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EFFECTS OF CHLORPROMAZINE AND ATROPINE ON ACETAMINOPHEN ABSORPTION IN RABBITS

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SUMMARY

The effects of chlorpromazine and atropine on the gastrointestinal absorption of acetaminophen were investigated in rabbits. Two doses of chlorpromazine and atropine were injected intraperitoneally 30 min prior to the oral administration of acetaminophen. Blood samples were collected before and 0.25, 0.5, 0.75, 1.0, 1.5, 2, 3, 4, 5 and 6 h after acetaminophen administration and were analyzed for acetaminophen contents using a HPLC method. Chlorpromazine at a 10 mg/kg dose significantly reduced the maximum plasma concentration (C_{max}) of acetaminophen from 64.2 ± 2.8 to 40.0 ± 6.3 μg/ml ($P < 0.05$). In addition, chlorpromazine at 5 and 10 mg/kg doses significantly increased the time taken to reach the maximum plasma concentration (T_{max}) of acetaminophen from 0.29 ± 0.04 to 0.67 ± 0.15 and 0.96 ± 0.21 h, respectively ($P < 0.05$). Atropine at 0.5 and 1.0 mg/kg doses also significantly reduced the C_{max} of acetaminophen from 69.6 ± 4.7 to 45.6 ± 3.7 and 45.9 ± 6.7 μg/ml, respectively ($P < 0.05$). However, atropine has little effect on T_{max} of acetaminophen. Both chlorpromazine and atropine did not seem to affect the area under the plasma concentration–time curve and the elimination half-life of acetaminophen. It was concluded that chlorpromazine and atropine affect the rate but not the extent of acetaminophen absorption, by delaying the gastric emptying.

INTRODUCTION

According to the pH-partition hypothesis, weakly acidic drugs would be absorbed more readily from the stomach than from the small intestine (Brodie, 1964). However, many investigators have demonstrated that acidic drugs such as aspirin, barbiturates and warfarin are absorbed much more slowly from the stomach than from the small intestine presumably because of the relatively large surface area of the latter (Siurala et al., 1969; Kojima et al., 1971; Kekki et al., 1971). Alteration of gastric emptying is therefore likely

to have important effects on the rate of drug absorption. For example, atropine, trihexyphenidyl and imipramine decrease the absorption of L-DOPA in man and rat by delaying the gastric emptying (Morgan et al., 1975; Algeri et al., 1976). On the other hand, metoclopramide increases the absorption of tetracycline and pivampicillin in man by accelerating the gastric emptying (Gothoni et al., 1972). Acetaminophen absorption in man has been shown to be related to the rate of gastric emptying (Heading et al., 1973). Propantheline delays gastric emptying and markedly retards the absorption of acetaminophen. Conversely, metoclopramide which stimulates gastric emptying accelerates the absorption of acetaminophen (Nimmo et al., 1973). The purpose of the present study is to elucidate whether chlorpromazine and atropine which have been shown to delay gastric emptying would decrease the rate of acetaminophen absorption in rabbits.

MATERIALS AND METHODS

Acetaminophen and atropine sulfate were obtained from Aldrich Chemicals and Mallinckrodt Chemicals respectively. Chlorpromazine hydrochloride was kindly supplied by Smith, Kline and French Labs.

Male New Zealand white rabbits weighing 2.6–3.1 kg were fasted for 36–40 h prior to the experiment, but water was allowed ad libitum. Food and water were withheld during the experiment. Chlorpormazine (5 and 10 mg/kg) and atropine (0.5 and 1.0 mg/kg) were dissolved in 5 ml saline and injected intraperitoneally 30 min prior to oral administration of acetaminophen. Acetaminophen was dissolved in 70 ml warm deionized water (30–35°C) and administered orally at a dose of 100 mg/kg. Blood samples (0.5 ml) were collected from the ear vein in heparinized vacutainers before and 0.25, 0.5, 0.75, 1.0, 1.5, 2, 3, 4, 5 and 6 h after oral administration of acetaminophen. The blood was immediately centrifuged and the plasma obtained was kept in a refrigerator until analysis.

Assays of acetaminophen were performed using a high performance liquid chromatographic method (Wang and Lee, submitted). A 0.2 ml aliquot of the rabbit plasma sample to be assayed was mixed with 250 μl of the vanillin internal standard solution (25 μg) and deionized water 550 μl to make up final volume of 1 ml. Subsequently 0.8 g of sodium chloride was added. The mixture was vortexed for 30 s and extracted with 8 ml ether for 15 min on a test tube rotator. After centrifugation of the samples for 4 min at 3600 rpm, the ether layer was transferred to another test tube and evaporated to dryness at room temperature under a stream of nitrogen. The residue was reconstituted in 2 ml of the mobile phase and 10–50 μl aliquot injected onto the column. Acetaminophen analyses were carried out under following conditions: column, uBondapak C18; mobile phase, methanol–water (35 : 65 v/v); flow rate, 2.5 ml/min; UV detector, 254 nm.

The area under plasma concentration–time curve (AUC_0^∞) was estimated according to the trapezoidal rule. The elimination half-life was calculated from the regression slope of the log-linear portion of the plasma concentration–time curve, assuming first order kinetics. Statistical analyses were performed with paired Student *t*-test. A *P*-value of 0.05 or less was considered significant.

RESULTS AND DISCUSSION

Chlorpromazine at a 10 mg/kg dose significantly reduced the maximum plasma concentration of acetaminophen from 64.2 ± 2.8 to 40.0 ± 6.3 μg/ml ($P < 0.05$, Table 1).

TABLE 1

EFFECT OF CHLORPROMAZINE ON THE MAXIMUM PLASMA CONCENTRATION (C_{max}) AND THE TIME TAKEN TO REACH THE MAXIMUM PLASMA CONCENTRATION (T_{max}) OF ACETAMINOPHEN IN RABBITS

Rabbit	C_{max} (μg/ml)			T_{max} (h)		
	Control	Chlorpromazine		Control	Chlorpromazine	
		(5 mg/kg, i.p.)	(10 mg/kg, i.p.)		(5 mg/kg, i.p.)	(10 mg/kg, i.p.)
A	77.5	89.0	48.2	0.25	1.00	1.50
B	62.7	39.3	22.9	0.50	1.00	1.50
C	62.8	26.3	22.4	0.25	1.00	1.00
D	63.5	61.1	36.9	0.25	0.50	0.50
E	61.4	32.8	47.9	0.25	0.25	0.25
F	57.4	47.4	61.4	0.25	0.25	1.00
Mean	64.2	49.3	40.0 [a]	0.29	0.67 [a]	0.96 [a]
S.E.	2.8	9.3	6.3	0.04	0.15	0.21

[a] Significantly different from control value, $P < 0.05$.

TABLE 2

EFFECT OF ATROPINE ON THE MAXIMUM PLASMA CONCENTRATION (C_{max}) AND THE TIME TAKEN TO REACH THE MAXIMUM PLASMA CONCENTRATION (T_{max}) OF ACETAMINOPHEN IN RABBITS

Rabbit	C_{max} (μg/ml)			T_{max} (h)		
	Control	Atropine		Control	Atropine	
		(0.5 mg/kg, i.p.)	(1.0 mg/kg, i.p.)		(0.5 mg/kg, i.p.)	(1.0 mg/kg, i.p.)
A	77.5	51.4	71.9	0.25	0.25	0.50
B	62.7	56.2	29.6	0.50	0.50	0.25
C	62.8	53.2	50.0	0.25	0.50	0.25
D	63.5	38.3	55.9	0.25	0.25	0.25
E	61.4	35.3	34.2	0.25	0.25	0.50
G	89.7	39.3	33.5	0.25	0.25	0.50
Mean	69.6	45.6 [a]	45.9 [a]	0.29	0.33	0.38
S.E.	4.7	3.7	6.7	0.04	0.05	0.06

[a] Significantly different from control value, $P < 0.05$.

In addition, chlorpromazine at 5 and 10 mg/kg doses significantly increased the time taken to reach the maximum plasma concentration of acetaminophen from 0.29 ± 0.04 to 0.67 ± 0.15 and 0.96 ± 0.21 h, respectively ($P < 0.05$, Table 1). Atropine at 0.5 and 1.0 mg/kg doses significantly reduced the maximum plasma concentration of acetaminophen from 69.6 ± 4.7 to 45.6 ± 3.7 and 45.9 ± 6.7 μg/ml, respectively ($P < 0.05$, Table 2). However, atropine had little effect on the time taken to reach the maximum plasma concentration of acetaminophen (Table 2). These effects were also observed in the time course curves of mean acetaminophen concentration in plasma after oral administration of acetaminophen with chlorpromazine or atropine pretreatment (Figs. 1 and 2).

Since acetaminophen is a weakly acidic drug ($pK_a = 9.5$), it is largely nonionized both in the stomach and the small intestine and should be well absorbed from both sites

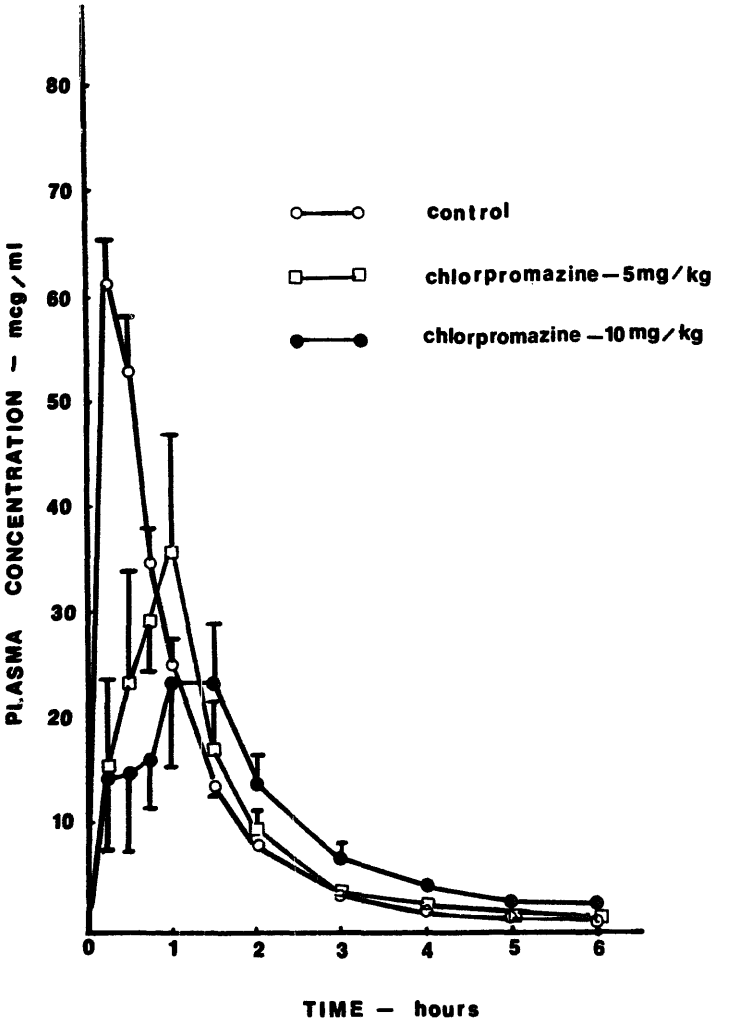

Fig. 1. Time course curves of acetaminophen plasma concentration in rabbits after oral administration of acetaminophen (100 mg/kg) alone or in combination with chlorpromazine (5 or 10 mg/kg, i.p., 30 min before acetaminophen). Each point represents the mean ± S.E. of 6 rabbits.

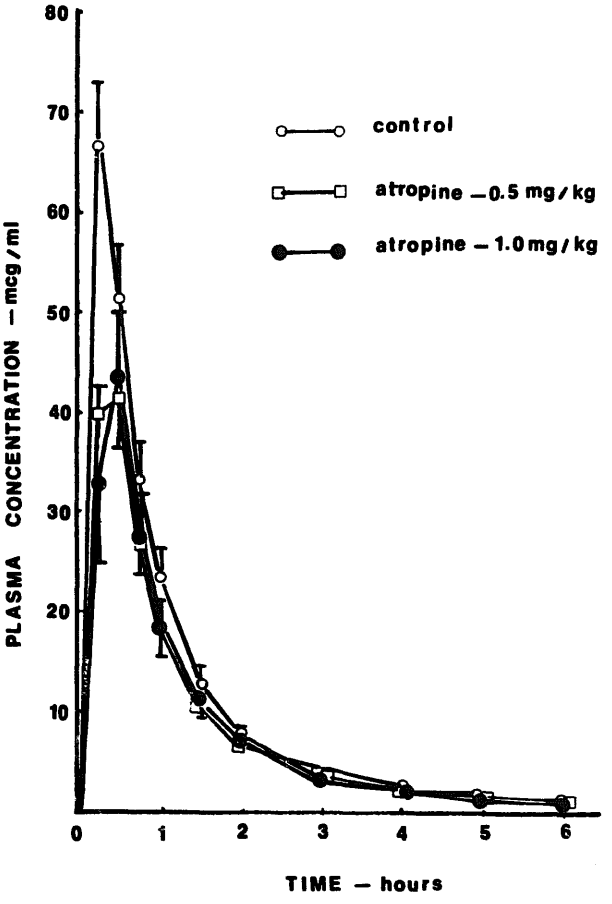

Fig. 2. Time course curves of acetaminophen plasma concentration in rabbits after oral administration of acetaminophen (100 mg/kg) alone or in combination with atropine (0.5 or 1.0 mg/kg, i.p., 30 min before acetaminophen). Each point represents the mean ± S.E. of 6 rabbits.

(Schanker et al., 1957, 1958). However, Heading et al. (1973) have demonstrated that the gastric absorption of acetaminophen is very slow and a significant correlation is observed between the rate of gastric emptying and the rate of acetaminophen absorption. Furthermore, chlorpromazine and atropine have been shown to delay the gastric emptying in rats (Consolo and Ladinsky, 1971). These literature facts and the present experimental results (Tables 1 and 2, Figs. 1 and 2) indicate that chlorpromazine and atropine decrease the rate of acetaminophen absorption by delaying the gastric emptying.

Chlorpromazine did not significantly affect the area under the plasma concentration–time curve (AUC_0^∞) and the elimination half-life of acetaminophen (Table 3). Similarly, atropine did not significantly affect the area under the plasma concentration–time curve (AUC_0^∞) of acetaminophen although the mean values were about 13% lower with 0.5 and 1.0 mg/kg doses of atropine (Table 4). Furthermore, atropine did not seem to affect the elimination half-life of acetaminophen (Table 4). These findings suggest that chlorpromazine and atropine have no effect on the acetaminophen elimination and alter only

TABLE 3

EFFECT OF CHLORPROMAZINE ON THE AREA UNDER THE PLASMA CONCENTRATION–TIME CURVE (AUC_0^∞) AND THE ELIMINATION HALF-LIFE ($t_{1/2}$) OF ACETAMINOPHEN IN RABBITS

Rabbit	AUC_0^∞ (μg · h/ml)			$t_{1/2}$ (h)		
	Control	Chlorpromazine		Control	Chlorpromazine	
		(5 mg/kg, i.p.)	(10 mg/kg, i.p.)		(5 mg/kg, i.p.)	(10 mg/kg, i.p.)
A	65.4	89.9	76.7	0.96	0.96	1.04
B	69.4	44.1	44.5	2.31	–	2.19
C	41.1	30.3	55.6	1.42	1.03	1.66
D	60.0	68.9	72.3	1.37	1.16	2.07
E	55.2	41.2	51.4	1.71	1.55	1.51
F	66.7	73.3	70.6	1.07	2.74	1.05
Mean	59.6	58.0	61.9	1.47	1.49	1.59
S.E.	4.3	9.3	5.3	0.20	0.30	0.20

the rate but not the extent of acetaminophen absorption. In addition, the fact that a similar half-life was observed for acetaminophen in the control and treatment groups justifies the omission of control intravenous administration in this study design. McGilveray and Mattok (1972) have also pointed out that concomitant intake of food which is shown to delay gastric emptying (Kojima et al., 1971) decreases the rate of acetaminophen absorption, but has little effect on the extent of acetaminophen absorption

TABLE 4

EFFECT OF ATROPINE ON THE AREA UNDER THE PLASMA CONCENTRATION–TIME CURVE (AUC_0^∞) AND THE ELIMINATION HALF-LIFE ($t_{1/2}$) OF ACETAMINOPHEN IN RABBITS

Rabbit	AUC_0^∞ (μg · h/ml)			$t_{1/2}$ (h)		
	Control	Atropine		Control	Atropine	
		(0.5 mg/kg, i.p.)	(1.0 mg/kg, i.p.)		(0.5 mg/kg, i.p.)	(1.0 mg/kg, i.p.)
A	65.4	50.1	68.3	0.96	0.97	0.99
B	69.4	46.6	36.1	2.31	2.00	2.13
C	41.1	52.7	46.4	1.42	1.26	1.21
D	60.0	63.6	66.1	1.37	1.18	1.24
E	55.2	41.0	46.5	1.71	1.51	1.96
G	46.4	39.6	30.5	2.36	2.39	2.37
Mean	56.3	48.9	49.0	1.69	1.55	1.65
S.E.	4.5	3.6	6.3	0.23	0.22	0.23

and the area under the blood concentration–time curve of acetaminophen. On the other hand, Algeri et al. (1976) have noted that trihexyphenidyl decreases not only the maximum plasma concentration but also the area under the plasma concentration–time curve of L-DOPA, probably as a consequence of an increased gastric metabolism of the drug due to a delayed gastric emptying.

Chlorpromazine is often used with improvement of psychotic states and is well known to possess anticholinergic activity. Our data showed that chlorpromazine decreased the rate of acetaminophen absorption by delaying the gastric emptying. A similar interaction was observed when atropine, a typical anticholinergic drug, was used instead of chlorpromazine. This indicates that the effect is due to the anticholinergic activity of chlorpromazine. Many drugs such as antihistamines, anti-Parkinsonism drugs and tricyclic antidepressants possess anticholinergic activity and might therefore influence drug absorption through effects on gastric emptying.

In man and rat, changes in drug absorption associated with delayed or accelerated gastric emptying have been reported for a number of drugs (Hurwitz and Sheehan, 1971; McGilveray and Mattok, 1972; Nimmo et al., 1973; Manninen et al., 1973; Lavigne and Marchand, 1973; Adjepon-Yamoah et al., 1973, 1974; Nimmo et al., 1975; Varga et al., 1975; Morgan et al., 1975; Algeri et al., 1976; Greenblatt et al., 1978). Nevertheless, there is no evidence for drug interaction involved in the gastric emptying in other laboratory animals besides rats. In this study we chose the rabbit as an animal model since it is convenient for periodical plasma sampling as opposed to many other laboratory animals. Chiou et al. (1969) and Crouthamel et al. (1975) have indicated that the rabbit did not appear to be a good animal model for drug absorption studies because of its slow gastric emptying and higher intestinal pH. However, control of the gastric emptying rate promoted the usefulness of rabbit in drug absorption studies and produced a good correlation in gastrointestinal drug absorption between rabbits and humans (Maeda et al., 1975, 1979). Although the gastric emptying rate of rabbits used in this study was not exactly controlled according to the method reported by Maeda et al. (1975), the rabbit was fasted over a period of 36–40 h and drug administration was accompanied by warm water intake. Under the controlled conditions, we were able to obtain reproducible data and clearly demonstrated the important role of gastric emptying in the rate of acetaminophen absorption.

Recently, Feldman and Putcha (1977) have reported that diphenhydramine markedly decreases the gastric emptying and intestinal transit in rats. In addition, diphenhydramine has been shown to inhibit the gastrointestinal absorption of *p*-aminosalicylate in rats and man by delaying the gastric emptying (Lavigne and Marchand, 1973). These facts suggest that dephenhydramine may decrease the rate of acetaminophen absorption by delaying the gastric emptying. Antihistamines such as diphenhydramine and chlorpheniramine are very often used in combination with acetaminophen in man. Because of this clinical implication, we are currently investigating the interactions of antihistamines and acetaminophen as they occur during gastrointestinal absorption in rabbits.

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