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The protective effect of deglycyrrhinized liquorice against aspirin and aspirin plus bile acid-induced gastric mucosal damage, and its influence on aspirin absorption in rats

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Little has been published concerning the mechanism of action of deglycyrrhinized liquorice, although in rats it has been shown to reduce acute aspirin-induced gastric mucosal damage when given with aspirin (Rees et al 1979; Bennett et al 1980) and injury due to pyloric ligation (Andersson et al 1971, Aarsen 1973).

A preparation (Caved S), combining deglycyrrhinized liquorice with antacids is of proven value in the healing of gastric ulceration and of equivalent efficacy in this respect to cimetidine and carbenoxalone (Morgan et al 1978, 1982).

In this study we have determined the effect of pre-treatment of the gastric mucosa with deglycyrrhinized liquorice on aspirin-induced damage, the effect of deglycyrrhinized liquorice on the bile acid potentiation of aspirin-induced injury and the effect of deglycyrrhinized liquorice on aspirin absorption in rats.

Materials and methods

Fasting male Sprague-Dawley rats were used as described by Carmichael et al 1976, 1977; Morgan et al 1980.

Deglycyrrhinized liquorice and aspirin-induced damage. Preliminary experiments determined that the dose of aspirin which produced haemorrhagic lesions in approximately 90% of the animals was 128 mg kg^{-1}. The dose of deglyrrhinized liquorice used was 2000 mg kg^{-1}, similar to that used by Rees et al (1979). Test solutions or suspensions were administered by intubation of the stomach through the mouth, using a syringe and olive-tipped needle. The design of study is shown in Table 1 and the volumes administered at time 0 and 30 min were 3·3 and 13·3 ml kg^{-1} respectively. Deglycyrrhinized liquorice suspended in water was given at time 0 in group 2 and contained in the aspirin suspension at 30 min in group 4. Aspirin consisted of acetylsalicylic acid (53·3 mmol $litre^{-1}$, Evans Medical Co, Liverpool U.K.), dextrose (28 mmol $litre^{-1}$) and sodium chloride (16·5 mmol $litre^{-1}$) in 0·5% carboxymethylcellulose.

Four hours after the final intubation, the rats were killed with ether, the stomachs removed, opened along the greater curvature and the mucosae washed under a constant stream of water. The observer, unaware of the rats grouping, examined the mucosa for haemorrhagic lesions and a scoring system was used to determine the amount of damage; lesions measuring <1, 1–2, 2–3, or > 3 mm across scored 1, 2, 3 and 4 points respectively. The median lesion score with quartiles was calculated for each group and groups were compared using the Mann-Whitney U-test (2 tail).

Deglycyrrhinized liquorice and aspirin plus bile acid-induced damage. The dose of aspirin was 64 mg kg^{-1} such as to cause haemorrhagic lesions in about 50% of the animals. The concentration of bile acid, taurodeoxycholic acid used was 5 mmol $litre^{-1}$ which is comparable with that found in post-prandial gastric aspirates of gastric ulcer patients (Rhodes et al 1969) and, alone, does not cause significant damage in rats (Semple & Russell 1975). Aspirin was administered alone to group 5, and with taurodeoxycholic acid, deglycyrrhinized liquorice or both, to groups 6, 7 and 8 respectively (Table 2). The volume of suspension administered was 13·3 ml kg^{-1}.

Deglycyrrhinized liquorice and aspirin absorption. Two groups of rats (n = 7) were used, receiving aspirin (128 mg kg^{-1}) or aspirin containing the liquorice preparation (2000 mg kg^{-1}). Immediately after intubation the animals were anaesthetized with intraperitoneal pento-

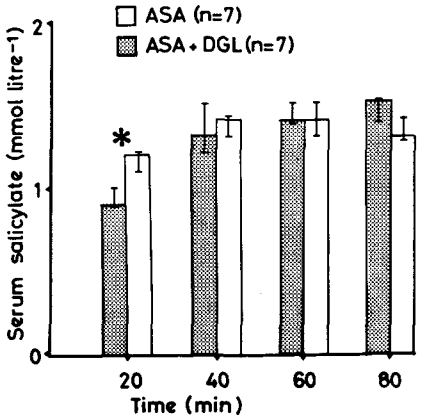

FIG. 1. The effect of deglycyrrhinized liquorice (DGL: 2000 mg kg^{-1}) on the absorption of aspirin (ASA: 128 mg kg^{-1}) expressed as median values with quartiles. * $P < 0.05$.

* Correspondence.

Table 1. The effect on aspirin-induced gastric mucosal damage of deglycyrrhinized liquorice given before or with aspirin.

	Group 1	2	3	4
	Treatment			
Time 0	H_2O	DGL	—	—
30 min	ASA	ASA	ASA	ASA DGL
n	24	24	23	24
Lower Quartile	6	10	12	1
Median Lesion Score	11	15	17	5
Upper Quartile	16	22	25	11

DGL—deglycyrrhinized liquorice (2000 mg kg^{-1}).
ASA—aspirin (128 mg kg^{-1}).
n = number of rats.

Table 2. The effect of deglycyrrhinized liquorice on aspirin- and aspirin plus bile acid-induced gastric mucosal damage.

	Group 5	6	7	8
	Treatment			
	ASA	ASA TDC	ASA DGL	ASA DGL TDC
n	22	22	21	22
Lower quartile	3	5	0	0
Median lesion score	6	12	1	3·5
Upper quartile	10	16	3·5	6

DGL—deglycyrrhinized liquorice (2000 mg kg^{-1}).
ASA—aspirin (64 mg kg^{-1}).
TDC—taurodeoxycholic acid (5 mmol $litre^{-1}$).
n = number of rats.

barbitone (45 mg kg^{-1}) and tail blood samples were taken at intervals of 20, 40, 60 and 80 min. Further sampling was not possible because the rats did not survive beyond 80 min. Total serum salicylates were measured using the method of Trinder (1954).

Results

Previous exposure of the gastric mucosa to deglycyrrhinized liquorice did not significantly affect the degree of aspirin-induced damage (Table 1—group vs group 2), whilst their combined administration caused a significant decrease in the number of lesions ($P < 0{\cdot}0005$; group 3 vs group 4).

The results shown in Table 2 confirm that combining taurodeoxycholic acid and aspirin causes a significant increase in the number of lesions ($P < 0{\cdot}05$: group 5 vs group 6), but not in the presence of deglycyrrhinized liquorice (NS: group 7 vs group 8) which decreased the damage caused by the combination ($P < 0{\cdot}0002$: group 6 vs group 8) and by aspirin alone ($P < 0{\cdot}0005$: group 5 vs group 7).

The aspirin absorption data in Fig. 1 shows that absorption is slightly delayed by deglycyrrhinized liquorice at 20 min when the median salicylate level for the deglycyrrhinized liquorice treated group was 0·9 compared with 1·2 mmol $litre^{-1}$ for aspirin alone ($P < 0{\cdot}05$). No differences were found at the other times.

Discussion

These studies show that deglycyrrhinized liquorice diminished acute gastric mucosal damage due to aspirin alone or in combination with taurodeoxycholic acid, prevented the potentiation of aspirin injury by bile acid, and did not greatly affect the aspirin absorption.

The failure of deglycyrrhinized liquorice to reduce injury when given before aspirin, suggests that its protective effect may be temporary, being diminished as a result of leaving the stomach or delayed because of absorption and distribution. A systemic effect for deglycyrrhinized liquorice following intraperitoneal injection (Andersson et al 1971; Aarsen 1973) implies that absorption could be a factor. Its ability to diminish aspirin plus taurodexoxycholic acid-induced damage and prevent the latter from potentiating aspirin-induced injury when given with these agents, may have value in man, in whom bile increases aspirin damage (Capron et al 1977) and may be of aetiological importance in gastric ulceration (du Plessis 1965; Rhodes et al 1969; Rhodes 1972). Morris et al's (1974) demonstration that deglycyrrhinized liquorice reduced bile acid-induced hydrogen ion back diffusion across canine gastric mucosa is consistent with our findings.

The results suggest that combining aspirin with deglycyrrhinized liquorice might lessen gastric mucosal injury, that this would not be compromised by biliary reflux, and that aspirin absorption would not be greatly impaired.

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A comparative study on the pharmacokinetics of valpramide after intravenous administration in dogs

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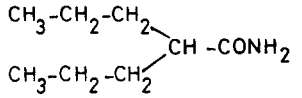
Valpramide (I), a primary amide of valproic acid, is commonly used as an antiepileptic and psychotic drug (Favel et al 1973; Musolino et al 1980; Pisani & Di Perri 1980; Pisani et al 1981, 1982b). After oral administration, valpramide is biotransformed to valproic acid before reaching the systematic circulation, leaving only traces of valpramide in the plasma of epileptics receiving it chronically (Pisani et al 1981). Biotransformation



Valpramide (I)

of valpramide to valproic acid in rats noted after oral administration of valpramide but not after intramuscular (i.m.) administration, was not inhibited in a group of rats pretreated with neomycin (Pisani et al 1982a). Food increased the bioavailability of valproic acid after oral administration of valpramide to healthy volunteers (Pisani et al 1982b). In man, the elimination half life of valpramide and valproic acid is 8–12 h (Pisani & Di Perri 1980). Valpramide has a slower absorption rate than valproic acid, resulting in fewer fluctuations in the drug plasma level during chronic valpramide treatment, which might allow for a dose reduction (Meijer & Klaff 1975; Pisani & Di Perri 1980; Pisani et al 1981). As intravenous (i.v.) administration avoids first pass effects, we have compared the pharmacokinetics of i.v. valpramide with those of valproic acid in five mongrel dogs.

Materials and methods

Four males and one female mongrel (16–21 kg) each received via a catheter into the cephalic vein a bolus injection of 200 mg of sodium valproate (Labaz, France) as a 50 mg ml^{-1} sterile aqueous solution (injected in 10 s), and 400 mg of valpramide (Labaz, France) in a 3·64 mg ml^{-1} sterile 0·9% NaCl(saline) solution. (110 ml of the valpramide solution were injected i.v. within 3 min and the data treated pharmacokinetically as an i.v. bolus). Starting 5 min after each administration, blood samples (7 ml) were taken via an indwelling catheter in the other cephalic vein into heparinized test tubes, for measurement of valpramide and valproic acid. Each blood sample was centrifuged immediately (at 2000 rev min^{-1} for 15 min), the plasma decanted and stored at −20 °C. Before assaying, the plasma was allowed to reach room temperature (22 °C), vortexed, centrifuged and the residual clot removed.

Valpramide and valproic acid were assayed by g.l.c. (Bialer et al submitted for publication). Each sample was extracted into chloroform and chromatographed on the same day and compared with an eight point calibration curve containing plasma (from each dog before either treatment administration-time = 0) spiked with known amounts of valproic acid and valpramide. Valpramide was stable in plasma at room temperature and 37 °C for 24 h. The solubility of valpramide used was 4·385 ± 0·14 mg ml^{-1} (mean ± s.d., n = 10) in purified water and 3·619 ± 0·101 mg ml^{-1} (mean ± s.d., n = 15) in saline. Each plasma sample was assayed three times.

Results and discussion

Mean plasma concentrations of valpramide and valproic acid after i.v. administration to the five dogs are presented in Fig. 1., and the pharmacokinetic parameters are summarized in Table 1. After valproic acid administration, a biphasic exponential decay of plasma concentrations was found in dogs 1, 3 and 5, so that a two-compartment open body model could be assumed (Loscher & Enswein 1978; Loscher 1978). The distribution half life ($t_{1/2\alpha}$) was about 10 min. Owing to a shorter distribution half life in dogs 2 and 4, the biphasic exponential decay of valproic acid plasma concentrations could not be easily determined. After valpramide administrations the $t_{1/2}$ was even shorter and hence a

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