Table III—Effect of Pretreatment with 5-Hydroxytryptaminergic Receptor Blocking Agents on the Body Temperature Response to Cobaltous Chloride in Mice

Pretreatment[a]	Treatment[b]			
	Water		Cobaltous Chloride	
	Initial Temperature °[c]	Temperature Change °[d] (Mean ± SE)	Initial Temperature °[c]	Temperature Change °[d] (Mean ± SE)
Water	36.83	+0.13 ± 0.09	36.96	−4.73 ± 0.33[e]
Methergoline[f]	36.83	+0.25 ± 0.14	37.02	−6.12 ± 0.47[g]
Cyproheptadine	37.28	+0.03 ± 0.23	37.22	−5.97 ± 0.48[g]
Xylamadine	36.85	+0.22 ± 0.13	36.74	−5.56 ± 0.34[g]

[a] Water (0.01 ml/g), methergoline (1 mg/kg), cyproheptadine hydrochloride (1 mg/kg), and xylamidine tosylate (1 mg/kg) were administered intraperitoneally to groups of 10 animals. [b] Intraperitoneal water (0.01 ml/g) and cobaltous chloride (25 mg/kg) treatments were given 4 hr following pretreatment injection. [c] Initial temperatures were recorded immediately prior to water or cobalt treatment. [d] Temperature changes represent the difference between body temperature recorded initially and that obtained 30 min after treatment. [e] Compared with water–water (Pretreatment–Treatment), $p < 0.05$. [f] Methergoline was solubilized in distilled water acidified to pH 3.8 with ascorbic acid. [g] Compared with water–cobalt (Pretreatment–Treatment), $p < 0.05$.

chloroamphetamine and *p*-iodoamphetamine. In addition, the finding that uptake inhibitors (fluoxetine and nisoxetine) failed to modify halogenated amphetamine reversal of cobalt hypothermia further supports an extraserotonergic role of these amines in their ability to antagonize body temperature depression by cobaltous chloride.

The results presented in this report do not support the suggestion that cobaltous chloride hypothermia is mediated through the release of serotonin from intraneuronal storage sites. For example, the serotonin receptor-blocking agents, cyproheptadine, methergoline, and xylamidine, were incapable of attenuating the body temperature response. While it seems inviting to postulate an influence of cobalt on the neuronal storage of dopamine and/or norepinephrine, previous studies utilizing 6-hydroxydopamine failed to reveal catecholaminergic involvement (2). It is likely that cobalt produces hypothermia through a mechanism or mechanisms which are at present undefined.

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Effect of Cimetidine on the Pharmacokinetics of Quinidine and Lidocaine in the Rat

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Received March 23, 1982, from the *Department of Pharmacology, Hahnemann Medical College and Hospital, Philadelphia, PA 19102.* Accepted for publication July 9, 1982.

Abstract □ Because of previously reported drug interactions involving cimetidine and liver-metabolized drugs, the intravenous pharmacokinetics of quinidine (25 mg/kg) and lidocaine (15 mg/kg) were investigated in anesthetized rats pretreated with a single intraperitoneal dose of cimetidine (60 mg/kg) and compared with saline pretreated controls. Significant reductions of 35 and 23% in the respective total clearances of quinidine and lidocaine were observed in the presence of cimetidine. The quinidine volume of distribution was significantly decreased in the cimetidine-treated rats, while the lidocaine volume of distribution was not altered significantly. There was no significant change in the elimination half-life for either drug in the presence of cimetidine. These results suggest cautious use of quinidine or lidocaine when cimetidine is prescribed concurrently.

Keyphrases □ Cimetidine—inhibition of lidocaine and quinidine clearances in the rat, kinetics □ Lidocaine—inhibition of clearance in the rat by cimetidine, kinetics □ Quinidine—inhibition of clearance in the rat by cimetidine, kinetics □ Kinetics—of the inhibition of lidocaine and quinidine clearances in the rat by cimetidine

Cimetidine, a histamine H_2-receptor antagonist, is prescribed widely for the therapy of peptic ulcers. Human pharmacokinetic studies have demonstrated that cimetidine in therapeutic doses impairs the elimination of drugs metabolized by cytochrome P-450-dependent pathways, such as antipyrine (1), theophylline (1), diazepam (2),

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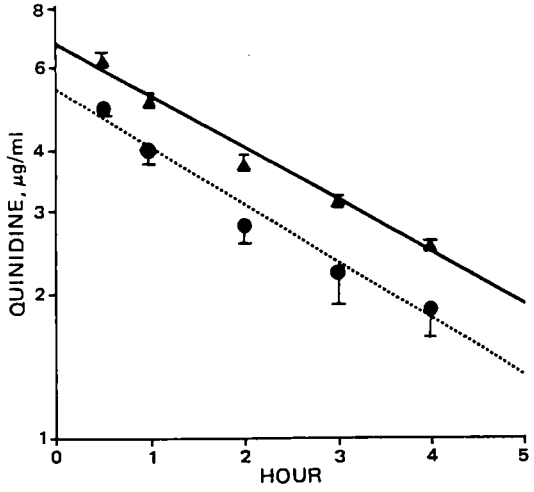

Figure 1—*Plasma disappearance curves of quinidine in rats pretreated with cimetidine (▲) or saline (●) intraperitoneally 30 min prior to the quinidine injection. Values are mean ± SE with n = 4–5 at each point.*

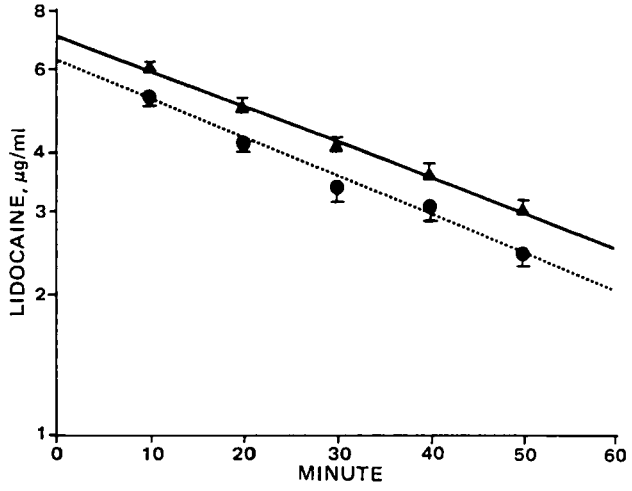

Figure 2—*Plasma disappearance curves of lidocaine in rats pretreated with cimetidine (▲) or saline (●) intraperitoneally 30 min prior to the lidocaine injection. Values are mean ± SE with n = 5–6 at each point.*

chlordiazepoxide (3), propranolol (4), warfarin (5), and phenytoin (6). The clearances of drugs such as lorazepam and oxazepam, which are eliminated by glucuronidation, are unaffected by cimetidine (7). Studies using *in vitro* rat liver homogenates have revealed that cimetidine inhibits aminopyrine *N*-demethylation and benzo[*a*]pyrene hydroxylation in a concentration-dependent manner (8). Similar results were found in homogenates obtained from human liver biopsies (9). Quinidine and lidocaine are two popular antiarrhythmic agents dependent on cytochrome P- 450 liver metabolism for inactivation (10). This present study investigates the effect of cimetidine on the pharmacokinetics of these drugs in the rat.

EXPERIMENTAL

Male Sprague–Dawley rats[1], weighing 220–250 g on the day of the study, were used. They were housed in groups of four in plastic cages over corn cob bedding in a well-ventilated room (24° ± 0.5°) with alternate 12-hr periods of light and dark. Food[2] and water were provided *ad libitum*.

After being acclimated to their cages for at least 5 days, the rats were anesthetized with 1.7 g/kg of urethane, an anesthetic that does not inhibit drug metabolism (11) and which has been reported to maintain hepatic blood flow at a level equal to that of an awake animal (12). The right and left jugular veins were surgically exposed by superficial skin incisions above both clavicles, and either 60 mg/kg of cimetidine or 1 ml/kg of saline was injected intraperitoneally. Thirty minutes after the injections, both groups of rats received either 15 mg/kg (free base) of lidocaine or 25 mg/kg (free base) of quinidine intravenously through the right jugular vein. Blood samples (0.4 ml) were taken at 10, 20, 30, 40, and 50 min postinjection (lidocaine) or at 0.5, 1, 2, 3, and 4 hr postinjection (quinidine). Samples were obtained by needle puncture of the left jugular vein using heparinized tuberculin syringes. Plasma lidocaine and quinidine concentrations were measured by commercially available enzyme immunoassay kits[3], as described previously (13).

The plasma disappearance of both drugs was treated as a one-compartment model and considered to follow the exponential function $C(t) = Ae^{-\lambda t}$ where $C(t)$ is the plasma concentration at time t, A is the time zero intercept, and λ is the elimination rate constant. The elimination half-life was calculated by $t_{1/2} = 0.693/\lambda$, the volume of distribution by V_D = dose/A, and the clearance by $CL = V_D\lambda$. The parameters were calculated for each animal by least-squares analysis of a semilogarithmic plot of drug concentrations *versus* time. Statistical calculations were performed using the two-tailed Student's t test.

[1] Charles River Breeding Laboratories, Wilmington, Mass.
[2] Rodent Chow, Ralston Purina Inc., St. Louis, Mo.
[3] EMIT System, Syva Co., Palo Alto, Calif.

RESULTS AND DISCUSSION

Figures 1 and 2 illustrate the respective average plasma disappearance curves for quinidine and lidocaine in cimetidine- and saline-pretreated rats; Table I shows the derived pharmacokinetic parameters. The administration of cimetidine caused a 35% reduction in quinidine clearance compared with saline-treated rats (significant at the $p < 0.05$ level). Likewise, cimetidine produced a significant (23%) reduction in lidocaine clearance ($p < 0.05$). There was a significant decrease in the quinidine volume of distribution in the cimetidine-treated rats ($p < 0.05$); however, the lidocaine volume of distribution was not significantly altered. There was no significant change in elimination half-life for either drug.

These results demonstrate that cimetidine, in a single dose, will prolong the clearance of either quinidine or lidocaine in the rat. They are similar to the findings of Desmond *et al.* (14), in which a single dose of cimetidine significantly prolonged the half-life of aminopyrine in the rat. All of the human pharmacokinetic studies reported to date were done after multiple doses of cimetidine; however, Patwardhan *et al.* (15) reported a decreased clearance of chlordiazepoxide as early as 24 hr after treatment with cimetidine, with recovery to baseline clearance 48 hr after discontinuing the cimetidine. Thus, it appears that a certain level of cimetidine is needed in the organism to manifest the inhibitory affect on drug metabolism. The exact mechanism by which cimetidine exerts its effect at the enzyme level is not entirely certain. Both competitive and noncompetitive inhibition of *in vitro* drug-metabolizing enzymes has been shown for various substrates (16).

There has been speculation that H_2-receptor blockade may play a role in the observed depression of drug clearances. However, a recent report demonstrated that the new H_2-receptor antagonist ranitidine did not inhibit drug metabolism (16). This fact supports the concept that the imidazole structure of cimetidine is responsible for its inhibitory effects, since similar structures are known to depress drug metabolism (17); ranitidine has a furan ring structure.

Table I—Effect of Cimetidine on the Pharmacokinetics of Quinidine and Lidocaine

Parameter	Quinidine[b] Treated: Saline Pretreatment (5)	Quinidine[b] Treated: Cimetidine Pretreatment (4)
$t_{1/2}$, hr	2.53 ± .25	3.09 ± .26
V_D, liter/kg	4.68 ± .21	3.82 ± .19[c]
CL liter/hr/kg	1.33 ± .13	0.86 ± .04[c]
	Lidocaine[b] Treated	
	Saline Pretreatment (5)	Cimetidine Pretreatment (6)
$t_{1/2}$, min	36.9 ± 1.2	42.4 ± 2.8
V_D liter/kg	2.45 ± .13	2.17 ± .07
CL ml/min/kg	46.5 ± 3.8	36.0 ± 2.1[c]

[a] Animals were pretreated with cimetidine 60 mg/kg ip or saline and received the test drug 30 min later. Results are means ± *SEM* with the number of animals in parentheses. [b] Dosage levels were 25 and 15 mg/kg iv, respectively, for quinidine and lidocaine. [c] $p < 0.05$ *versus* saline-treated animals, two-tailed Student's t test.

Quinidine and lidocaine are drugs that have intermediate-to-high hepatic extraction ratios and metabolites formed by the hepatic mixed-function oxidase system (10). Therefore, their clearances should be dependent both on liver blood flow and drug-metabolizing enzyme activity (18). The most likely explanation for the decreased clearances observed in this study is inhibited drug metabolism; however, decreased liver blood flow may play a role since a single dose of cimetidine has been shown to reduce hepatic blood flow 25% in humans (4). Since quinidine and lidocaine are drugs with narrow therapeutic ranges, decreases in their clearances could potentially lead to drug accumulation with resultant toxicity. Evaluated blood levels of quinidine have been associated with cinchonism, arrhythmias, and syncope, while increased lidocaine levels have been linked to confusion, seizures, and respiratory arrest (10). Therefore, frequent measurement of quinidine and lidocaine serum levels are recommended when cimetidine is prescribed concurrently, pending human pharmacokinetic studies on these interactions.

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Acetaminophen–Aluminum Hydroxide Interaction in Rabbits

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Abstract □ Acetaminophen–aluminum hydroxide interaction was investigated in a crossover study using six rabbits. Blood samples were collected at various time intervals for up to 6 hr following the oral administration of acetaminophen alone or in combination with aluminum hydroxide. Aluminum hydroxide at a 40-mg/kg dose did not appear to affect the rate and extent of acetaminophen absorption. The influence of aluminum hydroxide on gastric emptying could be compromised by gastric absorption of acetaminophen, resulting in a negligible effect on the overall bioavailability of acetaminophen.

Keyphrases □ Acetaminophen and aluminum hydroxide interaction—crossover study in rabbits, pharmacokinetics □ Aluminum hydroxide—effect on rate and extent of acetaminophen absorption in rabbits □ Pharmacokinetics—rate and extent of acetaminophen absorption in rabbits with and without aluminum hydroxide administration

Retarded drug absorption in the presence of aluminum hydroxide has been demonstrated in animals and humans (1). This pharmacokinetic interaction probably results from a slowed gastric emptying (1). *In vitro*, aluminum ion inhibits the contractile response of human and rat gastric strips to acetylcholine (2). This effect is possibly due to the antagonization by aluminum of calcium influx into smooth muscle cells during depolarization, leading to a delay in muscle contractions (3).

Acetaminophen (weak acid, pK_a 9.5) is a common, nonprescription, analgesic drug. It is not clear whether acetaminophen is completely free of damaging effects on the gastric mucosa, although minimal or no gastric structural damage has been found to be induced by acetaminophen in marked contrast to aspirin (4). Since acetaminophen is believed to cause less damaging effects, it has replaced aspirin as the analgesic of choice in many situations. However, acetaminophen is frequently used in combination with aspirin in nonprescription drugs (5), necessitating the use of antacids to avoid the gastric damage induced by aspirin, or perhaps acetaminophen.

Table I—Mean Plasma Acetaminophen Concentrations Following Oral Administrations of Acetaminophen Alone (100 mg/kg) and in Combination with Aluminum Hydroxide (40 mg/kg) to Rabbits

Time, hr	Acetaminophen		Acetaminophen Plus Aluminum Hydroxide	
	Mean[a]	*SEM*	Mean[a]	*SEM*
0.25	35.77	2.38	31.37	3.15
0.50	27.39	1.65	27.17	1.18
0.75	23.53	2.05	22.89	1.79
1.0	18.77	1.51	16.95	1.86
1.5	11.54	1.16	11.06	1.40
2.0	7.84	0.62	7.65	0.96
3.0	4.74	0.60	4.65	0.62
4.0	2.82	0.47	2.57	0.36
5.0	1.77	0.28	1.81	0.26
6.0	1.29	0.24	1.41	0.21

[a] Mean data of six rabbits.

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