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THE EFFECT OF SOME VISCOSITY-ENHANCING AGENTS ON THE INTESTINAL ABSORPTION OF SULFAFURAZOLE IN THE RAT

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SUMMARY

One of the biopharmaceutical factors that can influence the gastrointestinal absorption of a drug is viscosity and the physical properties of the viscosity-enhancing agent involved. In the present study the effects of some typical viscosity-enhancing agents on the intestinal absorption of sulfafurazole were investigated in the rat. The retarding effect of all the studied pharmaceutical adjuvants on absorption was clearly observed in the experiments. The area under the time concentration curve (AUC) had rank correlation with the reciprocal of viscosity and linear correlation with the logarithm of viscosity. In addition, maximum concentration (C_{max}) correlated statistically significantly with the logarithm of viscosity.

INTRODUCTION

From the biopharmaceutical point of view many factors should and do influence the gastrointestinal absorption of a drug from a liquid formulation, e.g. particle size and paticle size distribution in the bulk drug, static electrification of solids, type and amount of adjuvants such as diluents, suspending agents, surfactants etc., and storage conditions. In addition, many physiological factors are involved in gastrointestinal absorption; e.g. transit time, gastric emptying rate, site and effective surface area of absorption, blood flow rate to site, pH of luminal contents, body posture and relative activity, and the presence or absence of food in the digestive tract (Wagner, 1975).

One of the biopharmaceutical factors is viscosity and the physical characteristics of the viscosity-enhancing agent involved. The possible mechanisms by which changes in viscosity might affect drug absorption are: (1) modification of gastric emptying rate, (2) modification of intestinal transit rate, (3) hindrance of drug molecules moving from the lumen to the absorbing membrane, (4) altered ability of intestinal contents to contact the

entire surface of the microvilli, (5) possible complex formation, and (6) reduction in dissolution rate due to absorption effects, decreased diffusion rate and reduced agitation (Levy and Jusko, 1965).

Recently, small laboratory animals have become widely used in biopharmaceutical studies. For example, the retarding effect of sodium carboxymethylcellulose on the absorption of pentobarbital has been demonstrated in mice (Ritschel et al., 1974). However, the toxic effect of the drug (LD_{50}) was used as the parameter of absorption in this study, rather than blood concentrations or urinary excretion data as is usual in human experiments. In addition, experiments with rats using ethanol and salicylic acid as test substances have shown that increasing concentrations of methylcellulose delayed the disappearance of drugs from the stomach (Levy and Jusko, 1965). As a whole, information on the influence of viscosity on drug absorption is still limited in the literature. The purpose of the present study was: (1) to investigate the effect of some viscosity-enhancing agents on the intestinal absorption of a drug, using rats as test animals and blood concentrations as parameters of absorption; and (2) to find some correlation between viscosity and the pharmacokinetic parameters of the drug.

MATERIAL AND METHODS

Animals

In the experiments male Sprague–Dawley rats weighing 422 ± 42 g (mean ± S.D.) were used. The animals were fasted for 16–20 h before the experiments but access to water was allowed ad libitum.

Drugs, doses and analyses

For anesthesia sodium pentobarbital (Nembutal, Abbott A.S.), 50 mg/kg intraperitoneally, was used. The following viscosity-enhancing agents were employed: (1) agar (Ph. Nord.) at concentrations of 0.25, 0.5 and 0.75%, (2) bentonite (BDH Chemicals Ltd.) at concentrations of 1.25, 2.5 and 5%, (3) methylcellulose (MC) (Fluka AG) at concentrations of 0.5, 1 and 2%, (4) polyvinylpyrrolidone K30 (PVP) (Fluka AG) at concentrations of 2.5, 5 and 10%, and (5) tragacanth (Ph. Nord.) at concentrations of 0.125, 0.25 and 0.5% in 0.9% NaCl solution. As a test substance sulfafurazole (Gantrisin ampoules, F. Hoffmann-LaRoche and Co. AG) was used at a dose of 80 mg/kg. The sulfafurazole dose for each rat was diluted with 0.9% NaCl solution or with the viscosity-enhancing agent solution so that the total dose volume was always 10 ml. The free sulfonamide concentration in the blood samples was determined by a spectrophotometric method (Bratton and Marschall, 1939). Statistical evaluations were made using the Student's *t*-test, the rank correlation test and the linear correlation test.

Experimental procedure

The intestinal absorption of the drug was studied with an in situ technique described earlier (Marvola et al., 1978). Before every experiment the animal was anesthetized and the trachea cannulated in order to facilitate respiration. The abdomen of the rat was opened by a midline incision and the duodenum beneath the pylorus and the terminal ileum was cannulated. The lumen of the intestine was flushed with 0.9% NaCl solution

(warmed to 37°C) until the effluent was clear. The remaining perfusion solution was expelled by air, and 10 ml of drug solution was immediately introduced into the intestine through the duodenal cannula. Blood samples of 0.2 ml were taken by cardiac puncture at 5, 15, 30, 45, 60, 90, 120 and 180 min after the drug administration.

Pharmacokinetic analyses

The pharmacokinetics of 80 mg/kg of sulfafurazole following intravenous administration have been studied in the rat earlier (Marvola et al., 1978). The constants thus obtained were used in the present study for calculating pharmacokinetic parameters after intestinal administration. The areas under the curves were calculated by the trapezoidal method from the measured drug concentrations. The absorption rate constants were calculated by the method of Loo and Riegelman (1968).

Measurement of viscosity

A Brookfield micro-LVT viscometer serial 33330 was used to measure the viscosities of the solutions. The volume of the samples was 1 ml, at a temperature of 37°C. The following speeds were available: 0.3, 0.6, 1.5, 3, 6, 12, 30 and 60 min^{-1}. The measurements were started with the lowest speed, and at 2-min intervals the rate was increased. The mean of three consecutive measurements was calculated and usually the apparent viscosity obtained with the speed of 60 min^{-1} was used to describe the viscosity of each solution. If this was not possible the highest workable speed was used.

RESULTS

The pharmacokinetic data on sulfafurazole in the rat after bolus intravenous injection of the applied dose (80 mg/kg) are given in Table 1. The linear two-compartment open model was used.

The time concentration curves after intestinal administration of sulfafurazole in different vehicles are seen in Figs. 1–5 and the respective calculated pharmacokinetic parameters are given in Table 2. In the Student's *t*-tests sulfonamide concentrations after administration of different viscous solutions were compared with the time-matched values after administration of sulfafurazole in NaCl solution. Table 3 contains the apparent viscosities of the vehicles. The high viscosity of 0.75% agar solution could not be determined with the viscometer used. Rank correlation tests were made between the reciprocal of viscosity at the speed of 60 min^{-1} and k_a (absorption rate constant), t_{max} (time of maximum concentration of drug), C_{max} (maximum concentration of drug) and AUC (area under curve). The correlation coefficient of AUC/viscosity was 0.6084 and this value is statistically significant ($P < 0.05$). The other coefficients of rank correlation were lower. The best value was 0.4966 for C_{max}/viscosity, but this is significant only at the 0.1 level. When correlations within the groups of solutions containing the same viscosity-enhancing agent were tested many times, perfect rank-order correlations between the reciprocal of viscosity and AUC, C_{max} and k_a were obtained.

Table 4 shows the results of the linear correlation tests between the viscosities at 60 rpm and the pharmacokinetic parameters of different sulfafurazole solutions. No statistically significant correlation was noted. When the same tests between the values of solu-

TABLE 1

PHARMACOKINETIC DATA ON SULFAFURAZOLE IN THE RAT AFTER INTRAVENOUS INJECTION OF 80 mg/kg

C_p	= plasma concentration μg/ml.
C_0	= initial plasma concentration μg/ml.
V_d	= volume of distribution.
V_C	= volume of distribution central compartment.
V_T	= volume of distribution peripheral compartment.
AUC	= area under curve.
k_{el}, k_{12} and k_{21}	= rate constants for two-compartment model following i.v. dosing.
$t_{1/2\alpha}$	= initial half-life.
$t_{1/2\beta}$	= terminal half-life.

$$C_p = 262\, e^{-0.117t} + 179\, e^{-0.00364t}$$

C_0	= 141 μg/ml	k_{el}	= 0.0086 min^{-1}
V_d	= 142 ml	k_{12}	= 0.062 min^{-1}
V_C	= 63 ml	k_{21}	= 0.050 min^{-1}
V_T	= 79 ml	$t_{1/2\alpha}$	= 5.9 min
$AUC_{0-\infty}$	= 52373 μg · ml^{-1} · min	$t_{1/2\beta}$	= 190 min (3.2 h)

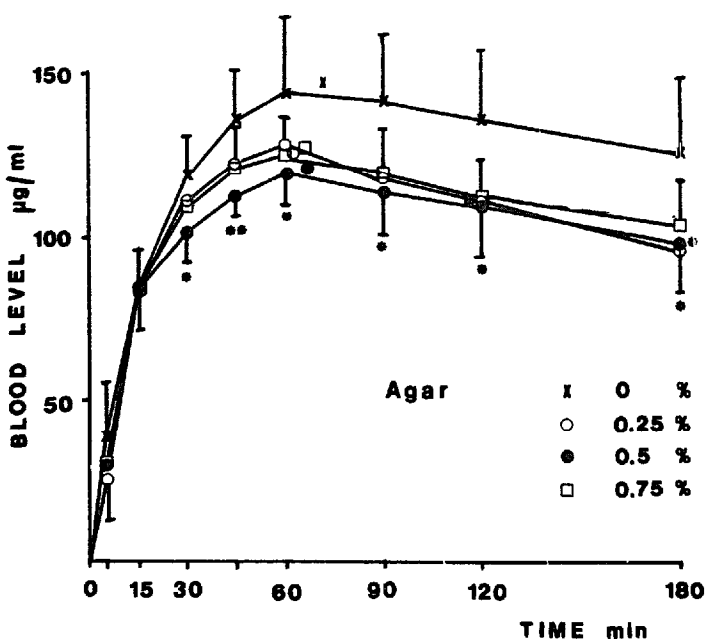

Fig. 1. The effect of different concentrations of agar on the absorption of sulfafurazole in situ in the rat. The vertical bars show the S.D. The symbols without bars = calculated C_{max}, t_{max}. Student's *t*-test: * = $P < 0.05$, ** = $P < 0.01$, *** = $P < 0.001$. N = 6.

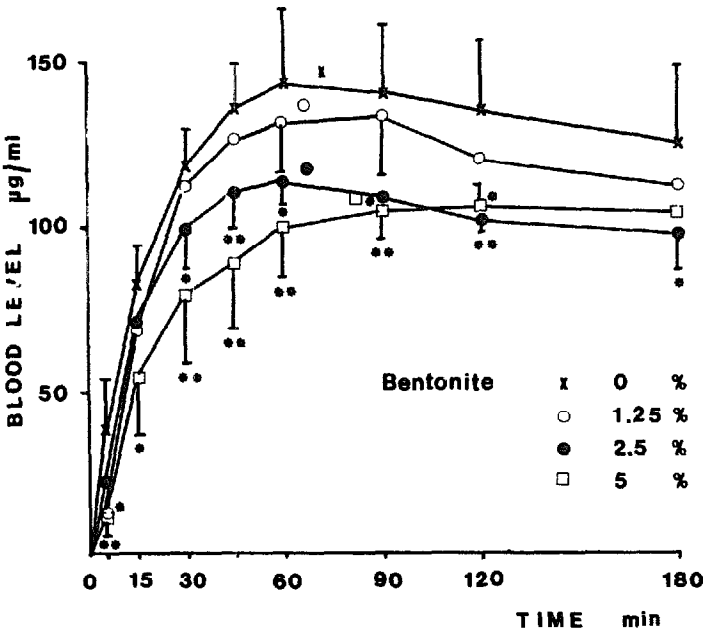

Fig. 2. The effect of different concentrations of bentonite on the absorption of sulfafurazole in situ in the rat. For explanations see Fig. 1.

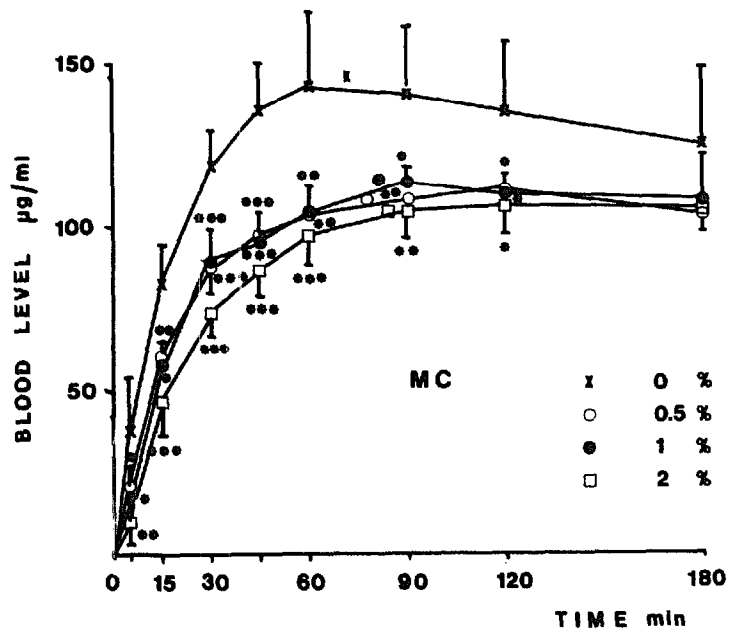

Fig. 3. The effect of different concentrations of methylcellulose (MC) on the absorption of sulfafurazole in situ in the rat. For explanations see Fig. 1.

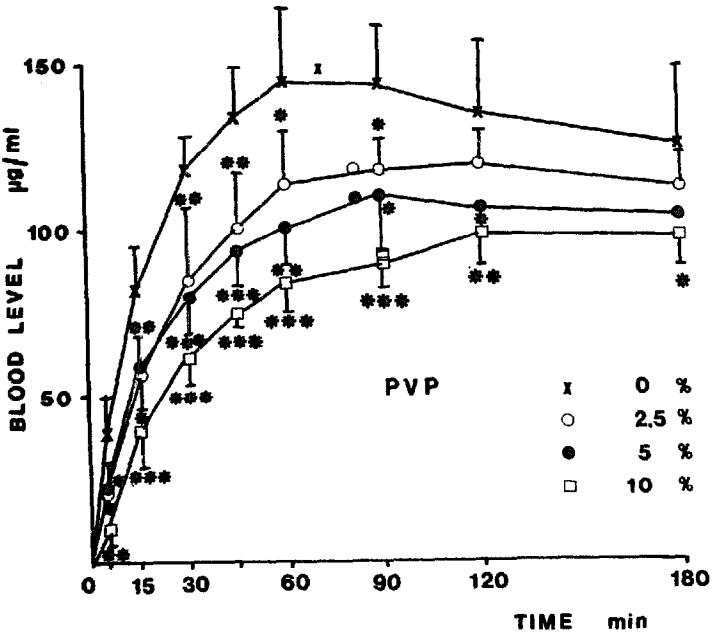

Fig. 4. The effect of different concentrations of polyvinylpyrrolidone (PVP) on the absorption of sulfafurazole in situ in the rat. For explanations see Fig. 1.

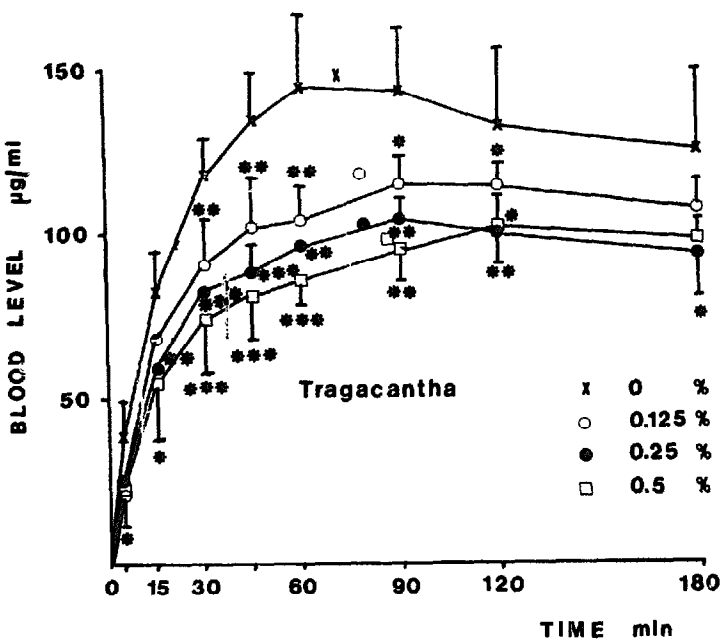

Fig. 5. The effect of different concentrations of tragacanth on the absorption of sulfafurazole in situ in the rat. For explanations see Fig. 1.

TABLE 2

THE PHARMACOKINETIC DATA DESCRIBING THE EFFECT OF DIFFERENT CONCENTRATIONS OF VISCOSITY-INCREASING AGENTS ON THE BIOAVAILABILITY OF SULFAFURAZOLE (80 mg/kg) IN THE RAT

Vehicle	Absorption rate constant (k_a) min^{-1}	Absorption half-life ($t_{1/2\alpha}$) min	Time of C_{max} (t_{max}) min	Maximum concentration (C_{max}) $\mu g/ml$	$AUC_{0-\infty}$ $\mu g \cdot ml^{-1} \cdot min$	$AUC_{0-\infty}$ % of the i.v. curve
0.9% NaCl	0.0209	33	72	146	56620	108
Agar 0.25%	0.0277	25	61	126	45276	86
Agar 0.50%	0.0236	29	67	120	44931	86
Agar 0.75%	0.0243	28	66	128	47547	91
Bentonite 1.25%	0.0238	29	67	136	50982	97
Bentonite 2.50%	0.0233	30	68	118	44483	85
Bentonite 5.00%	0.0163	42	83	109	45464	87
Methylcellulose 0.5%	0.0181	38	78	113	45939	88
Methylcellulose 1.0%	0.0171	41	81	115	47310	90
Methylcellulose 2.0%	0.0158	44	85	105	44552	85
PVP 2.5%	0.0166	42	82	118	49208	94
PVP 5.0%	0.0166	42	82	109	45531	87
PVP 10.0%	0.0142	49	90	94	41145	79
Tragacanth 0.125%	0.0185	37	77	118	47427	91
Tragacanth 0.250%	0.0182	38	78	103	41585	79
Tragacanth 0.500%	0.0151	46	87	100	42726	82

TABLE 3

THE APPARENT VISCOSITIES OF THE SOLUTIONS USED AS VEHICLES IN THE STUDY (TEMPERATURE 37°C)

Solution	Speed min^{-1}	Viscosity cP
NaCl 0.9%	60	0.72
Agar 0.25%	30	15.9
Agar 0.50%	60	8.5
Agar 0.75%	–	–
Bentonite 1.25%	60	1.7
Bentonite 2.50%	60	4.2
Bentonite 5.00%	60	8.3
Methylcellulose 0.5%	60	4.6
Methylcellulose 1.0%	12	25.8
Methylcellulose 2.0%	1.5	375.8
Polyvinylpyrrolidone 2.5%	60	1.2
Polyvinylpyrrolidone 5.0%	60	1.9
Polyvinylpyrrolidone 10.0%	60	4.0
Tragacanth 0.125%	60	1.9
Tragacanth 0.250%	60	2.6
Tragacanth 0.500%	60	4.2

tions containing the same viscosity-enhancing agent were carried out, correlation coefficients of 0.5969–0.9735 were found. Because of the small number of concentrations used ($n = 3$, $v = 1$) no significant ($P > 0.1$) correlations could be demonstrated in these experiments.

In the linear correlation tests in Table 5 logarithms of viscosity rather than viscosity were used. In this case statistically significant negative correlations were found between C_{max} and log viscosity ($P < 0.05$) and between AUC and log viscosity ($P < 0.02$). When the tests were made within the groups of the same viscosity-enhancing agent, r values of

TABLE 4

THE RESULTS OF THE LINEAR CORRELATION TESTS BETWEEN THE APPARENT VISCOSITIES AT THE SPEED OF 60 min^{-1} AND SOME PHARMACOKINETIC VALUES OF DIFFERENT SULFAFURAZOLE SOLUTIONS

Tested parameters	Correlation coefficient (r)	t	P
k_a/viscosity	0.0454	0.1437	>0.8
t_{max}/viscosity	−0.0112	0.0354	>0.8
C_{max}/viscosity	−0.3457	1.1650	>0.2
AUC/viscosity	−0.4730	1.6977	>0.1

TABLE 5

THE RESULTS OF THE CORRELATION TESTS BETWEEN THE LOGARITHMS OF THE APPARENT VISCOSITIES AT THE SPEED OF 60 min^{-1} AND SOME PHARMACOKINETIC VALUES OF DIFFERENT SULFAFURAZOLE SOLUTIONS

Tested parameters	Correlation coefficient (r)	t	P
k_a/log viscosity	−0.0542	0.1716	>0.8
t_{max}/log viscosity	0.0984	0.3127	>0.8
C_{max}/log viscosity	−0.5799	2.2511	<0.05
AUC/log viscosity	−0.7044	3.1383	<0.02

0.6944–0.9999 were obtained. However, correlation was significant only in the test between C_{max} and log viscosity of the PVP group ($P < 0.01$).

DISCUSSION

From the present results it can be concluded that after intestinal administration of sulfafurazole the viscosity of the vehicle correlated with some pharmacokinetic parameters of the drug. The best correlating parameter appeared to be the area under the time concentration curve (rank correlation with the reciprocal of viscosity and negative linear correlation with the logarithm of viscosity). The maximum concentration also had significant correlation with the logarithm of viscosity. It is notable that correlation was found even when the results from solutions containing different viscosity-enhancing agent were combined. In addition, the linear correlation of these two pharmacokinetic parameters (AUC and C_{max}) was always better with the logarithm of viscosity than with viscosity. Levy and Jusko (1965) have noted that absorption rate is not directly proportional to viscosity.

Although in the groups of the same viscosity-enhancing agent rank-order correlation between k_a and the reciprocal of viscosity was found, no correlation was left after combining the results of all groups. Thus it is obvious that other properties than the viscosity-enhancing effect of the adjuvant dominate in the absorption phase. For example, absorption rate constants for all the agar solutions were higher than that for NaCl solution.

In the present study attempts were made to exclude some of the mechanism by which changes in viscosity might affect drug absorption. Possible effects of viscosity on gastric emptying rate and intestinal transit rate were avoided by administering the drug into the ligated intestine. Reductions in dissolution rate were also excluded by using solutions of the drug. Possible complex formation between the drug and non-absorbable macromolecules was not observed in our study, but earlier it has been found with equilibrium dialysis that salicylic acid and ethanol do not complex with methylcellulose (Levy and Jusko, 1965). Thus it is obvious that the observed decrease of absorption rate with increasing viscosity is due to the slower rate of movement of drug molecules into the absorbing membranes and to the reduced ability of intestinal contents to contact the entire surface of the microvilli..

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