The interaction between H₂-receptor antagonists and β -adrenoceptor blockers

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1 The degrees of interactions between the H₂-receptor antagonists, cimetidine and ranitidine, and several β -adrenoceptor blockers were investigated in healthy volunteers following 7 days of oral monotherapy with penbutolol, propranolol, metoprolol, pindolol and atenolol, and after co-administration with each of the H₂-receptor antagonists.

2 The kinetic parameters of unmetabolised penbutolol and penbutolol glucuronide were unaffected, whereas the levels of 4-hydroxypenbutolol and 4-hydroxypenbutolol glucuronide were significantly reduced. Furthermore, cimetidine led to a marked increase in propranolol and metoprolol plasma levels. During co-administration with cimetidine, pindolol plasma levels were only slightly raised, whereas the pharmacokinetics of atenolol were not affected.

3 With regard to pharmacodynamics, the inhibition of exercise-induced tachycardia by each of the β -adrenoceptor blockers was not affected by cimetidine. Ranitidine did not alter atenolol plasma levels, but did raise the peak plasma concentration of metoprolol by about 30%.

4 It is concluded that cimetidine interactions do occur and can be predicted for substances metabolised by the cytochrome P-450 pathway.

Keywords β -adrenoceptor blockers cimetidine H₂-receptor antagonists pharmacokinetics ranitidine

Introduction

The histamine H₂-receptor antagonists cimetidine and ranitidine (Figure 1), are currently used in ulcer therapy. Cimetidine has been shown to interact particularly with hepatic elimination, elevating plasma levels of various drugs, for instance warfarin, benzodiazepines, phenytoin or theophylline. An increase in propranolol plasma levels has been reported as a result of β -adrenoceptor blocker co-administration with cimetidine (Feely *et al.*, 1980; Warburton *et al.*, 1979). Donavan and co-workers (1981) observed that a patient suffered from severe sinus bradycardia and hypotension after having taken propranolol and cimetidine concurrently. Two possible mechanisms for the pharmacokinetic interactions mentioned were

Figure 1 Structural formulas of histamine, cimetidine and ranitidine.

discussed, a reduction of liver blood flow and an inhibition of drug metabolising enzymes, especially of cytochrome P-450.

The study was designed to investigate the effect of the H_2 -receptor antagonists on the kinetics of β -adrenoceptor blockers with different physicochemical properties (lipophilic and hydrophilic) and different routes of elimination. The following β -adrenoceptor blockers were included in the investigations: penbutolol and propranolol as non-selective, highly lipophilic agents; metoprolol as a cardioselective, medium lipophilic β -adrenoceptor blocker; pindolol as a β -adrenoceptor blocker with ISA and medium lipophilicity; and atenolol as a cardioselective, hydrophilic agent.

Methods

Six to seven healthy volunteers were admitted to each study, each subject acting as his own control. The dosage schemes are given in Table 1. The β -adrenoceptor blockers were administered to the volunteers orally as monotherapy for 6 days.

Table 1 Dosage schemes

Substance	Dose (mg)	Regimen
Penbutolol	40	once daily
Propranolol	80	twice daily
Metoprolol	100	twice daily
Pindolol	10	twice daily
Atenolol	100	once daily
Cimetidine	200	three times daily
	400	at night
Ranitidine	150	twice daily

During this treatment plasma samples were taken prior to the morning dose and 3 h afterwards. Following the last oral dose on the morning of day 7, blood samples were taken up to 24 h after dosing. After a therapy-free interval the β -adrenoceptor blockers were co-administered with cimetidine. For metoprolol and atenolol, the influence of ranitidine was also investigated. The concentrations of propranolol, metoprolol, pindolol and atenolol were determined using fluorodensitometric methods (Mutschler *et al.*, 1984; Schäfer *et al.*, 1977; Schäfer & Mutschler, 1979a, b). Penbutolol and its metabolites were measured using reversed-phase h.p.l.c. with u.v. detection (Damm & Hajdu, 1984). Pharmacokinetic parameters were calculated from the plasma levels and urinary excretion on day 7 of each of the treatment periods. The β -adreno-

ceptor blockade produced by monotherapy and by co-administration with cimetidine and ranitidine was assessed by the inhibition of exercise-induced tachycardia 3 and 12 h after the morning dose.

Results

Effect of cimetidine on penbutolol and its metabolites

The plasma concentration time profiles of parent penbutolol are illustrated in Figure 2. There were no statistically significant alterations in any of the kinetic parameters on day 7; the same holds true for the penbutolol glucuronide metabolite. However, plasma levels of unconjugated 4-hydroxypenbutolol during monotherapy were very low, reaching a mean maximum concentration ($C_{\max}$) of 13 ng/ml (Figure 3). After combination therapy the plasma levels were below the level of detection for the analytical method used (< 5 ng/ml). Values of $C_{\max}$ for the corresponding 4-hydroxypenbutolol glucuronide were significantly reduced ($P < 0.05$) after cimetidine treatment (Spahn *et al.*, 1984).

Effect of cimetidine on propranolol

A pronounced increase in propranolol plasma levels was apparent when the β -adrenoceptor blocker was given together with cimetidine (Figure 4), a finding which is in agreement with previous studies (Feely *et al.*, 1980). The area under the plasma level time curve ($AUC_{0-24\text{ h}}$; day 7) was almost doubled. Values for $C_{\max}$ on day 7 averaged 126 ng/ml with monotherapy and increased to 251 ng/ml after co-administration of cimetidine ($P < 0.05$). Elimination half-life was prolonged from 5.6 h to 7.6 h during cimetidine co-administration (not significant).

Effect of cimetidine on metoprolol

Plasma metoprolol increased markedly during co-administration with cimetidine (Figure 5). Metoprolol $C_{\max}$ increased from 177 ng/ml with monotherapy to 284 ng/ml with co-administration of cimetidine ($P < 0.05$). AUC also rose significantly from 1167 ng ml⁻¹ h to 1885 ng ml⁻¹ h. Elimination half-life was prolonged from 4.4 h to 7 h (NS).

Effect of cimetidine on atenolol and pindolol

Whereas the plasma concentration of unmetabolised pindolol showed a slight increase, atenolol levels were not affected by concomitant therapy with cimetidine (Figure 6).

Figure 2 Mean plasma levels of penbutolol following the last oral dose of penbutolol 40 mg with (●) and without (Δ) cimetidine on day 7 ($n = 7$).

C_{max} , terminal half-life and AUC values of parent penbutolol, propranolol, metoprolol, pindolol and atenolol in different treatment periods are summarised in Table 2.

Effect of propranolol, metoprolol and atenolol on cimetidine

Regarding the influence of propranolol, metoprolol and atenolol on cimetidine, it was found

that none of the β -adrenoceptor blockers significantly altered cimetidine kinetics. A typical result, that for propranolol, is shown in Figure 7. The elimination half-life of cimetidine was slightly prolonged from 2.4 h (cimetidine monotherapy) to 3.6 h (propranolol co-administration). Mean maximum plasma cimetidine concentrations were 0.95 $\mu\text{g/ml}$ for monotherapy, 1.18 $\mu\text{g/ml}$ for propranolol co-administration, 1.21 $\mu\text{g/ml}$ for metoprolol co-administration and 1.05 $\mu\text{g/ml}$ for atenolol co-administration.

Figure 3 Mean plasma levels of 4-hydroxylated compounds in seven healthy volunteers (4-hydroxy-penbutolol plus 4-hydroxyphenbutolol glucuronide, calculated as 4-hydroxyphenbutolol equivalents) on day 7 of treatment with penbutolol (Δ) and penbutolol + cimetidine (●).

Figure 4 Mean plasma levels of propranolol following the last oral dose of propranolol 80 mg as monotherapy (Δ) and after combination with cimetidine 200 mg on day 7 ($\bullet$) ($n = 6$).

Effect of ranitidine on atenolol and metoprolol

Ranitidine did not influence atenolol kinetics, but enhanced peak plasma metoprolol concentrations by about 30%.

Effect of cimetidine on β -adrenoceptor blocker pharmacodynamics

The effect of H_2 -receptor antagonists on β -

adrenoceptor blocker pharmacodynamics was assessed in terms of effect on exercise-induced tachycardia 3 and 12 h after the morning dose on day 6. No differences were apparent between monotherapy and combination therapy, and a highly significant improvement in tachycardia was maintained relative to placebo. Systolic and diastolic blood pressure and pulse frequency were not significantly affected at any time when comparing β -adrenoceptor blocker monotherapy

Figure 5 Mean plasma levels of metoprolol following the last oral dose of metoprolol 100 mg as monotherapy (Δ) and after combination with cimetidine 200 mg on day 7 ($\bullet$) ($n = 6$).

Figure 6 Mean plasma levels of atenolol following the last oral dose of atenolol 100 mg as monotherapy (Δ) and after combination with cimetidine 200 mg on day 7 ($\bullet$) ($n = 6$).

and cimetidine/ β -adrenoceptor blocker co-administration (Kirch *et al.*, 1982; Spahn *et al.*, 1984).

Discussion

Using penbutolol the effects of cimetidine on phase I (oxidative metabolism) and phase II (glucuronide conjugation) metabolism were measured simultaneously. The amount of penbutolol conjugated with glucuronic acid was not altered, whereas the concentration of oxidation metabolites (4-hydroxypenbutolol and 4-hydroxypenbutolol glucuronide) was significantly reduced. These results correspond to those obtained by Klotz & Reimann (1980a, b) and

Desmond *et al.* (1980) from studies with benzodiazepines.

From this investigation of penbutolol metabolism, it is concluded that cimetidine inhibits oxidative metabolism of penbutolol and that the interaction is not caused by reduced liver blood flow. This conclusion is confirmed by the investigation of Mojaverian *et al.* (1982), who found no effect of cimetidine on the pharmacokinetics of morphine, a drug with a high hepatic extraction ratio. Since the concentration of oxidation products of penbutolol metabolism is rather small, and because the pharmacological activity of 4-hydroxypenbutolol is only 1/4 to 1/8 that of penbutolol, this interaction is unlikely to be of any therapeutic consequence, but is of theoretical interest.

Secondly, these investigations suggest that

Table 2 C_{max} , terminal half-life and AUC values of various β -adrenoceptor blocking agents in different treatment periods

	C_{max} (ng/ml)	$t_{1/2\lambda z}$ (h)	$AUC_{0-24 h}$ (ng ml ⁻¹ h)
Penbutolol	478	17.0	1272
Penbutolol + cimetidine	564	16.8	1466
Propranolol	126	5.6	948
Propranolol + cimetidine	251*	7.6	2112*
Metoprolol	177	4.4	1167
Metoprolol + cimetidine	284*	7.0	1885*
Pindolol	54	6.6	396
Pindolol + cimetidine	72	6.6	513
Atenolol	660	7.4	5787
Atenolol + cimetidine	610	7.5	5827

* $P < 0.05$, monotherapy vs co-administration

Figure 7 Mean cimetidine plasma levels following the last oral dose of cimetidine 200 mg on day 7 of treatment with cimetidine (Δ) and cimetidine + propranolol ($\bullet$) ($n = 6$).

cimetidine does not significantly affect the plasma levels and pharmacodynamics of unmetabolised penbutolol, pindolol and atenolol.

However, cimetidine co-administration elevates the plasma concentration of the oxidatively metabolised β -adrenoceptor blockers, propranolol and metoprolol. In spite of this, cimetidine did not alter the pharmacodynamics of the two β -adrenoceptor blockers. This is due to the shallow plasma concentration-response curve at higher plasma levels.

As expected, ranitidine did not influence the kinetics of atenolol. The interaction with metoprolol, however, cannot be explained completely, and further experiments are necessary.

In conclusion, H_2 -receptor antagonist/ β -adrenoceptor blocker interactions are clinically relevant only in those cases where β -adrenoceptor blockers are eliminated mainly by oxidative biotransformation, and are given concurrently with cimetidine to endangered patients.

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