Effects of Salicylate on Rectal Absorption of Theophylline

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Abstract □ The rectal absorption of theophylline in rats was facilitated by concurrent administration of salicylic acid or sodium salicylate. The absorption of theophylline depended on the simultaneous absorption of salicylate and increased with an increasing concentration of salicylate. Calcium and magnesium ions inhibited the effects of salicylate at pH 7.4 but not at pH 4.5. Sodium lauryl sulfate caused lasting changes in rectal absorption, whereas the effects of salicylate on absorption were observed only when salicylate was present. Strong chelating agents, such as ethylenediaminetetraacetic acid and sodium citrate did not affect the absorption of theophylline, except at very high concentrations (30%), where membrane damage was observed. Rectal drug absorption was not enhanced by vasodilation or inflammation alone since sodium nicotinate and histamine did not facilitate the disappearance of theophylline from the perfusate.

Keyphrases □ Theophylline—rectal absorption, effect of salicylate □ Absorption, rectal—theophylline, effects of salicylate □ Salicylate—effect on rectal absorption of theophylline

Although rectal administration of drugs is not particularly popular in the United States (~1% of all medications dispensed), it can overcome some problems associated with oral and parenteral administration. Such problems include drug inactivation in the upper GI tract or by the liver, medication of infants and debilitated patients, vomiting, and nausea. The factors that control the rate of absorption from the rectum are not fully understood. Rectal delivery also is hampered by poor and inconsistent absorption of many drugs.

Some antibiotics and polypeptides that generally are not well absorbed from the rectum have been formulated as suppositories or rectal capsules, using various surfactants as adjuvants, to enhance rectal absorption (1). However, many surfactants appear to damage the rectal membrane, which may limit their use. The present report describes studies of salicylate as an adjuvant to enhance the rectal absorption of theophylline. A preliminary report of this study was published recently (2).

EXPERIMENTAL

Animals—Sprague–Dawley male rats, 275–300 g, were fasted for 16 hr prior to the experiments. During the experiment, the rats were kept on a 38° surface and were anesthetized with pentobarbital (60 mg/kg).

***In Situ* Perfusion of Rat Rectum**—These experiments were carried out by a method similar to that reported by Crommelin *et al.* (3). The rectum was exposed by an abdominal incision, and a glass cannula was inserted in the distal direction and tied firmly to keep it in position. A second cannula was inserted through the anus 1 cm inside the rectum and secured by ligation. Thus, ~2 cm of the rectum was exposed to the perfusate. The perfusate (6 ml) was circulated at a rate of 2 ml/min at 38°. Phosphate buffer (0.067 *M*) was used as the perfusate, which was adjusted, with sodium chloride to maintain an ionic strength of 0.75.

***In Vivo* Absorption Studies**—The rectum was exposed by an abdominal incision, a 0.3-ml sample of the drug solution was injected into a 2-cm section of the rectum, and the drug solution was maintained in that section by ligating the rectum with thread. After rectal administration, blood samples were collected as a function of time from a leg vein using a cannula.

In another experiment, 0.3 ml of the drug solution was injected into the rectum using a cannula, after which the anus was tied firmly to prevent leakage. After rectal administration, blood samples again were taken from a leg vein.

Table I—Conditions for HPLC Assay [a] of Drug in the Blood and in the Perfusate

Compound	Mobile Phase	Flow Rate, ml/min	UV Detector Wavelength, nm
Salicylate	0.1 *M* acetate buffer (pH 4.5)–methanol (30:70)	1.0	280
Theophylline	Water–propanol (95:5)	1.5	280
Nicotinic acid	0.1 *M* acetate buffer (pH 4.5)	1.0	284
Histamine	0.1 *M* phosphate buffer (pH 8.0)–methanol (60:40)	1.0	254

[a] A 25-cm reversed-phase column was used.

Assay Methods—Theophylline, salicylate, nicotinate, and histamine were assayed by high-pressure liquid chromatography (HPLC) under the conditions shown in Table I.

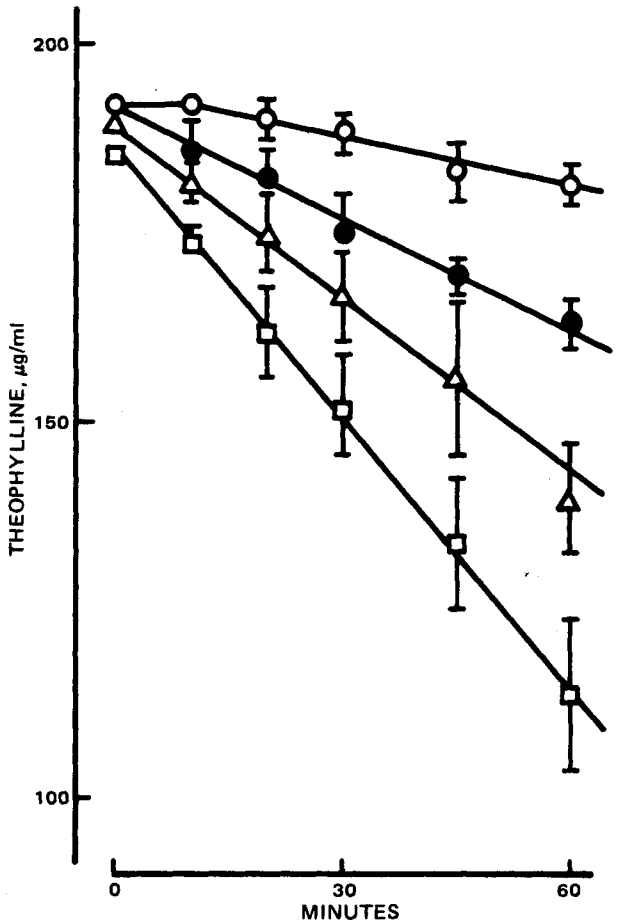

Figure 1—*Disappearance of theophylline from the perfusate at pH 7.4. Initial salicylate concentrations were 0 (○), 0.1 (●), 0.5 (△), and 1.0 (□)%.*

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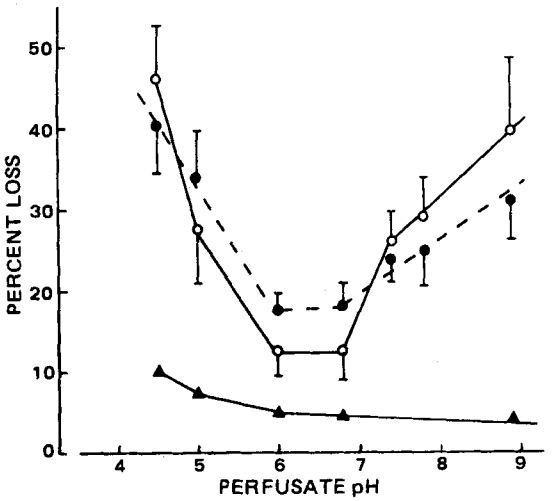

Figure 2—*Percent loss of salicylate or its acidic form (●) and theophylline (○ and ▲) after 1 hr from the perfusate. Initial concentrations were 0.5% sodium salicylate (●), 0.5% sodium salicylate and 200 μg of theophylline/ml (○), and 200 μg of theophylline/ml (▲). (Reproduced, with permission, from Ref. 2.)*

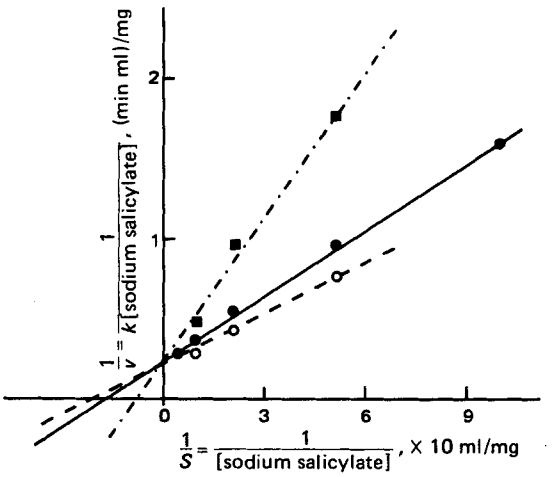

Figure 3—*Lineweaver–Burk plots for the disappearance of sodium salicylate at pH 6.8 (■), 7.4 (●), and 8.9 (○).*

The drug and adjuvants in blood were extracted with ether at a pH of <2.0 after deproteinization with 3.0% trichloroacetic acid. Following centrifugation, the ether layer was evaporated and the sediment was dissolved in methanol. This methanolic sample containing the drug was assayed by HPLC. The perfusate samples were assayed directly by HPLC.

The assay of ethylenediaminetetraacetic acid (I) and citrate was carried out using the turbidimetric titration method of Ogino and Hayashi (4). Ten milliliters of the sample containing I or citrate was mixed with 10 ml of 0.1% sodium lauryl sulfate. The resulting solution was maintained at 37° with mild stirring by a magnetic stirrer and was titrated with a solution of calcium chloride (equivalent to 0.1% $CaCO_3$) until precipitation of calcium lauryl sulfate was observed. A 0.02 *M* ammonium chloride–ammonium hydroxide buffer solution (pH 10.0) was used as the diluent.

RESULTS AND DISCUSSION

Effects of Perfusate pH and Salicylate on Disappearance of

Table II—Rate Constants ($k \times 10^3$, min^{-1}) for the Disappearance of Sodium Salicylate from the Rat Rectum as a Function of pH and Initial Salicylate Concentration [a]

Perfusate pH	Initial Concentration of Sodium Salicylate in Perfusate				
	0.1%	0.2%	0.5%	1.0%	2.0%
4.5	—	8.2 ± 1.85	8.0 ± 1.81	7.6 ± 1.58	—
5.0	—	6.0 ± 1.05	6.2 ± 1.49	5.9 ± 1.23	—
6.0	—	2.6 ± 0.25	2.1 ± 0.19	2.3 ± 0.32	—
6.8	—	2.8 ± 0.45	2.0 ± 0.32	1.7 ± 0.23	—
7.4	7.1 ± 0.56	5.5 ± 0.48	3.8 ± 0.26	3.1 ± 0.14	1.9 ± 0.24
7.8	—	5.2 ± 0.64	4.1 ± 0.32	3.2 ± 0.30	—
8.9	—	6.9 ± 0.92	4.5 ± 0.13	3.9 ± 0.05	—

[a] Uncertainties are expressed as the standard deviation among runs (usually five or six animals).

Table III—Effects of Magnesium and Calcium Ions on the Disappearance Rate Constants ($k \times 10^3$, min^{-1}) of Sodium Salicylate from the Perfusate through the Rat Rectum

Additive Concentration, %	Initial Concentration of Sodium Salicylate in Perfusate			
	0.1%	0.2%	0.5%	1.0%
Perfusate at pH 7.4				
None	7.1 ± 0.6	5.5 ± 0.5	3.8 ± 0.3	3.1 ± 0.1
Magnesium chloride 0.5	4.0 ± 0.2	3.2 ± 0.2	2.6 ± 0.6	2.4 ± 0.2
Magnesium chloride 1.0	3.4 ± 0.3	2.9 ± 0.2	2.5 ± 0.1	—
Calcium chloride 0.5	4.7 ± 1.0	3.9 ± 0.1	3.1 ± 0.2	2.5 ± 0.1
Perfusate at pH 5.0				
None	—	6.0 ± 1.1	6.2 ± 1.5	5.9 ± 1.2
Magnesium chloride 0.5	—	5.8 ± 0.8	6.0 ± 0.9	5.6 ± 0.8
Calcium chloride 0.5	—	6.1 ± 0.6	5.6 ± 1.0	5.5 ± 1.2

Table IV—Effect of Magnesium and Calcium Ions on the Disappearance (Percent Lost) of Theophylline [a] after 1 hr in the Presence of Varying Amounts of Sodium Salicylate

Additive Concentration, %	Initial Concentration of Sodium Salicylate in Perfusate					
	0%	0.1%	0.2%	0.5%	1.0%	2.0%
None	4.7 ± 0.2	18.3 ± 2.1	26.7 ± 1.9	29.2 ± 2.0	27.7 ± 4.4	48.1 ± 5.7
Magnesium chloride 0.5	—	9.5 ± 0.3	14.9 ± 0.4	19.3 ± 1.1	24.4 ± 1.3	—
Magnesium chloride 1.0	—	9.2 ± 0.3	12.2 ± 0.7	16.2 ± 0.7	—	—
Calcium chloride 0.5	—	8.5 ± 0.4	16.9 ± 0.8	22.7 ± 1.3	29.6 ± 2.2	—

[a] The initial theophylline concentration was 200 μg/ml at pH 7.4.

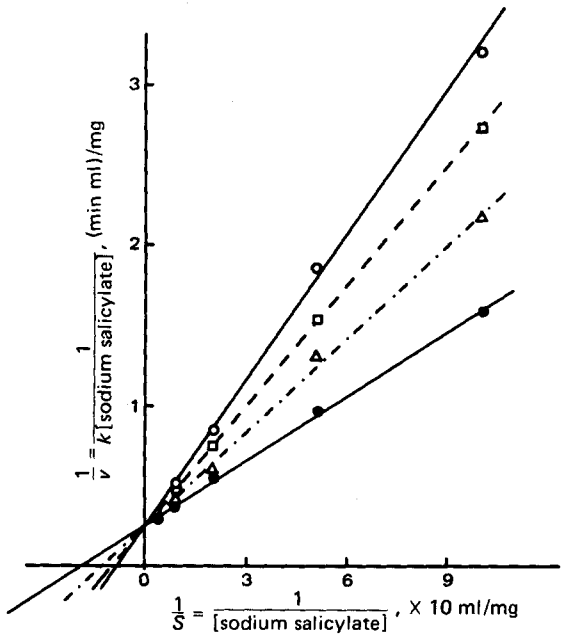

Figure 4—*Effects of calcium and magnesium ions on the Lineweaver–Burk plots for the disappearance of sodium salicylate at pH 7.4. The concentrations were 1.0% $MgCl_2$ (○), 0.5% $MgCl_2$ (□), and 0.5% $CaCl_2$ (△); the control also is shown (●).*

Theophylline—The disappearance of theophylline from the perfusate in the rat rectum in the absence of adjuvants was very slow, and the total loss of theophylline was <10% 60 min after the perfusion was begun at pH 4.5–8.9. However, a significant loss of theophylline was observed in the presence of salicylate. Figure 1 shows the disappearance of theophylline from the perfusate as a function of the salicylate concentration and time at pH 7.4. The higher the initial concentration of salicylate in the perfusate, the faster theophylline disappeared from the perfusate.

The effect of salicylate on the percent loss of theophylline from the perfusate was greater at pH values above 7.4 and below 5.0 (Fig. 2). The high loss of theophylline was accompanied by a high loss of salicylate. This result suggests that the disappearance of theophylline depends on the simultaneous disappearance of salicylate from the perfusate.

Table V—Absolute Bioavailability of Theophylline (F_{ab}) as a Function of the Salicylate Concentration with and without Ligation

Salicylate Dose, mg/kg	Percent Bioavailability	
	With Ligation	Without Ligation
0	18.2 ± 4.3 (n = 6)	35.6 ± 6.3 (n = 4)
1.0	42.2 ± 9.8 (n = 6)	37.1 ± 5.8 (n = 4)
2.5	59.3 ± 10.7 (n = 6)	60.7 ± 8.2 (n = 3)
3.75	56.8 ± 6.7 (n = 6)	74.6 ± 9.8 (n = 5)
7.5	98.6 ± 4.8 (n = 8)	96.2 ± 6.6 (n = 5)
15	97.5 ± 9.2 (n = 8)	100.3 ± 5.8 (n = 5)

Disappearance of Salicylate from Perfusate—The disappearance of salicylate from the perfusate appears to be a first-order process. However, in the basic pH region, the first-order disappearance followed an initial lag time. As shown in Table II, in the acidic region, the rate constant for the disappearance of salicylic acid did not depend on the initial concentration. However, in the basic region, the disappearance rate constant did depend on the initial concentration of salicylate.

In the acidic region, the disappearance of salicylic acid from the perfusate in the rectum may depend on the lipophilicity of salicylic acid, resulting in rapid distribution of salicylic acid to the rectal membrane. However, in the basic region, where the rate constant depended on the initial concentration, some type of saturable phenomenon may be involved.

Lineweaver–Burk plots obtained from the data in Table II for the basic region are shown in Fig. 3. Under these conditions, the V_{max} value did

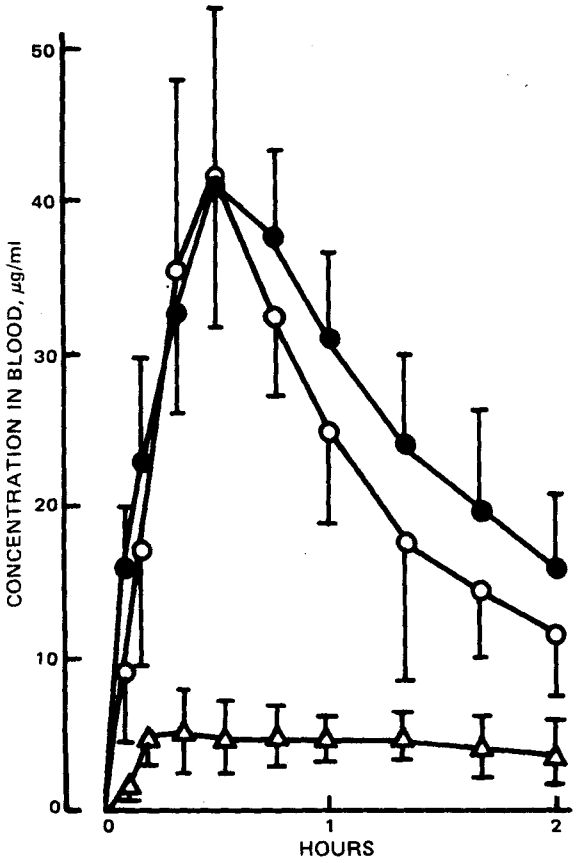

Figure 5—*Blood levels of theophylline (○ and △) and salicylate (●), in micrograms per milliliter, following the administration of 0.3 ml of a pH 8.0 buffer solution containing 15 mg of theophylline/kg (△) or 15 mg of theophylline and 15 mg of salicylate/kg (○ and ●) to a ligated 2-cm section of the rectum.*

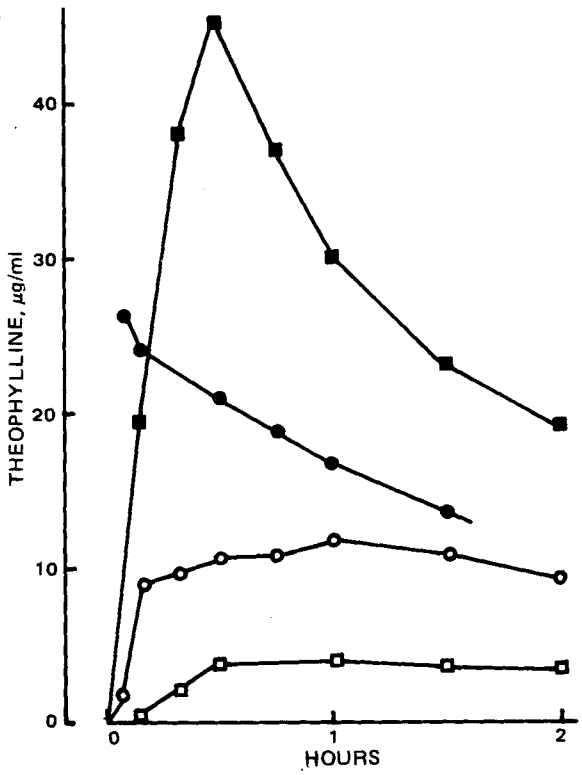

Figure 6—*Concentration of theophylline, in micrograms per milliliter, in blood following intravenous administration of 6 mg of theophylline/kg (●), rectal administration of 0.3 ml of a solution containing 15 mg of theophylline/kg with ligation (□) and without ligation (○), and rectal administration of 15 mg of theophylline and 15 mg of salicylate/kg without ligation (■).*

Table VI—Effect of Sodium Lauryl Sulfate on the Disappearance of Theophylline from the Rat Rectum after 1 hr as a Function of pH

Sodium Lauryl Sulfate Concentration, %	Percent of Theophylline Lost			
	pH 4.5	pH 6.0	pH 7.4	pH 8.9
0	9.8 ± 0.4	5.2 ± 0.3	4.7 ± 0.2	4.0 ± 0.1
0.5	10.9 ± 3.6	9.5 ± 1.3	14.2 ± 3.8	20.8 ± 4.4
2.0	12.8 ± 2.4	13.1 ± 1.5	24.7 ± 3.7	35.1 ± 3.4

not change but the K_m value depended on the pH of the perfusate. This finding suggests that the disappearance of the ionic form of salicylate depends on the affinity of salicylate for some feature of the rectal membrane. At every pH value of the perfusate, the disappearance rate constant of salicylate was not affected by the presence of theophylline. This result indicates that the formation of a complex between salicylate and theophylline is not the primary factor facilitating the transport of theophylline in the presence of salicylate.

Effect of Calcium and Magnesium Ions on Disappearance of Salicylate and Theophylline—Since salicylate interacts with calcium and magnesium ions, the effect of these cations on the disappearance rate constant of salicylate from the perfusate through the rat rectum was studied. Addition of calcium or magnesium ions to the perfusate at pH 7.4 led to a decrease in the rate constant for salicylate disappearance (Table *III*). However, at pH 5.0, addition of calcium or magnesium ions did not affect the disappearance rate constant of salicylic acid.

This result probably means that the disappearance of salicylate in the perfusate at pH 5.0 primarily involves the nonionic form and that the disappearance process is different for the ionic and nonionic forms.

Based on the Lineweaver–Burk plots of the effect of calcium or magnesium ions at pH 7.4, these ions did not affect V_{max} but led to an increase in K_m (Fig. 4). This result suggests that calcium and magnesium ions competitively inhibit the binding of salicylate to some feature in the membrane. On the other hand, calcium and magnesium ions did not affect penetration of the nonionic form through the rectal membrane.

Calcium and magnesium ions did not affect the disappearance of theophylline in the absence of salicylate. At pH 7.4, the effect of salicylate on the disappearance of theophylline from the perfusate was suppressed by the presence of calcium or magnesium ions in the perfusate (Table IV). However, at pH 4.5, the effect of salicylate was not affected by calcium or magnesium ions. This observation indicates that the disappearance of theophylline probably is controlled by the disappearance of salicylate. A possible explanation is that the action of salicylate as an effective adjuvant depends on the presence of salicylate in the rectal membrane.

Appearance of Theophylline in Rat Blood after Rectal Administration—The absorption of theophylline into the general circulation after rectal administration to rats was studied by measuring the blood levels of theophylline as a function of time.

After the administration of 0.3 ml of pH 8.0 buffer containing 15 mg of salicylate and theophylline/kg into a 2-cm section of the rectum, the blood levels of theophylline and salicylate increased rapidly and reached maximum levels at 30 min (Fig. 5). The absorption of theophylline and salicylate occurred simultaneously.

The absolute bioavailability, F_{ab}, after rectal administration was calculated using the $[AUC]_0^\infty$ values corrected for intraindividual variation in the elimination rate as follows:

$$F_{ab} = \frac{[AUC]^{\infty}_{0,\text{rectal}} k_{e,\text{rectal}}\ \text{dose}_{iv}}{[AUC]^{\infty}_{0,iv} k_{e,iv}\ \text{dose}_{\text{rectal}}} \qquad \text{(Eq. 1)}$$

where $k_{e,\text{rectal}}$ and $k_{e,iv}$ are the elimination rate constants after rectal administration and intravenous injection, respectively. The elimination rate constants were determined by a linear regression analysis of the log concentration *versus* time data.

Absolute bioavailability of theophylline after rectal administration is shown in Table V and Figs. 5 and 6. Absolute bioavailability and blood levels of theophylline in solution without salicylate after rectal administration were ~20% with ligation and ~35% without ligation. Bioavailability and blood levels of theophylline without ligation were higher than with ligation. This result suggests that the effective area of the rectum available for drug absorption without ligation was larger than with ligation.

For drug solutions containing >7.5 mg of salicylate/kg, absolute bioavailabilities were 100% under both conditions. However, the bioavailability of theophylline after administration of drug solutions containing 3.75 mg of salicylate/kg was 55% with ligation and 75% without ligation. Bioavailability after giving drug solutions containing 1.0 mg of salicylate/kg was not significantly different with or without ligation of the rectum, in spite of the increase in bioavailability found in the absence of salicylate without ligation. This result may indicate that the effect of salicylate in promoting drug absorption through the rectum depends on the amount of salicylate in a limited area of the rectum.

Comparison of a Surfactant and Salicylate—To examine further the mechanism of rectal absorption, the relative effects of a surfactant and salicylate were studied using sodium lauryl sulfate as a surfactant. The disappearance of theophylline from the perfusate was facilitated by the presence of sodium lauryl sulfate in the perfusate (Table VI). However, as shown in Fig. 7, the presence of sodium lauryl sulfate resulted in a lasting effect, whereas the promotive effect of salicylate did not reflect a permanent change in the rectal membrane. The effect of salicylate was eliminated by washing the rectum with buffer for 5 min after pretreatment with salicylate whereas the effect of pretreatment with sodium lauryl sulfate was not eliminated by washing. This result probably indicates that the action of salicylate does not involve a lasting change in the membrane, whereas lauryl sulfate appears to damage the membrane.

Comparison of Strong Chelating Agents with Salicylate—Salicylate is known to interact with calcium and magnesium ions. Therefore, the action of salicylate was compared with that of ethylenediaminetetraacetic acid (I) and sodium citrate. As shown in Table VII, a 15% concentration of I or citrate did not affect the disappearance of theophylline from the perfusate. However, with very high concentrations (30%) of I or citrate in the perfusate, disappearance of theophylline from the perfusate was facilitated, but, contrary to the situation with salicylate, the perfusate developed a red color. Apparently, I and citrate produced

Table VII—Disappearance of Theophylline (Percent Lost) in the Presence of Citrate and Ethylenediaminetetraacetic Acid after 1 hr of Perfusion

Chelating Agent	pH 7.4	pH 8.0
Citrate, 15%	8.1 ± 0.8	9.7 ± 1.2
Citrate, 30%	20.3 ± 5.2	23.2 ± 4.6
EDTA[a], 15%	10.4 ± 3.8	8.5 ± 4.3
EDTA, 30%	24.8 ± 2.8	28.7 ± 4.6

[a] Ethylenediaminetetraacetic acid.

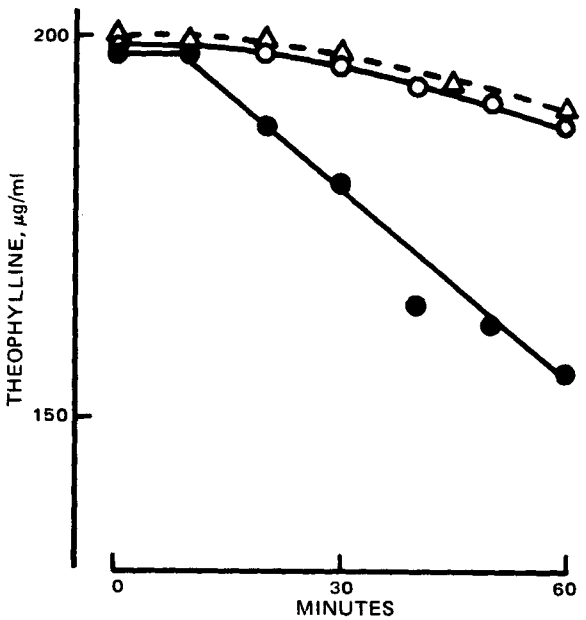

Figure 7—*Concentration of theophylline, in micrograms per milliliter, found in the perfusate after pretreatment of the rectum with salicylate (○) or with sodium lauryl sulfate (●). The control (△) involved no pretreatment.*

Table VIII—Effects of Nicotinic Acid and Histamine on the Disappearance of Theophylline from the Rat Rectum after 1 hr of Perfusion

Substance	Percent Lost				
	pH 4.5	pH 6.0	pH 6.8	pH 7.4	pH 8.9
Theophylline only	7.8 ± 1.5	5.2 ± 0.3	—	4.7 ± 0.2	4.0 ± 0.2
Nicotinic acid only	49.4 ± 1.3	—	4.6 ± 0.4	8.2 ± 3.2	5.5 ± 0.7
Theophylline in presence of 1% nicotinic acid	9.8 ± 2.8	—	5.9 ± 3.7	5.1 ± 0.9	6.1 ± 5.5
Theophylline in presence of 1% histamine	9.1 ± 4.7	9.1 ± 3.9	—	10.2 ± 3.7	12.2 ± 5.6

bleeding from the rectum, probably as a result of damage to the rectal membrane, and, thus, promoted the disappearance of theophylline from the perfusate.

Citrate and I do not appear to be absorbed from the rectum since the remaining chelating activity in the perfusate, measured according to the method of Ogino and Hayashi (4), was significant. This finding suggests that compounds that are not absorbed well themselves are not suitable adjuvants for rectal drug absorption.

Comparison of Sodium Nicotinate and Histamine with Salicylate—Another possible mechanism involves the effect of vasodilation and inflammation on the disappearance of theophylline from the perfusate. In this regard, the effects of nicotinate and histamine on the disappearance of theophylline were studied.

Neither histamine nor nicotinic acid significantly facilitated the disappearance of theophylline (Table VIII). At pH 4.5, the disappearance of theophylline from the perfusate was not facilitated by nicotinic acid, although nicotinate was lost from the perfusate. The action of salicylate as an adjuvant probably does not depend on vasodilation or an inflammatory action.

Mechanistically, the enhancement of rectal absorption of theophylline by salicylate still is unclear. The nonionic and ionic forms of salicylate apparently have different paths through the membrane. It is possible that salicylate reduces the lipophilicity or increases the permeability of the membrane, perhaps by interacting with some substance in the membrane, *e.g.*, calcium or magnesium ions, which may be present as structural features, and thus concurrently allows theophylline to pass through the rectal membrane.

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Time Course and Disposition of Methazolamide in Human Plasma and Red Blood Cells

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Abstract □ Methazolamide was determined in plasma, whole blood, and urine by a GLC–mass spectrometric method. Temporal patterns of methazolamide concentrations in plasma and red blood cells were obtained following single- and multiple-dose oral administration of the drug. The nonlinearity in the binding of the drug to the red blood cell carbonic anhydrase was evident from a comparison of plasma and red blood cell concentrations. The drug was cleared slowly from the red blood cells. The binding constants to the two isoenzymes of carbonic anhydrase were determined from the plasma and red blood cell concentrations and were in agreement with those determined by previous measurements. The half-life of elimination was 7.5 hr. The urinary recovery of unchanged drug was ~25% of the administered dose.

Keyphrases □ Methazolamide—time course and disposition in human plasma and red blood cells □ GLC–mass spectrometry—analysis, methazolamide, human plasma and red blood cells □ Distribution—methazolamide, time course and disposition in human plasma and red blood cells

Methazolamide (5-acetylimino-4-methyl-Δ^2-1,3,4-thiadiazoline-2-sulfonamide) is a carbonic anhydrase inhibitor used in the treatment of glaucoma. It is the methylated analog of the tautomer of acetazolamide. Both drugs reduce the transport of ions from the secretory cells of the ciliary body into the nascent aqueous humor and decrease aqueous secretion through a local osmotic effect (1). In particular, inhibition of the carbonic anhydrase in the secretory cells of dogs reduces the bicarbonate flux (2) and sodium-ion flux (3) into the posterior chamber of the eye.

The dynamics and distribution of drug following different patterns and routes of administration have been studied much more extensively for acetazolamide than for methazolamide. All work to date on the determination of methazolamide in biological fluids and tissues has employed the indirect enzymatic method developed by Maren and coworkers (4, 5). This method is based on two facts: (*a*) the rate of hydration of carbon dioxide catalyzed by carbonic anhydrase is reduced by an inhibitor present in a biological fluid; and (*b*) the rate of hydration or, equally, the rate of formation of carbonic acid or protons directly affects the time interval required to cause a given change in pH. Although methazolamide is metabolized significantly (only 25% is recovered as unchanged drug in the urine) in contrast to acetazolamide, which is not metabolized, the metabolites appear either to be very weak inhibitors of carbonic anhydrase or to lack inhibitory potential (6).

Plasma and red blood cell concentrations and the uri-

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