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Timolol and atenolol: relationships between oxidation phenotype, pharmacokinetics and pharmacodynamics

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1 The pharmacokinetics and pharmacodynamics of atenolol and timolol were studied in six extensive and four poor metabolisers of debrisoquine.
2 There was a significant correlation between the debrisoquine to 4-hydroxydebrisoquine ratio and the area under the plasma concentration time curve (AUC) for timolol ($r_s = 0.75$, $P < 0.02$). The mean of the AUC values for timolol was significantly greater in the poor metabolisers than in the extensive metabolisers ($P < 0.05$).
3 There was a significant correlation between the debrisoquine to 4-hydroxydebrisoquine ratio and β-adrenoceptor blockade 24 h after dosing with timolol ($r_s = 0.66$, $P < 0.05$). The mean degree of β-adrenoceptor blockade was significantly greater in the poor metabolisers than in the extensive metabolisers 24 h after dosing with timolol ($P < 0.01$).
4 There was no relation between the debrisoquine to 4-hydroxydebrisoquine ratio and the pharmacokinetics or pharmacodynamics of atenolol.

Keywords timolol atenolol oxidation phenotype pharmacokinetics pharmacodynamics

Introduction

The hydroxylation of debrisoquine in man exhibits genetic polymorphism, with approximately 9% of the white British population being the poor metaboliser (PM) phenotype and the remaining 91% the extensive metaboliser (EM) phenotype (Evans *et al.*, 1980). The metabolism of several drugs is linked to the debrisoquine oxidation phenotype (Lennard *et al.*, 1983b) including that of the β-adrenoceptor antagonist metoprolol (Lennard *et al.*, 1982).

On the basis of a single case report Alvan *et al.* (1982) suggested that the oxidation of timolol may be related to debrisoquine oxidation phenotype. The purpose of the present study was to determine whether such a relationship exists. To ensure that any relation observed for timolol was due to drug metabolism and not to some other mechanism, we also examined atenolol, a β-adrenoceptor antagonist which undergoes little metabolism (Smith & Tucker, 1980).

Methods

Ten healthy male volunteers participated in the study which was approved by the Ethics Committee of the Royal Hallamshire Hospital. Each gave written informed consent. Six of the volunteers (mean age ± s.d.: 30.7 ± 4.6 years; mean weight 69.0 ± 6.0 kg) were extensive metabolisers of debrisoquine (debrisoquine to 4-hydroxydebrisoquine ratio less than 12.5). Four subjects (mean age 29.0 ± 2.5

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years; mean weight 67.2 ± 2.5 kg) were poor metabolisers of debrisoquine (debrisoquine to 4-hydroxydebrisoquine ratio greater than 20). The subjects were phenotyped as described previously (Lennard *et al.*, 1982).

Each subject took 20 mg of timolol maleate and on a different occasion, 100 mg of atenolol, according to a randomised, balanced crossover design. The two phases of the study were separated by at least 1 week. The drugs were given orally together with 100 ml water after an overnight fast. Venous blood samples were taken at 0, 30, 60, 90, 120 min and at 3, 4, 6, 8, 12 and 24 h for the measurement of drug concentration in plasma.

Atenolol was measured by the h.p.l.c. method of Yee *et al.* (1979), with a coefficient of variation of less than 5% at a concentration of 0.5 μg ml^{-1}. These authors reported that prolonged storage of samples led to a decrease in plasma atenolol concentration. During the present work we found no loss of drug over a period of 6 months when plasma samples were stored at −20°C.

Timolol was assayed by h.p.l.c. with u.v. detection (Lennard & Parkin, 1985). The coefficients of variation at 5 and 50 ng ml^{-1} were 5.9% and 5.7% respectively. The minimum detectable concentration of drug in plasma was 2 ng ml^{-1}.

The area under the plasma drug concentration-time curve (AUC) was calculated by the linear trapezoidal method with extrapolation to infinity.

The degree of β-adrenoceptor blockade was determined using bicycle ergometry as described by Freestone *et al.* (1982). The subjects performed a stepped exercise regimen preselected to achieve a heart rate which exceeded 140 beats/min at the end of 4 min. Exercise tests were repeated at 2, 6, 12 and 24 h after dosing. β-adrenoceptor blockade was expressed as the percentage reduction in post exercise heart rate compared with pre-dosing values.

The statistical methods used were the Mann Whitney U test and Spearman's rank correlation (r_s). Significance was accepted when P was equal to or less than 0.05.

Results

The results are summarised in Table 1.

Timolol

The mean plasma concentrations of timolol were higher in the poor metabolisers of debrisoquine than in the extensive metabolisers throughout the 24 h study period (Figure 1a). The mean of the AUC values for timolol was significantly higher in the poor metabolisers than in the extensive metabolisers (625 ± 175 ng ml^{-1} h *vs* 294 ± 153 ng ml^{-1} h; $P < 0.05$). The mean half-life of timolol was longer in the poor metabolisers than in the extensive metabolisers (3.46 ± 0.69 h *vs* 2.75 ± 0.79 h) but this difference was not significant. There was a significant correlation between the debrisoquine to 4-hydroxy debrisoquine ratio and the AUC of timolol ($r_s = 0.75$, $P < 0.02$).

The mean degree of β-adrenoceptor blockade following timolol was greater in the poor metabolisers than in the extensive metabolisers at 2, 6, 12 and 24 h after dosing (Figure 2a). At 24 h the mean degree of β-adrenoceptor blockade was 15.9% in the poor metabolisers and 5.9% in the extensive metabolisers ($P < 0.01$). There was a significant correlation between the debrisoquine to 4-hydroxydebrisoquine ratio and percentage β-adrenoceptor blockade at 24 h ($r_s = 0.66$; $P < 0.05$).

Atenolol

The mean plasma atenolol concentrations were similar in the extensive metabolisers and poor metabolisers (Figure 1b) with AUC values of 6.3 ± 2.1 μg ml^{-1} h and 6.1 ± 1.4 μg ml^{-1} h respectively. The mean half-life of atenolol was 6.70 ± 1.70 h in the extensive metabolisers and 6.44 ± 1.03 h in the poor metabolisers. The debrisoquine to 4-hydroxydebrisoquine ratio did not correlate with either the AUC or the half-life of atenolol.

The mean degree of β-adrenoceptor blockade following atenolol was similar in the extensive and poor metabolisers at all times (Figure 2b) and there was no correlation between the debrisoquine to 4-hydroxydebrisoquine ratio and β-adrenoceptor blockade at 24 h.

Discussion

These findings indicate that the pharmacokinetics and pharmacodynamics of timolol are related to debrisoquine oxidation phenotype, with poor metabolisers having significantly higher AUC values and significantly greater β-adrenoceptor blockade at 24 h after treatment than extensive metabolisers. In addition there was a significant correlation between the urinary debrisoquine to 4-hydroxydebrisoquine ratio and both the AUC and β-adrenoceptor blockade at 24 h. There was no relation between oxidation phenotype and the pharmacokinetics and pharmacodynamics of atenolol.

Table 1 The pharmacokinetic and pharmacodynamic effects of oral timolol maleate (20 mg) and atenolol (100 mg) in extensive (EM) and poor (PM) metabolisers of debrisoquine

Phenotype	*Subject*	*D/HD ratio*	*AUC* ($ng\ ml^{-1}\ h$)	$t_{1/2}$ (*h*)	*β-adrenoceptor blockade (%)* 2 *h*	6 *h*	12 *h*	24 *h*
Timolol								
EM	1	0.85	253	3.21	28.8	17.1	9.5	5.4
	2	0.57	505	3.87	40.1	32.0	24.8	11.0
	3	0.41	91	2.36	35.5	32.6	20.9	8.2
	4	0.90	251	2.36	29.5	26.7	15.5	2.8
	5	0.57	219	1.58	33.1	26.3	10.0	2.5
	6	0.48	442	2.99	35.1	26.0	7.8	5.2
	Mean	0.63	294	2.75	33.7	26.8	14.8	5.9
	s.d.	0.18	153	0.79	3.8	5.1	6.3	3.0
PM	1	41	767	4.33	34.5	36.3	23.8	12.0
	2	33	391	2.80	33.3	27.2	16.1	19.7
	3	208	750	3.68	29.8	25.5	20.5	18.4
	4	40	590	3.04	39.5	32.0	22.0	13.6
	Mean	81	625	3.46	34.3	30.3	20.6	15.9
	s.d.	74	175	0.69	3.5	4.2	2.8	3.3
			($\mu g\ ml^{-1}\ h$)					
Atenolol								
EM	1	0.85	8.02	6.04	17.8	20.6	13.7	13.7
	2	0.57	3.42	6.46	22.5	23.2	12.7	11.2
	3	0.41	8.99	10.4	32.5	31.9	24.4	23.2
	4	0.90	4.87	5.99	26.8	33.5	19.7	20.4
	5	0.57	8.04	6.02	31.3	28.8	17.5	11.3
	6	0.48	4.46	5.24	27.0	19.5	18.2	14.4
	Mean	0.63	6.30	6.70	26.3	24.4	18.7	15.7
	s.d.	0.18	2.11	1.70	5.0	4.5	3.9	4.5
PM	1	41	5.44	7.62	30.5	23.9	21.7	13.0
	2	33	4.63	5.49	25.2	20.7	11.0	15.9
	3	208	7.77	6.97	26.2	23.4	19.1	17.7
	4	40	6.49	5.67	32.9	28.7	20.7	14.6
	Mean	81	6.1	6.44	28.7	24.2	18.1	15.3
	s.d.	74	1.40	1.03	3.1	2.8	4.2	1.7

AUC = area under the plasma drug concentration-time curve;
$t_{1/2}$ = elimination half-life;
β-adrenoceptor blockade (%) = % reduction in exercise heart rate.

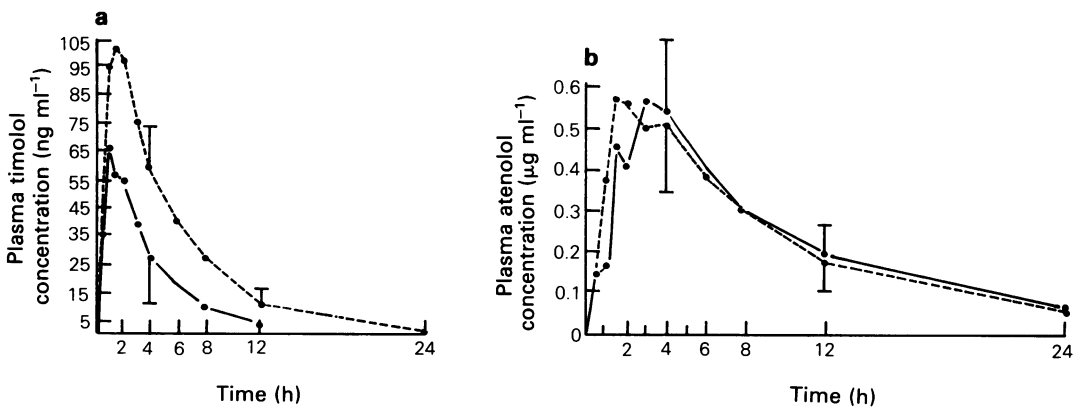

Figure 1 Plasma concentration of timolol (a) and atenolol (b) *vs* time in six extensive metabolisers (●—●) and four poor metabolisers (●---●) of debrisoquine. Vertical bars represent s.d.

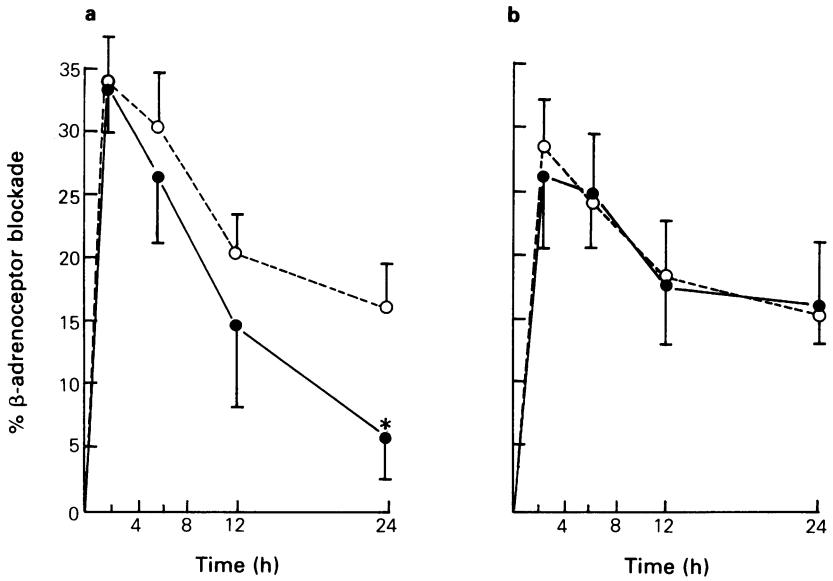

Figure 2 Percentage β-adrenoceptor blockade following timolol (a) and (b) *vs* time in six extensive (●) and four poor (○) metabolisers of debrisoquine. Vertical bars represent s.d. $*P < 0.01$.

The overlap between AUC values for timolol in the extensive and poor metabolisers might be expected, as the AUC of the parent drug is not the most sensitive discriminator between phenotypes, as has been discussed elsewhere (Jackson *et al.*, 1984). This overlap does not, therefore, invalidate our conclusions.

Between 2 and 12 h after dosing with timolol, β-adrenoceptor blockade was only slightly greater in the poor metabolisers than in the extensive metabolisers despite higher plasma timolol concentrations in the former. This may be explained by a maximum suppression of post exercise heart rate associated with relatively low plasma concentrations of timolol (Bobik *et al.*, 1979; Ferguson *et al.*, 1982). Only at 24 h after dosing, when plasma concentrations were much lower, were significant differences in β-adrenoceptor blockade observed. At this time drug effect was negligible in the extensive metabolisers. Plasma concentrations of timolol were at the lower limit of the assay at 24 h and it was therefore not possible to relate these concentrations to β-adrenoceptor blockade at this time.

The basis for the differences in timolol pharmacokinetics between debrisoquine phenotypes has not been established. At least 80% of an oral dose of timolol is thought to be metabolised in man (Tocco *et al.*, 1975). Cleavage of the morpholino ring constitutes the major pathway, the products of this reaction accounting for 40% of urinary recovery. It has been suggested that this cleavage reaction is the result of *o*-dealkylation subsequent to oxidative attack on the carbon atom adjacent to the morpholino oxygen atom (Wasson *et al.*, 1980). Defective *o*-dealkylation in poor metabolisers has been reported for phenacetin (Sloan *et al.*, 1978), encainide (Wang *et al.*, 1984), metoprolol (Lennard *et al.*, 1983a), and methoxyamphetamine (Kitchen *et al.*, 1979). There is no evidence that the metabolism of the isopropylamino side-chain of β-adrenoceptor antagonists is subject to polymorphic control of the debrisoquine type. One of the products of ring cleavage possesses weak β-adrenoceptor blocking activity in dogs (Wasson *et al.*, 1980), but the contribution of the metabolites of timolol to its pharmacological effects in man are unknown.

The significance of debrisoquine oxidation phenotype in the causation of adverse reactions to β-adrenoceptor antagonists has not been determined. Prospective studies are needed to explore a possible relation between metaboliser phenotype and the incidence and severity of side-effects.

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