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Famotidine lessens carbon tetrachloride-induced liver damage in rats: a possible implication in lessening volatile anesthetics-induced liver damage

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Introduction

Halothane is metabolized by the P450 mixed-function oxidase system (P450), and its metabolites have been thought to be responsible for fulminant hepatitis [1] or mild liver damage [2]. Cimetidine has been reported to interact with P450 to suppress the biotransformation of halothane, resulting in a reduction of halothane hepatotoxicity in experimental animals [3]. In contrast to cimetidine, famotidine is known to have almost no interaction with P450 [4].

Carbon tetrachloride (CCl_4) is also metabolized by P450, and some reactive intermediates, such as a trichloromethyl free radical, initiate lipid peroxidation [5]. Lipid peroxidation disrupts the biomembrane, and 4-hydroxyalkenals originating from the peroxidation of liver microsomal lipids inhibit calcium sequestration by microsomes [5]. A complex cascade of events links carbon tetrachloride metabolism, free-radical formation, lipid peroxidation, 4-hydroxyalkenal generation, calcium disorder, and cell death. Cimetidine has also been reported to lessen CCl_4-induced liver damage [6]. In this study, the effects of famotidine on CCl_4-induced liver damage were compared with those of cimetidine and ranitidine.

Materials and methods

All animal experiments were conducted in accordance with the Kyushu University guidelines for the care and use of laboratory animals. Seven-week-old male Wistar rats weighing about 200 g were used. Food deprivation was started 24 h before CCl_4 injection and continued until blood samples were taken. Water was offered ad libitum. A 1 ml·kg^{-1} dose of CCl_4 dissolved in olive oil (50% solution) was injected intraperitoneally. Control rats were given only olive oil (0.5 ml·kg^{-1}). Cimetidine (100 mg·kg^{-1}), ranitidine (25 mg·kg^{-1}), or famotidine (10 mg·kg^{-1}) was administered intraperitoneally 30 min before, and 8 h and 16 h after the CCl_4 injection. The dosages of H_2-receptor antagonists used were about ten times higher than the intravenous dosages reported to raise the pH of gastric juice in rats [7]. Blood samples from the right atrium were taken under anesthesia with diethyl ether 24 h after the CCl_4 injection. The CCl_4, analytical grade, was purchased from Nakarai Chemical (Kyoto, Japan).

Serum alanine aminotransferase (ALT) activity was measured with an Ektachem DT60 Analyzer (Eastman Kodak, Rochester, NY, USA) [6]. Serum ketone body concentrations were determined spectrophotometrically using the Ketone Test Sanwa (Sanwa Chemical Lab, Nagoya, Japan) [6]. Malondialdehyde formation was quantitated colorimetrically by means of the thiobarbituric reaction according to the method of Yagi [8].

All results are expressed as mean ± SD. Statistical analysis of the data obtained in each group was performed using the Student *t*-test. $P < 0.05$ was considered to be statistically significant.

Results

The administration of CCl_4 in starved rats caused a large increase in serum ALT activity (Table 1). Famotidine, as well as cimetidine and ranitidine, significantly lessened the CCl_4-induced increase in serum ALT activity. CCl_4 administration also induced a suppression of star-

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Table 1. Effects of pre-administration of H_2-receptor antagonists cimetidine, ranitidine, or famotidine on serum alanine aminotransferase (ALT) activity, serum total ketone body concentration, and serum lipid peroxide concentration in rats injected with or without CCl_4

		CCl_4			
	Oil alone ($n = 20$)	— ($n = 22$)	Cimetidine ($n = 10$)	Ranitidine ($n = 10$)	Famotidine ($n = 14$)
ALT activity ($IU \cdot L^{-1}$)	50 ± 10	3830 ± 3070#	750 ± 770*	1620 ± 1890*	1480 ± 1500*
Ketone body concentration (mM)	2.2 ± 0.9	0.8 ± 0.2#	1.1 ± 0.3*	1.1 ± 0.5*	1.1 ± 0.4*
Lipid peroxide concentration (μM)	4.3 ± 0.8	5.2 ± 2.1#	3.6 ± 0.5*	4.7 ± 0.6	4.5 ± 0.7

#$P < 0.05$ *vs* oil alone; *$P < 0.05$ *vs* CCl_4 without H_2-receptor antagonist.

vation ketosis and an increase in the serum concentration of lipid peroxide. All of the H_2-receptor antagonists tested partially reversed the CCl_4-induced decrease in serum concentrations of total ketone bodies. While cimetidine efficiently inhibited the CCl_4-induced increase in serum concentration of lipid peroxide, ranitidine and famotidine did not inhibit the change significantly.

Discussion

H_2-receptor antagonists have been widely used to prevent aspiration pneumonitis in perioperative and critically ill patients. Because cimetidine has been reported to affect the metabolism of drugs other than anesthetics (e.g., lidocaine, midazolam, propranolol, theophylline), to reduce hepatic blood flow, to produce central nervous system dysfunction, and to induce cardiovascular changes, the use of ranitidine and famotidine has been preferred. Famotidine is the most potent H_2-receptor antagonist available, and has been reported to have almost no interaction with P450, probably owing to the introduction of a thiazol ring instead of an imidazole ring [4]. Ranitidine, having a furan ring, is thought to have an intermediate place in terms of interaction with P450 [4].

The present findings indicated that famotidine had a cytoprotective effect on CCl_4-induced liver damage, as revealed by a reduction in ALT leakage, and ameliorated a functional disturbance, as revealed by the restoration of starvation ketosis. Because famotidine did not efficiently inhibit CCl_4-induced lipid peroxidation, and has been reported to have almost no interaction with P450 [4], it seems possible that famotidine lessened CCl_4-induced liver damage through a mechanism or mechanisms other than an interaction with P450. Ranitidine also lessened CCl_4-induced liver damage in a manner similar to that of famotidine rather than cimetidine.

The mechanism(s) for the observed amelioration of these H_2-receptor antagonists in CCl_4-induced liver damage are not clear. They may act via a H_2-receptor-mediated mechanism. The possible involvement of leukocytes in CCl_4-induced liver damage has been suggested [9], and cimetidine and ranitidine have been shown to inhibit the superoxide production of activated leukocytes [10]. Cimetidine has also been reported to interact with cuprum, and to display a superoxide dismutase-like activity [11]. It might be possible that H_2-receptor antagonists inhibit phagocyte-mediated deterioration of CCl_4-induced liver damage.

Humans are estimated to have 50–200 different P450s [12]. P450-2E1 has been identified as the primary catalyst of bioactivation of hydrocarbons, including CCl_4 and halogenated volatile anesthetics, in animals and, most likely, in humans as well [13]. The reported isozymes of P450 responsible for bioactivation of halogenated anesthetics are as follows: P450-2B4 and -2E1 for halothane; P450-2E1 and -3A for isoflurane; P450-2E1, -2A6, and -3A4 for sevoflurane [12]. Cimetidine has been shown to inhibit P450-3A, -2E, and -1A [14], which coincides with the reported amelioration of halothane hepatotoxicity by cimetidine [3]. Although famotidine has been thought to have almost no interaction with P450, at present we cannot rule out the possibility that famotidine interacts with some isozymes of P450.

Isoflurane and sevoflurane are bioactivated by P450, though not more than halothane. Although bioactivation of these two anesthetics does not produce reactive intermediates, their metabolites are considered to be responsible for liver damage [12]. Halogenated anesthetics have also been shown to cause a release of stored calcium into the intracellular fluid in isolated hepatocytes [15]. Furthermore, as discussed above, famotidine might have some protective effect against drug-induced liver damage by mechanisms independent of the interaction with P450. Therefore, the present study using CCl_4 raises the possibility that perioperative administration of famotidine plays some role in suppressing bioactivation of isoflurane and sevoflurane, and in preventing liver damage. The clinical implications of this finding should be further elucidated. It should also be noted that ranitidine has been reported

to induce liver damage by itself [16] and to inhibit liver regeneration [17].

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