THE EFFECT OF PRETREATMENT WITH CIMETIDINE ON THE BIOAVAILABILITY AND DISPOSITION OF ATENOLOL AND METOPROLOL

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1 Plasma levels of atenolol and metoprolol and their effects on exercise heart rate have been studied after oral administration of single doses of 100 mg of the two drugs in ordinary tablets alone and during concomitant cimetidine medication of 1 g per day.

2 Cimetidine caused no significant changes in the bioavailability of any of the two β -adrenoceptor blockers and the rate of elimination of metoprolol was unaffected by the histamine H_2 -receptor blocker. A slight but significant increase in the elimination half-life from 6.5 ± 0.6 to 7.9 ± 0.6 ($P < 0.05$) was noted for atenolol after pretreatment with cimetidine. The β -adrenoceptor blocking effect was about the same for the used doses of atenolol and metoprolol and it was not changed during cimetidine therapy.

Introduction

Reports on interactions between cimetidine and various other drugs have appeared in the literature with increasing frequency since Serlin *et al.* (1979) reported that the histamine H_2 -receptor antagonist prolonged the effect of warfarin and other oral anticoagulants on the prothrombin time because of reduced clearance. Another important interaction recently observed is the effect of cimetidine on the disposition of theophylline (Jackson *et al.*, 1980; Weinberger *et al.*, 1981) which might lead to severe adverse reactions unless the theophylline dose is adjusted properly in patients concurrently receiving cimetidine.

Other drugs the pharmacokinetics of which have been found to be affected by cimetidine, although the result might be less hazardous, include diazepam and antipyrine (Klotz & Reiman, 1980), chlordiazepoxide (Desmond *et al.*, 1980) and propranolol (Feely *et al.*, 1981; Heagerty *et al.*, 1981).

The reported cimetidine interactions all concern

drugs which primarily are eliminated by metabolism in the liver. Both low and high clearance drugs are represented indicating that the effect of cimetidine is not only an effect on the microsomal cytochrome P-450 system (Puurunen & Pelkonen, 1979) but also that hepatic blood flow might be reduced (Feely *et al.*, 1981). The dual effects on the hepatic function make extrapolations of results for one drug to another very uncertain. Thus, Klotz & Reiman (1980) found that pretreatment with cimetidine had a more pronounced effect on the disposition of diazepam than on that of antipyrine.

The present study was carried out to test the influence of cimetidine on the pharmacokinetics of the two selective β_1 -adrenoceptor antagonists atenolol and metoprolol, which have totally different routes of elimination. Metoprolol is mainly eliminated by metabolism (Regårdh & Johnsson, 1981) whereas atenolol is excreted to about 90% in unchanged form in the urine (Reeves *et al.*, 1978).

Table 1 Individual diagnoses and data of the patients.

Subject	Age (years)	Weight (kg)	Diagnosis
1	56	71	Cholecystopathy, hiatus hernia
2	29	60	Irritable colon
3	68	70	Coronary disease
4	46	50	Anorexia nervosa
5	62	72	Coronary insufficiency
6	45	70	Irritable colon
7	60	68	Spastic, irritable colon

Methods

Protocol

Four male and three female patients with varying diagnoses, (Table 1) volunteered for the study after informed consent. All patients had normal renal and hepatic function according to routine laboratory tests. Their age ranged from 29 to 68 years (mean 52 years). None of the patients had previously been treated with any β -adrenoceptor blocker or with cimetidine.

The study was carried out in a single-blind cross-over design. During day 1 and 3 the subjects received a single dose of 0.1 g of either β -adrenoceptor blocker after an overnight fast of 10 h. The dose was taken with 50 ml of water. After 3 h the patients were given a standard meal and after 6 h they got coffee and a sandwich. Blood samples were drawn immediately before the administration and then at 0.5, 1, 1.5, 2, 3, 4.5, 6, 8, 24 and 25 h.

The experiment was repeated on the third day with the other β -adrenoceptor blocker whereafter cimetidine therapy, 0.2 g three times daily and 0.4 g at night, was initiated on day 4 and continued throughout the study. After 3 to 4 days on cimetidine, single doses of the β -adrenoceptor blockers were again administered in randomized order one to two days apart and the experiment repeated accordingly. The β -adrenoceptor blocker was administered 1 h after the morning dose of cimetidine.

The day before starting the medication the patients were exercised on a bicycle-ergometer to their individual maximal work load by successively increasing the load from initially 30 W during 3 min to 40, 50, 70, 90, 120, 150, 170 and 200 W at an interval of 1 min. The lowest work load inducing maximal heart rate response was used in the assessment of the β -adrenoceptor blockade of atenolol and metoprolol 2 h after the tablet intake. The plasma concentrations of the two β -adrenoceptor blockers are then close to maximum and a change in the first-pass extraction of metoprolol by cimetidine would then be reflected in the exercise heart rate.

Assay methods

The plasma concentrations of metoprolol were determined by gas chromatography according to Ervik (1975) with the following modifications. Toluene was used as organic phase in the alkaline extraction and the internal standard was ($\pm$)1-(isopropylamino)-3-[*p*-(3 methoxypropyl)phenoxy]-2 propanol.

Atenolol was extracted from the plasma by methylene chloride containing 3% heptafluorobutanol. After evaporation of the organic solvent, atenolol was reacted with trifluoroacetic anhydride in diethylether. The organic solvent and the excess of reagent was evaporated and the derivative was dissolved in toluene and determined by gas chromatography with electron capture detection (Ervik *et al.*, 1980).

Data analysis

The effect of cimetidine on the fraction available systemically of atenolol and metoprolol was determined in each subject from the ratio of the area under the plasma concentration-time curve (AUC)_∞ obtained with and without pretreatment with cimetidine.

The linear trapezoidal rule was used to determine the AUC from time 0 to the time of the second sample after the maximum concentration. The log-linear trapezoidal rule (Yeh & Kwan, 1978) was used from this time to the time of the last sample. The remaining area to time infinity was determined by dividing the concentration of the last sample by the terminal rate constant. Student's *t*-test for paired observations was used to estimate the significance of the effect of cimetidine on the absorption characteristics and half-lives of atenolol and metoprolol.

Results

Pharmacokinetics

The mean plasma concentration-time curves of

Figure 1 Plasma levels of atenolol administered alone (—) and together with cimetidine (---).

atenolol and metoprolol with and without pretreatment with cimetidine are shown in Figures 1 and 2 respectively. The individual pharmacokinetic parameters studied and their mean values are given in the Tables 2 (atenolol) and 3 (metoprolol). Cimetidine therapy has no influence on the absorption rate or the systemic availability of any of the β -adrenoceptor blockers and the $t_{1/2\beta}$ of metoprolol

was the same with and without the gastric secretion inhibitor. A small but significant increase in $t_{1/2\beta}$ from 6.5 to 7.9 h ($P < 0.05$) was observed for atenolol when it was taken together with cimetidine.

β -adrenoceptor blockade

No significant differences were observed in the

Figure 2 Plasma levels of metoprolol administered alone (—) and together with cimetidine (---).

Table 2 Absorption characteristics and elimination half-life of atenolol administered alone and after treatment with 1.0 g of cimetidine for 4 to 5 days.

Subject	Without cimetidine				With cimetidine			
	t_{max} (h)	Cp_{max} ($\mu\text{mol l}^{-1}$)	AUC_x ($\mu\text{mol l}^{-1} \text{ h}$)	$t_{1/2\beta}$ (h)	t_{max} (h)	Cp_{max} ($\mu\text{mol l}^{-1}$)	AUC_x ($\mu\text{mol l}^{-1} \text{ h}$)	$t_{1/2\beta}$ (h)
1	1.5	4.19	35.0	9.2	2.0	3.44	33.3	11.2
2	3.0	4.04	37.9	6.8	1.5	4.58	50.6	8.6
3	3.0	4.94	42.5	7.0	3.0	6.58	62.7	7.7
4	3.0	3.79	40.2	6.4	2.0	4.36	37.1	5.9
5	2.0	4.88	36.1	5.3	3.0	4.20	43.0	6.9
6	3.0	5.39	44.7	6.3	2.0	4.54	39.4	7.2
7	1.5	6.33	38.5	4.6	1.5	5.64	46.0	8.0
Mean	2.43	4.794	39.27	6.51	2.14	4.763	44.58	7.93
s.e. mean	0.28	0.334	1.31	0.55	0.24	0.390	3.71	0.64

resting and the exercise heart rates between the different treatment regimens. However, both of the β -adrenoceptor blockers significantly reduced the heart rate during rest and exercise in comparison with no medication (Table 4).

Discussion

Pharmacokinetically metoprolol is classified as a high clearance drug having a mean total body clearance of about 1 l/min. The systemic availability of single oral doses varies between 20 to 85 % (mean value about 50 %) in healthy individuals (Regårdh & Johnsson, 1980; Jordö *et al.*, 1980). The systemic availability appears to be related to the portal blood flow since food has been found to increase the AUC of orally administered metoprolol by about 50% (Melander *et al.*, 1977). Based on this information only, one would expect cimetidine to interfere with the pharmacokinetics of metoprolol since cimetidine has been found to approximately double the plasma concentrations of oral doses of propranolol and labetalol (Feely *et al.*, 1981; Heagerty *et al.*, 1981;

Daneshmend & Roberts, 1981). These two drugs have similar pharmacokinetic properties to metoprolol albeit they are more efficiently removed presystemically. It seems unlikely, however, that the difference in presystemic elimination would be the only reason for the lack of effect of cimetidine on the kinetics of metoprolol. Likewise the minor differences in cimetidine doses and treatment periods between our study and those on propranolol and labetalol can probably be neglected. According to Klotz & Reiman (1980) and Jackson *et al.* (1980) the inhibitory metabolic effects of cimetidine are established already after 1 to 2 days of treatment and the portal blood-flow is reduced already after the first dose of the histamine H_2 -receptor blocker (Feely *et al.*, 1981).

The lack of effect of cimetidine on the systemic availability and disposition of metoprolol stresses the importance of studying each combination with cimetidine separately and that results with one drug cannot be simply extrapolated to other drugs. It should be clarified, however, that although we did not find cimetidine to interact with metoprolol in our study we cannot ignore the possibility that the lack of

Table 3 Absorption characteristics and elimination half-life of metoprolol administered alone and after treatment with 1.0 g of cimetidine for 4 to 5 days.

Subject	Without cimetidine				With cimetidine			
	t_{max} (h)	Cp_{max} ($\mu\text{mol l}^{-1}$)	AUC_x ($\mu\text{mol l}^{-1} \text{ h}$)	$t_{1/2\beta}$ (h)	t_{max} (h)	Cp_{max} ($\mu\text{mol l}^{-1}$)	AUC_x ($\mu\text{mol l}^{-1} \text{ h}$)	$t_{1/2\beta}$ (h)
1	1.0	1.19	9.52	9.0	1.5	1.01	9.07	8.0
2	1.0	0.31	2.10	4.3	2.0	0.45	2.95	4.6
3	4.5	0.23	1.58	3.5	3.0	0.49	2.40	3.3
4	1.0	0.36	0.92	4.1	1.0	0.35	1.85	5.7
5	1.0	0.63	2.92	2.8	1.5	0.47	2.20	2.8
6	1.0	1.04	6.79	5.3	1.0	0.88	7.16	5.4
7	1.5	0.68	4.03	5.5	1.0	0.57	3.76	5.0
Mean	1.57	0.635	3.980	4.93	1.57	0.603	4.200	4.97
s.e. mean	0.49	0.139	1.179	0.77	0.28	0.093	1.058	0.65

Table 4 Resting heart rates and heart rates during exercise 2 h after administration of placebo and single 0.1 g oral doses of atenolol and metoprolol alone and together with cimetidine.

Subject	Heart rate (beats/min)									
	No medication		Atenolol		Atenolol Cimetidine		Metoprolol		Metoprolol Cimetidine	
	Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise
1	90	155	70	86	60	108	60	108	65	83
2	100	140	60	78	60	65	60	78	65	84
3	80	135	55	85	55	92	65	98	50	98
4	85	140	65	88	80	86	70	90	65	89
5	70	110	65	93	65	95	70	97	70	100
6	70	150	65	105	65	110	60	110	60	110
7	80	150	70	98	70	102	65	110	70	110
Mean	82	140	64	90	65	94	64	99	64	96
s.e. mean	4	6	2	3	3	6	3	4	3	4

interaction might be related to the group of subjects included in the study. Thus, Ambrose & Harralson (1981) have recently found that daily doses of 0.6 to 1.2 g of cimetidine per day for 3 to 10 days had essentially no effect on the theophylline clearance in acutely ill bronchospastic patients. The patients had much lower clearance than the group susceptible to cimetidine interaction (Jackson *et al.*, 1980; Weinburger *et al.*, 1981) which according to Ambrose & Harralson (1981) might account for the lack of interaction. The clearance of metoprolol was not studied since intravenous administration was avoided. The individual AUC and $t_{1/2\beta}$ values were, however, comparable with the values reported in young healthy individuals indicating normal metoprolol clearance values also in the patients studied.

The slight but significant prolongation of the elimination half-life of atenolol during cimetidine treatment is from pharmacokinetic point of view an interesting observation but the clinical consequence of this change would probably be negligible. Assuming once daily regimen the accumulation factor would only increase from 1.08 to 1.14 during repeated administration to steady state.

The effect of cimetidine seems too great, however, to be interpreted in terms of reduced metabolic capacity only, since no more than about 10% of an oral atenolol dose is metabolized (Reeves *et al.*, 1978). Therefore, even if cimetidine blocked the

metabolism of atenolol completely, this would only lead to 10 per cent increase in $t_{1/2\beta}$ at the most, provided other disposition factors remained unchanged. It, thus, appears that cimetidine also affects the clearance of atenolol probably by decreasing kidney function (Dutt *et al.*, 1981). Another explanation although less likely might be an increase in the volume of distribution of atenolol by cimetidine.

After this paper was submitted to the journal a short report by Kirch *et al.* (1981) indicated that continuous treatment with cimetidine for 1 week significantly increased the steady state plasma levels of metoprolol, but had no effect on the kinetics of atenolol. The conflicting results in the present study and those of Kirch and associates might be due to the difference in the treatment period with the β -adrenoceptor blocker since our results are based on a single dose of each β -adrenoceptor blocker while Kirch and associates (1981) determined the plasma levels after 7 days of treatment. Considering, however, that the 60% increase in AUC of metoprolol observed by Kirch and co-workers (1981) did not lead to an increase in the β -adrenoceptor blocking effect one would suspect that their analytical method based on fluorometric determination of thin-layer chromatograms was not sufficiently selective.

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