J. Pharm. Pharmacol. 1979, 31: 615–618 Received January 4, 1979

The effects of some sweetening agents and osmotic pressure on the intestinal absorption of sulfafurazole in the rat

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The effects of some sugars and osmotic pressure have been examined on the absorption of sulfafurazole in the rat. Statistically significant correlations were found among the hypertonic solutions between the reciprocal of osmotic pressure and AUC0–∞ or C_{max}. In addition, negative correlation existed between plasma concentrations at 15 min and osmotic pressure. No significant correlations were noted among the hypotonic solutions. More attention should be paid to the osmotic pressure of formulations. The osmotic pressure of hypertonic solutions, especially, might affect absorption of drug from its dosage form.

Osmotic pressure is a factor given attention in parenteral or ophthalmic preparations, usually these are made isotonic with blood serum or lacrimal fluid to prevent local irritation. However, investigations into the possible role of osmotic pressure in the absorption of a drug substance from its dosage form are few. Malone et al (1960) reported that absorption of phenobarbitone in the rat is higher from hypotonic than from hypertonic solutions.

We have investigated the effect of some sugars on the intestinal absorption of a drug, by rats we also sought some correlation between the osmotic pressure of the vehicles and the pharmacokinetic data of the drug.

MATERIALS AND METHODS

Animals

Female Wistar rats, 200–325 g were fasted for 16–20 h before the use but free access to water was allowed.

Drugs, doses and analyses

Anaesthesia was with sodium pentobarbitone (Nembutal, Abbot A.S.), 50 mg kg^{-1} intraperitoneally. The sweetening agents were: (1) dextrose (D-glucose BDH Chemicals Ltd), (2) sucrose (BDH Chemicals Ltd), and (3) xylitol (Sokerikemia Ltd). As a test substance sulfafurazole (Gantrisin ampoules, F. Hoffman-La Roche & Co) was used at a dose of 80 mg kg^{-1}. The sulfafurazole dose for each rat was diluted with the vehicles used so that the total dose volume was 50 ml kg^{-1}. The free sulphonamide concentration in the blood samples was determined by the method of Bratton & Marshall (1939). Statistical evaluations were made using Student's *t*-test, the rank correlation test and the linear correlation test.

Experimental procedure

The intestinal absorption of the drug was studied by an in situ technique (Marvola et al 1978). The abdomen of the rat was opened and the duodenum beneath the pylorus and the terminal ileum cannulated. The lumen of the intestine was flushed with 0·9% NaCl solution (at 37 °C). The remaining perfusion solution was expelled with air and the drug solution immediately introduced into the intestine through the duodenal cannula. Blood samples of 0·2 ml were taken by cardiac puncture 5, 15, 30, 45, 90, 120 and 180 min after the drug administration.

Pharmacokinetic analyses

The pharmacokinetics of 80 mg kg^{-1} of sulfafurazole following intravenous administration was also studied. The constants thus obtained were used for calculating pharmacokinetic parameters after intestinal administration. The areas under the curves (AUC0–∞) were calculated by the trapezoidal method from the measured drug concentrations. The absorption rate constants were calculated by the method of Loo & Riegelman (1968).

Measurement of viscosity

The viscosities of the vehicles at 37° C were measured with a Ostwald capillary viscometer in which

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the efflux time for water was 34·8 s. The densities of the solutions at 37 °C were measured with a 10 ml glass pycnometer.

RESULTS

The pharmacokinetic data on sulfafurazole in the rat after bolus injection of the applied dose (80 mg kg^{-1}) are given in Table 1.

The time concentration curves after intestinal

Table 1. Pharmacokinetic data of sulfafurazole in the rat after intravenous injection of 80 mg kg^{-1} (N = 6). C_b = concentration of drug in the blood at time t, k_{12} = rate constant for transfer of drug from compartment no. 1 to compartment no. 2, k_{21} = rate constant for transfer of drug from compartment no. 2 to compartment no. 1, k_{el} = rate constant for elimination from compartment no. 1, AUC0 $-\infty$ = area under the blood concentrations versus time curve from 0 to ∞.

$C_b = 280\ e^{-0.229t} + 199\ e^{-0.001t}$
$k_{12} = 0{\cdot}132\ min^{-1}$
$k_{21} = 0{\cdot}096\ min^{-1}$
$k_{el} = 0{\cdot}002\ min^{-1}$
AUC $0-\infty$ = 202 mg ml^{-1} min

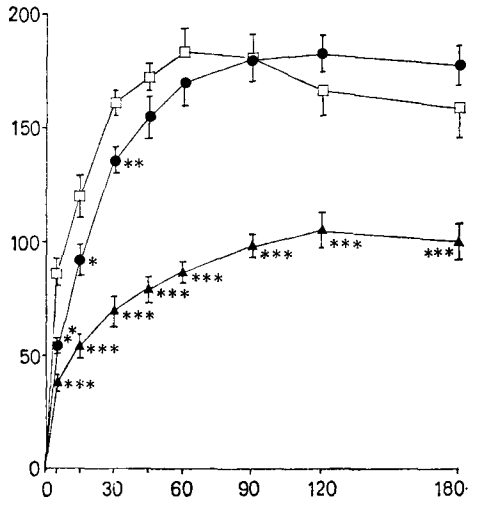

FIG. 1. The effect of different vehicles on the absorption of sulfafurazole in situ in the rat. ● = water; □ = 0·9% NaCl solution; ▲ = 1·8% NaCl solution. The vertical bars show the s.e.m. Student's *t*-test: * = $P<0{\cdot}05$; ** = $P<0{\cdot}01$; *** = $P<0{\cdot}001$. n = 6. Ordinate: blood concentrations ($\mu g\ ml^{-1}$). Abscissa: time (min).

Table 2. The pharmacokinetic data describing the effect of different vehicles on the bioavailability of sulfafurazole (80 mg kg^{-1}) in the rat. Each figure has been calculated from the means of six parallel experiments.

Vehicle	Absorption rate constant (k_a) min^{-1}	Absorption half-life ($t_{\frac{1}{2}a}$) min	Maximum concentration C_{max} $\mu g\ ml^{-1}$	Time of C_{max} (t_{max}) min	$AUC_{0-\infty}$ mg ml^{-1} min	$AUC_{0-\infty}$ % of the i.v. curve	Relative osmotic pressure
Water	0·0526	13	175	65	206	102	0
NaCl 0·9%	0·1060	7	175	38	188	93	1
NaCl 1·8%	0·0388	18	100	81	117	58	2
Dextrose 2·5%	0·0578	12	205	60	220	109	0·45
Dextrose 5%	0·0473	15	157	70	184	91	0·91
Dextrose 10%	0·0712	10	25	52	26	12	1·82
Dextrose 1·25% (in 0·9% NaCl)	0·0572	12	185	61	204	101	1·23
Dextrose 2·5% (in 0·9% NaCl)	0·0881	8	125	44	128	63	1·45
Dextrose 5% (in 0·9% NaCl)	0·0719	10	72	51	81	40	1·91
Sucrose 2·5%	0·0454	15	167	72	204	101	0·27
Sucrose 5%	0·0482	14	160	69	191	95	0·55
Sucrose 10%	0·0685	10	130	53	147	73	1·10
Sucrose 2·5% (in 0·9% NaCl)	0·0652	11	165	53	170	84	1·27
Sucrose 5% (in 0·9% NaCl)	0·0333	21	125	85	145	72	1·55
Sucrose 10% (in 0·9% NaCl)	0·0670	10	91	52	83	41	2·10
Xylitol 1·25%	0·0394	18	192	80	213	105	0·25
Xylitol 2·5%	0·0822	8	185	46	213	105	0·50
Xylitol 5%	0·0614	11	123	58	128	64	1·00
Xylitol 1·25% (in 0·9% NaCl)	0·0461	15	161	68	178	88	1·25
Xylitol 2·5% (in 0·9% NaCl)	0·0572	12	118	58	127	63	1·50
Xylitol 5% (in 0·9% NaCl)	0·0402	17	83	75	96	48	2·00

administration of sulfafurazole in water, 0·9% NaCl solution and 1·8% NaCl solution are seen in Fig. 1. Sulfonamide concentrations after administration in water or 1·8% NaCl were compared by Student's *t*-test with the time-matched values after administration of the drug in 0·9% NaCl solution.

Table 2 contains the calculated pharmacokinetic parameters of sulfafurazole from different vehicles, the relative osmotic pressures of the vehicles are also shown. The AUC-values above 100% do not differ significantly from 100%. In Table 3 the

Table 3. The results of the linear correlation tests between the relative osmotic pressure of the vehicles and some pharmacokinetic values of different sulfafurazole solutions. Student's *t*-test: * = $P<0.05$, ** = $P<0.01$, *** = $P<0.001$.

Tested parameters	Hypotonic vehicles (N = 8) r	Hypertonic vehicles (N = 13) r
Osmotic pressure/AUC	−0·6761	−0·8024***
Osmotic pressure/log AUC	−0·6886	−0·6707*
Osmotic pressure/C_{max}	−0·3100	−0·8018***
Osmotic pressure/log C_{max}	−0·3210	−0·6563*
Osmotic pressure/k_a	−0·4389	0·3204
Osmotic pressure/log k_a	−0·4717	0·3452

results of the linear correlation tests between the relative osmotic pressures and the pharmacokinetic parameters of different sulfafurazole solutions are seen. Statistically significant correlations were found in the hypertonic group between the reciprocal of osmotic pressure and AUC0–∞ or log AUC0–∞ ($P<0.001$ and $P<0.05$ respectively). The same correlation also exists between the reciprocal of osmotic pressure and the maximum drug concentration in the blood (C_{max}) or log C_{max}. In Fig. 2 the linear correlation between the blood sulfonamide level at 15 min and the relative osmotic pressures of the vehicles are shown. Significant correlation exists among the hypertonic solutions but not among the hypotonic solutions.

When correlations within the groups of solutions containing the same sugar and the same solvent were tested perfect rank-order correlation between the reciprocal of osmotic pressure and AUC and C_{max} was obtained every time. In contrast, no correlation was noted between osmotic pressure and the absorption rate constant (k_a) or the time of maximum concentration (t_{max}). Table 4 contains the viscosities of the vehicles used. No significant differences in viscosity were found between the sugar solutions prepared in water or 0·9% NaCl solution.

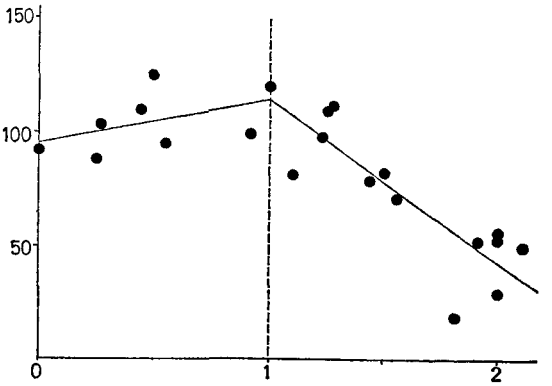

FIG. 2. The linear correlation test between blood concentrations at 15 min (ordinate: $\mu g\ ml^{-1}$) and relative osmotic pressures of the vehicles when the absorption of sulfafurazole from different vehicles was studied in situ in the rat. Abscissa: relative osmotic pressure. In A, $y = 95{\cdot}3 + 18{\cdot}7\ \times$, $r = 0{\cdot}4781$, $P<0{\cdot}3$. In B, $y = 184{\cdot}1 - 70{\cdot}4\ \times$, $r = 0{\cdot}8592$, $P<0{\cdot}001$.

DISCUSSION

If the effect of non-sugar-containing vehicles on the intestinal absorption of sulfafurazole is examined (Fig. 1; Table 2) it can be seen that the initial rate of absorption was significantly higher from 0·9% NaCl solution than from water or 1·8% NaCl solution. However, the bioavailability of sulfafurazole (AUCo–∞) was highest from pure water and very clearly lowest from 1·8% NaCl solution. The physical difference between the three solvents is osmotic pressure. These results suggest that the initial rate of intestinal absorption of a drug would be highest from an isotonic solution and that the amount of a drug absorbed would be lower from

Table 4. The viscosities of the vehicles used at 37 °C. Each figure represents the mean of ten measurements.

Vehicle	Viscosity, m N s^{-1} m^{-2}
Water	0·69
Dextrose 1·25%	0·69
Dextrose 2·5%	0·73
Dextrose 5%	0·79
Dextrose 10%	0·90
Sucrose 2·5%	0·71
Sucrose 5%	0·75
Sucrose 10%	0·88
Xylitol 1·25%	0·69
Xylitol 2·5%	0·70
Xylitol 5%	0·74

hypertonic than from hypotonic or isotonic solutions. The latter observation is in accordance with earlier findings (Malone et al 1960).

When different concentrations of sugars were added to the sulfafurazole solutions the absorption rate of hypotonic solutions had no significant correlation with osmotic pressure (Fig. 2; Table 2). The fact that low sugar concentrations (1·25–2·5%) seemed to increase the amount of the drug absorbed (AUC0–∞) might conceal the possible effect of osmotic pressure on absorption rate from hypotonic solutions. On the contrary, in the group of hypertonic solutions the effect of the added sugar concentrations on the absorption of the drug was very clearly seen. Blood sulphonamide concentrations at 15 min had highly significant negative correlation with osmotic pressure (Fig. 2). In addition, the bioavailability of sulfafurazole (AUC0–∞ and C_{max}) decreased with increasing osmotic pressure. It is noteworthy that although the initial osmotic pressure of the vehicles could be defined exactly the possible changes in it during the experiment were not examined. The loss of dextrose, sucrose, xylitol and NaCl by absorption might have occurred in different rates and this phenomenon might cause variation in the results.

It is also possible that the observed decrease in absorption was due to the increase in viscosity (Marvola et al 1979). However, the present results (Table 4) show that the difference between the least and most viscous vehicles was only about 40–50% and no significant differences were found between NaCl solutions and water solutions. Thus it can be concluded that the observed differences in the absorption of sulfafurazole from the hypertonic solutions are mostly due to the differences in osmotic pressure.

In pharmacological and toxicological studies in animals (e.g. for dose-response curves) it is usual to prepare the test solutions in 0·9% NaCl. When the dose is raised the dose volume is often kept constant while the amount of drug (concentration) is increased. But then the osmotic pressure of the test solution is also increased, which might lead to errors in results and conclusions. The extent of bioavailability and rate of initial absorption might be less for higher doses than for lower doses. When the effect of pH on gastrointestinal absorption has been investigated with in situ techniques the pH of the solution has often been adjusted with solutions of different ionic concentration. In such cases, observed changes in absorption may be due to altered osmotic pressure as well as to the change in pH.

Our present results suggest that more attention should be paid to the osmotic pressure of drug solutions. The osmotic pressure of hypertonic solutions, particularly, might modify the absorption of drugs from their dosage forms.

Acknowledgement

The authors are indebted to Hoechst-Fennica Research Foundation for financial aid.

REFERENCES

Bratton, A. C. Marshall, E. K. (1939) J. Biol. Chem. 128: 537–550

Loo, J. C. K., Riegelman, S. (1968) J. Pharm. Sci. 57: 918–928

Malone, M., Gibson, R. D., Miya, T. S. (1960) Ibid. 49: 529–534

Marvola, M., Tuomela, M-L., Komulainen, M., Inkinen, M., Pirjola, J. (1978) Acta Pharm. Suec. 15: 218–225

Marvola, M., Pirjola, J., Huikari, A. (1979) Int. J. Pharm. 2: in the press