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Studies on Absorption of Suppositories. VII.[1] Effect of the Amount of Base on Absorption of Sulfonamides from Rabbit Rectum

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To investigate the effect of the amount of a base on the absorption of drugs from the rectum, amount of rectal fluid and distribution region of a drug in the rectum after administration of a suppository were determined. The distribution region of a drug in the rectum increased in proportion to the volume of suppository, both in PEG and cacao butter base. The rectal fluid increased with increasing volume of the PEG base, but concentration of the base in rectal fluid was always about 30%, independent of the base volume, at 2 hr after administration. On the other hand, there was no detectable amount of the fluid but a little mucus in the rectum after administration of cacao butter suppository. The results of blood concentration studies showed that both the rate and extent of absorption of sparingly soluble sulfonamides were enhanced by the increasing amount of PEG and cacao butter base. The absorbability of water-soluble sulfonamide was reduced by the increased volume of PEG base, and a better absorbability of a soluble sulfonamide was obtained from cacao butter than from PEG base.

The results of *in vitro* membrane permeation experiment with isolated gut segments served sufficiently to explain the influence of the amount of base on *in vivo* rectal absorption of sulfonamides. From the results of *in vivo* and *in vitro* experiments, it was concluded that rectal absorption of sulfonamides from increased base volume of suppository depended mainly on the increment of the distribution area, that is, absorption area in rectum.

Keywords——suppository; rectal absorption; amount of suppository base; distribution area in rectum; volume of rectal fluid; membrane permeation; drug absorption; bioavailability; solubility; sulfonamides

Many investigators[3] reported that the kind of a base and additives of suppository affect the absorption of a drug from the rectum. Therefore, constitution of a base is important for the preparation of a suppository possessing high bioavailability.

In rat rectum circulation experiments of a drug solution containing various concentrations of water-soluble base, Kakemi, *et al.*[4] reported that the rectal absorption of sulfonamides depended directly on the concentration of a base, because the base decreases the partition between the vehicle and the lipoid. Pagay[5] also reported similar results in a rectal absorption of acetaminophen using human subjects.

In the drug absorption from a suppository, drug is first released from the base into the rectal fluid, the drug dissolves, and then is absorbed through the rectal membrane. If the amount of secreted fluid is varied by the amount or kind of a base, both the absorption area and the concentration of drug and base should differ greatly. However, no investigations from this point have been reported. Therefore, this experiment was undertaken to clarify the

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3) *a*) A.F. Cacchiro, *J. Am. Pharm. Assoc., Sci. Ed.*, **43**, 683 (1954); *b*) W. Lowenthal and J.F. Borzelleca, *J. Pharm. Sci.*, **54**, 1790 (1965); *c*) E.L. Parrott, *ibid.*, **60**, 867 (1971); *d*) R. Ovcharow, M. Pennova, and V. Kushew, *Pharmazie*, **26**, 693 (1971); *e*) T. Takubo, S. Tsuchiya, and M. Hiura, *Yakuzaigaku*, **31**, 292 (1971).

4) K. Kakemi, T. Arita, and S. Muranishi, *Chem. Pharm. Bull.* (Tokyo), **13**, 969 (1965).

5) S.N. Pagay, *Diss. Abstr. Int.*, 34, 1169B (1973).

volume of rectal fluid and distribution area of a drug in the rectum after administration of various amounts of a suppository base. Through the *in vitro* and *in vivo* experiment, the effect of the amount of the base on absorption of sulfonamides was discussed.

Experimental

Solubility——Ten ml of a solution containing 0, 10, 20, 30, or 40% polyethylene glycol (PEG) base was placed in a glass-stoppered flask with excess of each sulfonamide. The flask was immersed in a water bath (37°±1°) and shaken vigorously for 24 hr by which an equilibrium was established. An aliquot of the supernatant was removed with the aid of a cotton filter pipette and solubility of sulfonamides was determined by spectrophotometry according to the method described in the preceding report.[3e]

Partition Coefficient——Sulfonamides were dissolved in a concentration of 0.5 mmole/liter in the PEG solution, and 10 ml portion of the solution was shaken with an equal volume of isoamyl acetate at 37°±1°. The concentration of sulfonamide in both phases was determined after an equilibrium was established, and the partition coefficient was calculated.

Test Preparation——Sulfanilamide, sulfisomidine, sulfisoxazole, and sulfadiazine (200 mesh through) employed in this study were a commercial grade. As a suppository base, PEG and cacao butter were used. PEG base consists of 20% of PEG 400, 35% of PEG 1500, and 45% of PEG 6000. The suppositories were prepared by the hot-melting method. Each sulfonamide was dissolved or dispersed throughout the melted base and poured into PVC molds (Mutual Trading Co.) having 0.9, 1.1, 1.9, 2.9, and 5.8 ml in volume. The volume of suppository was defined by the volume (ml) of molds. Each suppository contained 200 mg of sulfonamide. The suppositories were stored in a refrigerator at 15° until use.

***In Vitro* Permeation Experiments**——Adult male rabbits weighing 2.0—3.0 kg were killed, the small intestine and rectum were isolated, and they were washed out with 20 ml of saline warmed to body temperature. A preliminary experiment was made using the rectum and the small intestine in length of 8 cm and containing 20% PEG solution of sulfanilamide. The amount of sulfanilamide permeated through the rectum and the small intestine obtained after 3 hr was 23.5 mg and 22.2 mg, respectively. The value of the permeation rate constant of sulfanilamide through the rectum was 10.0 mg/hr and the value through the small intestine was 9.9 mg/hr. Apparent difference was not observed between the values of the amount of the permeated sulfanilamide and the permeation rate constant through the rectum and the values through the small intestine. So the small intestine was used throughout in this experiment.

Cacao butter base suppository was placed in the intestine and both ends were ligated (Fig. 1-B). When the PEG base was employed, a suppository dissolved (10%, 20%, 30%) previously in distilled water was poured into the intestine and both ends were connected to glass tubings (Fig. 1-A). The length of intestine was varied according to the volume of cacao butter suppository or the solution of PEG suppository. These intestines were placed in a 500 ml beaker containing 200 ml of Tyrode solution, and this beaker was immersed in a water bath maintained at 37°±1°. The beaker was continuously gassed with air. One-half milliliter of outer solution was pipetted out at 0.5, 1.0, 1.5, 2.0, 2.5, and 3.0 hr, and concentration of sulfonamides was determined.

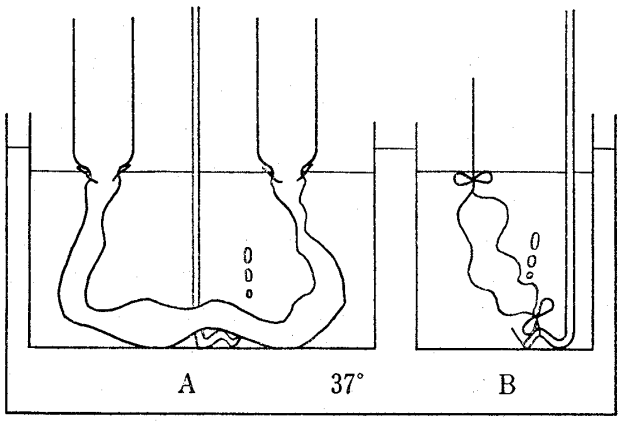

Fig. 1. Apparatus used for *in Vitro* Permeation Experiments

A: used for PEG base suppository
B: used for cacao butter base suppository

***In Vivo* Absorption Experiments**——Adult male rabbits weighing 2.0 kg were fasted for 24 hr before the absorption experiments but water was allowed freely. A suppository was placed in the rectum and the anal end was pinched with a clip for 4 hr to prevent expulsion of the suppository. Blood was withdrawn at 0.5, 1, 2, 4, 6, 8, 10, and 12 hr from the congested aural vein, and concentration of sulfonamide in it was determined.

To examine the absorption area of a drug and the amount of fluid secreted in the rectum, the rabbits were killed at 2 hr after administration of suppository containing 200 mg of charcoal instead of sulfonamide. The distribution region of charcoal was determined as the length from the anus to the foremost front of charcoal, and this region was presumed as the absorption area. The content in whole rectum was withdrawn into a 50 ml centrifuge tube. The volume of supernatant after centrifugation at 3000 rpm for 10 min was considered as the amount of rectal fluid.

Results and Discussion

Effect of PEG on Solubility and Partition Coefficient

The relationship between the apparent solubility of each sulfonamide (S) and the concentration (C) of PEG can be expressed by the following equation:

$$\log S = (Ks/2.303) \cdot C + \log Cs$$

where Cs is the solubility in water, and Ks is the constant specific to each sulfonamide (Fig. 2-A). The apparent partition coefficient (P) of sulfonamides between PEG solution and isoamyl acetate became lower with higher concentration of PEG (Fig. 2-B). This relationship is expressed as follows:

$$\log P = (-Kp/2.303) \cdot C + \log Cp$$

where Kp is a constant.

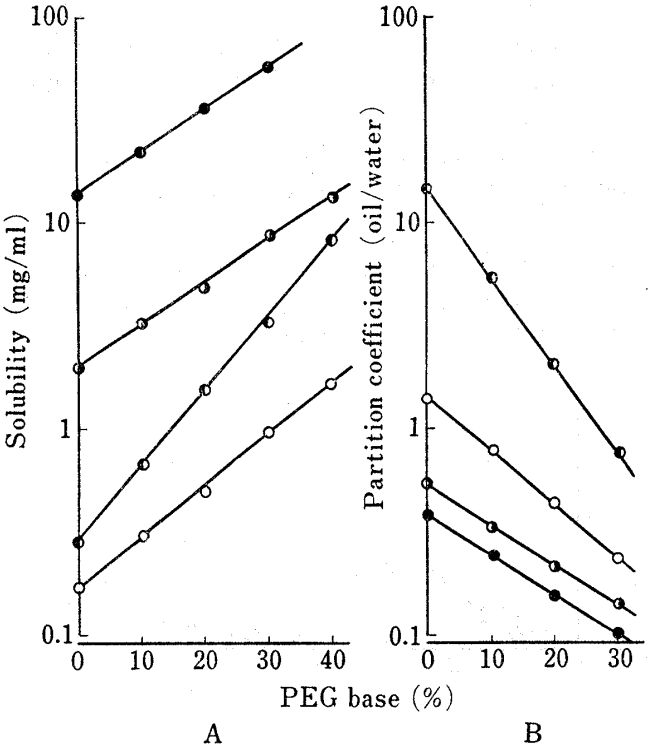

Fig. 2-A. Solubility of Sulfonamides in Various Concentrations of PEG Solution
2-B. Influence of the Concentration of PEG on Partition Coefficient of Sulfonamides

—●—: sulfanilamide —◐—: sulfisoxazole
—◑—: sulfisomidine —○—: sulfadiazine

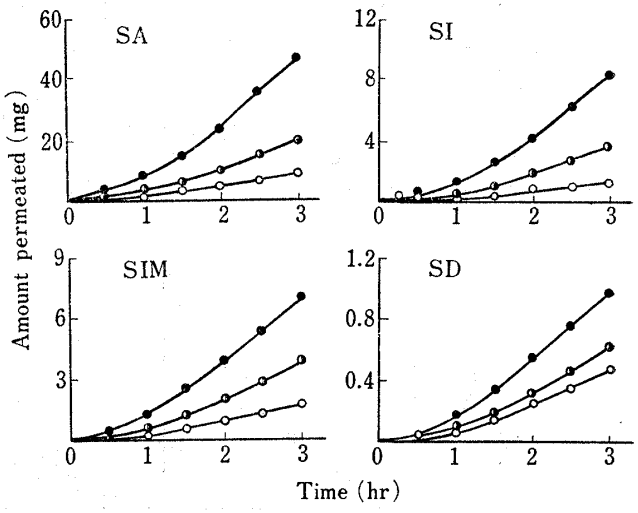

Fig. 3. Permeation Rate of Sulfonamides from Intestine (16 cm) containing Various Concentrations of PEG

SA: sulfanilamide, SIM: sulfisomidine, SI: sulfisoxazole, SD: sulfadiazine
—●—: 10%, —◑—: 20%, —○—: 30%

TABLE I. Increasing Rate of Solubility (Ks), Decreasing Rate of Partition Coefficient (Kp), and Ratio of Kp/Ks

Drug	Ks	Kp	Kp/Ks
Sulfanilamide	0.0461	0.0454	0.985
Sulfisomidine	0.0476	0.0475	0.998
Sulfisoxazole	0.0836	0.0871	1.042
Sulfadiazine	0.0594	0.0599	1.007

Kakemi, *et al.*[4] and Pagay, *et al.*[6] reported similar results, and stated that the increase of solubility and decrease of partition coefficient of drugs by the addition of a water-soluble base depended on the decreasing polarity of the solution.

*K*s and *K*p of each sulfonamide obtained in this experiment are listed in Table I. The relationship between the solubility and the partition coefficient can be expressed by the following equation:

$$\log P = -(Kp/Ks) \cdot \log S + \text{Const}$$

Since the ratio of *K*p to *K*s is equal to about 1 (Table I), increasing rate of solubility and decreasing rate of partition coefficient are compensated each other in PEG solution.

Effect of Amount of the Base on Membrane Permeation of Sulfonamide

PEG base suppository of a different volume, 0.9 ml (1 g), 1.9 ml (2 g), and 2.9 ml (3 g), was previously dissolved in distilled water at 37° to obtain the same final volume. The concentration of PEG in each solution was 10, 20, and 30%, respectively. The isolated intestine of 16 cm in length was filled with these solutions (Fig. 1-A).

As shown in Fig. 3, the permeation rate of sulfonamides was depressed by the increasing concentration of the base. In these solutions, the concentration of sulfonamide in 30% PEG was higher than that in 10% PEG, but the partition of a drug from PEG solution to membrane should decrease with increasing concentration of the base (Fig. 2).

Therefore, it would be considered that the rate of permeation of sulfonamides through the small intestine depends on the decrease of lipid solubility rather than the increase of solubility by PEG.

For determination of the permeation of sulfonamides from 20% PEG solution, 8, 16, and 24 cm of intestine were used for 0.9, 1.9, and 2.9 ml of PEG suppository, respectively. Amount of sulfonamide permeating from the whole and unit length of the intestine is shown in Fig. 4.

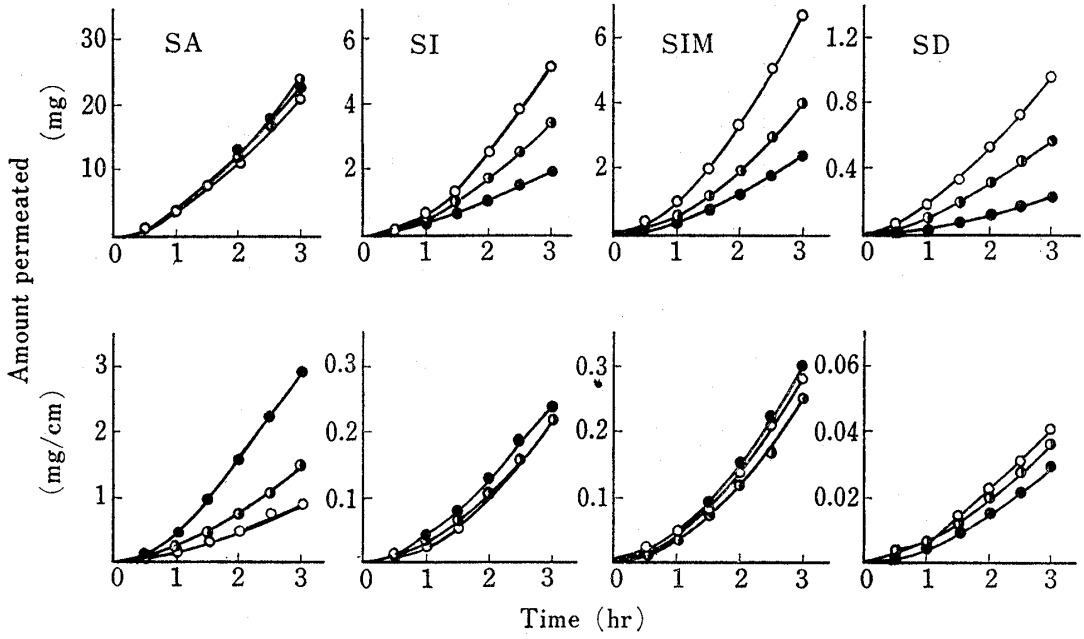

Fig. 4. Permeation Rate of Sulfonamides from Whole and Unit Length of Intestine containing 20% of PEG Solution

SA: sulfanilamide, SIM: sulfisomidine, SI: sulfisoxazole, SD: sulfadiazine
—●—: 8 cm (0.9 ml of base volume)
—◑—: 16 cm (1.9 ml of base volume)
—○—: 24 cm (2.9 ml of base volume)

6) S.N. Pagay, R.I. Poust, and J.L. Colazzi, *J. Pharm. Sci.*, **63**, 45 (1974).

Table II. Permeation Rate Constants of Sulfonamides from Whole and Unit Length of Intestine containing PEG and Cacao Butter Base

		PEG base							Cacao butter base		
Base volume (ml)		0.9	1.9	2.9	0.9	1.9	2.9		0.9	1.9	2.9
Concentration of base (%)		10.0	20.0	30.0	20.0	20.0	20.0		—	—	—
Length of intestine (cm)		16.0	16.0	16.0	8.0	16.0	24.0		4.0	8.0	12.0
Sulfanilamide	A)	22.70	9.20	3.50	10.00	9.80	9.60	Sulfanilamide	A) 4.50	7.70	11.90
	B)	1.42	0.58	0.22	1.26	0.61	0.40	(0—1.5 hr)	B) 1.13	0.96	0.99
	C)	0.90	0.85	0.85	0.75	0.75	0.75		C) 0.50	0.50	0.50
Sulfisomidine	A)	2.94	1.71	0.81	1.15	2.10	3.38	Sulfanilamide	A) 4.00	4.30	4.70
	B)	0.18	0.11	0.05	0.14	0.13	0.14	(1.5—3 hr)	B) 1.00	0.54	0.39
	C)	0.70	0.80	0.80	0.95	1.00	1.00				
Sulfisoxazole	A)	4.10	1.77	0.60	0.90	1.68	2.59	Sulfisoxazole	A) 0.39	0.84	1.33
	B)	0.26	0.11	0.04	0.11	0.11	0.11		B) 0.10	0.11	0.11
	C)	1.00	1.00	1.00	0.83	0.94	1.00		C) 0.20	0.20	0.40
Sulfadiazine	A)	0.42	0.27	0.21	0.11	0.26	0.42				
	B)	0.03	0.02	0.01	0.01	0.01	0.01				
	C)	0.75	0.75	0.80	0.80	0.75	0.74				

A: permeation rate constants of sulfonamides from whole intestine (mg/hr)
B: permeation rate constants of sulfonamides from unit length of intestine (mg/hr/cm)
C: lag time (hr)

The permeation rate constants were calculated from the slope of the linear portion of the permeation-time curves and summarized in Table II. The linear portion of the curvature has been extrapolated to abscissa and the lag time of permeation was determined.

The permeation rates of sparingly soluble sulfonamides (sulfisomidine, sulfisoxazole, and sulfadiazine) from whole length of the intestine increased in proportion to the length of the intestine (Fig. 4, upper), but the rate of unit length differed little in these sulfonamides (Fig. 4, lower). In the case of soluble sulfonamides (sulfanilamide), the permeation rate from whole segment of the intestine showed no detectable difference (Fig. 4, upper), but the rate of unit length decreased in proportion to the length of the intestine (Fig. 4, lower).

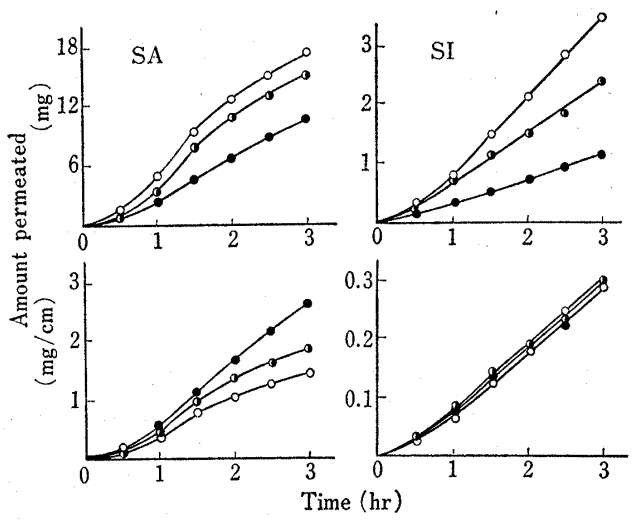

Fig. 5. Permeation Rate of Sulfonamides from Whole and Unit Length of Intestine from Various Volumes of Cacao Butter Suppository

SA: sulfanilamide, SI: sulfisoxazole
—●—: 4 cm (0.9 ml of base volume)
—◑—: 8 cm (1.9 ml of base volume)
—○—: 12 cm (2.9 ml of base volume)

As a reason for this result, it seems that sparingly soluble sulfonamides did not dissolve completely in 20% PEG solution at 37°, but sulfanilamide did and, therefore, a constant concentration was attained by these three kinds of sulfonamides but the concentration of sulfanilamide decreased in proportion to the increasing amount of the base in PEG suppository. From these considerations, it was recognized that the permeation rate of a sulfonamide through the intestinal membrane would be influenced by the concentration of a drug in the PEG solution.

Cacao butter base suppository of 0.9 ml (0.8 g), 1.9 ml (1.6 g), and 2.9 ml (2.4 g) were placed in a sac of 4, 8, and 12 cm of the intestine, respectively (Fig.

1-B). The permeation rate of sulfonamides is shown in Fig. 5 and the rate constants are summarized in Table II.

The permeation rate of sulfisoxazole from unit length of the intestine showed the same pattern, but that of sulfanilamide showed a little difference in three different volumes of the base (Fig. 5). As shown in Table II, the permeation rate constant of sulfanilamide from whole length of the intestine increased in proportion to the base volume and that of unit length was little different in the early stage (0—1.5 hr) but after 1.5 hr, the rate constant from whole length of intestine showed no differences and that of unit length decreased with increasing volume of the base.

As a reason for this result, it would be considered that the permeation of sulfanilamide after 1.5 hr was restricted by the release of drug from the base. On the other hand, if it assumes that the release of sulfisoxazole from the base should be controlled to the same degree as sulfanilamide, the permeation of sulfisoxazole may be restricted by the dissolution rate rather than the release rate because the dissolution rate of sulfisoxazole was very small compared with that of sulfanilamide.[7]

Distribution Area in Rectum and Amount of Rectal Fluid

When the water-soluble rectal suppository was administered, if a certain quantity of rectal fluid is secreted, concentration of the base in rectum should vary according to the amount of the base. If secretion of the rectal fluid varies according to the amount of the base, distribution area of a drug in the rectum should vary. Therefore, it would be important to determine the amount of rectal fluid and distribution area of a drug after administration of a suppository of various volumes. For this purpose, nonabsorbable and easily recognizable material, charcoal, was incorporated into the suppository.

As shown in Table III, rectal fluid was increased with the increasing amount of the PEG base. The concentration of PEG in the rectal fluid was about 30%, independent of the base volume, at 2 hr after administration. On the other hand, there was no detectable amount of the fluid but a little mucus in the rectum after administration of cacao butter base suppository.

Table III. Volume of Rectal Fluid and Distribution Area of Charcoal in Rectum at 2 hr after Administration of Various Volumes of Suppository

Suppository volume (ml)	PEG base			Cacao butter base		
	1.1	2.9	5.8	1.1	2.9	5.8
Rectal fluid (ml)	3.3	10.7	21.5	—	—	—
Concentration of base in rectal fluid (%)	33.0	27.2	27.0	—	—	—
Distribution area of charcoal (cm)	21.0	33.3	48.2	10.0	22.0	40.0

In physiological condition, it would be considered that the secreted rectal fluid is reabsorbed immediately but PEG base suppository is gradually dissolved from the surface, and soak up the rectal fluid until concentration of the base becomes about 30% in the rectum.

Since the concentration of PEG was constant, even though the amount of base was changed, the concentration of sparingly soluble sulfonamides was constant but the amount of the drug dissolved increased according to the amount of rectal fluid. Furthermore, the degree of the depression of partition of a drug from the base solution to rectal membrane should be a constant.

7) T. Takubo, S. Tsuchiya, and M. Hiura, *Yakuzaigaku*, **31**, 298 (1971).

Distribution area of a drug after administration of a suppository in the rectum increased in proportion to the base volume (Table III). It would be expected that the membrane area participating in absorption increased according to the base volume.

Effect of Amount of Base on Rectal Absorption

Since the more wide-spread distribution area has been obtained from the increased amount of the base, it can be anticipated that the drug absorption from the rectum will increase in proportion to the amount of the base.

The blood concentration pattern of sulfonamides after administration of PEG and cacao butter base suppositories with various base volumes to rabbit is shown in Fig. 6, A and B. Absorption and elimination rate constants of sulfonamides were calculated from the blood concentration by the same procedure as in the previous report[3e] and the values are summerized in Table IV. Absorption rate of each sulfonamide varied with the amount of the base, while elimination rate was little affected by the amount of the base.

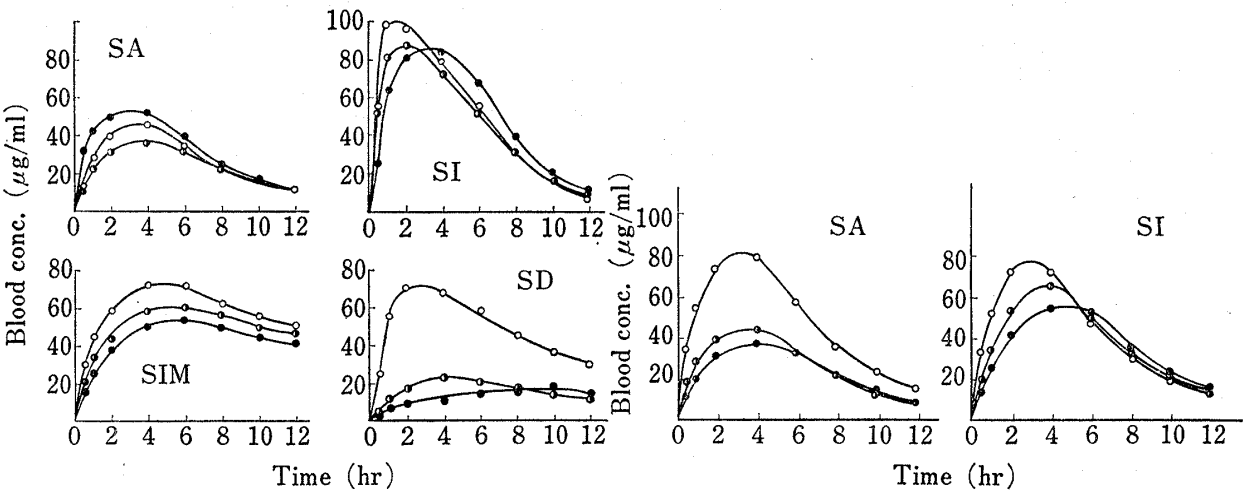

Fig. 6. Blood Concentration of Sulfonamides after Rectal Administration of Various Volumes of Suppository

SA: sulfanilamide, SIM: sulfisomidine, SI: sulfisoxazole, SD: sulfadiazine
—●—: 1.1 ml, —◑—: 2.9 ml, —○—: 5.8 ml

TABLE IV. Elimination Rate Constants (Kel) and Absorption Rate Constants (Ka) of Sulfonamides after Rectal Administration of Various Volumes of Suppository

Base volume (ml)	Kel (hr^{-1})			Ka (hr^{-1})		
	1.1	2.9	5.8	1.1	2.9	5.8
			PEG base			
Sulfanilamide	0.1959	0.1868	0.1853	0.7692	0.4985	0.6123
Sulfisoxazole	0.3254	0.3299	0.3157	0.5189	0.6065	0.8290
Sulfisomidine	0.0496	0.0438	0.0558	0.4761	0.5389	0.6923
Sulfadiazine	0.1050	0.1025	0.1115	0.2267	0.5267	0.9061
			cacao butter base			
Sulfanilamide	0.2111	0.2144	0.2135	0.4545	0.5466	0.6170
Sulfisoxazole	0.1936	0.2067	0.2009	0.4184	0.5548	0.7390

For PEG base suppository, absorption rate constant (Table IV) and maximum blood concentration (Fig. 6-A) of sparingly soluble sulfonamides were both high when a larger volume of suppository was administered. When taking the membrane permeation experiments into consideration, the rectal absorption of sparingly soluble sulfonamide increased in the presence of abundant rectal fluid because the absorption area of a drug in the rectum was increased. But the absorbability of sulfanilamide (water-soluble) was better from a small volume suppository (1.1 ml) than a larger one (2.9—5.8 ml). In this respect, when the suppository has been dissolved completely, the drug concentration of larger volume of suppository would become lower. The limited absorbability of sulfanilamide from 2.9 and 5.8 ml of PEG suppository suggests the possibility of greater influence of concentration rather than absorption area. The absorption of sulfanilamide and sulfisoxazole from cacao butter base suppository increased in proportion to the volume of the base (Fig. 6-B and Table IV), and these results could be explained by the increment of the absorption area in the rectum.

From these results, it is clear that the bioavailability of sparingly soluble sulfonamides was enhanced by the increasing amount of PEG and cacao butter base but the absorbability of water-soluble sulfonamide was reduced by the increasing volume of PEG base. The total areas under the blood concentration-time curve for sulfanilamide are greater from cacao butter than from PEG base when a larger volume of suppository is administered. Then, it would be considered that the bioavialability of soluble drug following rectal administration as suppository is higher from cacao butter than PEG base. It would be important, therefore, to select the kind and amount of suppository base carefully with consideration of the dissolution characteristics of drugs.