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Effect of domperidone on acetyl salicylic acid and acetaminophen absorption in rabbits

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Summary

Interactions between acetyl salicylic acid (ASA) and acetaminophen (AC) with domperidone were investigated by oral administration of ASA (50 mg/kg) or AC (100 mg/kg) alone or in combination with domperidone (1 mg/kg) to rabbits. Plasma samples were collected before and 5, 10, 15, 20, 25, 30 and 45 min and 1, 2, 3, 4, 6, 10, 24 and 30 h after ASA administration. Similarly, plasma samples were collected before and 0.25, 0.5, 0.75, 1.25, 2, 3, 4.5 and 6.0 h after AC administration. Assays of ASA and AC in plasma were performed using HPLC methods. Domperidone had no significant effect on the maximum plasma concentration (C_{max}), the time taken to reach C_{max} (T_{max}), the area under the curve (AUC) to infinity and the elimination half-life ($t_{1/2}$) of ASA and AC. However, domperidone significantly increased the plasma AC concentrations at 1.25 and 2.0 h in comparison with the control. Also, domperidone consistently demonstrated an increase in AUCs up to 6 h and to infinity for AC after domperidone administration in all of 5 rabbits. It was concluded that domperidone (1 mg/kg) does not significantly affect ASA and AC absorption in rabbits.

Introduction

Domperidone is a dopamine antagonist which has been shown to be effective in treating nausea and vomiting by increasing esophageal sphincter pressure and gastric emptying (Kessler et al., 1979; Weihrauch et al., 1979). It appears to be as effective as metoclopramide for antiemetic indications and for the treatment of gut motility with the absence of extrapyramidal side-effects (Debontridder, 1980; Sol et al., 1980). Recently, few anecdotal cases of cardiac arrest and arrhythmias have been reported after high intravenous doses of domperidone (Joss et al., 1982; Roussak and Carey, 1984).

Drugs associated with delayed or accelerated gastric emptying may change the rate of drug absorption in man. Propantheline delays gastric emptying and decreases acetaminophen (AC) absorption while metoclopramide accelerates gastric emptying and increases AC absorption (Nimmo et al., 1973). Volans (1974) found that concomitant metoclopramide (i.m.) and acetyl salicylic acid (ASA) therapy increases the rate of absorption of ASA in patients with migraine. Since ASA or AC may be given together with domperidone, this study was designed to investigate whether any interaction at the level of absorption occurs in rabbits.

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Materials and Methods

Materials

ASA, *p*-toluic acid and physostigmine sulfate were obtained from BDH Chemicals (Poole, U.K.) and AC was supplied by Arab Pharmaceuticals (Jordan). Domperidone was a kind gift from Janssen Pharmaceutica (Belgium). Salicylic acid (SA) and salicylamide were obtained from Hopkin and William (Essex, U.K.) and methanol, spectrographic grade from Winlab (Maidenhead, U.K.). Acetonitrile, chromatographic grade was supplied by E. Merck (Darmstadt, F.R.G.) and preformulated tetrabutyl ammonium phosphate (P.I.C. 'A', low UV) reagent was supplied by Waters Associates (Milford, MA). Polyethylene glycol 400 was obtained from Fluka AC (Buchs, F.R.G.).

Methods

Male New Zealand white rabbits weighing 2.7–3.8 kg were fasted overnight prior to the experiment, but water was allowed ad libitum. Food and water were withheld during the first 6 h of the experiment. ASA (50 mg/kg) or AC (100 mg/kg) alone or in combination with domperidone (1 mg/kg) were orally administered with 20 ml of distilled water. Each treatment was separated by at least 14 days. ASA solution was freshly prepared as described by Bakar and Niazi (1983). Domperidone (1 mg/kg) suspension and AC (25 mg/ml) solution were used. Blood samples (0.5 ml) were collected from the ear vein before and 5, 10, 15, 20, 25, 30 and 45 min and 1, 2, 3, 4, 6, 10, 24 and 30 h after oral ASA administration. Similarly, blood samples were collected before and 0.25, 0.5, 0.75, 1.25, 2.0, 3.0, 4.5 and 6.0 h after oral AC administration. ASA samples were immediately treated with 20 μl of 0.01 M physostigmine sulfate (Calvo et al., 1978), centrifuged, plasma separated and analyzed for ASA and SA on the same day. AC plasma aliquots were refrigerated until analysis.

The area under the plasma concentration–time curve (AUC) was estimated according to the trapezoidal rule. The elimination half-life ($t_{1/2}$) was calculated from the regression slope of the log-linear portion of the plasma concentration–time curve, assuming first-order kinetics.

ASA and SA analysis

ASA and SA were analyzed by a modified HPLC method reported by Waters Associates Publication (1981). ASA and SA standards were made up with rabbit plasma and treated with physostigmine sulfate as described before. To a 150 μl of plasma aliquot to be assayed, 150 μl of 10 mg/liter of *p*-toluic acid (internal standard) prepared in acetonitrile was added and vortexed. After centrifugation, 25 μl of the supernatant was injected onto the column. The column consisted of μBondapak phenyl cartridge (10 cm × 8 mm i.d., Waters Associates) with a Guard-Pak pre-column module fitted with a cyano cartridge (Waters Associates). The mobile phase consisted of 28% methanol in 0.005 M P.I.C. 'A' with pH 7.5. The flow-rate set at 4 ml/min with an operating pressure of 940 psi. The effluent was monitored at 233 nm with a full detection scale of 0.01 A or higher as needed. The retention times for ASA, *p*-toluic and SA were 3.2, 5.5 and 8.6 min, respectively. The standard curve for ASA and SA ranged from 0.5 to 10 μg/ml and 5 to 200 μg/ml, respectively. This procedure provided a low detection limit of 0.2 μg/ml and 1.0 μg/ml for ASA and SA, respectively.

AC analysis

AC analysis were performed using a modified HPLC method (Wang and Lee, 1980). In a testtube containing 0.2 ml aliquot of plasma to be assayed, is added 2 μl of 1 mg/liter salicylamide (internal standard) solution prepared in methanol and 1 g of sodium chloride. The mixture was extracted with 5 ml of ether for 5 min by vortexing. After centrifugation, the ether layer was decanted and evaporated to dryness at 40°C under a stream of nitrogen. The residue was reconstituted in 0.2 ml of the mobile phase and 25 μl aliquot was injected onto the column. The column consisted of μBondapak C_{18} cartridge (10 cm × 8 mm i.d., Waters Associates). The mobile phase consisted of 30% methanol in distilled water. The flow-rate was set at 3 ml/min with an operating pressure of 900 psi. The effluent was monitored at 247 nm with full detection scale of 0.005 or higher as needed. The retention times for AC and salicylamide were 2.2 and 4.3 min, respectively. The

standard curve for AC ranged from 0.5 to 10 μg/ml. This method provided a low detection limit of 0.1 μg/ml for AC.

Statistical analysis

The significance of difference between any two treatments was evaluated by using paired Student's *t*-test. A probability value (P) of 0.05 or less was considered significant.

Results and Discussion

The computed parameters for ASA after oral administration of ASA alone and in combination with domperidone is shown in Table 1 and the mean plasma concentrations depicted in Fig. 1. Domperidone did not significantly affect the plasma ASA concentrations. Also no significant differences were observed between AUC up to 60 min, and AUC up to infinity, maximum plasma concentration (C_{max}), time taken to reach C_{max} (T_{max}) and $t_{1/2}$ after oral administration among the two treatments. However, only 2 of the 5 rabbits demonstrated an increase in AUC up to 60 min for ASA with domperidone treatment. Reduction of T_{max} and increase in C_{max} was observed in 4 of the 5 rabbits with combined administration.

The computed parameters after oral administration of AC is presented in Table 2 and mean plasma concentrations are depicted in Fig. 2. Domperidone significantly increases the plasma concentrations at 1.25 and 2.0 h in comparison with the control ($P < 0.05$). No significant differences were observed between AUC up to 6 h,

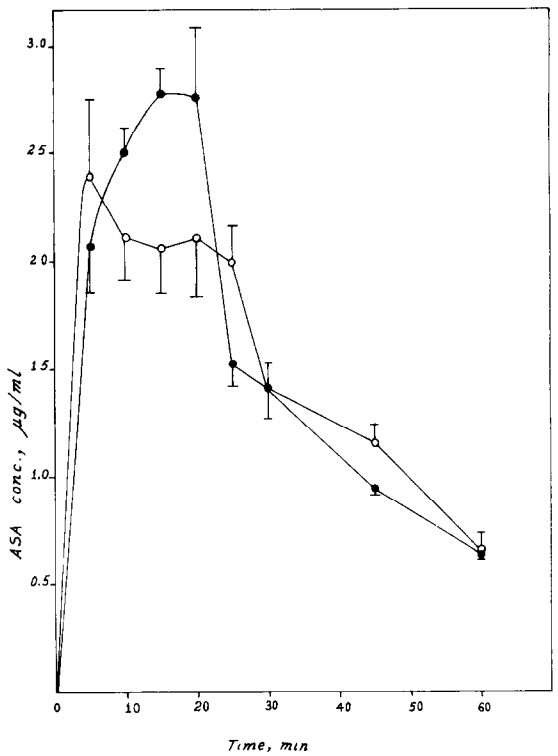

Fig. 1. Plasma ASA concentration–time curves for 50 mg/kg oral dose of ASA alone (●) and in combination with domperidone (○). Each point represents the mean ± S.E. for 5 rabbits in each group.

T_{max}, AUC up to infinity and $t_{1/2}$ of AC between two treatments. However, increase in AUC up to 6 h and AUC up to infinity was observed in all of the 5 rabbits with domperidone treatment compared to the control. Also 4 of the rabbits showed an increase in C_{max} of AC with domperidone treatment.

TABLE 1

MEAN COMPUTED PARAMETERS AFTER ORAL ADMINISTRATION OF ASA ALONE OR IN COMBINATION WITH DOMPERIDONE IN RABBITS

Parameter	Mean ± S.E.		Statistics (paired *t*-test)
	Control	Domperidone	
AUC up to 60 min (μg · min/ml)	90.3 ± 4.5	87.2 ± 7.6	NS
Time of maximum concentration (min)	13.0 ± 1.1	16.1 ± 1.6	NS
Maximum concentration (μg/ml)	3.7 ± 0.2	3.2 ± 0.3	NS
AUC up to infinity (μg · min/ml)	108.6 ± 6.2	108.0 ± 10.7	NS
Terminal log-linear half-life (min)	33.6 ± 1.0	29.2 ± 1.8	NS

TABLE 2

MEAN COMPUTED PARAMETERS AFTER ORAL ADMINISTRATION OF AC ALONE OR IN COMBINATION WITH DOMPERIDONE IN RABBITS

Parameter	Mean ± S.E.		Statistics (paired *t*-test)
	Control	Domperidone	
AUC up to 6 h (μg · h/ml)	33.9 ± 2.1	53.4 ± 5.3	NS
Time of maximum concentration (h)	0.6 ± 0.1	0.8 ± 0.1	NS
Maximum concentration (μg/ml)	19.6 ± 1.3	34.1 ± 3.4	NS
AUC up to infinity (μg · h/ml)	37.2 ± 2.2	54.9 ± 5.5	NS
Terminal log-linear half-life (h)	1.8 ± 0.2	1.3 ± 0.1	NS

Table 3 lists the mean plasma SA concentrations and its computed parameters after oral administration of ASA alone and in combination with domperidone. Domperidone significantly reduced the plasma SA concentration at 15 and 20 min from 84.8 ± 3.9 to 53.6 ± 2.9 and from 95.4 ± 1.8 to 71.6 ± 2.9 μg/ml, respectively ($P < 0.05$). No significant differences were found in AUC up to 2 h, C_{max}, T_{max} and AUC up to infinity for SA among treatments.

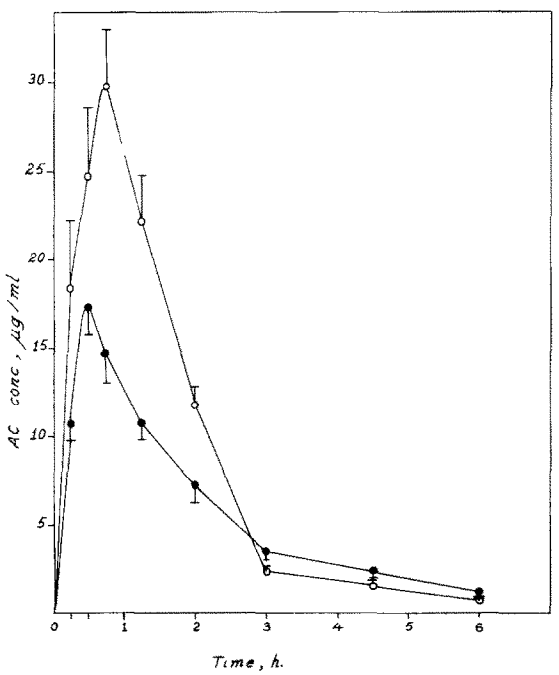

Fig. 2. Plasma AC concentration-time curves for 100 mg/kg oral dose of AC alone (●) and in combination with domperidone (○). Each point represents the mean ± S.E. for 5 rabbits in each group.

These results indicate that bioavailability of ASA and AC does not change the domperidone (1 mg/kg) concurrent oral administration in rabbits.

TABLE 3

MEAN PLASMA SA DATA AND COMPUTED PARAMETERS AFTER ORAL ADMINISTRATION OF ASA ALONE OR IN COMBINATION WITH DOMPERIDONE IN RABBITS

Parameter time	Mean ± S.E. μg/ml	
	Control	Domperidone
5 min	23.8 ± 3.9	15.4 ± 0.8
10 min	57.4 ± 5.3	32.8 ± 1.9
15 min	84.8 ± 3.9	53.6 ± 2.9 [a]
20 min	95.4 ± 1.8	71.6 ± 2.9 [a]
25 min	106.8 ± 2.8	86.0 ± 2.6
30 min	105.3 ± 3.0	91.9 ± 2.4
45 min	124.3 ± 4.1	109.3 ± 2.6
1 h	136.8 ± 4.4	129.5 ± 3.3
1.5 h	149.4 ± 3.1	136.0 ± 3.6
2.0 h	148.2 ± 4.0	144.7 ± 1.7
3.0 h	126.0 ± 6.1	137.7 ± 1.9
4.0 h	109.9 ± 8.1	132.8 ± 4.6
6.0 h	83.2 ± 9.5	98.1 ± 3.3
10.0 h	41.9 ± 5.4	53.8 ± 8.2
24.0 h	8.7 ± 2.6	8.7 ± 2.8
30.0 h	2.2 ± 0.6	1.0 ± 0.5
AUC up to 2 h (μg · h/ml)	242.3 ± 5.4	216.6 ± 4.7
Time of maximum concentration (h)	1.7 ± 0.1	2.7 ± 0.2
Maximum concentration (μg/ml)	151.9 ± 3.3	151.7 ± 2.4
AUC up to infinity (μg · h/ml)	1327.4 ± 128.4	1493.0 ± 106.0
Terminal log-linear half-life (h)	5.2 ± 0.5	4.3 ± 0.2

[a] Indicates significantly different from control, $P < 0.05$ (paired *t*-test).

No significant differences in $t_{1/2}$'s for ASA and AC were observed (Tables 1 and 2) which indicates that domperidone does not effect the $t_{1/2}$ of either drug under consideration. In addition, $t_{1/2}$ of AC is similar to that reported earlier (Imamura et al., 1981).

The pharmacological action of domperidone appears to be similar to that of metoclopramide with regard to the increased gastric motility (De Loore, 1979; Moriga, 1981; O'Shea, 1980). In rabbits, oral domperidone did not affect the rate and the extent of absorption of ASA. Volans (1975a) has shown that concomitant metoclopramide (i.m.) and ASA therapy increases the rate of absorption of ASA in patients with migraine. This is most likely related to impairment of salicylate absorption during migraine attacks secondary to impaired GI motility and delayed gastric emptying (Volans, 1974, 1975a and b).

Heading et al. (1973) have demonstrated a highly significant correlation between the rate of gastric emptying and rate of AC absorption. Nimmo et al. (1973) have reported that metoclopramide, which accelerates gastric emptying, markedly increases the rate of AC absorption in man. Our results indicate an increase in C_{max} after domperidone treatment, although not significant, which is similar to those reported by Nimmo et al. (1973). Crome et al. (1981) found no difference in the AUC of AC in normal volunteers after simultaneous oral administration of metoclopramide and AC which is similar to our results using rabbits. AUC up to 6 h and to infinity for AC tend to increase after domperidone treatment but failed to reach statistical significance. An increase in dosage of domperidone may cause the AUCs of AC to become significantly different.

In summary, this study demonstrates that domperidone, 1 mg/kg, does not significantly affect C_{max}, T_{max}, AUC and $t_{1/2}$ of ASA and AC in rabbits.

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