previous dose. At intervals over the next 24 h, blood for the estimation of metoprolol concentrations was taken and an exercise test was performed to determine β -adrenoceptor blockade.

β -adrenoceptor blockade was calculated as a % reduction in exercise heart rate from control (untreated) values. These had been previously determined over a 24 h period using the same protocol for each individual but before dosing. Each person performed an exercise test on at least two occasions prior to the day of the control tests to familiarize themselves with the procedure.

Exercise test

This was performed on a bicycle ergometer (Siemens 380B) for 4 min with incremental work loads at minute intervals in order to achieve a post-exercise heart rate when untreated which was consistently above 140 beats/min. Typically this required work loads of 50 w, 100 w, 150 w, 200 w. Post-exercise heart rate was measured on a continuous ECG recording and was defined as the mean heart rate calculated from the first four beats after stopping exercise. This was an open study and therefore the ECG was read by two observers, one of whom was always unaware of the drug taken by the volunteer. The exercise test was performed at 0, 2, 4, 8, 12 and 24 h in relation to dosing.

Metoprolol kinetics

When dosing with metoprolol blood was taken at 0, 1, 2, 4, 6, 8, 12 and 24 h. Plasma metoprolol concentrations were measured by h.p.l.c. (Lefebvre *et al.*, 1981). The internal standard was ($\pm$)-1-(4-butyramido-2-butyrylphenoxy)-2-hydroxy-3-isopropylaminopropane hydrochloride. The intra-assay coefficient of variation was 4.7% at 100 ng/ml and the

lowest measurable concentration was about 5 ng/ml. The area under the plasma concentration-time curve between 0–24 h (AUC) was calculated using the trapezoidal rule.

Oxidation status

This was estimated from an 8 h urine collection after a 10 mg single oral dose of debrisoquine administered 1 week after the last dose of β -blocking agents. The ratio of debrisoquine/4-hydroxydebrisoquine (D/HD) in poor metabolisers is >20 ; that in extensive metabolisers is <12 (mode <1) (Mahgoub *et al.*, 1977; Tucker *et al.*, 1977).

Statistics

Analysis of variance was used to assess the differences in post-exercise heart rate before and during treatment, in β -adrenoceptor blockade and in plasma concentrations with different treatments. The variables considered were patients, order of treatment and drugs.

The post-exercise heart rates during the first treatment phase were significantly higher than expected from heart rates during subsequent phases, implying some training effect. This was taken into account by the analysis of variance. A *t*-test was applied to the data obtained from the analysis of variance and significance was taken as $P < 0.05$.

Results

Metoprolol kinetics

There was wide inter-subject variability in AUC and half-life following administration of conventional metoprolol (Table 1). The systemic availability of metoprolol was not influenced by the formulation used, but the time to peak was delayed and peak concentrations were lower after SA and SR formulations ($P < 0.001$) (Figure 1). Plasma metoprolol concentrations at 0 h and 24 h were higher after metoprolol SA than after conventional metoprolol (0 h: $P < 0.025$, 24 h: $P < 0.005$). In contrast, dosing with metoprolol SR was not associated with a consistent difference in plasma concentrations at these times when compared to the conventional compound (0 h: NS, 24 h $P < 0.05$).

Exercise heart-rates

The post-exercise heart rates are shown in Table 2. Atenolol and metoprolol SA were associated with a reduction in post-exercise tachycardia which remained significant at both 0 h and 24 h ($P < 0.01$); with metoprolol SR the reduction was significant at

Table 1 Metoprolol kinetics in relation to formulation and oxidation status

	AUC_{0-24h} ($ng\ ml^{-1}\ h$)			C_{max} (ng/ml)			t_{max} (h)			C_0 (ng/ml)			C_{24} (ng/ml)			$t_{1/2}$ (h)	D/HD
	M	SA	SR	M	SA	SR	M	SA	SR	M	SA	SR	M	SA	SR		
1	7799	9384	8482	937	616	645	2	4	4	76	159	108	76	146	118	7.13	41.0
2	8493	8004	9400	889	572	767	2	4	4	78	126	119	99	125	125	6.92	40.0
3	4458	3940	4292	627	290	369	2	4	6	29	50	32	12	57	46	3.84	1.23
4	2259	1521	1678	395	144	140	1	4	2	0	9	0	0	20	0	2.97	0.84
5	4128	3974	2574	662	287	192	2	2	6	0	42	0	6	49	17	3.15	0.66
6	2707	2630	2518	382	218	242	2	4	4	0	10	9	5	18	9	3.34	0.57
7	864	972	1081	194	131	168	2	2	2	0	0	0	0	0	0	2.07	0.41
8	914	428	777	206	50	92	2	4	4	10	0	0	0	0	0	1.78	0.19
Mean	3953	3857	3850	537	289	327				24	50	34	25	52	39	3.90	
$\pm$ s.d.	2900	3269	3331	288	205	250				34	61	51	39	56	53	2.04	

M = metoprolol; SA = metoprolol SA; SR = metoprolol SR; C_{max} = maximum plasma concentration; t_{max} = time of C_{max} ; C_0 , C_{24} , plasma concentration at 0 h and 24 h; $t_{1/2}$ = half-life of conventional metoprolol; D/HD = debrisoquine/4-hydroxydebrisoquine ratio in 8 h urine.

Figure 1 Mean plasma metoprolol concentrations on the seventh day of once daily treatment with each of 3 formulations of metoprolol. ● conventional metoprolol, ○ metoprolol SA and □ metoprolol SR.

0 h ($P < 0.05$) but not at 24 h ($P > 0.1$). Reduction in tachycardia with conventional metoprolol was significant only between 2 and 12 h after the dose. At 24 h atenolol and metoprolol SA were superior to conventional metoprolol ($P < 0.02$ and < 0.01 respectively) and to metoprolol SR (atenolol: $P < 0.05$; metoprolol SA: < 0.02) (Figure 2). Atenolol was superior to conventional metoprolol at 0 h ($P < 0.025$). The latter compound caused significantly less reduction in exercise tachycardia than the other preparations at 12 h (metoprolol SR: $P < 0.025$; atenolol and metoprolol SA: $P < 0.05$). Following each of the metoprolol formulations, wide inter-subject variability in β -adrenoceptor blockade at 0 h and 24 h was observed (Figure 3).

Table 2 Mean ($\pm$ s.d.) post-exercise heart rates for each drug and control at each time.

Time (h)	Control	Atenolol	Conventional metoprolol	Metoprolol SA	Metoprolol SR
0	162 $\pm$ 13	136 $\pm$ 13	147 $\pm$ 10	141 $\pm$ 18	143 $\pm$ 11
2	159 $\pm$ 13	114 $\pm$ 10	111 $\pm$ 6	118 $\pm$ 7	115 $\pm$ 6
4	163 $\pm$ 14	117 $\pm$ 10	117 $\pm$ 7	119 $\pm$ 8	116 $\pm$ 6
8	162 $\pm$ 14	119 $\pm$ 11	125 $\pm$ 9	123 $\pm$ 7	116 $\pm$ 8
12	168 $\pm$ 14	130 $\pm$ 11	137 $\pm$ 9	129 $\pm$ 9	128 $\pm$ 7
24	161 $\pm$ 14	139 $\pm$ 11	148 $\pm$ 7	137 $\pm$ 12	147 $\pm$ 10

Oxidation status (Table 1)

The AUC and half-life were much greater in the two poor hydroxylators of debrisoquine than in the remaining six extensive metabolisers. Significant reduction in exercise tachycardia at 24 h was achieved in poor metabolisers, regardless of the formulation used; however, reduction of post-exercise heart rate at 24 h was often negligible in extensive metabolisers particularly following conventional and SR metoprolol. In contrast, oxidation status did not correlate with 24 h β -adrenoceptor blockade after atenolol which is largely excreted unchanged (Figure 3).

Discussion

The AUC and half-life of metoprolol differed widely between subjects. These parameters in two subjects

were much greater than those generally reported (Johnsson *et al.*, 1975; Regardh & Johnsson, 1980). The drug is known to be completely absorbed; we have already submitted (Lennard *et al.*, 1982) that these findings can only be explained by impaired metabolism since the urinary recovery of the parent drug is usually only 10% of the dose (Regardh & Johnsson, 1980). This conclusion is supported by the observations in one subject by Jordo *et al.* (1980) in whom a greatly increased AUC and half-life were associated with an unusually high urinary recovery of unchanged metoprolol while negligible quantities of the α -hydroxymetabolite were excreted in the urine. The likelihood that this phenomenon represents genetically impaired drug oxidation is supported by the observation that the subjects in question have all been poor metabolisers of debrisoquine (Lennard *et al.*, 1982; Alvan *et al.*, 1982).

The formulation of metoprolol did not affect its

Figure 2 Mean % reduction of exercise tachycardia on the seventh day of once daily treatment with each of 3 formulations of metoprolol and atenolol. ■ atenolol, ● conventional metoprolol, ○ metoprolol SA and □ metoprolol SR.

*Significantly greater than conventional metoprolol.

Figure 3 % reduction of exercise tachycardia (mean of 0 h + 24 h) for each individual in relation to drug and oxidation phenotype. ● extensive metabolisers and ○ poor metabolisers. (Bars indicate group mean values). M conventional metoprolol, SR metoprolol, SR, SA metoprolol, SA and A atenolol.

bioavailability but the SA and SR compounds were associated with lower peak concentrations and a delay in the time to peak. However, in comparison

only the SA preparation was associated with significantly higher plasma metoprolol concentrations at the end of a dosage interval.

β -adrenoceptor blockade mirrors plasma drug concentration data (Johnsson *et al.*, 1975). Thus metoprolol SA was superior to conventional metoprolol and metoprolol SR 24 h after the dose. Therefore, like slow oxprenolol (Petrie *et al.*, 1980; Bobik *et al.*, 1979; Leahey *et al.*, 1980) metoprolol SR offers no clinical advantage over its conventional counterpart. There has previously been no direct comparison of the two new formulations of metoprolol. However, these data confirm previous suggestions that over 24 h the SA preparation is likely to be superior to metoprolol SR (Harron & Shanks, 1981) and that the latter is no better than the conventional compound (Quarterman *et al.*, 1979).

At the end of a dosage interval mean β -adrenoceptor blockade with atenolol and metoprolol SA was similar. The former was superior to conventional metoprolol at both 0 h and 24 h. However, in our small series there were two poor metabolisers of metoprolol while the expected incidence of this phenotype in the population is only 9% (Evans *et al.*, 1980). Therefore, a more extensive study may show that the mean reduction of exercise tachycardia at 24 h is greater following atenolol than that following metoprolol SA. Indeed, previous volunteer studies demonstrated that mean reduction in exercise heart rate at 24 h was only 10% following metoprolol SA (Harron & Shanks, 1981; Johnsson *et al.*, 1980). This is the same value as that obtained in our extensive metabolisers. β -adrenoceptor blockade was not sustained in the most extensive metabolisers of metoprolol even with the slow-release preparations while the variability in response at 24 h following atenolol was small. It is not certain how much β -adrenoceptor blockade is required to confer antianginal or cardio-protective effects. However, in the absence of prior knowledge of oxidation phenotype this study suggests that, in the doses used, atenolol is most likely to produce at least a 10% reduction in exercise tachycardia 24 h after once daily administration.

We are grateful to Stuart Pharmaceuticals and ICI Pharmaceuticals Limited for financial support.

References

- ALVAN, G., VON BAHR, C., SEIDMAN, P. & SJOQVIST, F. (1982). High plasma concentrations of β -receptor blocking drugs and deficient debrisoquine hydroxylation. *Lancet*, **i**, 333.
- BOBIK, A., JENNINGS, G.L., KORNER, P.I., ASHLEY, P. & JACKSON, G. (1979). Absorption and excretion of rapid and slow release oxprenolol and their effects on heart rate and blood pressure during exercise. *Br. J. clin. Pharmac.*, **7**, 545–549.
- EVANS, D.A.P., MAHGOUB, A., SLOAN, T.P., IDLE, J.R. & SMITH, R.L. (1980). A family and population study of the genetic polymorphism of debrisoquine oxidation in a white British population. *J. med. Genet.*, **17**, 102–105.
- HARRON, D.W.G. & SHANKS, R.G. (1981). Comparison of the duration of effect of metoprolol and a sustained release formulation of metoprolol (Betoloc SA). *Br. J. clin. Pharmac.*, **11**, 518–520.
- JOHNSSON, G., REGARDH, C-G. & SOLVELL, L. (1975).

- Combined pharmacokinetic and pharmacological studies in man of the adrenergic β_1 -receptor antagonist metoprolol. *Acta Pharmac. Tox.*, **36** (Suppl V), 31–44.
- JOHNSSON, G., JORDO, L., LUNDBORG, P., REGARDH, C.-G. & RONN, O. (1980). Plasma levels and pharmacological effects of metoprolol administered as controlled release (Durules) and ordinary tablets in healthy volunteers. *Int. J. clin. Pharmac. Ther. Tox.*, **18**, 292–297.
- JORDO, L., ATTMAN, P.D., AURELL, M., JOHNSSON, L. & REGARDH, C.-G. (1980). Pharmacokinetic and pharmacodynamic properties of metoprolol in patients with impaired renal function. *Clin. Pharmacokin.*, **5**, 169–180.
- LEAHEY, W.J., NEILL, J.D., VARMA, M.P.S. & SHANKS, R.G. (1980). Comparison of the activity and plasma levels of oxprenolol, slow release oxprenolol, long acting propranolol and sotalol. *Eur. J. clin. Pharmac.*, **17**, 419–424.
- LEFEBRE, M.A., GIRAULT, J. & FOURTILLAN, J.B. (1981). β -blocking agents: Determination of biological levels using HPLC. *J. liquid Chromatogr.*, **4**, 483–500.
- LENNARD, M.S., SILAS, J.H., FREESTONE, S. & TREVETHICK, J. (1982). Defective metabolism of metoprolol in poor hydroxylators of debrisoquine. *Br. J. clin. Pharmac.*, **14**, 301–303.
- MAHGOUB, A., IDLE, J.R., DRING, L.G., LANCASTER, R. & SMITH, R.L. (1977). Polymorphic hydroxylation of debrisoquine in man. *Lancet*, **ii**, 584–586.
- PETRIE, J.C., JEFFERS, T.A., ROBB, O.J., SCOTT, A.K. & WEBSTER, J. (1980). Atenolol, sustained-release oxprenolol, and long acting propranolol in hypertension. *Br. med. J.*, **280**, 1573–1574.
- QUARTERMAN, C.P., KENDALL, M.J. & WELLING, P.G. (1979). Plasma levels and negative chronotropic effect of metoprolol following single doses of conventional and sustained-release formulations. *Eur. J. clin. Pharmac.*, **15**, 97–103.
- REGARDH, C.-G. & JOHNSSON, G. (1980). Clinical pharmacokinetics of metoprolol. *Clin. Pharmacokin.*, **5**, 557–569.
- REYBROUCK, T., AMERY, A., FAGARD, R., JOUSTEN, P., LIJNEN, P. & MEULEPAS, E. (1978). β -blockers: once or three times a day? *Br. med. J.*, **1**, 1386–1388.
- TUCKER, G.T., SILAS, J.H., IYUN, A.O., LENNARD, M.S. & SMITH, A.J. (1977). Polymorphic hydroxylation of debrisoquine. *Lancet*, **ii**, 718.

(Received April 2, 1982,
accepted June 21, 1982)