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Influence of cimetidine co-administration on the pharmacokinetics of acebutolol enantiomers and its metabolite diacetolol in a rat model: the effect of gastric pH on double-peak phenomena

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Abstract

Acebutolol (AC) is a chiral β-adrenergic receptor-blocking agent, which has been shown to be clinically effective in hypertension. The plasma concentration–time profiles of AC exhibit two peaks following oral administration of racemate for both *R*- and *S*-enantiomers. In the present study, the absorption of AC after a single dose was studied as a function of gastric pH in male Sprague–Dawley rats. Furthermore, the effect of cimetidine (CIM) on pharmacokinetic parameters of AC and its metabolite diacetolol (DC) was evaluated. CIM (50 mg kg^{-1}) was administered via jugular vein 30 min prior to AC administration to elevate the intragastric pH. AC (50 mg kg^{-1}) was administered orally by gavage and serial blood samples were collected before and for 8 h after AC administration. Plasma samples were assayed for AC and DC, pharmacokinetic parameters were estimated and compared with those of control. The concentration–time profiles and the pharmacokinetics of AC were unchanged after co-administration of CIM. The oral absorption of AC, as assessed by the area under the plasma concentration–time curve (AUC) and the amount of unchanged drug recovered in the urine were not affected by CIM. The amount of metabolite recovered in the urine and the rate of absorption, however, were significantly altered. These are unlikely to be of clinically importance as we have found that the extent of absorption was not changed. We, therefore, concluded that intragastric elevation of pH has no effect either on generation of multiple peaking or on pharmacokinetic parameters of AC.

Keywords: Acebutolol; Cimetidine; Double-peaks; Pharmacokinetics; Interaction

1. Introduction

Acebutolol (AC) is a chiral β-adrenergic receptor antagonist, which is widely used in the treatment of hypertension (Chatterji, 1978) and cardiac arrhythmias (Gradman et al., 1977). Although AC is manufactured as the racemate its β-blockade activity resides predominantly with *S*-enantiomer (Walle et al., 1988). AC is rapidly absorbed in the rat (Mostafavi and Foster, 1998) and human (Meffin et al., 1978; Gulaid et al., 1981) with similar extents of absorption for both enantiomers (Piquette-Miller et al., 1991). Peak plasma concentrations and the area under the plasma concentration–time curve (AUC) of AC enantiomers are different among individuals suggesting stereoselective first-pass metabolism for AC in man (Piquette-Miller et al., 1991; Singh et al., 1986) and the rat (Mostafavi and Foster, 1998). When AC is

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administered orally, the plasma concentration–time profile frequently shows two maxima (Piquette-Miller and Jamali, 1992a,b), the first at about 0.25 h and the second at about 1.5 h in the rat (Mostafavi and Foster, 1998). Furthermore, the "erratic" plasma concentration–time profile of AC (Meffin et al., 1978; Winkle et al., 1977; Zaman et al., 1984; Piquette-Miller and Jamali, 1992a,b; Zaman et al., 1985; Roux et al., 1980) and diacetolol (DC) (Fouvat et al., 1981) has been reported after p.o. administration. As expected, a double-peak effect disappears if the drug is administered intravenously (Mostafavi and Foster, 1997, 1998; Roux et al., 1980; Meffin et al., 1977). Double-peaks have been observed in the plasma concentration profile of several other drugs including acetaminophen (Clements et al., 1978), aspirin (Oberle and Amidon, 1986), cimetidine, (CIM, Pederson and Miller, 1980), furosemide (Hammarlund et al., 1984), penicillamine (Bergstrom et al., 1981), and ranitidine (Grag et al., 1983), following p.o. administration.

Several mechanisms have been suggested for occurrence of more than a single concentration maxima including the effect of gastric emptying (Clements et al., 1978). Gastric emptying is altered due to drugs and disease (Nimmo, 1976). Drugs may alter the rate of gastric emptying by effects on the smooth muscle, influencing the release of intestinal hormones, which modulate gastric activity, or by influencing the gastric pH. It has been reported that gastric emptying is reduced (Hunt and Knox, 1972) by both weak (e.g. lactic, tartaric and ascorbic acids) and strong acids (e.g. hydrochloric and nitric acids) while the basic (e.g. sodium bicarbonate or disodium phosphate) solutions were found to increase the rate of emptying in healthy subjects (VanLiere and Sleeth, 1940). Therefore, elevation of gastric pH may increase the gastric emptying rate, with a substantial amount of the drug emptying into the duodenum soon after administration. The fast gastric emptying may produce a rapid increase in plasma concentration and also result in the appearance of a single peak in the plasma profile of drugs. The disappearance of multiple peaks due to increasing pH has recently been reported for CIM (Mummaneni et al., 1995).

The objective of this study were to determine whether gastric pH plays an important role in the generation of double-peaks following p.o. administration of AC. CIM was administered as a method to increase intragastric pH (Smout et al., 1995; Thomson et al., 1999). We further addressed the influence of CIM co-administration on the pharmacokinetics of AC and DC enantiomers in the rat model. This study was conducted in the rat model as the rat has been shown to be a good animal model for studying the double-peak phenomena of AC (Piquette-Miller et al., 1992a).

2. Materials and methods

2.1. Chemicals

CIM, racemic AC and the internal standard (IS), racemic pindolol, was bought from Sigma (Illinois, USA). The metabolite, (DC, as hydrochloride salts) were obtained from Rhone-Poulenc Rorer Canada Inc. (Montreal, Que., Canada). All other chemicals and reagents were HPLC or analytical grade.

2.2. Surgery and animal maintenance

Twelve male Sprague–Dawley rats weighing between 220 and 350 g were chosen for this study. The protocol was approved by the animal ethics committee of the University of Alberta. Rats were fasted for about 8 h prior to, and for 2 h following the AC administration, with free access to water. Animals were anesthetized with pentobarbital (i.p.) and right jugular vein was catheterized with silastic tubing (i.d. = 0.025, o.d. = 0.037 Dow Corning, Midland, MI, USA). The animals were allowed to recover overnight prior to the experiments. During this time the animals were individually stored in 18 in. × 9.5 in. × 8 in. polycarbonate rodent cages.

2.3. Dosing and sample collection

CIM was administered as a bolus 50 mg kg^{-1} in normal saline at time zero to raise intragastric pH. Racemic AC dissolved in normal saline was administered orally in dose of 50 mg kg^{-1} after 30 min. Blood (0.25 ml) was collected from the jugular vein cannula at 0, 2, 15, 30, and 45 min. and at 1, 1.5, 2, 2.5, 3.5, 5.5 and 8 h after AC administration. Between each blood sample collection 0.25 ml normal saline was administered via the jugular vein cannula as fluid replacement and the cannula was heparinized (10 U ml^{-1}). Blood

samples were immediately centrifuged and the plasma was separated and immediately frozen at −20 °C until analyzed. Urine was collected and pooled for 24 h following drug administration. Urine samples were kept frozen at −20 °C until analyzed.

2.4. Stereospecific HPLC assay of AC and DC

Concentrations of *R*- and *S*-AC and *R*- and *S*-DC in plasma and urine were determined utilizing a previously reported stereospecific HPLC method (Piquette-Miller et al., 1990a,b). For urine sample analysis, specimens were diluted 1:10 (v/v) in HPLC grade water, derivatized, and subsequently analyzed.

2.5. Pharmacokinetic data analysis

The area under the plasma concentration–time curve ($AUC_{0-\infty}$) was calculated by the linear trapezoidal rule. The area from the last concentration point C_{last} to infinity was calculated as C_{last}/β, where β was the terminal elimination rate constant calculated by regression through at least three data points in the terminal elimination phase. We could not calculate the β for metabolite due to low concentration. Therefore, the AUC values reported for DC are the AUC from 0 to 3.5 h post dose. The terminal elimination half-life ($t_{1/2}$) was calculated by 0.693/β. Oral clearance ($Cl_{p.o.}$) was calculated as $D/AUC_{0-\infty}$, where *D* was the enantiomeric dose administered. Volume of distribution (V_d/F) was calculated by dividing corresponding $Cl_{p.o.}$ by β. As the urinary excretion of AC is almost complete within the first 24 h after single dose administration, renal clearance (Cl_R) of each enantiomer was estimated by dividing the cumulative 24-h urinary excretion of each enantiomers by the corresponding $AUC_{0-\infty}$. The relative bioavailability was calculated by dividing enantiomeric $AUC_{0-\infty}$ of AC after co-administration of CIM over the same value after administration of AC alone

2.6. Statistical analysis

Statistical comparisons of the pharmacokinetic parameters of enantiomers after administration of racemate were made by a two-tailed Student's *t*-test for paired. Statistical comparison of pharmacokinetic data of AC after co-administration of CIM versus administration of AC alone for *R*-versus *R*- and *S*- versus *S*-AC were made by two-tailed Student's *t*-test for two samples assuming equal variance. Significance was assumed at 5% level. Results are expressed as mean ± S.D.

3. Results

The plasma concentration versus time profiles of AC exhibited two concentration maxima after p.o. administration. CIM co-administration had no effect on the appearance of this phenomenon for either *R*- or *S*-AC (Figs. 1 and 2).

Pharmacokinetic parameters of *R*- and *S*-AC after co-administration of CIM (50 mg kg^{-1}) to the rat are summarized in Table 1. A slight but statistically significant difference in the AUC of the AC enantiomers in favor of *R*-AC was observed after administration of CIM. The $Cl_{p.o.}$ of AC enantiomers did not change significantly in co-administration with CIM although a trend of increase in this value was observed.

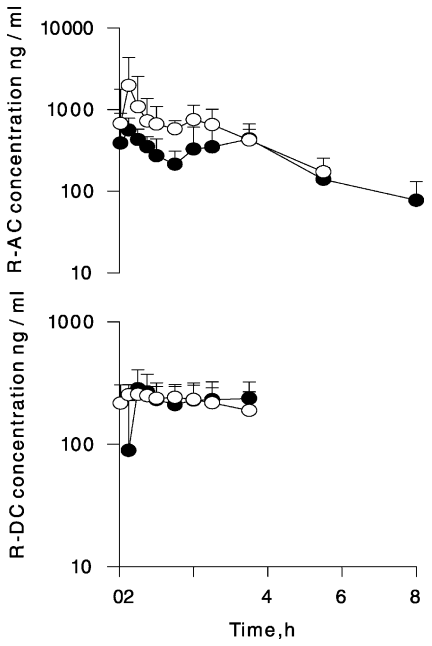

Fig. 1. The average plasma concentration vs. time profiles for *R*-AC and *R*-DC after administration of AC alone (○) and after co-administration of cimetidine (●) mean ± S.D. Six rats in each group.

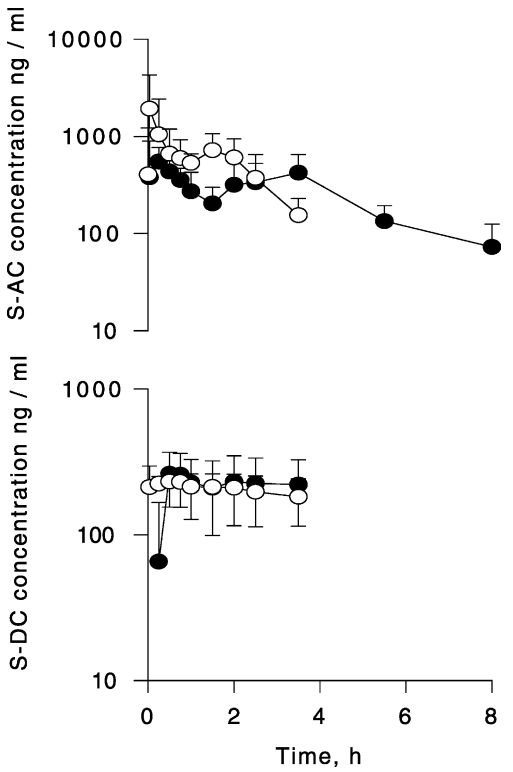

Fig. 2. The average plasma concentration versus time profiles for *S*-AC and *S*-DC after administration of AC alone (○) and after co-administration of cimetidine (●) mean ± S.D. Six rats in each group.

Disposition of DC was not stereoselective after co-administration of CIM. However, the amount of *R*-DC recovered in urine, was significantly greater than that of *S*-DC ($R{:}S = 1.63 \pm 0.16$) after 24 h post dose. The $AUC_{0-3.5}$ value of DC did not change during combined treatment with CIM. The amount of DC collected in urine however, was increased significantly for both enantiomers.

The mean fraction of AC recovered in urine was about 20% after administration of AC alone. A trend of decrease in this value was observed after co-administration of CIM for both enantiomers.

4. Discussion

The results of present study demonstrated that concomitant CIM administration did not change the concentration–time profiles of AC enantiomers. In fact, CIM was co-administered to increase the intragastric pH, as it has been shown that CIM is increasing the gastric pH, which in turn, increases the gastric emptying rate (Mummaneni et al., 1995). After increasing the gastric emptying rate, the substantial amount of drug emptying into the duodenum soon after administration which can make a rapid increase in plasma concentrations resulting in disappearance of double-peaks in the plasma profile of drugs. With

Table 1
Pharmacokinetic parameters of acebutolol enantiomers after administration of racemate and after co-administration of cimetidine to rats

Pharmacokinetic parameters	Acebutolol[c]		Acebutolol + cimetidine	
	R-AC	*S*-AC	*R*-AC	*S*-AC
AUC ($\mu g\,h\,l^{-1}$)	3155[a] (1003)	3007 (895)	2454[a] (734)	2367 (705)
$CL_{p.o.}$ ($ml\,min^{-1}\,kg^{-1}$)	138[a] (39)	149 (42)	183[a] (55)	189 (54)
$t_{1/2}$ (h)	1.92 (0.60)	1.86 (0.60)	2.31 (0.72)	2.44 (0.98)
T_{max} (h)	0.37 (1.37)	0.37 (1.37)	0.20 (2.50)	0.20 (2.50)
First and second peaks	0.25 (0.6)	0.26 (0.6)	0.09 (1.08)	0.09 (1.08)
C_{max} ($\mu g\,ml^{-1}$)	2114 (2310)	2084 (2248)	692 (471)	683 (458)
First and second peaks	1923 (1760)	1906 (1768)	316,222	314,213
Clr ($ml\,min^{-1}\,kg^{-1}$)	25 (6)	25 (6)	27 (10)	30 (11)
V_d/F ($l\,kg^{-1}$)	23 (9)	24 (9)	27 (9)	29 (11)
$\sum X_U$ of Diacetolol (μg)	165[a,b] (49)	80 (27)	389[a,b] (140)	248 (109)
$Ae_{0-\infty}$ (%)	20 (11)	19 (11)	15 (3)	16 (3)

Data are presented as mean (S.D.) $Ae_{0-\infty}$, percent of AC excreted intact in the urine.
[a] Significantly different from corresponding enantiomer, $P < 0.05$.
[b] Significantly different from corresponding enantiomer for the cimetidine group, $P < 0.05$.
[c] Adapted from Clements et al. (1978), $\sum X_U DC$ = amount recovered in the urine as metabolite.

AC however, two concentration maxima retained after CIM administration (Figs. 1 and 2). Recently, the double-peaks observed in concentration–time profiles of CIM after p.o. administration was found to be disappeared as the gastric pH was increased (Mummaneni et al., 1995). In this report, the double-peaks were observed more frequently when gastric pH was low however, the double-peak is disappeared at high gastric pH.

Another area where concomitant administration of CIM with other drugs may play a role is the drug interaction. The changes in pharmacokinetic parameters of several agents have been reported in concomitant administration with CIM. In our knowledge, however, there is no report on interaction between AC and CIM. Our data are shown that the pharmacokinetics of AC were not significantly affected by co-administration of CIM.

The most widely known effect of CIM is the inhibition of hepatic metabolism mediated by cytochrome *P*-450, the reduction in liver blood flow, and inhibition of the proximal tubular secretion of organic cations (Somogyi and Muirhead, 1987). Co-administration of CIM did not change the AUC of AC or its metabolite, DC, indicating that CIM did not inhibit the metabolism of AC. In fact, if the inhibition of AC were occurred in this sample of the rats we should see the increase in AUC of AC as well as decrease in DC concentrations. By contrast, we observed a trend of decrease in the AUC of AC. Furthermore, the amount of metabolite recovered in the urine after 24 h slightly, but significantly increased after co-administration of CIM. This finding may be explained by induction of the rat hepatic enzymes by CIM (Ioannoni et al., 1986; Wright et al., 1991).

AC is metabolized primarily by hydrolysis of its butyramide group. This gives the primary amine, acetolol, which then undergoes *N*-acetylation to produce DC. The differences in the metabolism of AC between treatments may be linked to induction of either hydrolysis or acetylation pathways. The metabolism of isoniazid (Paulsen et al., 1986;) and procainamide (Christian et al., 1984), drugs that also undergo acetylation, has been investigated by co-administration of CIM. Although renal clearance of procainamide was significantly reduced by CIM, there was no evidence of altered acetylation. Nevertheless, Svenssen and Tmilo, 1992 have reported that CIM did not induce the *N*-acetyl transferase activity responsible for drug acetylation in the rats. We therefore, did not expect CIM to have influenced AC metabolism by alteration of acetylation pathway. The hydrolysis stage however, remains a possibility, which could be responsible for these differences. In addition to enzymatic hydrolysis of AC, an increase in the gastric pH induced by CIM perhaps may influence its hydrolysis resulting in elevation of the concentration of intermediate metabolite, acetolol. Nonetheless, an increase in acetolol concentrations could result in elevating DC concentrations that in turn were recovered in urine (Table 1). In fact, the conversion of AC to acetolol either in gastrointestinal tract or after first pass through the liver could result in decreasing the amount of available AC in plasma. Interestingly, a trend of decrease in percent of AC recovered in urine which is a reflection of bioavailability, was observed after CIM co-administration which is consistence with the relative availability of 70% that was estimated after CIM co-administration. A decrease in availability produced by CIM could affect the $CL_{p.o.}$, C_{max} as well as V_d/F. We found a trend of increase in $CL_{p.o.}$ as well as V_d/F and a trend of decrease in C_{max} for AC after this treatment (Table 1).

Overall, this study identifies that gastric pH have no influence on appearance of double-peaks phenomena observed after p.o. administration of AC. Furthermore, the rate and the extent of absorption did not changed significantly. Thus, no special precautions would seem necessary if AC is taken with CIM.

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