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CIMETIDINE INCREASES STEADY STATE PLASMA LEVELS OF PROPRANOLOL

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1 The influence of cimetidine (1000 mg daily) on propranolol steady state plasma levels has been studied in seven normal volunteers. Cimetidine was used as a 200 mg normal release tablet whereas propranolol was given as a 160 mg slow release formulation once daily.

2 After 1 day of cimetidine treatment (day 9 of the study) the mean ($\bar{C}_{ss}$) and minimal (C_{ss} min) propranolol steady state plasma levels increased significantly from 24.1 ± 14.9 ng/ml (mean ± s.d.) to 39.2 ± 27.7 ng/ml ($P = 0.01$) and from 14.8 ± 9.3 ng/ml to 27.1 ± 21.2 ng/ml ($P = 0.03$), respectively. The apparent oral clearance (Cl_o) was reduced from 6.7 ± 4.3 l/min to 4.6 ± 3.1 l/min ($P = 0.006$).

3 A prolongation of cimetidine administration to 5 days (day 13 of the study) intensified this effect significantly ($P = 0.02$): $\bar{C}_{ss}$ of propranolol was elevated from 23.2 ± 14.4 ng/ml to 44.9 ± 26.7 ng/ml ($P = 0.003$); C_{ss} min was increased from 14.1 ± 10.2 ng/ml to 28.4 ± 17.9 ng/ml ($P = 0.02$) while Cl_o decreased from 6.9 ± 4.1 l/min to 3.3 ± 1.6 l/min ($P = 0.006$).

4 We conclude that the drug interaction between propranolol and cimetidine leads to significant elevations of propranolol steady state plasma concentrations which may cause a clinically relevant enhancement of the effect of a given dosage. This requires careful observation of patients under concomitant treatment with propranolol and cimetidine.

Introduction

Cimetidine, a histamine H_2-receptor blocking agent, is widely used in the treatment of gastroduodenal ulcer disease. Animal experiments demonstrated a prolonged hexobarbitone sleeping time and inhibition of aminopyrine breath test in cimetidine pretreated rats (Puurunen & Pelkonen, 1979). *In vitro* investigations revealed cimetidine-dependent inhibition of microsomal *N*-demethylation and hydroxylation processes (Puurunen & Pelkonen, 1979). These observations initiated a series of pharmacokinetic studies in man. Already short-term pretreatment with therapeutic doses of cimetidine impaired the elimination of warfarin (Serlin *et al.*, 1979), antipyrine (Puurunen, Sotaniemi & Pelkonen, 1980; Klotz & Reimann, 1980a), chlordiazepoxide (Desmond *et al.*, 1980), diazepam (Klotz & Reimann, 1980a) as well as its active metabolite desmethyldiazepam (Klotz & Reimann, 1980b). All of these drugs are eliminated by hepatic phase I reactions (e.g. desmethylation, hydroxylation), whereas the pharmacokinetics of oxazepam (Klotz & Reimann, 1980b) and lorazepam (Patwardhan *et al.*, 1980), conjugated to glucuronides (phase II reaction), are unaffected by cimetidine.

Another drug which undergoes extensive liver first pass effect by different phase I metabolization steps is propranolol (Paterson, Conolly & Dollery, 1970; Walle & Gaffney, 1972). Propranolol is one of the most widely used, non-selective β-adrenergic receptor blocking agents for treatment of hypertension, tachyarrhythmias as well as coronary heart disease. Cimetidine conceivably could affect propranolol pharmacokinetics by decreasing first pass elimination and thus increasing its pharmacological effect. Therefore, we have investigated the influence of cimetidine on steady state propranolol levels in healthy volunteers.

A preliminary report of this work was presented at the Spring 1981 meeting of the Deutsche Pharmakologische Gesellschaft, Mainz, Germany.

Methods

Subjects

Seven normal volunteers, four males and three females, age ranging from 21–42 years, participated in the study. All subjects were normal in body weight and were without further medications; all but one were non-smokers (Gardner, Cady & Ong, 1980).

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Drinking alcohol was not allowed during the course of the study (Grabowski *et al.*, 1980). Written informed consent was given by all participants before entering the study.

Study design

The study consisted of two parts each lasting for 13 days. Both parts of the study were separated by a drug free interval of at least 14 days. In both parts of the study racemic propranolol hydrochloride was given once daily at 08.00 h in a dose of 160 mg in a slow release preparation (Dociton retard®, Rhein Pharma, Plankstadt). During one of the two study periods the participants received in randomized order cimetidine (Tagamet ® tablets, Smith Kline, Dauelsberg, Göttingen) concomitantly with propranolol, starting on the 8th day of propranolol administration. The doses of cimetidine were 200 mg at 07.00 h, 12.00 h, 17.00 h and 400 mg at 22.00 h. Twenty-four hour propranolol plasma concentration profiles were obtained on day 6, 7, 9 and 13 of both parts of the study. For this, blood samples for determination of propranolol plasma concentrations were collected prior to and at 2 h intervals for 12 h as well as 24 h after propranolol intake.

Blood sampling

In order to avoid the *in vivo* interaction between heparin and plasma propranolol binding the venous blood was drawn from a forearm vein by separate venepuncture into a plastic syringe (Routledge & Shand, 1979). It was immediately transferred to a heparinized plastic tube with plastic stopper (avoiding rubber stoppers which contain plasticisers), mixed gently and centrifuged; plasma was transferred to plastic tubes and stored at −20°C until analysis.

Analytical methods

Chemicals Racemic propranolol HCl was kindly supplied by ICI-Rhein Pharma. *N*-ethylpropranolol, used as internal standard, was prepared according to the method of Wood *et al.* (1978). Organic solvents and chemicals were p.a. quality and obtained from E. Merck, Darmstadt, FRG.

Instrumentation A 'Waters' model 6000A high performance liquid chromatograph equipped with a Jobin Yvon Spectrofluo JY 3 D L.C. Fluorimeter, a 'Waters' u-Bondapak C_{18} column (30 cm × 4 mm i.d.) and a 'Knauer' RP-2 precolumn (12 cm × 4.6 mm) were used. The excitation and emission wave lengths were 295 nm and 340 nm, respectively. The flow rate of the mobile phase (distilled water: methanol: phosphoric acid = 315: 185: 0.5) was 2 ml/min.

The intraassay coefficient of variation of propranolol was 7.0 ± 2.5%, the limit of sensitivity of the assay method is about 0.5 ng propranolol/ml plasma.

Extraction procedure To 1.0 or 2.0 ml of plasma the internal standard (*N*-ethylpropranolol) and 0.5 ml of 2_N NaOH were added. After mixing, extraction with 8 ml of heptane/isoamyl alcohol (98.5 : 1.5) and centrifugation the organic phase was transferred to a tube containing 1 ml of 1_N HCl. After further mixing and centrifugation the organic phase was discarded, 1 ml of 5_N NaOH and 8 ml heptane/isoamyl alcohol (98.5 : 1.5) were added for a back extraction. The organic phase was completely transferred to a conical test tube and evaporated to dryness. The residue was dissolved in 200 μl of the mobile phase and injected into the h.p.l.c system.

Pharmacokinetic analysis

During steady state the areas under the curve (AUC) of propranolol were calculated according to the trapezoidal rule from the plasma propranolol concentration-time profiles over a 24 h dosing interval for each subject. Mean steady state propranolol plasma concentrations ($\bar{C}_{ss}$) were calculated from the equation $\bar{C}_{ss} = AUC^{\tau}/\tau$, the dosing interval τ being 24 h. The minimal steady state plasma concentrations of propranolol (C_{ss} min) were measured in blood samples taken at 08.00 h just before administration of the next propranolol capsule. The apparent oral plasma clearance (Cl_o) was derived from the ratio of the administered propranolol dose (assuming complete absorption from the sustained release capsules) to the area under the plasma concentration-time curve over 24 h ($AUC_{24\,h}$). Statistical analysis was performed by Wilcoxon rank test and by paired Student's *t*-test, $P = 0.05$ being the minimal level of significance. The values are given as mean ± s.d.

Results

Figure 1 shows the time course of the effect of cimetidine on propranolol plasma levels. Table 1 summarizes the pharmacokinetic data of all participants of the study. Cimetidine significantly increases $\bar{C}_{ss}$ as well as C_{ss} min and, accordingly, the $AUC_{24\,h}$ of propranolol. Although, in accordance with data in the literature (Routledge & Shand, 1979), the inter-individual variations in plasma propranolol concentrations are high in the present study ($\bar{C}_{ss}$ = 8.9–44.0 ng/ml following a dose of 160 mg propranolol as sustained release preparation) cimetidine increases propranolol mean steady state plasma levels in each subject to an extent ranging from 15.6 to 92.7% (mean ± s.d.: 55.2 ± 28.3%) after one day of cimetidine pretreatment (comparing day 9 of the

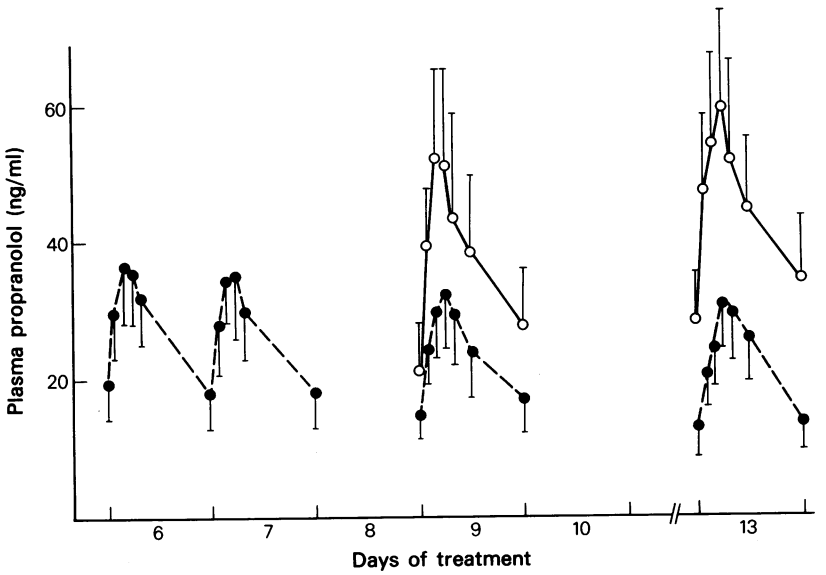

Figure 1 Plasma level time profiles of propranolol (●—●) and during concomitant cimetidine treatment (○—○) in seven subjects (mean ± s.e. mean).

propranolol phase to day 9 of the propranolol/cimetidine phase) and from 44.6 to 161.1% (mean ± s.d.: 104.2 ± 41.4%) after 5 days of simultaneous administration of propranolol and cimetidine (comparing day 13 of the propranolol trial to day 13 of the propranolol/cimetidine trial). This effect of cimetidine is mirrored in a statistically significant decrease in Cl_0 of 33.9 ± 11.9% (range 15.7–48.1%) on day 9 of the trials and of 50.7 ± 11.2% (range 30.7–61.6%) on day 13 of the trials, respectively. The minimal steady state plasma levels of propranolol are elevated by 73.8 ± 62.5% (range 3.5–203.6%) after 24 hours of cimetidine medication (day 9) and by 140.6 ± 123.6% (range 5.6–348%) after 5 days of cimetidine administration (day 13). The effect of cimetidine on propranolol kinetics was significantly greater on day 13 than on day 9 ($P = 0.02$). A correlation between the propranolol plasma concentration before cimetidine and the increase in propranolol plasma concentration during cimetidine administration treatment could not be demonstrated.

Discussion

Propranolol is completely absorbed in the gastrointestinal tract and highly extracted by the liver where the main metabolic pathways include several phase I reactions which are catalyzed by mixed function oxidases (Paterson *et al.*, 1970; Walle & Gaffney, 1972). After oral administration the amount of unchanged propranolol reaching the systemic circulation depends more on the activity of the hepatic drug metabolizing enzymes than on liver blood flow (Routledge & Shand, 1979). Assuming complete absorption, bioavailability of propranolol will be highly sensitive to variations in the activity of the hepatic mixed function oxidase system. Cimetidine has been shown to inhibit the microsomal cytochrome P-450 system, probably by ligand interaction (Rendić *et al.*, 1979).

The results of this study show that cimetidine in fact causes a decrease in apparent oral clearance of propranolol paralleled by an increase in minimal and mean propranolol steady state plasma levels. This effect can be seen already 24 h after intake of 1000 mg of cimetidine and is still further intensified during the following 5 days of cimetidine treatment. One of the metabolites of cimetidine, cimetidine sulphoxide, did not influence the aminopyrine breath test in rats in a single dose experiment (Speeg *et al.*, 1980); hence, it can be assumed that this metabolite will not play a major role in the propranolol/cimetidine drug interaction.

The most attractive explanation for the currently described interaction is a reduction in liver first pass elimination of propranolol by cimetidine. Other possibilities include variations in gastric emptying and/or gastric pH and digestive function, which in principle could affect rate and/or extent of propranolol absorption. In 1978 Castleden, George & Short showed that differences in gastric emptying

Table 1 Effect of cimetidine (C, 1000 mg daily) on pharmacokinetic parameters (mean ± s.d.) of propranolol (P, 160 mg as slow release preparation once daily) under steady state conditions in seven healthy volunteers (day 9 = 1 day of cimetidine treatment, day 13 = 5 days of cimetidine treatment).

Subject (sex, age in years)	*Day*	*AUC (ng ml^{-1} h)* P 9	P 13	P + C 9	P + C 13	$\overline{C}_{ss}$ *(ng/ml)* P 9	P 13	P + C 9	P + C 13	C_{ss} *min (ng/ml)* P 9	P 13	P + C 9	P + C 13	Cl_o *(l/min)* P 9	P 13	P + C 9	P + C 13
U.S. (F, 34)		978	934	1807	1504	40.8	38.9	75.3	62.7	22.7	21.9	39.4	48.4	2.7	2.8	1.5	1.8
C.S. (F, 42)		479	442	638	638	19.9	18.4	26.6	26.6	11.8	11.4	13.6	13.7	5.6	6.0	4.2	4.2
G.K. (F. 26)		1057	762	1582	1535	44.0	31.8	65.9	64.0	19.4	16.3	58.9	55.3	2.5	3.5	1.7	1.7
J.R. (F. 41)		323	243	383	506	13.5	10.1	15.6	21.1	11.6	7.5	12.0	13.0	8.3	11.0	7.0	5.3
F.S. (M, 29)		787	1026	1516	2135	32.8	42.8	63.2	89.0	29.0	32.2	48.0	34.0	3.4	2.6	1.8	1.3
B.B. (M, 21)		214	271	365	663	8.9	11.3	15.2	27.6	6.0	5.0	12.8	22.4	12.5	9.8	7.3	4.0
B.R. (M, 21)		219	217	304	565	9.1	9.0	12.7	23.5	3.3	4.3	5.2	11.9	12.2	12.3	8.8	4.7
Mean		579.6	556.4	942.1	1078	24.1	23.2	39.2	44.9	14.8	14.1	27.1	28.4	6.7	6.9	4.6	3.3
± s.d.		358.1	344.8	662.3	640.8	14.9	14.4	27.7	26.7	9.3	10.2	21.2	17.9	4.3	4.1	3.1	1.6
Significance			NS		NS		NS		NS		NS		NS		NS		NS
			$P = 0.01$				$P = 0.01$				$P = 0.03$				$P = 0.006$		
				$P = 0.003$				$P = 0.003$				$P = 0.018$				$P = 0.006$	

induced by anticholinergic drugs or metoclopramide have some influence on the height of propranolol peak concentration and the time at which this occurs. However, a valid correlation between gastric emptying and the bioavailability of propranolol has not been substantiated. Moreover, gastric emptying rate in man seems not to be influenced by cimetidine (Brogden *et al.*, 1978), whereas propranolol itself could be shown to speed it up (Rees *et al.*, 1980). However this effect cannot account for the differences seen in our study between the propranolol and propranolol plus cimetidine period. Enhanced absorption of propranolol due to cimetidine coadministration would be another, though rather unlikely, explanation which cannot be conclusively decided from the experiments reported here.

Compared to data in the literature (Wood *et al.*, 1978) our values for oral propranolol clearance seem rather high. The most probable reason may be that the small amounts of sustained released drug are highly exposed to the liver first pass effect and that propranolol absorption from the slow release formulation may not be as complete as originally assumed. This has lately been confirmed (McAinsh *et al.*, 1981) after we had finished our study.

Besides its inhibiting effect of hepatic drug-metabolizing enzymes cimetidine has recently been shown to reduce liver blood flow, thereby decreasing the systemic clearance of those drugs which, like intravenous propranolol, primarily depends on liver blood flow (Feely, Wilkinson & Wood, 1981).

The pharmacokinetic drug interaction between propranolol and cimetidine may lead to clinically relevant reinforcement of the β-adrenergic receptor blocking effects of a certain propranolol dosage. In support of an enhanced pharmacodynamic effect of a given dose of propranolol by cimetidine is a case report showing that cimetidine caused a clinically dangerous reduction in heart rate and blood pressure in a patient receiving propranolol for coronary heart disease (Donovan *et al.*, 1981).

If concomitant treatment with both drugs is inevitable, close supervision of the pharmacological effects of propranolol appears advisable.

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