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Studies on Characteristics of Drug Exsorption across the Membrane of Rat Small Intestine

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The exsorption of sulfanilamide into the small intestinal lumen after intravenous administration of the drug was studied with perfusion solution without any drugs having three different tonicities such as hypotonicity (0.45%), isotonicity (0.90%), and hypertonicity (1.35%) with sodium chloride employing an *in situ* single perfusion method devised by Schanker and his co-workers. The intraluminal single perfusion was conducted principally at a rate of 1 ml/min. The exsorption rate of the drug into the isotonic perfusate was dose-dependent and the rate was decreased with time obeying the first-order kinetics as well as the decrease in blood level of the drug. The amount of the drug exsorbed in the isotonic perfusate for 180 min represented as the percentage of dose was almost constant (about 17%) in the dose ranges from 10 mg/kg to 50 mg/kg used in the present study. The effect of tonicity of perfusion solution on the exsorption was examined and it was found that the exsorption rate and the amount exsorbed in the perfusate of the drug were increased with increasing the tonicity of the perfusate. Although the exsorption rate and the amount exsorbed in the lumen were changed by different experimental conditions, the existence of the drug in the perfusate was not negligible. These evidences suggest that the small intestinal lumen may be an important organ in the distribution of the drug. Moreover, the excretion of the drug in the bile juice was remarkably smaller than the exsorption of the drug into perfusate. Hence it is able to conclude that the distribution of the drug in the small intestinal lumen might be conducted across the intestinal membrane rather than through the agency of bile juice.

Keywords——bile juice; distribution; drug excretion in bile juice; drug exsorption into perfusate; effect of tonicity; exsorption; osmolality of perfusion solution; sulfanilamide; small intestine

Several investigators have reported the presence of organic bases in the stomach after parenteral administration. Dawson and Ivy[2] have pointed out that thirteen of thirty-three dyes administered intravenously were eliminated by the gastric glands and the parietal cells were the cells of the gastric mucosa most intimately concerned with dye elimination. Kobayashi[3] have also found similar phenomena in the same period. Sung and Way[4] reported that rather large amounts of acetylmethadol in the stomach contents were found in studying the fate of parenterally administered drug in rats. Shore and his co-workers[5] have shown that when levorphanol, a synthetic analgesic, was intravenously administered to dogs it appeared in the gastric juice in a concentration about 40 times that in the plasma. Moreover, they[6] have studied in detail and found that only the basic drugs appeared in gastric juice at a higher concentration than in plasma and the concentration ratio calculated by dividing the level of drug in the gastric juice by that in the plasma increased with the basicity of drugs. Based on these observations, they proposed pH-partition hypothesis.

On the other hand, the fragmental evidence has been accumulated concerning the existence of some sulfa drugs in the small intestinal lumen after parenteral administration of the

1) Location: *a*) *Kawara-cho, Shogoin, Sakyo-ku, Kyoto*; *b*) *Mitahora, Gifu.*
2) A.B. Dawson and A.C. Ivy, *Am. J. Physiol.*, **73**, 304 (1925).
3) K. Kobayashi, *Acta Scholae Med.*, **8**, 465 (1926).
4) C. Sung and E.L. Way, *J. Pharmacol. Exptl. Therap.*, **110**, 260 (1954).
5) P.A. Shore, J. Axelrod, C.A.M. Hogben, and B.B. Brodie, *J. Pharmacol. Exptl. Therap.*, **113**, 192 (1955).
6) P.A. Shore, B.B. Brodie, and C.A.M. Hogben, *J. Pharmacol. Exptl. Therap.*, **119**, 361 (1957).

drugs. Nogami and others[7] have reported that when sodium sulfisomezole was intravenously injected to rats, the drug was found in perfusion solution without any drugs which was perfused through the small intestinal lumen. Kakemi, Kimura and their co-workers,[8] using sulfaguanidine and sulfadimethoxine, found that these drugs injected intravenously were secreted in the small intestinal lumen (exsorption) and the exsorption of drugs was increased by the addition of a bile salt in intraluminal perfusate. The effects of various factors on the exsorption of drugs into the lumen, however, were hardly examined and not discussed fully in these papers.

In our previous studies,[9] it has been clarified using the *in situ* recirculating perfusion method[10] with perfusion solution having different tonicities that the absorption of drugs from the small intestine in rat was increased with increasing the transmucosal fluid inflow (absorption of fluid from the lumen).

The present study was undertaken to elucidate the characteristics of exsorption of the drug, sulfanilamide, after intravenous administration of the drug more in detail and the effect of tonicity of intraluminal perfusion solution on the exsorption rate of the drug.

Materials and Methods

Materials——Sulfanilamide and other chemicals were of reagent grade and obtained from commercial sources. These were used without further purifications.

Preparation of Drug Solution for Intravenous Injection——Sulfanilamide of 200 mg was dissolved in 5 ml of N,N-dimethylacetamide, which has been well employed as a solubilizing agent to inject intravenously sulfonamides,[8a,b,11] and isotonic sodium chloride solution was added to the solution to make 10 ml and an aliquot volume of the solution was intravenously injected.

Preparation of Perfusion Solution——An aliquot of sodium chloride was dissolved to purified distilled water and osmotic pressure of the solution was adjusted to hypotonicity (0.45%), isotonicity (0.90%), and hypertonicity (1.35%), respectively.

Animal Procedures——Male albino rats of the Wistar strain weighing about 200 g were used in all experiments. The animals were fed a standard laboratory diet and given tap water *ad libitum* prior to exsorption experiments. With the rats under sodium pentobarbital (Nembutal, 50 mg/kg *i.p.*) anesthesia, the small intestine was exposed by a midline abdominal incision. Both the upper duodenum and the ileo-cecal junction were opened and the entire small intestine was cleared with physiological sodium chloride solution which had been maintained at 37°. Both of the openings were cannulated with silicon tubings. The common bile duct was also ligated to avoid any inflow into the perfusate during the exsorption experiments unless otherwise specified. In order to examine the excretion of sulfanilamide in bile juice, the bile juice was collected separately from the common bile duct which was cannulated with polyethylene tubing. The intestine was replaced in the abdomen and the incision was closed with a metal clip. The blood sample to determine the blood level of the drug was collected from the left femoral artery, which was cannulated with polyethylene tubing, at a given interval. With the purpose to collect the blood samples during the course of the perfusion experiment, 0.1 ml of heparin solution (1000 Unit/ml solution, Novo Industri, A/S Copenhagen, Denmark) was injected intravenously.

Exsorption Procedures——Following the single perfusion method, which was devised by Schanker and collaborators,[10] isotonic sodium chloride solution (0.90%) which had been maintained at 37° was perfused intraluminally with the perfusion rate of 1 ml/min from duodenum to ileum using a pump (CV-1 type, Tokyo Kagaku Seiki Co.). The perfusate was recovered in an adequate volumetric cylinder from the outlet terminal of silicon tubing cannulated into the ileo-cecal junction. After the recovery of perfusate was almost constant, that is, the rate of the single perfusion was kept constant and uniformal flow of the perfusate was obtained, the drug solution was injected attentively from the right femoral vein. The collection of perfusate was started immediately after the injection was through. The volumetric cylinder used as a reservoir of perfusate was renewed at a given interval and the volume was read. The perfusate collected was used for analysis and the exsorption rate of the drug into the perfusate was determined.

7) H. Nogami, M. Hanano, and H. Yamada, *Chem. Pharm. Bull.* (Tokyo), **11**, 395 (1963).
8) *a*) K. Kakemi, H. Sezaki, R. Konishi, T. Kimura, and A. Okita, *Chem. Pharm. Bull.* (Tokyo), **18**, 1034 (1970); *b*) T. Kimura, K. Inui, and H. Sezaki, *Yakuzaigaku*, **31**, 167 (1971).
9) *a*) S. Kitazawa, H. Ito, and H. Sezaki, *Chem. Pharm. Bull.* (Tokyo), **23**, 1856 (1975); *b*) S. Kitazawa, H. Ito, and M. Iinuma, *ibid.*, **23**, 2128 (1975); *c*) S. Kitazawa and I. Johno, *ibid.*, **24**, 2832 (1976).
10) L.S. Schanker, D.J. Tocco, B.B. Brodie, and C.A.M. Hogben, *J. Pharmacol. Exptl. Therap.*, **123**, 81 (1958).
11) T. Komuro, S. Kitazawa, and H. Sezaki, *Chem. Pharm. Bull.* (Tokyo), **23**, 400 (1975).

Measurement of Osmolality of Perfusate——The osmolality of perfusate collected from the outlet terminal of silicon tubing cannulated into the ileo-cecal junction was determined with Advanced Osmometer model 3D (Advanced Instruments, Inc., Massachusetts, U.S.A.) applying freezing point depression.

Analyses——The drug in the perfusate, blood, and bile juice samples was diazotized with the regular manner[12] and coupled with 2-diethylaminoethyl-1-naphthylamine (Tsuda's reagent). The color developed was extracted with isopentyl alcohol by salting-out with sodium chloride and the organic phase was determined spectrophotometrically at a wave length of 550 nm using a Hitachi spectrophotometer model 124.

Results

Dose Dependency in Exsorption of Sulfanilamide

The dose dependency in the exsorption of sulfanilamide in the isotonic perfusate across the small intestinal membrane was examined using the dose ranges from 10 mg/kg of body weight of the animal to 50 mg/kg. The time course observations in blood level and exsorption rate of the drug were in Fig. 1. The dose dependency in the exsorption rate was observed, that is, the exsorption rate was increased with increasing the dose of the drug. As well as

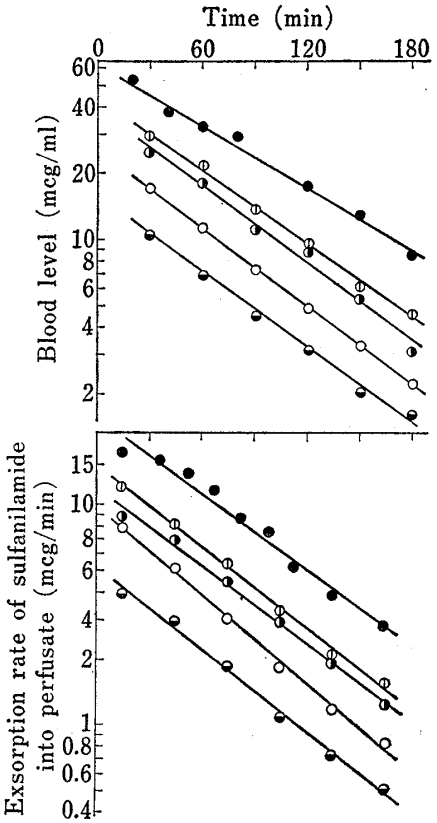

Fig. 1. Dose Dependency and Time Course Observations in Blood Level and Exsorption Rate of Sulfanilamide into an Isotonic Perfusate across the Small Intestinal Membrane

The drug was intravenously administered. The straight regression lines were calculated and drawn by the least squares method. The tonicity of perfusion solution was adjusted to isotonic with sodium chloride. In the dose of 25 mg/kg, five replicate determinations were conducted and essentially similar pattern was obtained in all cases. ●: 50 mg/kg, ◫: 30 mg/kg, ◑: 25 mg/kg, ○: 20 mg/kg, ◒: 10 mg/kg.

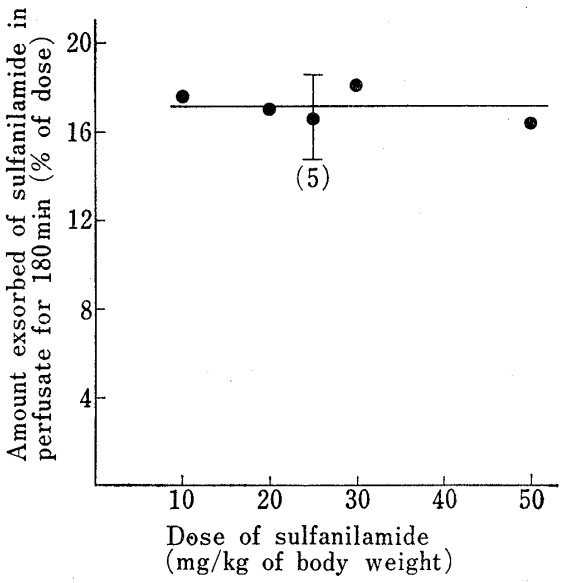

Fig. 2. Amount Exsorbed of Sulfanilamide in an Isotonic Perfusate across the Small Intestinal Membrane for 180 Minutes Obtained with Various Doses

The tonicity of perfusion solution was adjusted to isotonic with sodium chloride. The amount of the drug in the perfusate was represented as the percentage of dose. Five replicate determinations were conducted in the dose of 25 mg/kg and the mean value was plotted in the figure. Number in parenthesis indicates number of experiments.
⊥: mean±S.D.

12) A.C. Bratton and E.K. Marshall, Jr., *J. Biol. Chem.*, **128**, 537 (1939).

TABLE I. The Slopes of Respective Regression Lines Representing the Relation between Blood Level or Exsorption Rate of Sulfanilamide on the Vertical Axis and Time on the Horizontal Axis, and Half-lives of the Blood Level and the ExsorptionRate Obtained with Different Doses of the Drug

Dose (mg/kg)	$n^{a)}$	Blood		Exsorption rate	
		Slope (min^{-1})	Half-life (min)	Slope (min^{-1})	Half-life (min)
10	1	-5.57×10^{-3}	54.0	-6.22×10^{-3}	48.4
20	1	-5.91×10^{-3}	50.9	-6.76×10^{-3}	44.5
25	5	-4.95×10^{-3} *b)*	60.8 *b)*	-5.63×10^{-3} *b)*	53.5 *b)*
30	1	-5.56×10^{-3}	54.1	-6.20×10^{-3}	48.6
50	1	-4.76×10^{-3}	63.2	-5.76×10^{-3}	52.3

The perfusion solution through the intestinal lumen was isotonic (0.90%).
a) Number of experiments.
b) Mean values of five rats.

the elimination of the drug from blood, the exsorption rate of the drug into the perfusate was decreased obeying the first-order kinetics. The half-lives of the exsorption rate and the elimination from blood calculated from the data in Fig. 1 were listed in Table I. The half-life in the elimination of the drug from blood under the experimental condition used in the present study was almost in agreement with that of the exsorption rate. These observations suggest that the rate of exsorption of the drug might follow the blood level.

The amount of the drug exsorbed in the isotonic perfusate for 180 min calculated due to the data shown in Fig. 1 and those obtained with the dose of 25 mg/kg using more four animals were depicted in Fig. 2. The amount of the drug exsorbed in the perfusate representing as the percentage of dose was approximately constant (about 17% of dose) in the dose ranges of the drug used in the present study.

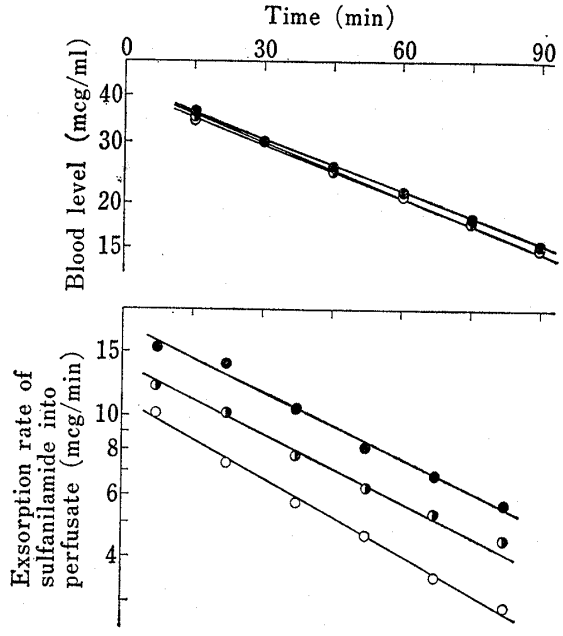

Fig. 3. Time Course Observations in Blood Level and Exsorption Rate across the Small Intestinal Membrane of Sulfanilamide Obtained Using Perfusion Solution Having Three Different Tonicities

The perfusion solution was adjusted to hypotonic (0.45 %), isotonic (0.90%), and hypertonic (1.35%) with sodium chloride, respectively. The drug was intravenously administered in the dose of 25 mg/kg in all cases. Three replicate determinations were made and essentially similar pattern was obtained respective cases. The regression lines were illustrated after calculations following the least squares method.
○: hypotonic, ◑: isotonic, ●: hypertonic.

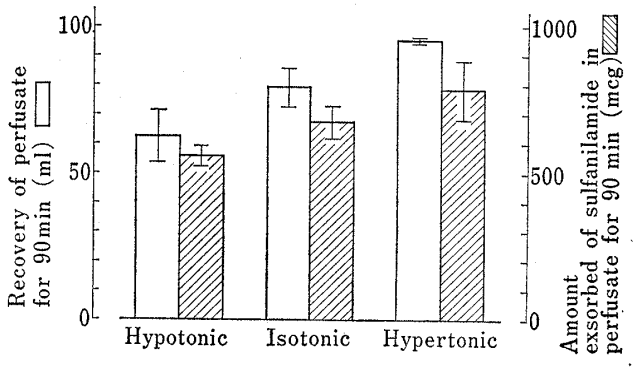

Fig. 4. Recovery of Perfusate and Amount Exsorbed of Sulfanilamide in Perfusate for 90 Minutes

All values are the mean of three determinations. The perfusion solution was adjusted to hypotonic (0.45%), isotonic (0.90%), and hypertonic (1.35%) with sodium chloride, respectively.
I: mean ± S.D.

Effect of Tonicity of Perfusion Solution on Exsorption of Sulfanilamide

The tonicity of perfusion solution through the intestinal lumen was adjusted to hypotonic, isotonic, and hypertonic with sodium chloride, respectively, however, the dose of sulfanilamide was kept at 25 mg/kg of body weight of the animal in all cases to examine the effect of tonicity of perfusion solution on the exsorption of the drug. The time course observations in blood level and exsorption rate of the drug were depicted in Fig. 3. The exsorption rates obtained with three different tonicities were decreased obeying first-order kinetics and were increased with increasing the tonicity of perfusate, although no difference in the blood level of the drug was found.

The recovered volume of perfusate and the amount of sulfanilamide exsorbed in perfusate for 90 min were shown in Fig. 4. Both of these values were increased with increasing the tonicity of perfusate, that is, the increase in the recovery of perfusate, in other words, the decrease in the transmucosal fluid inflow resulted in the increase in the exsorption of the drug. The average recovery of perfusate represented as the percentage of infused volume was 69.1% for hypotonic, 87.9% for isotonic, and 106.1% for hypertonic, respectively. The average amount of the drug exsorbed represented as the percentage of dose was 10.2, 13.0, and 16.0% for hypotonic, isotonic, and hypertonic, respectively. From these values, a good correlation between the recovery of perfusate on the vertical axis and the amount of the drug exsorbed in perfusate on the horizontal axis was found (regression equation: $y=4.46\ x+29.38$; n: 9; r: 0.793, $p<0.02$), although the figure was not shown in the present study. These results obtained were reverse phenomena, compared with those observed in the absorption rate of the drug across the small intestinal membrane of rat as was represented by our previous reports,[9a,c] in which the absorption rate of the drug was increased with decreasing the tonicity of perfusion solution containing the drug.

The rate of decrease in the blood level with time was similar degree with that of the exsorption rate and the mean and standard deviation of these values obtained with respective three animals were listed in Table II. As is evident from Table II, the average slope of

Table II. The Slopes of Respective Regression Lines Representing the Relations between Blood Level or Exsorption Rate of Sulfanilamide on the Vertical Axis and Time on the Horizontal Axis, and Half-lives of the Blood Level and the Exsorption Rate of the Drug Obtained with Perfusion Solution Having Three Different Tonicities

Tonicity[a]	n[b]	Blood		Exsorption rate	
		Slope $\times 10^3$ (min^{-1})	Half-life (min)	Slope $\times 10^3$ (min^{-1})	Half-life (min)
Hypotonic	3	-4.80 ± 0.19	62.9 ± 2.4	-6.04 ± 0.89	50.8 ± 6.9
Isotonic	3	-5.15 ± 0.21	58.5 ± 2.4	-5.71 ± 0.26	52.8 ± 2.3
Hypertonic	3	-5.64 ± 0.44	53.6 ± 3.9	-6.12 ± 0.11	49.3 ± 0.9

All values are mean $\pm$ S.D.
a) Each tonicity of perfusion solution was adjusted to hypotonic (0.45%), isotonic (0.90%), and hypertonic (1.35%) with sodium chloride, respectively.
b) Number of experiments.

respective straight regression lines obtained with the least squares method and the average of respective half-lives in the blood level were in approximately agreement with those in the exsorption rate in all tonicities of perfusate. In the strict sense of the term concerning these values, the half-life of the drug elimination from blood tended to decrease with increasing the tonicity of perfusate and a significant difference between the half-life obtained with the hypotonic perfusate and that obtained with the hypertonic perfusate was found ($p<0.05$),

although no significant difference between respective tonicities in the half-life of the exsorption rate was observed.

Relation between Exsorption Rate of Sulfanilamide into Perfusate and Excretion Rate of the Drug in Bile Juice

The excretion rate of sulfanilamide in bile juice was compared with the exsorption rate of the drug into perfusate with a dose of 25 mg/kg. The results obtained were shown in Fig. 5. The excretion rate of the drug in bile juice was also decreased with time obeying the first-order kinetics as well as the decrements in the exsorption rate into perfusate and the blood level of the drug with times. The slope of straight regression line obtained using the least squares method and the half-life in the excretion rate of the drug in bile juice were somewhat similar to those in the blood level and the exsorption rate of the drug into perfusate. However, the excretion rate of the drug in bile juice was appreciably small, compared with the exsorption rate of the drug into the isotonic perfusate.

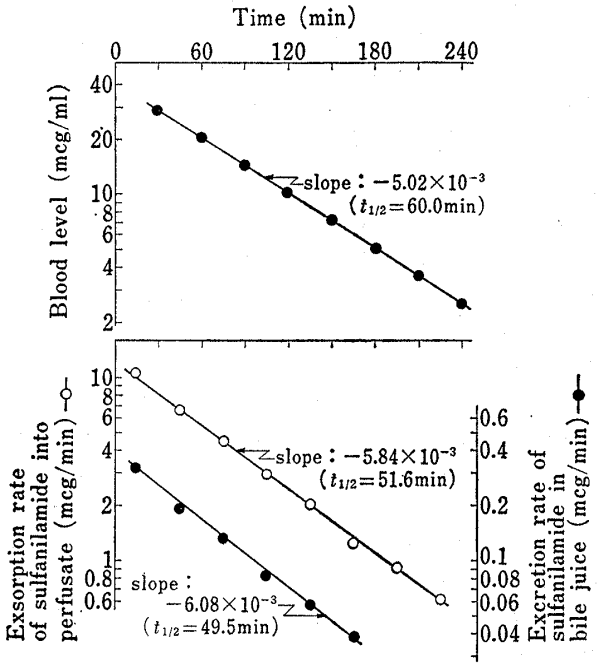

Fig. 5. Time Course Observations of Sulfanilamide in Blood Level, Exsorption Rate into an Isotonic Perfusate across the Small Intestinal Membrane, and Excretion Rate in Bile Juice

The tonicity of perfusate was adjusted to isotonic (0.90%) with sodium chloride. The dose of the drug was 25 mg/kg of body weight of the rat. The regression lines were illustrated after calculations following the least squares method. The $t_{1/2}$ indicates respective half-lives.

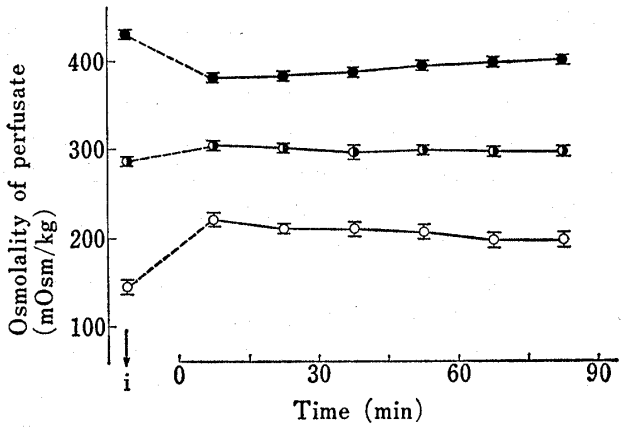

Fig. 6. Time Course Observations in Osmolality of Intraluminal Perfusate

The perfusate was initially adjusted to hypotonic (0.45%), isotonic (0.90%), and hypertonic (1.35%) with sodium chloride, respectively. The perfusate was collected at 15 min intervals from the outlet terminal of silicon tubing cannulating into the ileo-cecal junction. The i in the figure indicates the osmolality of respective initial perfusates prior to the intraluminal perfusion. All values are mean ± S.D. obtained with respective three determinations.

○: hypotonic, ◑: isotonic, ●: hypertonic.

I: mean±S.D.

Discussion

Average half-life of the drug elimination from blood obtained under the condition of exsorption experiment employed in the present study was revealed 60 min in approximation (Table I and II). This half-life was apparently shortened, compared with that of the intact animal which was about 80 min in separate control experiments. Possible mechanisms in explanation of this shortening might be considered as that the reabsorption process was lacking in the experimental condition such as the exsorption and that the concentration gradient of the drug between blood and the lumen was kept always in considerable difference in such condition of single perfusion experiment. To demonstrate these considerations, a series of

exsorption experiments were conducted with different rates of single perfusion. Although the results obtained will be reported in detail from our laboratories in future,[13] the half-lives of the drug elimination were gradually increased with decreasing the rate of perfusion; on the contrary, the drug concentration in the perfusate was increased with decreasing the rate. However, in such condition as the rate was less than 1 ml/min the exsorption data were found fluctuate and it seemed to be impossible to draw any conclusion without introducing another technique in the experiment.

The exsorption rate of sulfanilamide into the isotonic saline perfusate was dose-dependent in the dose ranges from 10 mg/kg to 50 mg/kg used in the present study, *i. e.*, the exsorption rate was increased with increasing the intravenous dose of the drug (Fig. 1). Moreover, the rate of elimination of the drug from blood was similar to the rate of decrement in the exsorption rate in all cases under the experimental condition mentioned above (Table I). It seemed that similar phenomena might be observed employing perfusion solution having different tonicities, because the exsorption of the drug into hypotonic or hypertonic solution was similar in pattern to that into the isotonic solution, although the exsorption rate and the amount exsorbed in respective solutions of the drug were different as will be mentioned below in detail. So far we have not encountered the reports in which sulfanilamide was actively transported from the intestinal lumen to blood. These observations suggest that the transport of the drug from the lumen to blood (absorption) and from blood to the lumen (exsorption) may be carried out by a similar mechanism such as passive diffusion.

It is well known that solution in the duodenum and upper jejunum rapidly come into osmotic equilibrium with the blood; and chyme, which may have any osmolality when it enters the duodenum, it brought about quickly to isotonicity and remains isotonic as it moves down the rest of the small intestine.[14] However, it was found under the condition used in this report that there is still a osmotic difference between respective perfusates when the osmolality of perfusate collected from the outlet terminal of silicon tubing cannulated into the ileo-cecal junction was measured, although all the perfusates tend to come into isotonicity owing to the bidirectional transmucosal fluid movement as shown in Fig. 6. The osmolality of perfusate prior to the luminal perfusion was smaller than that after the perfusion in the hypotonicity; on the contrary, in the hypertonicity the osmolality prior to the perfusion was greater than that after the perfusion. The osmotic pressure in the isotonic perfusate was kept almost constant during the course of the experiment. However, it was recognized that the osmolality of hypotonic or hypertonic solution perfused intraluminally tend to approach to the respective initial values. The intensity of these physiological regulations in the small intestine, with which the luminal solution come into osmotic equilibrium, might be reduced gradually with time. These phenomena suggested that there might be limitations in capacity of osmotic regulation owing to the bidirectional transmucosal fluid movements in the lumen of the animal with which a intraluminal solution having abnormal osmolality such as hypotonic or hypertonic state is attained to normal tonicity.

Under these physiological circumstances in the small intestinal lumen, the effect of tonicity of perfusion solution on the exsorption of the drug was examined. Almost all the animals were died for 120—150 min after the intravenous administration of the drug when the hypertonic solution, with which apparent outflow of fluid into the lumen was observed (Fig. 4), was intraluminally perfused. It seemed that the apparent outflow of fluid to regulate the abnormal high osmolality might be one of the mortal causes. Hence the perfusion time was set up for 90 min. The exsorption rate and the amount exsorbed in perfusate for 90 min of the drug were increased with increasing the tonicity of perfusate (Fig. 3 and 4). Namely,

13) S. Kitazawa, I. Johno, and H. Ito, "in preparation."
14) H.W. Davenport, "Physiology of the Digestive Tract," 3rd ed., Year Book Medical Pub., Inc., Chicago, 1971, p. 174.

the exsorption rate and the amount exsorbed in perfusate was decreased with increasing the transmucosal fluid absorption. Kitazawa and his co-workers[9] have reported that the absorption of drugs from the lumen was increased with increasing the transmucosal fluid absorption. These evidences strongly demonstrate that the bidirectional transports of sulfanilamide across the small intestinal membrane, *i.e.*, absorption and exsorption of the drug, were affected remarkably by the transmucosal fluid movement and when the direction of drug transport across the intestinal membrane coincided with that of the transmucosal fluid movement, the drug transport was increased following an increased transmucosal fluid movement.

The amount of sulfanilamide exsorbed in the isotonic perfusate for 180 min representing as the percentage of dose was about 17% in all doses used in the present study (Fig. 2). However, it has to be noted that this observation was obtained with the perfusion rate of 1 ml/min. Although the exsorption rate and the amount exsorbed in the intestinal lumen of the drug were changed by different experimental conditions as mentioned above, the existence of the drug in the perfusate was observed in all cases used in this study. Davenport and his collaborators[15] have reported that sulfanilamide is secreted in the gastric juice. These evidences suggest that the gastrointestinal tract is not negligible as one of distribution organs of the drug. Furthermore, the drug exsorbed in the small intestinal lumen might be absorbed once more, because the drug was favorably absorbed from the lumen;[9a,c] and this entero-hemato circulation might result in the durability in pharmacological action of the drug. In fact, sulfanilamide has been classified as one of medium-long-acting or long-acting sulfonamides in spite of a low protein binding.[16] Considering from evidence such as reabsorption of the drug exsorbed in the lumen, it seems that the accurate measurement in the exsorption rate and the amount exsorbed of the drug using non-treated intact animals might be fairly difficult.

The small intestinal motility[17] and the transit time of luminal contents[18] are affected by various intestinal conditions. Moreover, although osmotic equilibrium in the intestinal lumen is attained by absorption of solutes and by net movement of water from blood to lumen,[14] these balance in the osmolality of luminal contents might be broken down at a time by several intestinal conditions such as the decrease in the absorption rate of intestinal contents. Hence it seems that the exsorption rate and the amount exsorbed in the lumen of the drug might be also affected by these physiological alterations in the digestive tract.

When a drug is secreted in one part of the body and resorbed in another a cyclic process results and the best-known example of this phenomenon is the secretion of substances in the bile and resorption in the small intestine.[19] When the excretion rate of sulfanilamide in bile juice was compared with the excretion rate of the drug into the luminal perfusate, it was recognized that the former, which was only about 0.5% of dose, was remarkably smaller than the latter (Fig. 5). The results obtained demonstrate that the drug might be mainly distributed in the small intestinal lumen across the intestinal membrane. Czok and Dammann[20] have reported that bromsulphthalein was secreted about 80% of dose in bile within 30 min after intravenous administration of the compound (5—6 micromol/kg). Takada and others[21] have shown that bromphenol blue, a non-metabolizing organic compound, was secreted about 55% of dose in bile juice within 30 min. Their observations suggest that these organic com-

15) M. Cooke, H.W. Davenport, and L.S. Goodman, *Yale J. Biol. Med.*, **14**, 13 (1941); H.W. Davenport, *ibid.*, **14**, 589 (1941).
16) T. Struller, *Antibiot. Chemotherap.*, **14**, 179 (1968).
17) H.W. Davenport, "Physiology of the Digestive Tract," 3rd ed., Year Book Medical Pub., Inc., Chicago, 1971, pp. 61—69.
18) T. Hukuhara, "Mechanism of Gastrointestinal Motility," 1st ed., Bunko-do, Tokyo, 1973, pp. 27—28 (in Japanese).
19) T.H. Wilson, "Intestinal Absorption," W.B. Saunders Co., Philadelphia, 1962, p. 253.
20) G. Czok and H.G. Dammann, *J. Pharm. Pharmacol.*, **24**, 820 (1972).
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pounds might be eliminated principally in the intestinal lumen through the agency of bile juice.

These lines of evidences and findings obtained in the present study demonstrated that the small intestine is apparently one of the target organs of drug distribution. In these several years, studies on drug transfer in biological system and drug distribution into various organs were often undertaken with purposes of evaluating efficacy and safety of the drug. Although many skilful devices have been developed and data were accumulated, the freezing whole-body autoradiography method originally devised by Ullberg[22] was recognized as one of the most appropriate and comprehensive methods in investigating the distribution of labeled compound. The method has contributed in elucidating minute distribution of the drug throughout the animal body. However, the present report arouses attentions in analysing the distribution data especially when the drug was administered through oral route. Investigators should discriminate the exsorbed and unabsorbed portions from total amount of the drug existed in the small intestine of the subjected animal.

The present study demonstrates that drug is exsorbed into the small intestinal lumen and the technique of measuring the rate and extent of the drug exsorption is rather simple. The simple method may open the way speculating the extent of distribution of the drug into the small intestine after the administration.

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