PHARMACEUTICAL EVALUATION OF HOLLOW TYPE SUPPOSITORIES. V.¹⁾ PREPARATION OF VALPROIC ACID SUPPOSITORY AND RECTAL ABSORPTION OF VALPROIC ACID IN RABBITS*

YOSHITERU WATANABE, YOSHITO TONE, SEIKO NISHIHARA AND MITSUO MATSUMOTO

Department of Pharmaceutics, Showa College of Pharmaceutical Sciences, 1-8, Tsurumaki 5-chome, Setagaya-ku, Tokyo, 154, Japan

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Seven kinds of suppositories were constructed with oleaginous base materials (Witepsol H-15 (H-15) and E-85 (E-85)): a conventional type suppository containing valproic acid (VPA) mixed with E-85 (I), a conventional type suppository containing sodium salt of VPA (sodium valproate) (S-VPA) mixed with H-15 (II), hollow type suppositories containing VPA in the forms of oily liquid (free acid) (III), macrogol 1000 or 6000 mixture (IV or V), powder (S-VPA) (VI) and aqueous solution (S-VPA was dissolved in 0.9% NaCl solution) (VII) in each cavity.

The content of VPA in type I was decreased considerably by volatility and type II was found to be hygroscopic. Therefore conventional type suppositories containing VPA or S-VPA were not of practical use, whereas III and VI prevented volatility of VPA and minimized the hygroscopic property of S-VPA.

Plasma concentration of VPA was measured in rabbits after rectal administrations of III, IV, VI and VII. By using VI, the highest values of the mean of the peak plasma VPA concentration ($C_{\max}$) ($49.8 \pm 2.6 \mu\text{g/ml}$) and the mean of the area under the plasma concentration-time curve (AUC) ($90.0 \pm 3.7 \text{ h} \cdot \mu\text{g/ml}$) were obtained. The $C_{\max}$ and the AUC estimated after administration of VII were not significantly different from those of VI. The $C_{\max}$ and the AUC were lower with III than with IV, VI or VII but the extent of bioavailability (EBA) of III was about 80%.

These data on bioavailability suggested that VPA was efficiently absorbed into the rectum of rabbits after the administration of hollow type suppositories. Thus, it was concluded that hollow type suppositories containing VPA or S-VPA can be produced as practical preparations for use.

Keywords — hollow type suppository; valproic acid; sodium valproate; rectal absorption; valproic acid added form; rabbit; volatility; hygroscopicity

INTRODUCTION

Valproic acid (2-propylpentanoic acid) (VPA) is one of the efficient antiepileptics and is used clinically in the treatment of generalized tonic-clonic and partial seizures²⁾ but the usual daily doses (1000 to 3000 mg in adults)³⁾ are large. The most common side effects of VPA are gastrointestinal symptoms, including anorexia, nausea and vomiting in about 16% of patients⁴⁾ and oral administration of VPA may be ineffective because absorption is often impaired by paralytic ileus and vomiting in patients. In these cases, a suitable dosage form of VPA for the rectal administration is available.^{5,6)} However, at present, VPA suppositories can not be obtained commercially.

The reason for this is that VPA causes lowering of the melting points of the suppository base

materials when the conventional type suppository containing a therapeutic dose of VPA is prepared with oleaginous bases, and therefore, the suppository obtained is too soft to insert into the rectum. Furthermore, VPA becomes lost by volatilization from conventional suppositories, and furthermore, the sodium salt of VPA (sodium valproate) (S-VPA) is very hygroscopic.

Previously, Watanabe *et al.*¹⁾ confirmed that the rectal administration of hollow type suppositories containing propranolol (PPL) (hydrochloride salt powder and aqueous solution) in rabbits attained higher bioavailability compared with the use of a conventional type suppository prepared with the same oleaginous base material since PPL was released faster from a hollow type than from a conventional one.

In this report, it was proved that VPA was ef-

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ficiently absorbed by the rectum of rabbits after administrations of hollow type suppositories containing VPA in the forms of (free acid (oily liquid), VPA-macrogol 1000 mixture, S-VPA powder or S-VPA aqueous solution).

MATERIALS AND METHODS

Materials — VPA (content (>99%), d_{20}^{20} 0.91) was purchased from Tokyo Kasei Kogyo Co., Ltd., Tokyo, Japan and S-VPA (mp 360 °C (dec.)) was a gift from Kyowa Hakko Kogyo Co., Ltd., Tokyo, Japan. S-VPA was stored in a tight container and desiccated with silica gel *in vacuo*. Witepsol H-15 (H-15) and E-85 (E-85) (Dynamit Nobel, Witten, F.R.G.) were used as suppository bases. Macrogol 1000 (M-1000) and 6000 (M-6000) were obtained from Wako Pure Chemical Industries, Ltd., Tokyo, Japan. Chloroform and methanol (Kanto Chemical Co., Inc., Tokyo, Japan) were of spectro grade. All other chemicals were commercial products of reagent grade.

Preparation of Suppositories — Hollow type suppositories (Fig. 1) were prepared through the fusion process with a metallic suppository mold equipped with an adapter by which the hollow cavity can be constructed in the same way as described in previous reports.^{1,7)}

A sample of H-15 was melted at 45 °C, poured into a mold equipped with an adapter at 30 °C and then allowed to solidify at room temperature (20–25 °C). After the construction of a hollow cavity of the solidified H-15, the amount of VPA, calculated as the free acid, in various added forms was accurately weighed and added to each cavity (Table I). Then, a disc plug (Fig. 1 (c)) which had been separately prepared with H-15 was used to seal the opening of

FIG. 1. Schematic Illustration of a Hollow Type Suppository

Keys: (A), body of suppository (Witepsol H-15); (B), valproic acid (VPA, free acid (oily liquid), free acid-macrogol 1000 mixture, sodium salt (S-VPA, powder, aqueous solution)); (C), disc plug (Witepsol H-15).

A disc plug (C) separately prepared was sealed to the opening at the rear part of the suppository after addition of VPA.

the rear part of suppository (Fig. 1). The suppositories which had been stored in a refrigerator (4 °C) overnight after preparation were tested.

Melting Behavior of Mixture of Base Material with VPA or S-VPA — VPA or S-VPA was mixed with H-15 or E-85 at a concentration of 20% or 23% (equivalent to 20% of VPA), respectively. The mixtures had been stored at 4 °C overnight after preparation.

A differential scanning calorimetry (DSC) was used for the melting test under the following conditions: apparatus, DT 30 system (Shimadzu Seisakusho Ltd., Kyoto, Japan); heating rate, 5 °C/min from 5 to 50 °C; range, ± 10 mJ/s; nitrogen. The accuracy of the temperature was checked by measuring the melting points of

TABLE I. Suppositories (Cylindrical Shape, About 3 g of Weight) Containing 300 mg of VPA for *in Vitro* Test

Suppository	Base	Form of VPA or S-VPA added	Number
Conventional	E-85	VPA (oily liquid)	I
	H-15	S-VPA (powder)	II
Hollow	H-15	VPA (oily liquid)	III
		VPA-M-1000 (liquid) ^{a)}	IV
		VPA-M-6000 (semisolid) ^{b)}	V
		S-VPA (powder)	VI

^{a)} VPA (50%) mixed with M-1000. ^{b)} VPA (50%) mixed with M-6000.

methyl stearate and indium. The solid fat index (SFI) of the mixture was determined by DSC thermogram according to the method of Maruyama *et al.*⁸⁾ and Yoshino *et al.*⁹⁾ The weight fraction of liquid phase of the mixture was regarded as $100 - \text{SFI}$.

Determination of VPA Content in Suppository during Storage — The suppositories which had been stored in the refrigerator overnight after preparation were regarded as the initial samples. Each of the suppositories prepared was wrapped with a paraffin powder paper and was placed in a polyvinylchloride envelope with a fastener. These enveloped suppositories were stored at 5, 20 and 30 °C for a predetermined time.

After these storage experiments, each VPA suppository was dissolved, diluted with chloroform and then assayed by a gas chromatographic (GC) method. An aliquot (1 ml) of VPA in chloroform was transferred to a stoppered glass tube (10 ml) containing 0.1 ml of methanol which contained *n*-octanoic acid as an internal standard (concn. 600 $\mu\text{g/ml}$). The mixture was stirred with a Vortex mixer for 30 s, and 5 μl of the mixture were injected into a gas chromatograph (Model GC-5A, Shimadzu Seisakusho Ltd., Kyoto, Japan) equipped with a flame ionization detector and a 3.0 mm $\times$ 2.0 m glass column packed with 20% of PEG-20M on 60–80 mesh Chromosorb W AW DMCS (Gasukuro Kogyo Inc., Tokyo, Japan). GC was carried out under the following conditions: temperature of injection ports, 250 °C; column oven temperature, 210 °C; carrier gas (nitrogen) flow rate, 60 ml/min.

Determination of Hygroscopicity — Conventional and hollow type suppositories containing S-VPA and S-VPA powder as reference sample were placed in open glass containers (10 ml). These containers were stored at 30 °C and 75% relative humidity (RH) for a predetermined time.

During these storage experiments, the suppositories and the reference samples were weighed to a precision of 1 mg every 24 h for 7 d, and every 7 d for 2–4 weeks. Water contents in suppositories and S-VPA powder were measured according to the Karl Fischer method using the Karl Fischer Moisture Meter (Model MK-AII, Kyoto Electronics Manufacturing Co. Ltd., Kyoto, Japan).

Animal Experiments — Male albino rabbits

weighing 3.0 ± 0.04 kg were fasted for one night prior to the experiments but water was given freely. The animals were secured in a crouching posture in the same manner as described in the previous paper¹⁾ and a suppository containing a dose of 10 mg/kg, calculated as free acid, (about 30 mg of VPA per suppository) was inserted into the rectum. The anus was then closed with a surgical cyanoacrylate adhesive (Aron Alpha A, Toa Gosei Kagaku Kogyo Co. Ltd., Tokyo, Japan) to prevent leakage of the melted suppository.

For intravenous bolus administration, S-VPA dissolved in isotonic NaCl solution (100 mg calculated as free acid/ml) was injected through the auricular vein at a dose of 10 mg VPA/kg. After administration, blood samples were withdrawn into heparinized syringe at predetermined intervals from a marginal ear vein and centrifuged at 3000 rpm for 15 min. The plasma layer was transferred to stoppered polyethylene tubes and stored at 4 °C until analyzed.

Measurement of VPA in Plasma — A GC method reported by Grgurinvich *et al.*¹⁰⁾ was applied with a slight modification as follows: 0.5 ml of plasma was added to a 10 ml stoppered glass centrifuge tube containing 0.4 ml of 4 N HCl, 0.1 ml of the internal standard solution (60 mg of *n*-octanoic acid was dissolved in 100 ml of methanol) and 1 ml of chloroform. The mixture was vigorously shaken for 5 min and then centrifuged at 3500 rpm for 5 min. An aliquot (5 μl) of the chloroform layer was then injected into a gas chromatograph with the same equipment system and experimental conditions described in the section of Determination of VPA Content in Suppository during Storage.

Pharmacokinetic Analysis — Bioavailability parameters such as the peak plasma VPA concentration (C_{max}), the peak concentration time (t_{max}), and the area under the plasma concentration-time curve (AUC), were obtained from the plasma VPA concentration measured after the administrations. AUC_{0-4} was calculated according to the trapezoidal rule for the observed blood levels from 0 to 4 h after administration. To obtain the absorption rate constant (k_a) and the elimination rate constant (k_e), plasma level data were analyzed by the one-compartment model^{11,12)} with first-order process using a non-linear iterative least-square regression analysis, MULTI.¹³⁾

Statistical analysis was performed using the one-way ANOVA and the Dunnett's test and the differences were assumed to be significant when $p < 0.05$.

RESULTS AND DISCUSSION

VPA and S-VPA Suppositories Prepared by the Conventional Method

According to the usual dosage regimen for patients, each suppository is required to contain at least 300–600 mg of VPA. Since the concentration of VPA is 10 to 20% of the base material, the commonly used size suppository is 3 g.

Figure 2 shows the relationship between the SFI estimated by a DSC thermogram and the temperature when the concentration of VPA was increased from 0 to 20% in H-15 (A) or E-85 (B). The SFI-temperature curves were broadened and shifted to lower temperatures by increasing the concentration of VPA in H-15 (Fig. 2 (A)). When 20% of VPA was mixed in H-15, the SFI at 25 °C was 60% and the suppository base containing 20% of VPA was found to be markedly softened at 25 °C. Consequently, the conventional type suppository made of H-15 is not suitable for practical use.

The SFI-temperature curves of E-85 with a higher melting range (mp about 42 °C) (Fig. 2 (B)) were shifted to a higher temperature than those of H-15 with the same concentrations of VPA (10 and 20%) (Fig. 2 (A)). Therefore, it was confirmed that VPA with E-85 was sufficiently solidified at room temperature. Despite the complete solidification required for the use of E-85, a strong odor of VPA was noted.

In order to estimate the volatility of VPA, VPA conventional type suppositories prepared

FIG. 2. Solid Fat Index (SFI)-Temperature Curves of VPA Conventional Type Suppositories Prepared with H-15 (A) and E-85 (B)

VPA concentration (%): —○—, 0; —■—, 10; —●—, 20.

Each point represents the mean of three samples.

with E-85 (I) were stored at 5, 20 and 30 °C for 4 weeks and the content of VPA in each suppository was determined. The remaining percentages of VPA in I were 84% (5 °C), 80% (20 °C) and 78% (30 °C) after 4 weeks. The content of VPA in I was considerably decreased even at 5 °C (Table II).

TABLE II. Remaining Percentages (%) of VPA Added in Suppository at Various Storage Temperature for 4 Weeks

Storage temperature (°C)	Suppository ^{a)}	
	I	III
5	84	100
20	80	100
30	78	Softened and deformed

a) Each suppository contained 300 mg of VPA as free acid. Values are expressed as the mean of three suppositories.

$$\text{Remaining percentage of VPA added (\%)} = \frac{\text{amount of VPA in suppository after storage}}{\text{amount of VPA in suppository before storage}} \times 100$$

FIG. 3. *SFI-Temperature Curves of S-VPA Conventional Type Suppository Prepared with H-15*
S-VPA concentration (%): —○—, 0;
—●—, 23 (20% of VPA).
Each point represents the mean of three samples.

When a S-VPA conventional type suppository prepared with H-15 (II) was tested, no difference in SFI-temperature curve profile was found between II and H-15, even when 23% of S-VPA (equivalent to 20% of VPA) was mixed (Fig. 3) and the odor of VPA was not detected. However, droplets of water were observed on the surface of II during storage under high humidity.

II and S-VPA powder, as a reference sample, were then stored at 30 °C and 75% RH and the change of weight was determined. Figure 4 illustrates the percentages of weight increased during storage. The weight of II increased about 8% after 4 weeks. The weight of S-VPA powder was immediately increased on storage, and the powder was liquefied within only a day. The increased weight of II and S-VPA powder corresponded to the water content determined by the Karl Fischer method (Table III). Thus, II was

FIG. 4. *Increase of Weight of Suppository Containing S-VPA (345 mg) at 30°C and 75% RH*
Suppository (see Table I): —●—, II;
—○—, VI and —×—, S-VPA powder (reference).
S-VPA (%)

$$= \frac{(\text{weight after storage}) - (\text{weight before storage})}{\text{amount of S-VPA in suppository or reference}} \times 100$$

found to be hygroscopic.

From these results, conventional type suppositories containing VPA or S-VPA were found unsuitable for practical use except when they are used immediately after preparation since the contents of drugs and their properties are liable to change. Water-soluble bases such as macrogols were prone to soften and to be hygroscopic whereas those of oleaginous base materials lacked these properties.

Hollow Type Suppositories Containing VPA or S-VPA

The use of hollow type suppositories are expected to eliminate interaction between drugs and base materials since the two are separated. In

TABLE III. *Hygroscopicity of S-VPA (345 mg) at 30°C and 75% RH*

Sample	Storage (week)	Increased weight (mg)	Water content ^{a)} (mg)
S-VPA powder	1	222 ± 1	220 ± 8
Suppository II	4	28 ± 1	28 ± 1
Suppository VI	4	1 ± 1	3 ± 1

a) Determined by Karl Fischer method. All values represent the mean ± S.E. of three samples.

this report, a hollow type suppository (cylindrical shape) weighing about 3 g with 0.7 cm³ inner volume of cavity (inner diameter, 6 mm; thickness of wall, 3 mm) was prepared and was sufficiently hard for use (stress required to break was about 3 kg).¹⁴⁾

When a hollow type suppository containing 300 mg of VPA prepared with H-15 (III) was stored at 5 and 20 °C for 4 weeks, there was no loss of VPA in III whereas there was some loss of VPA in I (Table II). Odor of VPA and the change of appearance of III were not observed during storage at 5 and 20 °C, while III stored at 30 °C became soft and deformed within a week. The reason why III became soft at 30 °C may be due to the penetration of VPA into the H-15 since VPA was detected in the exterior base material of III.

Previously, Watanabe *et al.*¹⁵⁾ reported that indomethacin dissolved in water-miscible solvents such as macrogol 300, which has low affinity for H-15, could be added into hollow type suppositories. Hollow type suppositories containing VPA mixed with M-1000 (IV) and M-6000 (V) (concn. of VPA, 50%) were then prepared and stored at 30 °C. Although softening in IV and V was slightly delayed, the problem of softening of the suppository was not essentially improved. It may be assumed that III will be a suitable dosage form as a suppository when it is stored at a temperature at least below 20 °C.

A hollow type suppository containing 345 mg of S-VPA (equivalent to 300 mg of free acid) prepared with H-15 (VI) was stored at 30 °C and 75% RH for 4 weeks and weight of VI was determined. The result shown in Figure 4 indicated that the increased in weight of VI was less than 1% after 4 weeks.

FIG. 5. Semi-Logarithmic Plots of Plasma Concentrations of VPA against Time in Rabbits after Rectal Administration of Hollow Type Suppositories at the Dose of 10 mg/kg

Lines and Points are the computer-calculated and experimentally observed plasma VPA concentrations, respectively.

Each Point represents the mean $\pm$ S.E. (vertical bar) of five rabbits.

Suppository (see Table IV): — Δ —, VII; — $\blacktriangle$ —, VIII; — $\circ$ —, IX.

Rectal Absorption of VPA after Administration of Hollow Type Suppositories

Four kinds of hollow type suppositories containing VPA (free acid, oily liquid) (VII), VPA mixed with M-1000 (concn. of VPA, 50%) (VIII), S-VPA powder (IX) and S-VPA aqueous solution (X) in their cavities (Table IV) were prepared with H-15 and then administered rectally. For animal experiments, in order to insert the suppositories with ease into the rectum of rabbits, a hollow type with a torpedo shape (weight, about 2 g; inner volume, 0.5 cm³; inner diameter, 5 mm; thickness of wall, 2 mm) was

TABLE IV. Hollow Type Suppositories ^{a)} (Torpedo Shape, About 2 g of Weight) Containing Dose of 10 mg/kg of VPA for *in Vivo* Test

Form of VPA or S-VPA added	Number
VPA (oily liquid)	VII
VPA-M-1000 (liquid) ^{b)}	VIII
S-VPA (powder)	IX
S-VPA (aqueous solution) ^{c)}	X

^{a)} Base: H-15. ^{b)} See Table I. ^{c)} S-VPA was dissolved in isotonic NaCl solution (100 mg calculated as free acid/ml), and then 100 μ l of this solution per kg of body weight were added to each cavity.

FIG. 6. Semi-Logarithmic Plots of Plasma Concentrations of VPA against Time in Rabbits after Rectal or Intravenous Administration at the Dose of 10 mg/kg

Lines and Points are the computer-calculated and experimentally observed plasma VPA concentrations, respectively.

Each point represents the mean $\pm$ S.E. (vertical bar) of five rabbits.

Suppository (see Table IV): —○—, IX; —●—, X and - - -●- - -, i.v. (S-VPA aqueous solution).

prepared.

The mean semi-log plasma concentration-time curves after the intravenous or rectal administration of the four kinds of VPA suppositories with the same dose of VPA (10 mg/kg) are shown in Fig. 5 and 6, and their bioavailability parameters are summarized in Table V. The plasma concentrations of VPA were increased (lag time 4–6 min) after the administration of each suppository.

In comparing VII with IX, the means of

$C_{\max}$ ($34.1 \pm 1.6 \mu\text{g/ml}$) and AUC_{0-4} ($70.2 \pm 4.7 \text{ h} \cdot \mu\text{g/ml}$) of VII were lower ($p < 0.01$) than the means of $C_{\max}$ ($49.8 \pm 2.6 \mu\text{g/ml}$) and AUC_{0-4} ($90.0 \pm 3.7 \text{ h} \cdot \mu\text{g/ml}$) of IX, respectively, and $t_{\max}$ ($45 \pm 5 \text{ min}$) of VII was larger than those of IX ($27 \pm 3 \text{ min}$) (Table V). The mean of k_a ($3.22 \pm 0.65 \text{ h}^{-1}$) of VII was lower than that ($8.77 \pm 2.24 \text{ h}^{-1}$) of IX. Moolenaar *et al.*¹⁶⁾ reported that $t_{\max}$ obtained after the rectal administration of a conventional type suppository containing VPA was smaller than after the administration of a conventional suppository containing S-VPA in human patients. It is probable that the difference of $t_{\max}$ between the VPA conventional suppository and the S-VPA conventional one is related to the fact that SFI-temperature curves were shifted to lower temperature when VPA was mixed with the base material. It is presumed that the differences of $C_{\max}$, $t_{\max}$ and k_a between VII and IX are related to the difference of solubility in rectal fluid between VPA and S-VPA.

Patients with epileptic seizures need rapid increase of plasma VPA concentration after rectal administration. In the therapeutic use of VPA, the hollow type suppository containing S-VPA is a suitable device for absorption by the rectum since the shortest $t_{\max}$ and the largest k_a are obtained. The extent of bioavailability (EBA) of IX was 98% while EBA of VII was approximately 80%. These results suggested that VPA (free acid) was well-absorbed from the rectum of rabbits.

Previously, we found that the plasma concentration of indomethacin after the rectal administration of a hollow type suppository containing indomethacin in macrogol 300 was significantly higher than that after the administration of a

TABLE V. Bioavailability Parameters of VPA in Rabbits after Rectal or Intravenous Administration

Administration		$C_{\max}$ ($\mu\text{g/ml}$)	$t_{\max}$ (min)	AUC_{0-4} ($\text{h} \cdot \mu\text{g/ml}$)	k_a (h^{-1})	k_{el} (h^{-1})	EBA (%)
Suppository ^{a)}	VII	34.1 ± 1.6	$45 \pm 5^d)$	70.2 ± 4.7	3.22 ± 0.65	0.71 ± 0.06	77
	VIII	$46.6 \pm 0.9^c)$	$45 \pm 0^d)$	$84.8 \pm 4.5^b)$	5.55 ± 1.76	0.74 ± 0.07	93
	IX	$49.8 \pm 2.6^c)$	27 ± 3	$90.0 \pm 3.7^c)$	8.77 ± 2.24	0.67 ± 0.07	98
	X	$44.6 \pm 1.9^c)$	39 ± 4	$85.7 \pm 2.6^c)$	3.61 ± 0.36	0.74 ± 0.03	94
Intravenous	—	—	—	$91.6 \pm 4.7^c)$	—	0.72 ± 0.03	100

a) Suppository, see Table IV. VPA dose: 10 mg/kg. Each value represents the mean $\pm$ S.E. of five rabbits. Statistically significant differences: b) $p < 0.05$, c) $p < 0.01$ against VII; d) $p < 0.05$ against IX.

$EBA (\%) = AUC_{\text{rectal}} / AUC_{\text{i.v.}} \times 100$

hollow type suppository containing indomethacin powder.¹⁷⁾ A hollow type suppository containing VPA mixed with M-1000 (concn. of VPA, 50%) (VIII) was prepared and then administered. After rectal administration of VIII, the plasma VPA concentration-time curve was higher than that of VII (Fig. 5), the means of $C_{\max}$ ($46.6 \pm 0.9 \mu\text{g/ml}$) and AUC_{0-4} ($84.8 \pm 4.5 \text{ h} \cdot \mu\text{g/ml}$) were significantly ($p < 0.01$, $p < 0.05$) increased (Table V), but the plasma concentration of VPA of VIII was not higher than IX.

The plasma concentration-time curves of VPA for IX and X were close together after intravenous administration (Fig. 6) and the means of AUC_{0-4} for IX ($90.0 \pm 3.7 \text{ h} \cdot \mu\text{g/ml}$) and X ($85.7 \pm 2.6 \text{ h} \cdot \mu\text{g/ml}$) were not statistically different from that of intravenous injection ($91.6 \pm 4.7 \text{ h} \cdot \mu\text{g/ml}$) (Table V).

The plasma VPA concentration after the administration of a hollow type suppository containing S-VPA aqueous solution (as 100 mg of VPA/ml) (X) was compared to that of IX. The mean plasma VPA concentration-time curve profile of X was similar to that of IX (Fig. 6) and there was no statistically significant difference between the means of bioavailability parameters. These data on bioavailability suggest that the powder of S-VPA in the hollow type suppository dissolved rapidly into the rectal fluid and was absorbed from the rectum of rabbits after administration. When hollow type suppositories containing a drug with high solubility in water (*e.g.*, salt) are administered, bioavailability in the form of powder was similar to that in the form of solution since no difference in the release of water-soluble drugs into the rectal fluid was observed.^{1,7)} Therefore, these results in S-VPA were similar to the case of hollow type suppository containing PPL hydrochloride.¹¹⁾ In the production of VPA hollow type suppositories, the use of solution is more convenient than powder.

From these experimental data, it may be concluded that VPA and S-VPA were efficiently absorbed from the rectum of rabbits and that hollow type suppositories containing VPA or S-VPA are useful as practical preparations for storage and for use.

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