EFFECT OF RIFAMPICIN ON METOPROLOL AND ANTIPYRINE KINETICS

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- 1 Effects of rifampicin on the pharmacokinetics of single oral doses of metoprolol and antipyrine are reported.
- 2 Rifampicin, administered daily for 15 days, reduced the area under the plasma concentration-time curve (AUC) of metoprolol but the rate constant for elimination (β) of metoprolol from plasma did not alter significantly.
- 3 Administration of rifampicin for 13 days reduced AUC and increased β of antipyrine. Thirteen days after discontinuing rifampicin, AUC and β of antipyrine remained significantly different from the initial values.
- 4 Some loss of β -adrenoceptor blockade should be anticipated if rifampicin is administered to patients who are receiving metoprolol.

Introduction

The β -adrenoceptor antagonist metoprolol is eliminated from the body almost entirely by metabolism in the liver. Enzyme induction with phenobarbitone reduces plasma concentrations of metoprolol in man (Haglund *et al.*, 1979) but not in rat (Arfwidsson *et al.*, 1976). Rifampicin, a first-line antituberculous drug, is also a potent enzyme inducer in man (Mignet *et al.*, 1977; Ohnhaus & Park, 1979; Brodie *et al.*, 1980). We report here our investigation of the effect of rifampicin on the kinetics of metoprolol.

Methods

Drug assays

Metoprolol was assayed in plasma by gas-liquid chromatography (g.l.c.) using the method of Degen & Riess (1976). Antipyrine was assayed in plasma by g.l.c. using the method of Prescott *et al.* (1973).

Subjects

The subjects were 12 male volunteers aged 21–35 years (mean 28 years) and weighing 62–82 kg (mean 71 kg). Physical examination, haemoglobin, leucocyte count, blood urea, serum electrolytes, creatinine,

plasma albumin, aspartate transaminase, alkaline phosphatase and bilirubin were normal in all subjects. Plasma gamma glutamyl transpeptidase was normal in eleven subjects and was 105 IU/l in subject 7 (normal < 50 IU/l). Haematological and biochemical measurements were repeated on days 18 and 33. Subjects 7 and 10 were smokers and all other subjects were non-smokers. All subjects except numbers 2 and 6 habitually consumed alcohol. Each subject maintained a personal daily record of cigarettes smoked and of consumption of alcohol and caffeine-containing drinks and was requested to maintain his normal use of these for the duration of the study. No subject took drugs other than metoprolol, rifampicin and antipyrine during the study except subject 6 who took paracetamol for 3 days for coryza. The study was approved by the Bath hospitals ethics committee and all subjects gave written, informed consent to participate.

Design of study

Metoprolol and antipyrine kinetics were studied (a) before rifampicin, (b) after a period of daily administration of rifampicin and (c) after a further period during which no rifampicin was taken. On each occasion antipyrine was taken by mouth in a single dose and blood was collected for assay before dosing

and at 3, 6, 9, 12 and 24 h thereafter. Urine was collected in 12 h periods for 48 h after each administration for assay of antipyrine metabolites. The result of metabolite analysis will be presented in a separate communication (Toverud *et al.*, 1981). On each occasion metoprolol was taken in a single dose by mouth and blood was collected for assay before dosing and 0.5, 0.75, 1.5, 2, 3, 4, 6, 8 and 12 h after each dose.

The scheme of dosing was as follows:

- Day 1 antipyrine 1200 mg by mouth
- Day 3 metoprolol 100 mg by mouth in the morning; rifampicin 600 mg by mouth at night and thereafter nightly discontinuing after day 17
- Day 16 antipyrine 1200 mg by mouth
- Day 18 metoprolol 100 mg by mouth
- Day 31 antipyrine 1200 mg by mouth
- Day 33 metoprolol 100 mg by mouth

Pharmacokinetic analyses

The apparent first order rate constant for drug elimination from plasma (β) was calculated from the log-linear phase of the plasma concentration-time curve by least squares regression. Area under the plasma concentration-time curve from zero time to time t (AUC_0^t) was estimated by the trapezoidal rule and AUC from zero time to infinity was calculated from the equation

$$AUC_0^\infty = AUC_0^t + \frac{C_t}{\beta}$$

where C_t is plasma concentration at time t .

Apparent distribution volume (V_d) was calculated from the equation

$$V_d = \frac{D}{C_0}$$

where D is dose and C_0 is the concentration at zero time estimated by extrapolation of the log C v time plot to zero time. Clearance (CL) was calculated from the equation

$$CL = \frac{D}{AUC_0^\infty}$$

Statistics

Unless otherwise stated, Student's paired t -test was used.

Results

Metoprolol

Mean plasma concentrations of metoprolol (Figure 1) were lower after rifampicin (day 18) at all sampling

Figure 1 Mean plasma concentrations of metoprolol ($\pm$ s.e. mean) in 12 normal males after single doses of metoprolol, 100 mg p.o. before rifampicin (O, day 3), immediately after rifampicin (600 mg p.o. daily for 15 days) (■, day 18) and 15 days after ceasing rifampicin (▲, day 33).

times than were concentrations before rifampicin (day 3) or 15 days after administration of rifampicin had ceased (day 33) ($P < 0.007$ by Repeated Measures Variance Analysis; Winer, 1971). AUC_0^∞ on day 18 was significantly lower than the value on day 3 ($P < 0.01$) or day 33 ($P < 0.01$) but there was no significant change in AUC_0^∞ between days 3 and 33 (Table 1) (Friedman Rank Test; Friedman, 1956). In subjects 10 and 12 AUC_0^∞ was markedly greater than in the other subjects but no adverse effects of metoprolol were observed in these individuals. β was greater after rifampicin (day 18) than on day 3 but the difference was not statistically significant ($0.05 < P < 0.1$) (Table 1).

Antipyrine

Mean plasma concentrations of antipyrine (Figure 2) were lower after rifampicin (day 16) at all sampling times than were concentrations before rifampicin (day 1) or 13 days after administration of rifampicin had ceased (day 31) ($P < 0.001$ by Repeated Measures Variance Analysis). AUC_0^∞ on day 16 was significantly lower than that on day 1 ($P < 0.001$) or on day 31 ($P < 0.001$) and AUC_0^∞ on day 31 remained less than the value before rifampicin (day 1) ($P < 0.01$). Compared with the value on day 1, there was a significant increase in β on day 16 ($P < 0.001$) which was maintained on day 31 ($P < 0.01$) (Table 2). V_d on day 16 was 41.0 ± 2.0 l and was not significantly different from the value on day 1 (39.6 ± 1.5 l). Clearance of antipyrine was 38.7 ± 3.6 ml h^{-1} kg^{-1} on day 1, 90.8 ± 5.5 on day 16 ($P < 0.001$) and 51.3 ± 4.0 on day 31.

Table 1 Kinetics of metoprolol (100 mg p.o. in a single dose) in normal males before, immediately after rifampicin (600 mg p.o. per day for 15 days) and 15 days after ceasing rifampicin

Subject	β (h^{-1})			AUC_0^∞ ($\mu g l^{-1} h$)		
	Before rifampicin (day 3)	Immediately after rifampicin (day 18)	15 days after ceasing rifampicin (day 33)	Before rifampicin (day 3)	Immediately after rifampicin (day 18)	15 days after ceasing rifampicin (day 33)
1	0.467	0.450	0.340	476	331	642
2	0.145	0.470	0.321	783	336	538
3	0.211	0.151	0.112	467	434	625
4	0.331	0.439	0.280	664	510	1176
5	0.267	0.414	0.397	432	288	312
6	0.388	0.522	0.250	200	183	417
7	0.287	0.319	0.522	268	194	347
8	0.415	0.352	0.613	326	213	244
9	0.350	0.628	0.539	215	105	76
10	0.046	0.065	0.045	5366	3264	4435
11	0.343	0.288	0.248	566	424	923
12	0.157	0.173	0.116	1392	624	1440
Mean	0.284	0.356	0.315	930	624	932
s.e. mean	0.036	0.048	0.052	414	254	338

Figure 2 Mean plasma concentrations of antipyrine ($\pm$ s.e. mean) in 12 normal males after single doses of antipyrine 1200 mg p.o. before rifampicin ($\circ$, day 1), immediately after rifampicin (600 mg p.o. daily for 13 days) ($\blacksquare$, day 16) and 13 days after ceasing rifampicin ($\blacktriangle$, day 31).

Haematological and biochemical values

No abnormal haematological or biochemical values were recorded after rifampicin (day 18) except in the case of subject 7 in whom plasma gamma glutamyl transpeptidase was 105 IU/l before and 107 IU/l after rifampicin. Mean $\pm$ s.e. mean plasma bilirubin at the start of the study was $14.1 \pm 1.7 \mu\text{mol/l}$ and after rifampicin fell in all subjects, the mean value being $8.2 \pm 0.63 \mu\text{mol/l}$; on day 33 mean plasma bilirubin was still below the pretreatment value at $9.3 \pm 0.81 \mu\text{mol/l}$.

Discussion

Rifampicin reduced plasma concentrations of metoprolol in our subjects (Figure 1) causing a mean decrease in AUC_0^∞ of 32.9%; within 15 days these changes had reverted to the initial values. Metoprolol is eliminated from the body by hepatic metabolism and only about 3% of a single oral dose is recovered unchanged in the urine (Regardh *et al.*, 1975). We believe that the changes in the kinetics of metoprolol were due to induction of hepatic microsomal enzymes since rifampicin also increased β and reduced AUC_0^∞ of antipyrine, a drug which is widely used as an indicator of hepatic mono-oxygenase activity. Since V_d did not alter, the increase in β cannot be ascribed to volume change. Several recent reports have concluded that rifampicin increases elimination of antipyrine by enzyme induction (Mignet *et al.*, 1977; Ohnhaus & Park, 1979; Brodie *et al.*, 1980). Additional evidence of rapid biotransformation of antipyrine was obtained in a separate part of the study in which rates of formation of the three principal metabolites of antipyrine were found to increase after administration of rifampicin (Toverud *et al.*, 1981).

In man 85% of the total urinary excretion of metoprolol is accounted for by three main metabolites which result from oxidative deamination, o-dealkylation with subsequent oxidation and from aliphatic hydroxylation of the parent drug (Borg *et al.*, 1975). Antipyrine is also metabolised to hydroxylated and de-alkylated products. However there was no significant correlation between the extent of increase in metabolism of metoprolol as indicated by percentage reduction in AUC_0^∞ compared to that for antipyrine

Table 2 Kinetics of antipyrine (1200 mg p.o. in a single dose) in normal males before, immediately after rifampicin (600 mg p.o. per day for 13 days) and 13 days after ceasing rifampicin

Subject	β (h^{-1})			AUC_0^∞ ($mg\ l^{-1}\ h$)		
	Before rifampicin (day 1)	Immediately after rifampicin (day 16)	13 days after ceasing rifampicin (day 31)	Before rifampicin (day 1)	Immediately after rifampicin (day 16)	13 days after ceasing rifampicin (day 31)
1	0.063	0.109	0.079	540	272	423
2	0.063	0.145	0.085	400	198	291
3	0.054	0.157	0.077	552	161	363
4	0.052	0.115	0.072	468	199	333
5	0.042	0.095	0.054	518	217	393
6	0.064	0.147	0.082	477	199	316
7	0.111	0.161	0.072	248	162	284
8	0.041	0.104	0.040	611	241	496
9	0.077	0.162	0.100	383	164	269
10	0.057	0.151	0.079	518	147	399
11	0.071	0.132	0.117	337	146	218
12	0.054	0.110	0.064	607	239	436
Mean	0.062	0.132	0.076	472	195	352
s.e. mean	0.005	0.007	0.006	32	11	23

for each individual ($r = 0.279$). Administration of pentobarbitone 100 mg daily for 10 days to normal subjects reduced AUC of metoprolol by an average of 32% indicating that enzyme induction by barbiturate also increases metabolism of metoprolol (Haglund *et al.*, 1979).

Sixteen days after discontinuation of rifampicin the kinetics of metoprolol had returned to the initial value but the AUC_0^∞ for antipyrine was only 75% of the initial figure 13 days after cessation of rifampicin, a finding compatible with relatively slow turnover of some induced enzymes in man (Breckenridge *et al.*, 1973).

A perfusion-limited model has been used to describe hepatic drug elimination (Rowland, 1972; Wilkinson & Shand, 1975). For oral dosing this model predicts that when hepatic metabolism is increased, drugs with low hepatic extraction will exhibit reduction in AUC and increase in elimination rate constant whereas for highly hepatically cleared drugs AUC will be reduced without change in elimination rate

constant. Hepatic extraction ratio of antipyrine is low (≈ 0.1) and of metoprolol is in the intermediate range (0.55) (Johnsson *et al.*, 1975). The observations in the present study are consistent with the predictions of this model in that for both drugs AUC decreased with enzyme induction but the increase in elimination rate constant was greater for antipyrine than for metoprolol.

Percentage reduction of exercise tachycardia with metoprolol is linearly related to logarithm of plasma concentration (Johnsson *et al.*, 1975). Any contribution to β -adrenoceptor blockade from metabolites would probably be minimal as animal evidence suggests that the principal biotransformation products of metoprolol have only weak antagonistic activity (Borg *et al.*, 1975). Some reduction in β -adrenoceptor blockade is therefore to be anticipated if rifampicin is administered to patients who are receiving metoprolol.

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