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Effect of cimetidine on acetaminophen pharmacokinetics in rats

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Summary

The purpose of this investigation was to determine the effect of acute cimetidine administration on the elimination kinetics of acetaminophen in rats. Cimetidine, 80 mg/kg i.p., 30 min before i.v. injection of acetaminophen, 30 mg/kg, caused a small but statistically significant decrease in the total clearance and an increase in the biological half-life of acetaminophen in adult male rats. The partial metabolic clearance of acetaminophen to acetaminophen sulfate was decreased by cimetidine. The magnitude of the acute interaction of cimetidine with acetaminophen was not increased at a higher (150 mg/kg) dose of acetaminophen.

Introduction

The histamine H_2-receptor antagonist, cimetidine, is a potent inhibitor of microsomal drug metabolism in man and animals. Clinical studies have shown or suggested that cimetidine administration is associated with a decreased metabolic clearance of antipyrine (Breckenridge et al., 1979; Klotz and Reimann, 1980),warfarin (Breckenridge et al., 1979), diazepam (Klotz and Reimann, 1980), chlordiazepoxide (Desmond et al., 1980); phenytoin (Hetzel et al., 1981), orally administered propranolol (Heagerty et al., 1981; Feely et al., 1981), carbamazepine (Telerman-Toppet et al., 1981), and theophylline (Jackson et al., 1981). In vitro, cimetidine has been found to inhibit the hydroxylation of benzo(a)pyrene and coumarin, and the O-deethylation of 7-ethoxycoumarin by human liver homogenates (Puurunen et al., 1980). Studies in animals have revealed that cimetidine prolongs the hexobarbital (Puurunen and Pelkonen, 1979) and pentobarbital sleeping time and the zoxazolamine paralysis time (Breckenridge et al., 1979), and inhibits the metabolic clearance

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of aminopyrine (Desmond et al., 1980; Puurunen and Pelkonen, 1979), warfarin (Serlin et al., 1980) and caffeine (Desmond et al., 1980). The mechanisms of these interactions have not yet been elucidated but it has been demonstrated that there occurs a ligand interaction between cimetidine and cytochrome P-450 (Rendić et al., 1979). However, cimetidine inhibits drug biotransformation processes that are mediated by cytochrome P-450 as well as by cytochrome P-448 and it may act by more than one mechanism (Desmond et al., 1980).

Acetaminophen, the widely used analgesic and antipyretic agent, can produce severe and sometimes fatal hepatotoxicity when taken in large overdoses (Zimmerman, 1981). The liver damage is produced by a minor but highly reactive metabolite generated by the cytochrome P-450 system. Certain inhibitors of that system can reduce acetaminophen-induced hepatotoxicity while inducers such as phenobarbital have the opposite effect (Hinson et al., 1981). A limited study in mice to determine the effect of cimetidine on acetaminophen-induced hepatic necrosis yielded equivocal results which the authors interpreted as 'a favorable trend' (Rudd et al., 1981). In this laboratory, cimetidine administration had no significant effect on the acute median lethal dose of acetaminophen in mice; the i.p. LD_{50} (95% confidence interval) was 409 (291–574) mg/kg in control animals and 342 (259–453) mg/kg in animals treated with cimetidine, 75 mg/kg i.p. 1 h before and again 1 h after acetaminophen (Pond et al., 1982).

Inhibition of the oxidative metabolic pathway of acetaminophen elimination will reduce the fractional conversion of that drug to its reactive and potentially hepatotoxic metabolite only if the parallel, major pathways of acetaminophen elimination (glucuronide[1] and sulfate formation) are not similarly inhibited. No information is available concerning the potential effect of cimetidine on the formation of acetaminophen glucuronide and sulfate. However, we have recently observed that an acetaminophen-intoxicated patient who received repeated doses of cimetidine eliminated acetaminophen unusually slowly (Pond et al., 1982). While there are many possible reasons for the slow elimination of acetaminophen by an overdosed patient, one possibility is that cimetidine may have inhibited one or more of the major biotransformation pathways of acetaminophen. A study was initiated therefore to determine the acute effect of cimetidine on the elimination kinetics of acetaminophen in experimental animals.

Materials and methods

Adult male Sprague–Dawley rats[2] weighing between 280 and 310 g had an indwelling cannula implanted in the right jugular vein one day before the study. Food and water were withdrawn in the morning before the experiment and animals

[1] Glucuronide formation is an important biotransformation pathway for acetaminophen in humans and becomes quantitatively significant in rats at high acetaminophen doses when inorganic sulfate becomes depleted and acetaminophen sulfate formation decreases (Galinsky and Levy, 1981).

[2] Holtzman, Madison, WI.

were housed individually in plastic metabolism cages. Acetaminophen, 30 mg/kg (5 mg dissolved in 1 ml of 0.9% saline) or 150 mg/kg (25 mg dissolved in 1 ml of 40% propylene glycol in water) was injected intravenously. Half of the animals received cimetidine[3], 80 mg/kg i.p., 30 min earlier. Control animals received an equivalent volume of 0.9% saline i.p. instead of cimetidine solution. The study with 150 mg/kg acetaminophen was performed 6 months after the 30 mg/kg study, with animals from the same source but obtained at a different time.

Blood samples (0.25 ml) were drawn periodically and urine was collected for 6 h (after the 30 mg/kg acetaminophen dose). One ml of 0.9% saline was injected i.v. after each blood withdrawal to clear the cannula of blood and to stimulate urine flow. Two additional animals received cimetidine alone and blood and urine samples were obtained to check for possible interference by cimetidine or its metabolites with the acetaminophen assay.

Plasma and urine were assayed for acetaminophen, acetaminophen sulfate and acetaminophen glucuronide by high-performance liquid chromatography (Galinsky and Levy, 1979). The apparent volume of distribution (Vd) and half-life ($t_{1/2}$) of acetaminophen (30 mg/kg dose) were calculated from the zero-time intercept and the slope of the regression line fitted to the log plasma concentration–time data by the method of least-squares. Total clearance was calculated as the product of Vd and $0.693/t_{1/2}$ or as the quotient dose/area under plasma concentration–time curve (for the 150 mg/kg dose because plasma concentrations did not decline mono-exponentially). Partial clearance for conversion of acetaminophen to a metabolite was determined as the product of total clearance and fraction of the dose recovered from the urine as the metabolite. Statistical analyses were performed by unpaired *t*-test for small samples.

Results and discussion

Plasma acetaminophen concentrations in control and cimetidine-treated rats after i.v. injection of the 30 mg/kg dose of acetaminophen are shown in Fig. 1 and pharmacokinetic constants are summarized in Table 1. Acute pretreatment with cimetidine caused a small but statistically significant decrease in the total clearance and increase in the biological half-life of cimetidine. The apparent volume of distribution was not affected.

Metabolic conversion of acetaminophen to its sulfate conjugate accounted for most of the elimination of the 30 mg/kg dose. The partial clearance of acetaminophen by this pathway was significantly reduced. The partial clearances for the minor elimination pathways of glucuronide formation and renal clearance were also lower, on the average, in cimetidine-treated animals but these differences were not statistically significant.

The effect of cimetidine on the time course of acetaminophen concentrations in plasma after injection of 150 mg/kg acetaminophen are shown in Fig. 2. The

[3] Tagamet[R], SK and F, Carolina, P.R., Lot no. 31 OT 22.

TABLE I

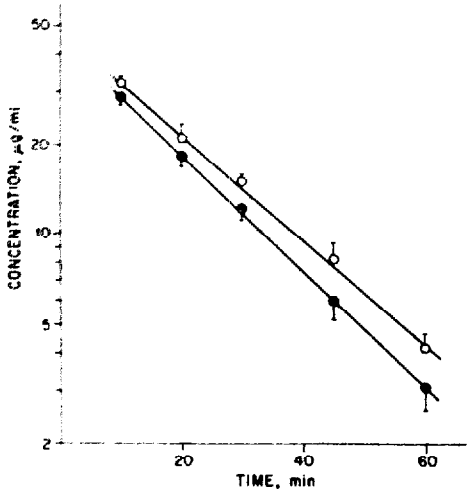
EFFECT OF CIMETIDINE ON THE PHARMACOKINETICS OF ACETAMINOPHEN (30 mg/kg) IN RATS

Pharmacokinetic constant	Control		Cimetidine-treated
Total clearance (ml/min/kg)	33.6 ± 2.4	$P<0.01$	28.0 ± 2.3
Half-life (min)	15.4 ± 0.8	$P<0.02$	17.5 ± 1.3
Volume of distribution (l/kg)	0.74 ± 0.04	N.S.	0.70 ± 0.03
Renal clearance (ml/min/kg)	0.72 ± 0.17	N.S.	0.61 ± 0.23
Partial metabolic clearance to acetaminophen sulfate (ml/min/kg)	29.2 ± 1.6	$P<0.005$	24.1 ± 2.6
Partial metabolic clearance to acetaminophen glucuronide (ml/min/kg)	1.79 ± 0.39	N.S.	1.58 ± 0.20

Results are expressed as mean ± S.D., n = 5.

time-average total clearance of acetaminophen was 8.8 ± 1.6 ml/min/kg in 4 control rats and 6.7 ± 1.1 ml/min/kg in 4 cimetidine-treated animals (mean ± S.D., difference between groups not statistically significant).

Plasma and urine from rats that received only cimetidine did not interfere in the assay of acetaminophen and its major metabolites by high-performance liquid chromatography.



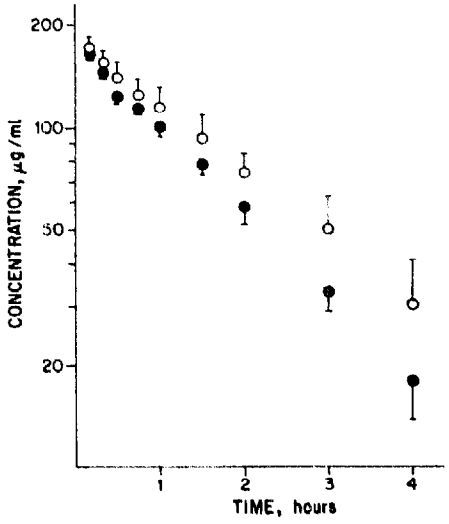


Fig. 1. Effect of cimetidine on the elimination kinetics of acetaminophen in rats. Shown are the plasma acetaminophen concentrations after i.v. injection of a 30 mg/kg dose. Treated animals (○) received cimetidine, 80 mg/kg i.p. at −30 min.; control animals (●) received an equivalent volume of normal saline solution. $\bar{Q}$ = mean ± S.D., n = 5.

Fig. 2. Effect of cimetidine on the elimination kinetics of acetaminophen in rats. Details as in Fig. 1 except that the dose of acetaminophen was 150 mg/kg and n = 4.

The dose of cimetidine used in this . .vestigation (80 mg/kg) is similar or higher than those used in other drug interaction studies in rats. Even a 20 or 30 mg/kg dose of cimetidine has a pronounced inhibitory effect on the metabolism of certain drugs in rats (Desmond et al., 1980; Serlin et al., 1980). The apparent absence of an inhibitory effect of cimetidine on the formation of acetaminophen glucuronide is consistent with the lack of effect of cimetidine on the elimination of lorazepam and oxazepam in humans (Patwardhan et al., 1980), both of the latter two drugs being eliminated almost entirely by glucuronidation.

Cimetidine itself is cleared from the body primarily by renal excretion and by conversion to a sulfoxide; humans and rats are similar in this respect (Taylor et al., 1978). There is no indication that cimetidine competes with acetaminophen for any of the major pathways of acetaminophen elimination. A possible inhibitory effect of cimetidine on the oxidative biotransformation of acetaminophen would not have a quantitatively significant influence on the total clearance of acetaminophen since only a small fraction of a dose of acetaminophen is metabolized by that pathway.

The cimetidine effect may be indirect. The drug could inhibit the microsomal metabolism of endogenous substances that are also subject to conjugation with sulfate, and thereby increase the competition by such endogenous substances with acetaminophen for sulfate conjugation. There are also indications that cimetidine can reduce hepatic blood flow (Feely et al., 1981), and this could affect the elimination of small doses of acetaminophen in rats because of the relatively high clearance of acetaminophen in the low dose range. In that case, the cimetidine effect would be relatively non-specific. The limited data obtained in this study on the cimetidine interaction with a large (150 mg/kg) dose of acetaminophen show that the magnitude of the interaction does not increase under conditions in which acetaminophen is subject to capacity-limited biotransformation (Galinsky and Levy, 1981).

In summary, cimetidine has only a small inhibitory effect on the total clearance of acetaminophen by rats. Since the metabolism of both drugs is qualitatively similar in man and rats, it appears unlikely that cimetidine will have an appreciable effect on the total clearance of acetaminophen in humans.

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References

Breckenridge, A.M., Challiner, M., Mossman, S., Park, B.K., Serlin, M.J., Sibeon, R.G., Williams, J.R.B. and Willoughby, J.M.T., Cimetidine increases the action of warfarin in man. Br. J. Clin. Pharmacol., 8 (1979) 392–393.

Desmond, P.V., Patwardhan, R., Parker, R., Schenker, S. and Speeg, Jr., K.V., Effect of cimetidine and other antihistaminics on the elimination of aminopyrine phenacetin and caffeine. Life Sci., 26 (1980) 1261–1268.

Desmond, P.V., Patwardhan, R.V., Schenker, S. and Speeg, K.V., Jr., Cimetidine impairs elimination of chlordiazepoxide (Librium) in man. Ann. Intern. Med., 93 (1980) 266–268.

Feely, J., Wilkinson, G.R. and Wood, A.J.J., Reduction of liver blood flow and propranolol metabolism by cimetidine. New Engl. J. Med., 304 (1981) 692–695.

Galinsky, R.E. and Levy, G., Dose- and time-dependent elimination of acetaminophen in rats: pharmacokinetic implications of cosubstrate depletion. J. Pharmacol. Exp. Ther., 219 (1981) 14–20.

Galinsky, R.E. and Levy, G., Effect of N-acetylcysteine on the pharmacokinetics of acetaminophen in rats. Life Sci., 25 (1979) 693–699.

Heagerty, A.M., Donovan, M.A., Castleden, C.M., Pohl, J.F., Patel, L. and Hedges, A., Influence of cimetidine on pharmacokinetics of propranolol. Br. Med. J., 282 (1981) 1917–1919.

Hetzel, D.J., Bochner, F., Hallpike, J.F., Shearman, D.J.C. and Hann, C.S., Cimetidine interaction with phenytoin. Br. Med. J., 282 (1981) 1512.

Hinson, J.A., Pohl, L.R., Monks, T.J. and Gillette, J.R., Acetaminophen-induced hepatotoxicity. Life Sci., 29 (1981) 107–116.

Jackson, J.E., Powell, J.R., Wandell, M., Bentley, J. and Dorr, R., Cimetidine decreases theophylline clearance. Am. Rev. Respir. Dis., 123 (1981) 615–617.

Klotz, U. and Reimann, I., Delayed clearance of diazepam due to cimetidine. New Engl. J. Med., 302 (1980) 1012–1014.

Patwardhan, R.V., Yarborough, G.W., Desmond, P.V., Johnson, R.F., Schenker, S. and Speeg, K.V., Cimetidine spares the glucuronidation of lorazepam and oxazepam. Gastroenterology, 79 (1980) 912–916.

Puurunen, J. and Pelkonen, O., Cimetidine inhibits microsomal drug metabolism in the rat. Eur. J. Pharmacol., 55 (1979) 335–336.

Puurunen, J., Sotaniemi, E. and Pelkonen, O., Effect of cimetidine on microsomal drug metabolism in man. Eur. J. Clin. Pharmacol., 18 (1980) 185–187.

Pond, S.M., Galinsky, R.E., Tong, T.G., Roberts, S.M., Kaysen, G.A., Menke, D.J. and Levy, G., Massive intoxication with acetaminophen and propoxyphene: unexpected survival and unusual pharmacokinetics of acetaminophen. Clin. Toxicol., in press.

Rendić, S., Sunjić, V., Toso, R. and Kajfez, F., Interaction of cimetidine with liver microsomes. Xenobiotica, 9 (1979) 555–564.

Rudd, D.G., Donn, K.H. and Grisham, J.W., Prevention of acetaminophen-induced hepatic necrosis by cimetidine in mice. Res. Commun. Chem. Path. Pharmacol., 32 (1981) 369–372.

Serlin, M.J., Challiner, M., Park, B.K., Turcan, P.A. and Breckenridge, A.M., Cimetidine potentiates the anticoagulant effect of warfarin by inhibition of drug metabolism. Biochem. Pharmacol., 29 (1980) 1971–1972.

Taylor, D.C., Cresswell, P.R. and Bartlett, D.C., The metabolism and elimination of cimetidine, a histamine H_2-receptor antagonist, in the rat, dog and man. Drug Metab. Disposition, 6 (1978) 21–30.

Telerman-Toppet, N., Duret, M.E. and Coërs, C., Cimetidine interaction with carbamazepine. Ann. Int. Med., 94 (1981) 544.

Zimmerman, H.J., Effects of aspirin and acetaminophen on the liver. Arch. Int. Med., 141 (1981) 333–342.