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Rectal Delivery of Antiinflammatory Drugs. I. The Influence of Antiinflammatory Drugs on Rectal Absorption of β-Lactam Antibiotics[1)]

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The effects of non-steroid antiinflammatory (NSAI) drugs on the rectal membrane were studied by measuring the change in the rectal absorption of ampicillin and cephalothin. All the NSAI drugs studied were found to case a remarkable enhancement of the rectal absorption of antibiotics which were not able to permeate readily through the rectal membrane in the absence of NSAI drugs. The optimum concentrations of NSAI drugs as adjuvants in triglyceride suppositories containing 10% ampicillin sodium were 1.5% for indomethacin sodium and diclofenac sodium, 5% for mepirizole, 7.5% for phenylbutazone, and 10% for sodium salicylate. These concentrations of NSAI drugs were used in a study of the promoting efficacy of the drugs as adjuvants for the rectal absorption of antibiotics. The promoting effects of adjuvants in dogs were inferior to those in rabbits. From simultaneous measurements of NSAI drugs and antibiotic, it was found that the absorption of antibiotic started at the early stages after the administration of suppositories and the peak blood level was reached while the blood concentration of NSAI drug was still increasing. From these results, it was suggested that the NSAI drugs made the mucosal barrier leaky to water-soluble antibiotics at the early stages of permeation of the NSAI drugs through the rectal membrane, and that the barrier rapidly recovered its normal properties even while the permeation of NSAI drug was continuing and a considerable amount of antibiotic still remained in the rectal cavity.

A linear correlation between the enhanced absorption of antibiotics and the antiinflammatory activity of NSAI drugs against carrageenan-induced edema was observed.

Keywords——indomethacin; diclofenac; salicylic acid; phenylbutazone; mepirizole; rectal absorption; promoter; ampicillin; cephalothin; HPLC-analysis

It is well known that many drugs can irritate the gastrointestinal mucosa in humans and experimental animals following oral administration, and administration *via* the routes of injection has been questioned because of possible disadvantages such as local irritation and amyotrophia.[2)] Recently, rectal administration has been tentatively studied as a delivery route to overcome these problems. It is also currently recognized that, after rectal administration, drugs absorbed at the lower and middle parts of the rectum mainly enter the general circulation without the possibility of bioinactivation by the so-called first-pass effect in the liver.[3)] Fifty percent or more of drugs absorbed rectally can be transferred into the systemic circulation in contrast to complete passage through the liver after oral administration.[4)] Thus, rectal administration is recommended as a noninvasive alternate for drugs easily metabolized in the liver. Indeed, for certain drugs, rectal administration produces comparable or better results than oral administration in terms of clinical effectiveness.[5)]

Kakemi *et al.*[6)] reported that sulfonamides were absorbed from the rat rectum by passive transport and the patterns of absorption were similar to those of gastrointestinal absorption according to the pH-partition theory.[7)]

Thus, a drug which is unable to permeate readily through the rectal membrane alone because of its unfavorable lipid affinity requires some adjuvant(s) to enhance its membrane permeability.

To promote rectal permeability, chelating agents[8)] and surface-active agents[9)] have been extensively used, but the mechanism(s) of the promoting processes remain to be clarified.

Concerning the intestinal absorption of salicylic acid, it is rapidly absorbed from the small intestine despite nearly complete dissociation at the physiological pH region of the intestine because of its low pK_a of 3.0.[10] Kunze *et al.*[11] studied the absorption of salicylic acid through the rat jejunum and considered that salicylic acid was mainly absorbed in the ionized state and that the contribution of chelation of divalent metal ions, be it Ca^{2+} of cell membranes or other ions inside the cells essential for their metabolism and integrity, was important for the permeation of the hydrophilic salicylate ions.

Recently, Nishihata *et al.*[12] demonstrated the promoting efficacy of salicylic acid on the membrane permeability of some drugs through the rat rectum by an *in situ* perfusion method.

The present study was performed to clarify the effect of non-steroid antiinflammatory (NSAI) drugs on the rectal absorption of hydrophilic drugs. As hydrophilic drugs, β-lactam antibiotics were used because of their possible usefulness for clinical purposes and the convenience of their assay in the blood.

Experimental

Materials——NSAI drugs used were salicylic acid (SA) and its sodium salt (SANa), phenylbutazone (PB) and its sodium salt (PBNa), indomethacin (IM) and its sodium salt (IMNa), diclofenac (DC) and its sodium salt (DCNa), and mepirizole (MP). β-Lactam antibiotics used were the sodium salts of ampicillin (ABPCNa) and cephalothin (CETNa). SA, SANa, PB, PBNa, IM, and IMNa were purchased from Wako Pure Chemicals Co., Ltd. and DCNa was obtained from Nippon Bulk Yakuhin Co., Ltd. These drugs were used without further purification. DC was prepared from DCNa. MP was extracted from commercial tablets and routinely purified. Other reagents and solvents used were of analytical reagent grade and were used without further purification.

Preparation of Suppositories——All drugs were passed through a 100 mesh sieve. As a suppository base, Witepsol H-15 (Dynamit Nobel A. G., Chemishe Werke Witten, German Federal Republic) was used. For all experiments involving rectal and intravenous administration, a fixed dose of 15 mg/kg (0.04 mmol/kg of ABPCNa and 0.036 mmol/kg of CETNa) was selected. The suppositories were prepared by the fusion method, *i.e.*, aliquots of an NSAI drug and antibiotic were mixed with a mortar and pestle, the mixed powder was suspended in the molten base at 40°C, the suspension was homogenized by sonication for 2 min at 30—35°C employing an ultrasonic cleaner (Branson 220, Branson Co., Ltd., U.S.A.) and the suspension was poured into 1 ml plastic molds (Nippon Elanco Co., Ltd.) at 28°C. Suppositories prepared were 10% (w/w) of ABPCNa or CETNa and 0.5—10% (w/w) of one of NSAI drugs. The drug contents in suppositories were determined by a microbiological assay for the antibiotics and by a high-performance liquid chromatographic method for the NSAI drugs and found to be within ±0.5% of the stated amounts.

***In Vivo* Absorption Study**——Adult male rabbits weighing 2.3—2.5 kg and adult beagle dogs of either sex weighing 10—12 kg were used. Animals were fasted for 24 h before the experiments, but water was given freely. After the insertion of a suppository into the rabbit rectum, the anus was closed with a plastic clip for 20 min. The expulsion and leakage of the suppository during the experimental period was prevented by this short-term clipping. For the experiments with dogs, the clipping was omitted because no leakage was observed during the experimental period. Blood samples were withdrawn into heparinized syringes at the designated intervals from the marginal ear vein in rabbits and from the jugular vein in dogs. They were taken into 10 ml glass tubes and centrifuged at 3000 rpm for 5 min. The plasma layer was taken into stoppered glass tubes and kept at 4°C until assays were carried out. Oral administration was carried out using gelatine capsules. In case of intravenous administration, saline solution of a drug was injected into the marginal ear vein in rabbits and the jugular vein in dogs.

Analysis of Antibiotics——An aliquot of 0.2 ml of plasma was diluted with 1.0 ml of water in the case of ABPC and 0.4 ml of water in the case of CET, and the concentrations of antibiotics were routinely measured by microbiological assay using *Micrococcus luteus* (ATCC 9341) as the test organism. The paper disk diffusion method and the penicillin cup diffusion method were used for the determination of ABPC and CET, respectively.

Analysis of SA, PB, IM, and DC——The concentrations of these four NSAI drugs were measured by a high-performance liquid chromatographic method (HPLC). An aliquot of 0.5 ml of plasma sample was mixed with 0.5 ml of water and 0.5 ml of 0.3 N HCl in a stoppered 10 ml centrifuge tube. After the addition of 7 ml of a solvent, the tube was shaken for 10 min in a KM shaker (Iwaki Co., Ltd.) at room temperature. Solvents used were benzene for PB, IM and DC, and ethyl ether for SA. After centrifugation for 2 min at 1800 rpm, 6 ml of the organic layer was pipetted into a 10 ml centrifuge tube. The organic layer was concentrated at 40°C under reduced pressure in a Vapor-Mix (Tokyo Rikakikai Co., Ltd.). Twenty-five μl of a mobile phase (Table I) containing an internal standard was taken into the tube. Ten μl of the solution was

Table I. Analytical Conditions for High-Performance Liquid Chromatography in the Determination of IM, DC, SA, and PB

	IM	DC	SA	PB
Mobile phase	0.01 M PBS, pH 7.4 containing 0.03 mol $NaNO_3$	0.01 M PBS, pH 7.0 containing 0.2 mol $NaNO_3$	0.01 M PBS, pH 6.5	0.01 M PBS, pH 6.0
Detector	UV 268 nm	UV 275 nm	UV 295 nm	UV 275 nm
Retention time	Sample 3.8 min I.S. 5.5 min	Sample 5.8 min I.S. 4.8 min	Sample 4.0 min I.S. 6.0 min	Sample 4.8 min I.S. 6.8 min
I.S.	DC	NPA	SNS	NPA

Instrument, JASCO TRIROTAR-II; column, 500 mm × 3.15 mm; packing material, Permaphase AAX; flow rate, 1.0 ml/min. PBS, phosphate buffer; I.S., internal standard; NPA, N-phenylanthranilic acid; SNS, sodium 1-naphthalenesulfate.

injected onto the HPLC column. From the ratio of the peak height of a drug to that of the internal standard, the concentration of the drug was routinely obtained. Analytical conditions for HPLC are listed in Table I. The recoveries of all NSAI drugs assayed in plasma samples were essentially complete under the analytical condition stated in Table I.

Analysis of MP——The concentration of MP in plasma samples was measured by a thin-layer chromatographic method employing a Shimadzu CS-900 chromatogram scanner equipped with a dual-wave length spectrophotometer. Five-tenths ml of plasma was taken into a 10 ml glass tube, and 0.5 ml each of water and 1 N aqueous NH_3 and 7 ml of benzene were taken into the tube. The mixture was shaken for 10 min at room temperature with the shaker. After centrifugation for 2 min at 1800 rpm, 6 ml of the organic layer was taken into a 10 ml glass tube. Benzene was evaporated off at 50°C under reduced pressure. The residue was redissolved by the addition of 25 μl of methanol containing phenylbutazone (1μg/ml) as an internal standard. Ten μl of the solution was applied at the bottom of a thin-layer chromatography plate (Silica 60F 254, E. Merck). After development with a mixture of MeOH–benzene (1: 9) to about 10 cm, the amounts of drugs in the spots were measured by means of a scanner. The ratio of the area under the recorded curve of MP to that of the internal standard was used to calculate the concentration of MP. The analytical procedures are presented in Table II. The recovery of MP from the plasma samples was essentially complete in the present analytical procedures. The lowest detectable amount of MP in plasma was 0.05 μg/ml.

Table II. Analytical Conditions for Chromatoscanner and TLC in the Determination of MP

Instrument	Shimadzu CS-900 Dual-Wave Length Chromatoscanner with Auto Zero Suppressor and Expansion System
Detector	Sample UV 255 nm Reference UV 330 nm
Slit	0.5 mm × 10 mm
Sensitivity	0.1 AUFS
Scanning	Linear Scan (40 mm/min)
TLC plate	Silica Gel 60F 254 (E. Merck)
Solvent system	MeOH–Benzene (1: 9)
Rf value	MP 0.22 I.S. 0.44
I.S.	Phenylbutazone

I.S.; internal standard.

Partition Coefficient——Drugs were dissolved in 0.05 M phosphate buffer (pH 7.4, μ 0.15) at a concentration of 1 mM. An aliquot of 10 ml of the solution was shaken with an equal volume of *n*-octanol, previously saturated with the buffer at 37°C, for 60 min at 37°C. The mixture was allowed to stand for 30 min at 37°C, then 2 ml of the aqueous layer was taken into a test tube and diluted with the buffer. The absorbance at λ_{max} of each sample was measured employing a Shimadzu UV-200 spectrophotometer, and the partition coefficient (P) was calculated from the absorbance of the aqueous layer before and after the distribution experiments ($P = C_{n\text{-octanol}}/C_{H_2O}$).

***In Vitro* Release Study**——The *in vitro* release of drugs from the suppositories at 37°C was determined using a dissolution-test apparatus for suppositories (Toyama Sangyo Co., Ltd.) according the method of

Muranishi *et al.*[13] Three hundred ml of phosphate buffer (pH 7.4, μ 0.15), the dissolution medium, was taken into the releasing glass vessel and maintained at 37°C under stirring at 100 rpm. A 0.5 g suppository was placed on a Millipore filter (PSED 0471) fitted at the lower end of a plastic cylindrical cell, and the molten suppository was stirred with a stainless steel rod stirrer. An aliquot of 3 ml of dissolution medium was taken and the medium was replenished with the same volume of the phosphate buffer. The amounts released were followed by means of microbioassay and spectrophotometry for antibiotics and NSAI drugs, respectively.

Results and Discussion

Effect of Antiinflammatory Drugs on Rectal Absorption of ABPCNa and CETNa

Many β-lactam antibiotics are poorly absorbed through the rectal membrane in the living body due to their unsuitable lipid affinity in relation to the membrane. Thus, some adjuvant-(s) many enhance their rectal absorption. This was confirmed for the absorption of ABPCNa and CETNa in preliminary experiments, in which, indeed, they were hardly absorbed in the absence of adjuvant(s).

The results of rectal absorption of ABPCNa in rabbits in the presence of various amounts of one of the NSAI drugs in the suppositories are presented in Figs. 1 and 2 in terms of the area under the plasma concentration–time curve (AUC of 0—120 min, μg·min/ml) and peak plasma level (μg/ml) in relation to the concentration of NSAI (%(w/w)), respectively. Suppositories were prepared so as to contain 10% ABPCNa and various amounts of an NSAI drug and the dose of ABPCNa was adjusted to 15 mg/kg by whittling the suppositories to a designated amount.

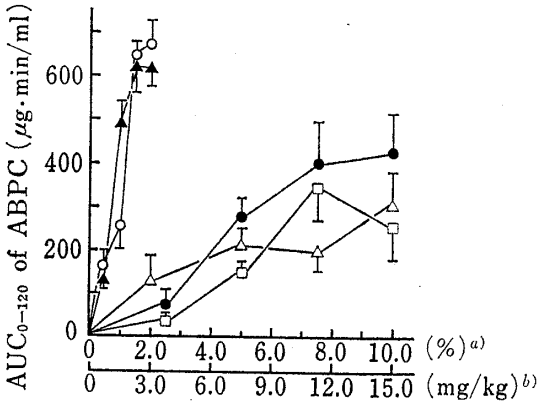

Fig. 1. AUC of 0—120 min for ABPC following Administration of Suppositories containing 10% ABPCNa and Various Concentrations of NSAI Drugs to Rabbits

—○—: DC, —▲—: IM, —●—: SA, —□—: PB, —△—: MP.
Dose of ABPCNa; 15 mg/kg.
Each point represents the mean ± S.D. of six animals.
a) Concn. of NSAI drugs in suppositories.
b) Dose of NSAI drugs.

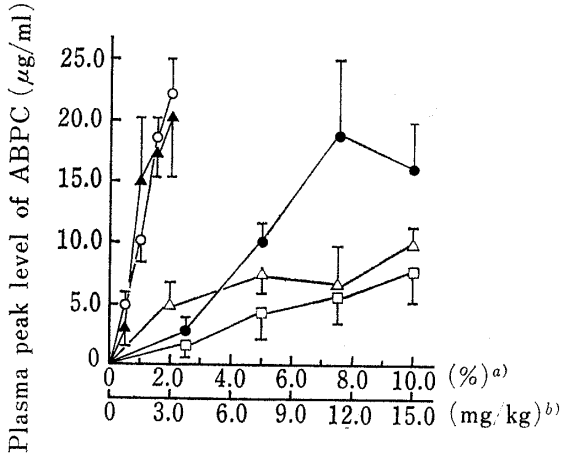

Fig. 2. Peak Plasma Level of ABPC following Administration of Suppositories containing 10% ABPCNa and Various Concentrations of NSAI Drugs to Rabbits

—○—: DC, —▲—: IM, —●—: SA, —□—: PB, —△—: MP.
Dose of ABPCNa; 15 mg/kg.
Each point represents the mean ± S.D. of six animals.
a) Concn. of NSAI drugs in suppositories.
b) Dose of NASI drugs.

The promoting effects of SA and SANa were observed at 2.5% incorporation and increased in a sigmoidal manner with the concentration. The effects were considered to reach the maximum at about 7.5%. At 10% incorporation, the values of AUC for both drugs reached about 400 μg·min/ml, equivalent to 46% bioavailability relative to the results of intravenous administration of ABPCNa alone.

The promoting effects of PB and PBNa were also observed at 2.5% and reached the maximum at about 7.5%. The promoting efficacy of PB seemed to decrease at 10% incorporation but no significant difference was obtained between 10% and 7.5%. Among the NSAI

drugs studied, IMNa and DCNa showed the strongest promoting effects on the rectal absorption of ABPCNa in rabbits. A significant absorption of ABPCNa was observed even at the concentration of 0.5% and the absorption increased with increase of concentration. The bioavailability of ABPC reached more than 69% upon coadministration of only 1.5% of these drugs. MP, one of the basic NSAI drugs, was reported to be less irritative to the gastrointestinal mucosa than acidic ones after oral administration.[14] Even so, it retained a remarkable promoting efficacy for the rectal absorption of ABPCNa. The AUC_{0-120} curve had a shoulder between 5% and 8% (Fig. 1). An increase in the efficacy at 10% was observed but the reason is unclear at present.

From the results in rabbits, the optimum concentrations of NSAI drugs incorporated in suppositories were tentatively fixed at 1.5% for IM, IMNa and DCNa, 7.5% for PB and PBNa, 10% for SA and SANa, and 5% for MP in the following experiments.

From the results obtained in our laboratory,[15] it is well established that the rectal absorption of many drugs in rabbits with and without adjuvants is greater than that in dogs and humans. Thus, to study the differences of promoting efficacy between animal species, suppositories containing one of the NSAI drugs at the concentration stated and 10% ABPCNa were rectally administered to dogs (Fig. 3). The results are presented in histograms in terms of bioavailability of ABPC. For ease of comparison, the results for rabbits are also presented in the open histograms. In general, the promoting efficacy in rabbits was greater than that in dogs.

Because ABPC has cationic and anionic groups in the molecule, a possible contribution of electrostatic interaction with the ionized NSAI drugs should be considered in relation to the promoting effects of NSAI drugs on the rectal absorption of ABPCNa.

CETNa has an anionic group in the molecule and has been clinically used by the routes of injection because of its poor absorbability *via* the gastrointestinal route. The promoting effects of NSAI drugs on the rectal absorption of CETNa in rabbits were studied following the administration of suppositories containing 10% CETNa and the designated concentration of

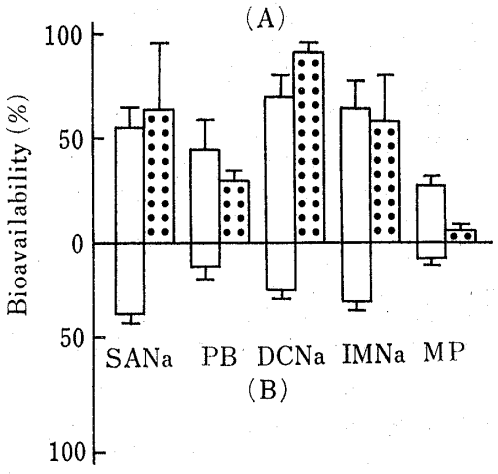

Fig. 3. Bioavailability of ABPC and CET following Administration of Suppositories containing 10% ABPCNa or CETNa and One of the NSAI Drugs (1.5% for IMNa and DCNa, 10% for SANa, 7.5% for PB, or 5% for MP) to Rabbits (A) and Dogs (B)

Dose; 15 mg/kg for ABPCNa or 15 mg/kg for CETNa.
Each histogram represents the mean±S.D. of six animals.
□ ABPC, ⁞⁞⁞ CET

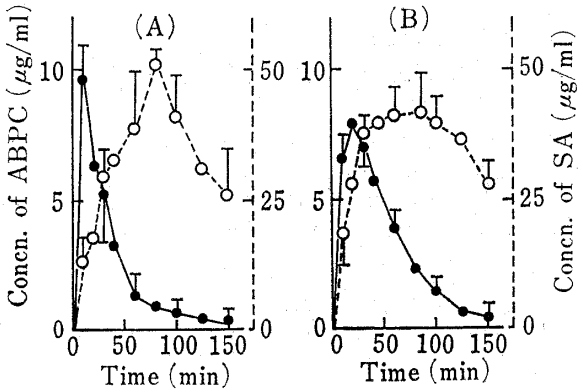

Fig. 4. Time Course of Plasma Concentrations of SA and ABPC following Administration of Suppositories containing 10% ABPCNa and 10% SANa to Rabbits (A) and Dogs (B)

—○—: SA, —●—: ABPC.
Dose; 15 mg/kg for ABPCNa and 15 mg/kg for SANa.
Each point represents the mean±S.D. of six animals.

one of NSAI drugs. The results are presented by dotted bars in Fig. 3. The promoting effects were found to have the same tendency as found in the case of ABPCNa.

Plasma Levels of ABPC and Antiinflammatory Drugs

Suppositories containing 10% ABPCNa and the designated concentration of one of NSAI drugs were rectally administered in rabbits and dogs and the plasma concentrations of both drugs were followed. The results are presented in Figs. 4—8.

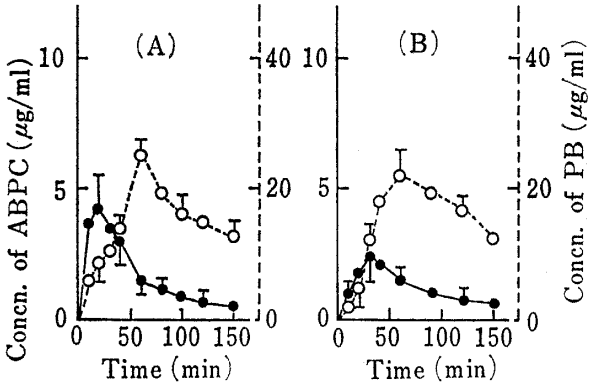

Fig. 5. Time Course of Plasma Concentrations of PB and ABPC following Administration of Suppositories containing 10% ABPCNa and 7.5% PB to Rabbits (A) and Dogs (B)

—○—: PB, —●—: ABPC.
Dose; 15 mg/kg for ABPCNa and 11.3 mg/kg for PB.
Each point represents the mean±S.D. of six animals.

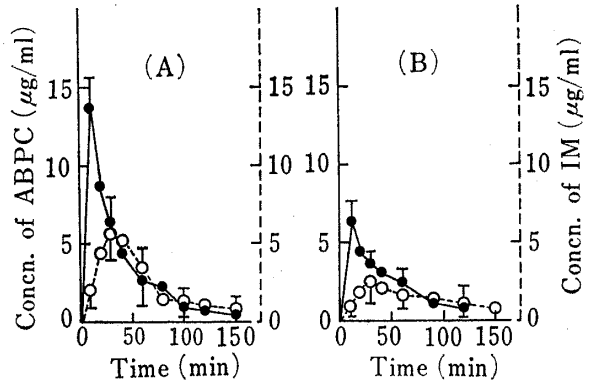

Fig. 6. Time Course of Plasma Concentrations of IM and ABPC following Administration of Suppositories containing 10% ABPCNa and 1.5% IMNa to Rabbits (A) and Dogs (B)

—○—: IM, —●—: ABPC.
Dose; 15 mg/kg for ABPCNa and 2.3 mg/kg for IMNa.
Each point represents the mean±S.D. of six animals.

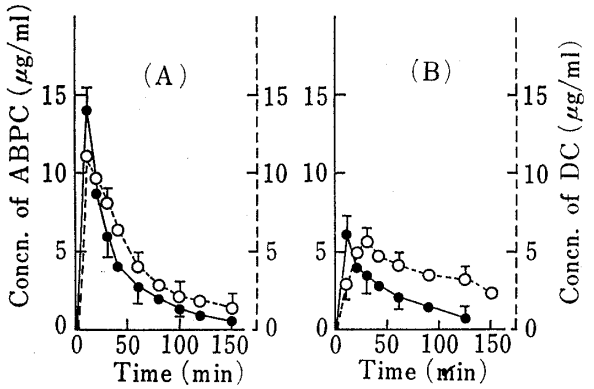

Fig. 7. Time Course of Plasma Concentrations of DC and ABPC following Administration of Suppositories containing 10% ABPCNa and 1.5% DCNa to Rabbits (A) and Dogs (B)

—○—: DC, —●—: ABPC.
Dose; 15 mg/kg for ABPCNa and 2.3 mg/kg for DCNa.
Each point represents the mean±S.D. of six animals.

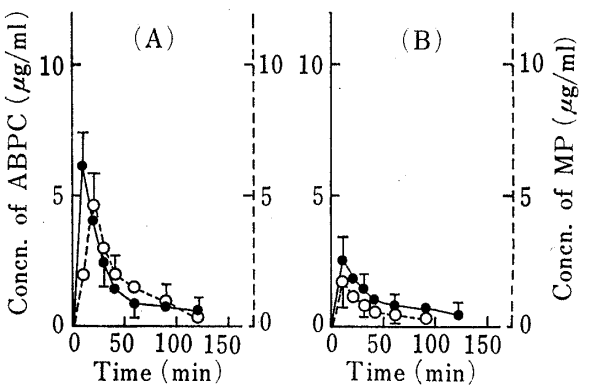

Fig. 8. Time Course of Plasma Concentrations of MP and ABPC following Administration of Suppositories containing 10% ABPCNa and 5% MP to Rabbits (A) and Dogs (B)

—○—: MP, —●—: ABPC.
Dose; 15 mg/kg for ABPCNa and 7.5 mg/kg for MP.
Each point represents the mean±S.D. of six animals.

In general, the absorption of ABPCNa started at an early stage after administration and the peak blood level was observed before those of the NSAI drugs.

To clarify the duration of promoting effects of NSAI drugs on the rectal absorption of ABPCNa, the elimination rates of ABPC from the blood were calculated by employing the declining curves in the figures on the basis of assumed apparent first-order kinetics (Table III). It was noted that the elimination parameters of ABPC after rectal administration were not significantly different from those after intravenous administration except for PB. From these results, it may be considered that NSAI drugs dissolved in the rectal fluid immediately

after administration and enhanced membrane permeation. The effect vanished rapidly, even though the absorption of NSAI drugs was presumably continuing in view of the considerable amounts of ABPCNa remaining in the rectum. The protective property of rectal mucosa against the permeation of hydrophilic compounds may be easily modified by the presence of NSAI drugs at low concentration, but apparently it rapidly recovers. While the permeation of NSAI drugs through the rectal membrane may occur mainly through the lipid barrier, subject to adequate lipid affinity, the permeation of hydrophilic antibiotics through the rectal membrane may be considered to progress *via* hydrophilic pathway(s) under the influence of NSAI drugs. However, further work is to determine the precise mechanism(s) involved.

Table III. Elimination Rate Constants and Half-Times of ABPC Absorption from the Rectum as promoted by Various Antiinflammatory Drugs in Rabbits and Dogs

	Adjuvants	Rabbits		Dogs	
		k (min^{-1})	$t_{1/2}$ (min)	k (min^{-1})	$t_{1/2}$ (min)
Rectal	SANa	0.0359±0.0035	19.3±2.3	0.0276±0.0011	25.2±1.0
	SA	0.0365±0.0028	19.0±1.5		
	PBNa	0.0340±0.0078	21.2±4.9		
	PB	0.0221±0.0052	31.3±3.2	0.0202±0.0057	35.0±8.4
	IMNa	0.0348±0.0070	19.1±3.9	0.0249±0.0070	29.2±7.2
	IM	0.0324±0.0024	21.3±1.6		
	DCNa	0.0325±0.0053	21.8±2.2	0.0191±0.0006	36.6±6.5
	DC	0.0341±0.0018	20.3±1.1		
	MP	0.0449±0.0095	15.4±5.2	0.0219±0.0020	31.6±9.8
i.v.		0.0453±0.0035	15.3±2.0	0.0242±0.0043	28.3±5.6

k; elimination rate constant, $t_{1/2}$; half-time.
Dose of ABPCNa; 15 mg/kg.
Each value represents the mean±S.D. of six animals.

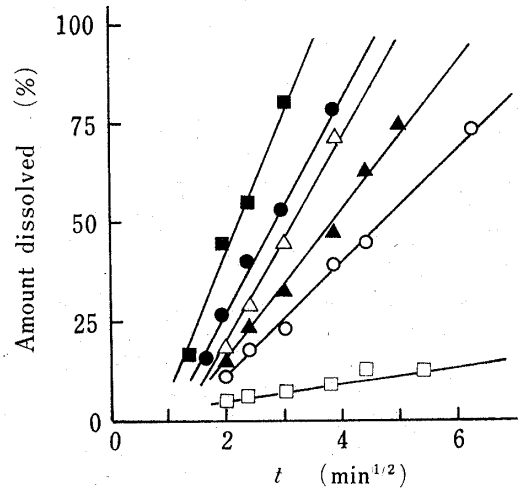

Fig. 9. Amount of Drug released from Suppositories *versus* the Square Root of Time

—■—: ABPC, —○—: DC, —▲—: IM, —●—: SA, —□—: PB, —△—: MP.
Suppositories used contain 10% ABPCNa and one of the NSAI drugs (1.5% for DCNa and IMNa, 10% for SANa, 7.5% for PB, or 5% for MP).
Each point represents the mean of six experiments.

The dissolution profiles of ABPCNa and NSAI drugs from suppositories containing ABPCNa and NSAI drug are presented in Fig. 9. Ninety percent of ABPCNa incorporated with NSAI drug into the suppositories was found in the aqueous phase within the first 10 min. NSAI drugs except for PB were also rapidly released from suppositories and 50% of the drugs were found within the first 10 min. The slow dissolution of PB was considered to be partly responsible for the large $t_{1/2}$ of ABPC at its elimination phase (Fig. 5 and Table III).

Ralationship of Promoting Effect of Antiinflammatory Drugs with Their Partition Coefficient and Antiinflammatory Activity

The promoting efficacy of NSAI drugs on the rectal absorption of ABPCNa was analyzed on the basis of the results for suppositories containing the designated concentrations of NSAI drugs (Table IV).

The values of corrected bioavailability, A_{bio}, were obtained by dividing the value of bioav-

TABLE IV. Physicochemical and Biological Parameters

Drugs	Concn. % [a]	Concn. mmol/g (M) [b]	B(%) [c]	log A_{bio} [d]	log P [e]	log 1/ED_{50} [f]
SANa	10.0	0.725	54.6±29.1	1.88	−1.86	−0.75
PB	7.5	0.244	41.5±28.1	2.23	0.55	0.79
DCNa	1.5	0.047	75.6±19.7	3.20	1.18	2.13
IMNa	1.5	0.039	69.7±29.6	3.25	0.69	1.84
MP	5.0	0.241	25.6±17.6	2.08	1.34	0.40

a) Percent of NSAI drugs in suppositories.
b) *M*; amount (mmol) of NSAI drugs in one gram of suppositories.
c) *B* (bioavailability); [AUC_{0-120} (rectal)/AUC_{0-120} (*i.v.*)]×100, the mean±S.D. of six animals.
d) A_{bio} (corrected bioavailability); *B*/*M*.
e) *P*; apparent partition coefficient ($C_{n\text{-octanol}}/C_{H_2O}$).
f) Carageenan-induced paw edema inhibition.

ailability (*B*) by the amount (mmol) of the NSAI drug (*M*) in one gram of suppository (*cf.* Table IV). The partition coefficients of NSAI drugs were found to have little correlation with their promoting efficacy. However, a linear correlation was obtained between the value of A_{bio} and the antiinflammatory activity (Eq. 1).

$$\log A_{bio} = 0.5263 \log 1/ED_{50} + 2.064 \quad (r=0.941, n=5) \qquad \text{Eq. 1}$$

The antiinflammatory activity in the inhibition of carrageenan-induced paw edema reported by Heiger[16] is presented in the table in term of mmol/kg, ED_{50}, by dividing his values by the molecular weights of the NSAI drugs, Thus, it may be reasonable to compare the antiinflammatory activity with the promoting efficacy of NSAI drugs derived from the present experiments. On the other hand, the degree of antiinflammatory activity of NSAI drugs was reported to be correlated with the extent of the irritation of gastroenteric mucosa.[17] This finding led us to speculate that histological changes in the rectal mucosa might be induced by the NSAI drugs and that the induced alteration led to the increased permeation of hydrophilic ABPCNa through the membrane. However details of the actual mechanism remain to be investigated.

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References and Notes

1) Part of this work presented at the 29th Annual Meeting of the Kinki Branch, Pharmaceutical Society of Japan, Kyoto, November 1979.
2) M. Moritani, *Rinshyoseikeigeka*, **12**, 447 (1977); T. Negishi, *Seikeigeka*, **21**, 349 (1970).
3) T. Fujii, *Rinshyoseijinbyo*, **8**, 303 (1978); S. Muranishi, *Yakkyoku*, **18**, 69 (1967).
4) K. Bucher, *Helv. Physiol. Pharmacol. Acta.*, **6**, 821 (1968); T. Takao, S. Tuchiya, and M. Hiura, *Yakuzaigaku*, **31**, 292 (1971).
5) B.L. Kabacoff, A.W. Wohlman, M. Umhey, and S.A. Kian, *Nature* (London), **199**, 815 (1963); T. Matuzaki and E. Noda, *Yakuzaigaku*, **26**, 25 (1966).
6) K. Kakemi, T. Arita, and S. Muranishi, *Chem. Pharm. Bull.*, **13**, 861 (1965).
7) C.A.N. Hogben, D.J. Tocco, and B.B. Brodie, *J. Pharmacol. Exptl. Therap.*, **125**, 275 (1959).
8) T. Nishihata, T. Murakami, J. Kim, M. Yamamoto, M. Yamazaki, K. Kubo, N. Yata, and A. Kamada, "7th Symposium on Pharmacological Activity and Mechanism" sponsored by the Pharmaceutical Society, Tokyo, November 1978.
9) Y. Nishioka and N. Kawamura, *Yakuzaigaku*, **37**, 119 (1977).
10) H. Nogami and T. Matuzawa, *Chem. Pharm. Bull.*, **9**, 532 (1961).
11) H. Kunze, G. Rehback, and W. Vogt, *Nanuyn-Schmiedeberg's Arch. Pharmacol.*, **273**, 331 (1972).
12) T. Nishihata, J.H. Rytting, and T. Higuchi, *J. Pharm. Sci.*, **69**, 744 (1980).
13) S. Muranishi, Y. Okubo, and H. Sezaki, *Yakuzaigaku*, **39**, 1 (1979).

14) K. Tsurumi, K. Kyuki, and H. Fujimura, *J. Pharm. Dyn.*, 3, 659 (1980).
15) Unpublished.
16) S.H. Heiger, *Scan. J. Rheumatology*, **29**, 613 (1972); K. Akimoto, T. Tukuda, T. Yamazaki, H. Kizima, A. Kasahara, A. Akashi, K. Yamaguchi, and Y. Oshima, *Nippon Yakurigaku Zasshi*, **65**, 387 (1967).
17) Y. Harada and M. Katori, *Rinshyoseijinbyo*, **8**, 263 (1978).