subjects is open to question, but the reasons for ileostomy were different and subjects with a resection were not those showing the shortest transit times.

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J. Pharm. Pharmacol. 1981, 33: 792–793
Communicated April 2, 1981

0022–3573/81/120792–02 $02.50/0

Bioavailability of magnesium salicylate

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Intensive salicylate therapy is commonly associated with gastrointestinal disturbances and acute blood losses (Leonards & Levy 1972). Davison et al (1966) have shown that the extent of aspirin-induced gastrointestinal bleeding is higher when the drug is given as a suspension rather than as a solution buffered at pH 6·5. After esterification of the carboxylic group, aspirin retains its pharmacological activity while producing less gastric irritation (Rainsford & Whitehouse 1976). Sorenson (1977) has shown that copper complexes of aspirin and salicylates are as effective as the parent compound but they seem to cause less gastric irritation. Magnesium salicylate has been reported to produce less gastrointestinal irritation than aspirin (Rotschild 1979). Recent reports (Cohen 1978; Cassell et al 1979) suggested that choline magnesium trisalicylate can effectively deliver salicylate without the gastric irritation associated with aspirin. Mason (1980) has shown that commercially available tablets of aspirin, magnesium salicylate and choline magnesium trisalicylate are bioequivalent in man.

In view of the importance of salicylate therapy in the treatment of rheumatoid arthritis, we have investigated the pharmacokinetics of magnesium salicylate and of a commercially available aspirin tablet using a cross-over study in dogs. The tetrahydrate form of magnesium salicylate, which has been shown to be a crystalline, non-hygroscopic material (Alam & Gregoriades 1981) was used in these studies.

Materials

Two tablet formulations of magnesium salicylate were used. Tablet A (Magan, Adria Laboratories, Inc.) contained gelatin as a binder; tablet B contained pregelatinized starch as a binder. A commerial aspirin tablet (Bowman Pharmaceuticals, Inc., U.S.A.) and an aqueous solution of magnesium salicylate were also used in these studies.

In vitro dissolution. The in vitro dissolution of tablets was determined by placing one tablet in the rotating basket which was immersed in 900 ml of distilled water (United States Pharmacopeia 1980). The basket was rotated at 100 rev min^{-1}. At various time intervals, 1 ml sample was withdrawn, filtered through a 0·45 μm membrane filter, diluted to 10 ml with distilled water and an aliquot taken for u.v. absorbance at 296 nm (magnesium salicylate) and 275 nm (aspirin). The amount dissolved was determined and the cumulative percent dissolved was calculated based upon assayed values. Six individual tablets were run for each product. t50% was determined from a plot of cumulative percent dissolved vs time (Alam & Parrott 1971).

In vivo studies. Four female beagle-type mongrel dogs, each ca 10 kg were used. The study was a 4 × 4 Latin square design with a one week wash-out period between treatments. Doses of 325 mg magnesium salicylate (½ tablet) and aspirin, each providing the equivalent of approximately 26 mg salicylic acid per kg were used.

Following an overnight fast, the dogs were given 200 ml water by gavage; 30 min later, the dogs were dosed with one of the test substances. The solution of magnesium salicylate was administered with an oral feeding tube. Immediately following dosing, the dogs were administered an additional 25 ml water to wash down the medication.

Table 1. In vitro dissolution of magnesium salicylate and aspirin tablets in distilled water using USP apparatus at 100 rev min^{-1}.

Product*	Dissolution time means (with s.d.) n = 6	
	t50% (min)	k_d (min^{-1})
Tablet A	12 (2·4)	0·058 (0·012)
Tablet B	33 (8·8)	0·021 (0·003)
Aspirin tablet	3 (1·2)	0·231 (0·039)

* Tablet A, 650 mg magnesium salicylate with gelatin binder.
Tablet B, 650 mg magnesium salicylate with pregelatinized starch binder.
Aspirin (325 mg), commercial tablet.

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A 10 ml blood sample was withdrawn from the jugular vein into heparinized tubes at 0, 0·5, 1, 2, 3, 4, 6 and 12 h. The plasma was separated by centrifugation and was frozen. The total plasma salicylate concentrations were determined spectrophotofluorometrically (Harris & Riegelman 1967).

Pharmacokinetic analysis. The pharmacokinetic parameters were calculated using one compartment open model with first order elimination kinetics (Wagner 1971). The area under the plasma curve (AUC) was determined by the trapezoidal method (Notari 1971). The statistical parameters were obtained by analysis of variance.

Results and discussion

The dissolution t50% for tablet A and B were 12 and 33 min, respectively and 3 min for aspirin tablet (Table 1). The dissolution rate constant was calculated from t50% by the first-order equation: $k_d = 0{\cdot}693/t50\%$. The total plasma salicylate concentration from each of the four dogs receiving the four preparations was regressed to first-order absorption and elimination kinetics. There was no statistically significant difference ($P > 0{\cdot}5$) in total plasma salicylate between the two magnesium salicylate formulations. Also, there was no statistically significant difference ($P > 0{\cdot}05$) between the tablet formulations and the oral solution of magnesium salicylate. However, at 0·5 h, the plasma salicylate concentration from the aspirin tablet was significantly lower ($P < 0{\cdot}01$) than that from each of the three magnesium salicylate preparations. From 1 to 12 h after dosing, plasma salicylate concentrations from each of the four preparations were equivalent.

The mean pharmacokinetic parameters calculated from each dog are shown in Table 2. The C_{max} of salicylate ranged from 117 to 119 μg ml^{-1}. The t_{max} for the magnesium salicylate solution was 1 h, and for tablets A and B were 1·6 and 1·2 h, respectively. However, the t_{max} for the aspirin tablet was 2·9 h. The plasma t½ was 8 h for the magnesium salicylate solution, 7·4 h and 6·5 h for tablets A and B, respectively and 5·4 h for the aspirin tablet. There was no statistically significant difference ($P > 0{\cdot}5$) in t½ between aspirin and magnesium salicylate preparations. The apparent difference in t½ may be explained by the fact that magnesium salicylate is absorbed more rapidly (3–4 fold) which caused a saturation of enzyme capacity at the dose given. This is consistent with findings described in man (Levy et al 1972). Thus, the apparent t½ values from magnesium salicylate were slightly longer than for aspirin. The bioavailability, as measured by AUC ratios of the solution to the tablets, were 101 and 86% for tablets A and B, respectively. The bioavailability of the aspirin tablet was 89%. No statistically significant differences in overall bioavailability were observed among these preparations. The analysis of variance also indicated no significant effects due to dogs ($F = 4{\cdot}095$), weeks of treatment ($F = 3{\cdot}59$) or treatment ($F = 0{\cdot}73$).

The results indicate that the bioavailability of magnesium salicylate as either a tablet or a solution was comparable to that of aspirin. Although the dissolution rates from the two tablets of magnesium salicylate differed by some 3-fold, the overall bioavailabilities were not significantly different.

The slower rate of absorption (k_a and t_{max}) observed for the aspirin tablet is consistent with the results of previous studies showing that aspirin is absorbed more slowly than salicylates (Rowland et al 1972). The reason for the slower absorption rate of aspirin compared with salicylates is not known. However, it is unlikely to be due to differences in dissolution rates since the results presented here demonstrate that the aspirin tablets dissolved more rapidly than the magnesium salicylate tablets.

Table 2. Pharmacokinetic parameters of salicylate in dogs.

	Treatments*			
	Magnesium salicylate			Aspirin tablet
Parameters	Solution	Tablet A	Tablet B	
C_{max} (μg ml^{-1})	117.0 ± 0.2†	119.0 ± 7.9	119.0 ± 8.9	117.0 ± 14.2
t_{max} (h)	1.0 ± 0.2	1.6 ± 0.4	1.2 ± 0.2	2.9 ± 0.7
k_a (h^{-1})	4.5 ± 0.8	3.7 ± 2.1	3.4 ± 0.9	1.2 ± 0.5
k_{el} (h^{-1})	0.09 ± 0.02	0.10 ± 0.01	0.11 ± 0.01	0.14 ± 0.02
t½ (h)‡	8.0 ± 1.1	8.4 ± 1.1	6.5 ± 0.8	5.4 ± 1.8
$(AUC)_{0-12\,h}$ (μg h ml^{-1})	920 ± 48	966 ± 67	888 ± 54	932 ± 65
$(AUC)_{0-\infty}$ (μg h ml^{-1})	1451 ± 167	1469 ± 147	1249 ± 91	1290 ± 124
Bioavailability**	100	101	86	89

* Approximately 26 mg kg^{-1} salicylic acid.
† Data are mean ± s.e.m., n = 4.
‡ $t½ = \frac{0{\cdot}693}{k_{el}}$
** Bioavailability $= \frac{(AUC)_{0-\infty}\ \text{Tablet}}{(AUC)_{0-\infty}\ \text{Solution}} \times 100.$

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