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76. Hiroshi Fukuchi, Yasuo Arimoto, Akira Kamada, Kanjiro Kobayashi, and Masaru Aoki : The Absorption of Organomercurial Compounds from the Vaginal Route of the Rabbits. I.

Comparative Study on the Effect of Suppository Vehicles on the Absorption of ω-Ethylmercurithio-*n*-undecanoic Acid, Phenylmercuric Acetate and Ethylmercuric Chloride after Single Dose Administration.

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The authors' previous study[1] revealed that phenylmercuric acetate (PMA) was favorable when used with a water soluble vehicle in enhancing the mercurial absorption into the vaginal membrane. The absorption was more enhanced when PMA was used in the form of triethanolamine salt. Very few reports seem to have been made of an intravaginal absorption of PMA. Laug and Kunze[2] were among the few authors who reported an intravaginally administered PMA being absorbed into the kidney and liver, when used with a jelly base and in the form of aqueous solution.

In the meantime ω-ethylmercurithio-*n*-undecanoic acid (EMU) was developed by one of the colleagues, Kobayashi,[3] which has proved to be as effective as PMA for antimicrobial purposes especially for anti-trichomonal purposes.

A detailed study on the antimicrobial and anti-trichomonal effect will be published elsewhere. Some of the results obtained are shown in Table I (a) and (b).

Table I (a). Minimum Inhibiting Concentration of EMU and PMA against Microorganisms (μg./ml.)

Agents / Microorganisms	EMU		PMA	
	n	s	n	s
E. coli	1	8	2	8
S. aureus	1	8	0.25	2
S. hemolyticus	2	16	0.5	8
C. albicans	1	4	0.125	1
B. doderlein	2	2	2	4

s : with 10% rabbit serum
n : without rabbit serum

Table I (b). Minimum Inhibiting Concentration of EMU and PMA against *Trichomonas Vaginalis* (μg./ml.)

EMU	5	5[a)]	0.625[b)]
PMA	2.5	5[a)]	5[b)]

a) with 0.5% of cream base Rx 6_1·M_6, being used as modified Rx 6 employed in absorption test.
b) with 0.25% of the cream base.
The cream base (Rx 6_1·M_6) was composed as follows : mineral oil 36%, stearic acid 4%, MYS-10 6%, MYS-25 4%, distilled water 50%.

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1) M. Aoki, *et al.* : Yakuzaigaku, **19**, 31 (1959).
2) E. P. Laug, F. M. Kunze : J. Pharm. Exptl. Therap., **95**, 460 (1949).
3) K. Kobayashi : Japan Pat. No. 278,995 (June 26, 1961); U. S. Pat. No. 2,973,379 (Feb. 28, 1961).

Primarily EMU and PMA are agents for topical application. In the present study, they are meant to attack microorganisms in the vagina. However, since they are of mercurial nature, they are preferably to be used with the least possible intracorporeal absorption.

Thus, an attempt was made to investigate a possibility of minimizing a harmful intratissue absorption during local application of mercurial compounds such as EMU and PMA. EMU, being a newly introduced agent, should be first checked up as to its mode of absorption depending upon the modification of vehicles employed.

Little is known of the adjusting of absorption of mercurials from the vaginal tract by means of selective vehicles. During the present experiments the changes of blood level were pursued between EMU and PMA with cream base used in various compositions in comparison with Carbowax vehicle.

In treating *trichomonas vaginalis,* care was taken to prepare EMU suppository with an adequate non-irritable vehicle. Preliminary study of the present series of experiments revealed that various degrees of irritation were experienced by the materials employed. A cream base Rx 6 was experimentally evidenced to be the least irritable *in vivo* and to be favourable in enhancing anti-trichomonal activities *in vitro.* Thus during the present experimentation Rx 6 was used as a standard vehicle, in which a comparative study was made between EMU and PMA as to their vaginal absorption.

Various changes were made of constituent percentages and components in Rx 6 in order to observe varying influences on intravaginal absorption. Also Carbowax 2000 was employed for comparison's sake. The organomercurial compounds employed were all labelled with radio active Hg^{203}.

Method

Young matured female rabbits, weighing from 2.3 to 3.3 kg. were used during their non menstrual period. They were fed once daily with a solid meal; water was given *ad lib.* In order to avoid a risk of the suppository administered as single dose being washed away by urination, the rabbit was kept fasting for 24 hr. prior to the experiment. In repeated administration, the animal's vagina was ligated loosely enough to let out only the minimum amount of urine required.

In the case of single dose administration, the animal's vagina was kept clamped for 7 hr., while the animal's blood level was checked up.

0.2 g. of each suppository containing 0.1% labelled mercurial compound (Hg^{203}-PMA or Hg^{203}-EMU) was put into 1 ml. tuberculine syringe whose upper-most barrel part had been cut off tip and the cut end blunted so as not to damage animals' vaginal wall.

After insertion of a suppository, 0.5 ml. of blood was chronologically taken from the ear lobe by intravenous puncture. The blood was transfered into a glass tube, 1 cm. in diameter and 5 cm. in length, followed by cleansing with 0.5 ml. of H_2O. Concentrations of a labelled mercurial compound in the blood were determined by direct counting of gamma radiation with a well-type scintillation counter (Phillips Gloelampenfabrieken). In each experiment, the concentrations were represented as PMA, EMU, and EMCl (ethylmercuric chloride) respectively from the values simultaneously counted with standard solution of each 0.2 μg. of Hg^{203}-PMA, Hg^{203}-EMU, or Hg^{203}-EMCl which was dissolved in conc. HNO_3 respectively. The counting was made for 10 min.

Determination of the Water Solubility of Hg^{203}-EMU——Ten mg. of Hg^{203}-EMU was placed in an L-formed glass tube with a ground glass stopper being added by 10 g. of dist. H_2O. The glass tube was kept in a rocking device in a constant temperature bath at 25±1°. After being shaked for 24 hr., the solution was filtered from the glass tube and centrifuged at 3,000 r.p.m. for 10 min. The radio-activity of 78 mg. of the supernatant was counted directly. The water solubility of Hg^{203}-EMU was calculated to be 2.67 μg./g. from the value simultaneously counted with the standard solution of Hg^{203}-EMU which was mentioned previously.

Determination of Oil/Water Partition Coefficient of Hg^{203}-PMA and Hg^{203}-EMU——The same device for determining water solubility of Hg^{203}-EMU was employed in this experiment.

A stock solution of Hg^{203}-PMA was prepared by dissolving 200 mg. of Hg^{203}-PMA in 100 g. of dist. H_2O. Three g. of the stock solution was placed in an L-formed glass tube being added with the same amount of liquid paraffin and shaken for 24 hr. at 30±1°. Each 10 mg. of oil and H_2O phase was taken out of the glass tube and their radio-activity were counted directly.

In case of Hg^{203}-EMU, as an oil phase, oleyl alcohol was employed instead of liquid paraffin because of Hg^{203}-EMU's poor solubility into the latter. The rest of the procedures were carried out as in the determination of Hg^{203}-PMA.

Material

The Ingredients of Vehicles——Carbowax 2000 : mixture of equal amounts of polyoxyethylene glycol 400 and polyoxyethylene glycol 4000 (U. C. C.). MYS-4, MYS-10, and MYS-25 are polyoxyethylene monostearate produced by Nihon Surfactant Co. and having HLB values of 6.7, 10.8, and 15.2 respectively, MGS-B (glyceryl monostearate, HLB 3.7), Nihon Surfactant Co.

The Radioactive Reagents——Radioactive mercurial compounds*2 were obtained from the Abbott Radio-Pharmaceuticals as phenylmercuric acetate (Hg^{203}-PMA) and ethylmercuric chloride (Hg^{203}-EMCl).

The radioactive ω-ethylmercurithio-*n*-undecanoic acid (Hg^{203}-EMU) was prepared as follows :

Hg^{203}-C_2H_5HgCl (0.54 g.) was dissolved in a mixture of 10% NaOH (0.815 g.) and 95% EtOH (7 ml.) on a water bath. After being cooled, the solution was filtered. The filtrate was added under stirring with a solution which had been prepared by dissolving ω-mercapto-*n*-undecanoic acid (0.445 g.) in 10% NaOH (0.815 g.) and H_2O (5 ml.) on a water bath.

Na salt of Hg^{203}-EMU was immediately separated as colorless scale-shaped crystals. Two hr. later, they were filtered, washed with H_2O, and dried in air. When the Na salt was completely dissolved in boiling H_2O (12 ml.), the solution thus obtained was acidified with 10% AcOH (1.7 ml.). Hg^{203}-EMU was precipitated as colorless crystals. After being cooled for 3 hr., it was filtered, washed with H_2O, dried *in vacuo*, and then purified by recrystallization in MeOH (9 ml.). Pure Hg^{203}-EMU (0.67 g.) was obtained as colorless scale-shaped crystals, having melting point of 85~87°.

The reaction sequence is as follows :

$$C_2H_5HgCl + 2NaOH + HS(CH_2)_{10}COOH \longrightarrow C_2H_5HgS(CH_2)_{10}COONa + NaCl + 2H_2O$$

$$C_2H_5HgS(CH_2)_{10}COONa + AcOH \longrightarrow C_2H_5HgS(CH_2)_{10}COOH + AcONa$$

It was found that unlabeled EMU, Hg^{203}-C_2H_5HgCl and Hg^{203}-PMA were stable in the dark at room temperature, but Hg^{203}-EMU gradually became greyish during a few days even in the dark and changed partially insoluble in hot MeOH. This insoluble product was found to be $[HOOC(CH_2)_{10}S]_2$ Hg having melting point of 155~157°.

Unlabeled EMU was exposed to γ-radiation of Hg^{203}-PMA which was filled in a glass ampule. Recrystallization of the greyish product which was obtained in 5 months recovered mostly to an undecomposed EMU having melting point of 81~85° except for a negligible amount of Hg and $[HOOC(CH_2)_{10}S]_2$ Hg which corresponded to 1% of the initial compound.

Thus, it was suggested that self-decomposition of Hg^{203}-EMU occurred not only due to β- but also γ-radiation and Hg^{203}-EMU decomposed mostly by the following disproportionation reaction.

$$2C_2H_5HgS(CH_2)_{10}\cdot COOH \longrightarrow [HOOC(CH_2)_{10}S]_2Hg + C_2H_5HgC_2H_5$$

Hence, just before each experiment labelled EMU, being low in its decomposition rate, was purified by recrystallization in hot MeOH. Standard solutions of Hg^{203}-PMA and Hg^{203}-EMU were prepared after dissolving each agent in conc. HNO_3 in order to keep the solutions stable.

At the beginning of the experiments, standard solutions containing each 0.2 μg. of Hg^{203}-PMA and Hg^{203}-EMU showed 12,000 c.p.m./μg. PMA and 2,945 c.p.m./μg. EMU, respectively.

Formulae for Suppository Vehicles——Prior to this investigation, experiments on formulation of cream vehicles and a test on local irritation had been made in relation to their composition from a stand point of practical application.[4]

Among formulae which showed a suitable consistency and the minimum irritating effect for vaginal use, the formula Rx 6 was chosen as basic one because of its minimum irritation. This vehicle showed another advantage of enhancing the antitrichomonal activity of EMU *in vacuo* (Table I (a) and (b)). The primarily formulated Rx 6 and its modified vehicles employed in this experiment are presented in Table II (a) and (b).

In formulating Rx 9 oleic acid was employed instead of stearic acid in Rx 6, in order to see a different influence on the absorption of an incorporated Hg compounds. Part of liquid paraffin in Rx 9 was replaced by paraffin wax to formulate Rx 10 in order to increase consistency during the hot season.

*2 Supplyed by the courtesty of Mead Johnson Co. U. S. A.

4) M. Aoki, *et al.* : Yakuzaigaku, in print.

Table II(a). Formulae of Suppository Vehicles

Components	Vehicles				
	Rx 6 (%)	Rx 9 (%)	Rx 110 (%)	Rx 110 (%)	Carbowax 2000
Liquid paraffin	45	45	30	30	a mixture of polyethylene
Parffin wax	—	—	15	15	glycol-400 and polyethylene
Stearic acid	5	—	5	—	glycol-4000 in equal weight
Oleic acid	—	5	—	—	
Oleyl alcohol	—	—	—	5	
Water	40	40	40	40	
MYS-10	8	8	7	9	
MYS-25	2	2	3	1	

Table II(b). Formulae of Suppository Vehicles

Components	Vehicles			
	Rx 6(w/o)(%)	Rx 9(w/o)(%)	Rx 10_7(%)	Rx 6_3(%)
Liquid paraffin	45	45	42	27
Paraffin wax	—	—	21	—
Stearic acid	5	—	7	3
Oleic acid	—	5	—	—
Oleyl alcohol	—	—	—	—
Water	40	40	20	60
MYA-10	—	—	7	8
MYS-25	4	2	3	2
MYS-4	6	8	—	—

A modification was attempted to study the influence of replacement reaction in which PMA turns to PM-stearate or PM-oleate in the cream base. The use of oleyl alcohol in Rx 110 meant to avoid such replacement reaction that would have developed if stearic acid or oleic acid had been employed in Rx 6 or Rx 9. A comparative study was made of Carbowax 2000 which was used as typical H_2O soluble vehicle. (Table II (a)).

An attempt was also made to study the state of absorption depending upon different types and phase ratios of emulsions using modified formulae with various amounts of components. (Table II(b)).

Results and Discussion

Absorption of Phenylmercuric Acetate (PMA)

The results obtained with PMA which is incorporated into Carbowax 2000 in two stages of concentration (0.05% and 0.1%) are presented in Fig. 1 which shows the blood concentrations following a single vaginal administration. And the results with cream vehicles having a composition shown in Table II (a) are summarized in Fig. 2. For comparison's sake the result obtained with an administration of 0.2 g. of Carbowax suppository which contains 0.1% of PMA is also presented.

The data shown in Fig. 1 indicates that the absorption of PMA which is incorporated into Carbowax 2000 suppository is markedly influenced by the concentration and absolute amount of the drug administered.

When the same amount of PMA is administered, the higher the concentration of the drug in a suppository, the more absorption of PMA is observed. When a suppository containing the same concentration of the drug is given, the larger the absolute amount, the higher the blood level.

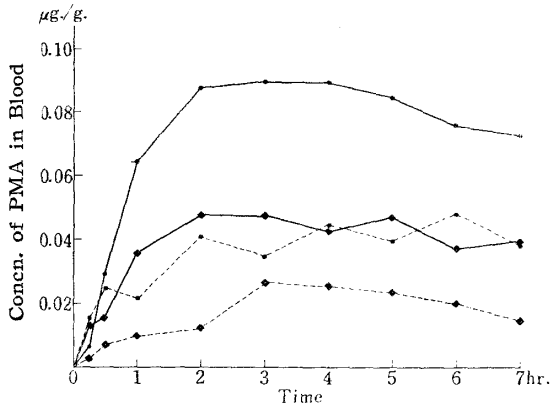

Fig. 1. Absorption of PMA Contained in Carbowax 2000 Suppositories Following Insertion into Rabbit's Vagina

●—● 0.1%, 0.2 g. ●---● 0.1%, 0.1 g.
◆—◆ 0.05%, 0.4 g. ◆---◆ 0.05%, 0.2 g.

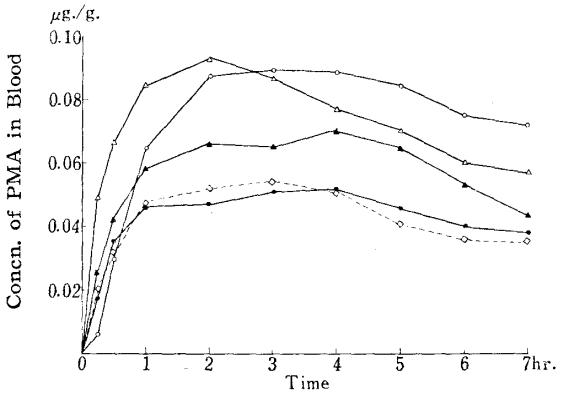

Fig. 2. Absorption of PMA Contained in various Suppository Vehicles Following Insertion into Vagina

○—○ Carbowax 2000 ●—● Rx 6
◇---◇ Rx 9 ▲—▲ Rx 10 △—△ Rx 110
Concentration of PMA 0.1% Dosage 0.2 g.

From the results shown in Fig. 2, the influences of vehicles on the absorption rate of PMA are understood to be especially related to the composition of cream base. A similar blood level of PMA observed after the usage of Rx 6 or Rx 9 cream base revealed that either stearic acid or oleic acid can be employed in the vehicles with little or no effect on absorption.

A rather higher blood level is observed after the usage of Rx 10 the highest being disclosed by Rx 110 or Carbowax 2000. This observation can be explained by an assumption that absorption rate of the drug from vaginal mucosa depends upon the oil-water partition coefficient of the drug. A detailed discussion will be given later with Table Ⅲ. PMA is very soluble to a liquid paraffin containing 10% of stearic acid or oleic acid. This may be ascribed to an easy turn over of PMA into phenylmercuric stearate (PM-stearate) or oleate (PM-oleate) which is more oil soluble than the parent substance.

During the preparation of suppositories with Rx 6 or Rx 9 cream base, the turn over was first suggested by the smelling out of acetic acid and then experimentally confirmed.

Similar blood level patterns observed with Rx 6 and Rx 9 are in accordance with the above assumption, being fortified by a similarity of oil-water partition coefficient (Table Ⅲ).

In any case, it is suggested that a large amount of PMA was distributed in oil phase being converted into oil soluble derivatives under the influences of Rx 6, Rx 9, and Rx 10 vehicles, which contain fatty acids such as stearic or oleic acid.

Table Ⅲ. Oil/Water Partition Coefficient of Mercurials

Oils	Partition coefficient (oil/water)	
	PMA	EMU
Liquid paraffin[a)]	0.06	0.83
Oleyl alcohol[a)]	1.98	3.85
10% Oleyl alcohol + 90% Liquid paraffn[a)]	0.60	—
10% Oleic acid + 90% Liquid paraffin[b)]	17.24	1.29
10% Stearic acid + 90% Liquid paraffin[b)]	18.68	4.26

a) Measured at 30°.
b) Measured at 40°.

However when Rx 110 is used PMA is supposed rather markedly distributed in water phase because of the non-existence of fatty acid in the vehicle. When Carbowax is employed, PMA is very likely to be interwoven with water soluble Carbowax base.

The blood concentration curves obtained with Rx 110 and Carbowax 2000 show higher patterns than with those containing fatty acids. Thus, the absorption rate of PMA from the vaginal mucosa seems to be related to the amount of the drug distributed in the water phase of a vehicle.

A rapid rise of blood level followed by a rather sharp reduction after the usage of Rx 110 than after Carbowax 2000 may be related with a fact that PMA in Carbowax 2000 requires an additional time needed to be dissolved into water phase.

A slightly higher blood level of PMA resulting from Rx 10 than that from Rx 6 or Rx 9 seems to be noteworthy. The opposite result is expected, since a replacement of liquid paraffin with paraffin wax raises the melting point of oily phase, leading to a possible decrease in drug absorption. The above finding seems to remind one of the result of the preliminary test in which Rx 10 was found more responsible to skin irritation test than Rx 6 or Rx 9.[4]

No significant differences have been observed of the influences of different types and phase ratios of emulsion base on the absorption rate of mercurials (Figs. 3 and 4).

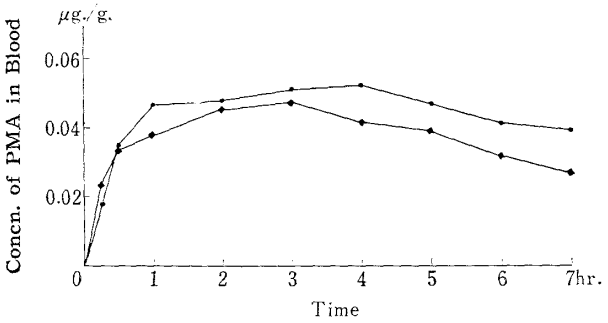

Fig. 3. Absorption of PMA Contained in Suppository Vehicles of Various Emulsion Types Following Insertion into Rabbit's Vagina

●—● Rx 6 (o/w) ◆—◆ Rx 6 (w/o)
Concentration of PMA 0.1% Dosage 0.2 g.

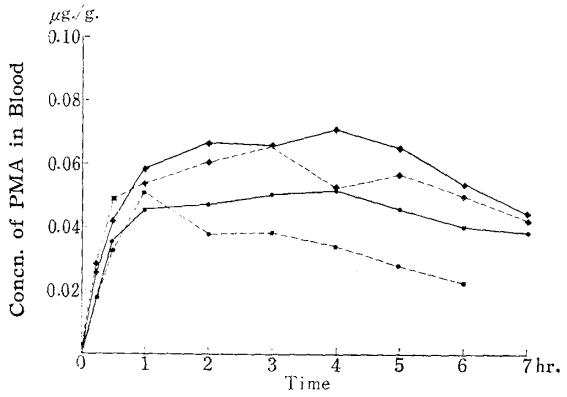

Fig. 4. Absorption of PMA Contained in Suppository Vehicles of Various Different Phase Ratios of Emulsion Following Insertion into Rabbit's Vagina

●—● Rx 6_5 ●---● Rx 6_3 ◆—◆ Rx 10_5
◆---◆ Rx 10_7 Concentration of PMA 0.1%
Dosage 0.2 g.

The use of water-in-oil type emulsion base (Rx 6, w/o) results in a slightly lower blood level than oil-in-water type (Rx 6, o/w). This result advocates the previous interpretation that PMA in water phase is more responsible for the absorption from the vaginal mucosa. When oil phase was raised from 50% to 70% no significant difference in the absorption rate was observed (Rx 10_5 and Rx 10_7 curves in Fig. 4). A decrease of oil phase from 50% to 30% found in modification of Rx 6 was followed by a decrease of the absorption rate (Rx 6_5 and Rx 6_3 curves in Fig. 4). A similar decrease was also observed in modification of Rx 10.

Absorption of ω-Ethylmercurithio-*n*-undecanoic Acid (EMU)

Blood concentrations after a single vaginal administration of EMU which was incorporated into Carbowax 2000 in two stages of concentration of 0.05% and 0.1% (Fig. 5) reveals that the drug absorption is also influenced by dosage. Regarding the absorption

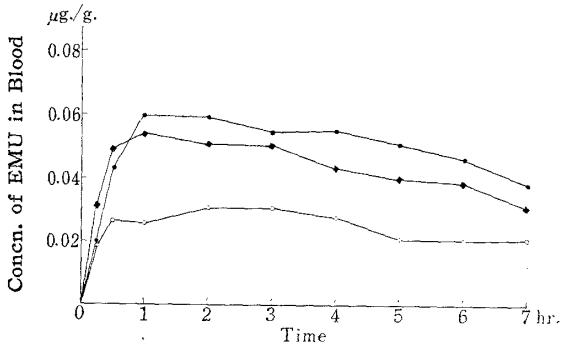

Fig. 5. Absorption of EMU Contained in Various Suppository Vehicles Following Insertion into Rabbit's Vagina

●—● Carbowax 2000, 0.1%, 0.2 g.
○—○ Carbowax 2000, 0.05%, 0.2 g.
◆—◆ Rx 6, 0.1%, 0.2 g.

of EMU, the difference such as shown with PMA is not observed between the usage of Carbowax 2000 and that of Rx 6 (Fig. 5). It is reasonably considered that EMU does not undergo replacement reaction such as observed between PMA and Rx 6.

The blood level of EMU obtained after absorption from Carbowax 2000 and Rx 6 has followed an analogous pattern when PMA is absorbed with Carbowax 2000 and Rx 110, although there is a considerable difference in the degree of blood concentration between the former and the latter.

The blood concentration of PMA is higher than EMU when Carbowax 2000 suppository is employed, but in case of Rx 6 a similar blood level is observed (Figs. 2 and 5). This may be explained, once again, by the assumption that absorption from the vaginal mucosa depends upon the oil-water partition coefficient of the drug employed.

Table III represents the oil-water partition coefficients of the two drugs against various oil phases which are employed in the cream bases mentioned earlier. On the water solubilities of these drugs including ethylmercuric chloride (EMCl) against their absorption rate discussions will be made below with reference to the absorption of EMCl.

Absorption of Ethylmercuric Chloride (EMCl)

The blood concentrations of EMCl observed after a single administration of Carbowax 2000 suppositories which contain EMCl in two stages of concentration (0.05% and 0.1%) are presented in Fig. 6.

A comparison of the absorption rate of the three drugs is made from the data obtained following administration of Carbowax 2000 suppositories (Figs. 1, 5, and 6).

PMA, EMU, and EMCl with reference to their water solubility, the ratios of blood concentration obtained after

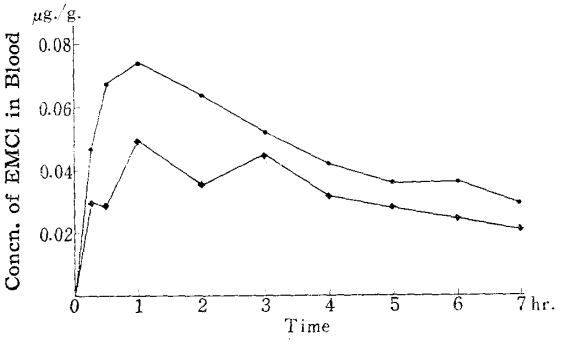

Fig. 6. Absorption of EMCl Contained in Carbowax 2000 Suppositories Following Insertion Rabbit's Vagina

●—● 0.1%, 0.2 g. ◆—◆ 0.05%, 0.2 g.

Table IV. Ratios of Blood Concentration at Time Intervals after Administration between $C_{0.1}$ and $C_{0.05}$ Mercurials Incorporated in Carbowax 2000 Suppositories

Mercurials	Ratios ($C_{0.1}/C_{0.05}$) (hr.)								
	¼	½	1	2	3	4	5	6	7
PMA	2.7	3.8	5.7	6.2	2.9	3.1	3.3	3.4	4.6
EMU	1.1	1.6	2.3	2.0	1.8	2.0	2.4	2.3	1.8
EMCl	1.5	2.4	1.5	1.8	1.2	1.3	1.3	1.5	1.4

Table V. Ratios of the Highest Blood Concentrations between 0.1% and 0.05% Mercurials Incorporated with Carbowax 2000 Suppositories, The Water Solubility of Mercurials at 25°

Mercurials	Concn. of mercurials in suppository (%)	Maximum concn. in blood (μg./g.)	Ratio ($C_{0.1}/C_{0.05}$)	Water solubility at 25° (μg./g.)
PMA	0.1	0.089	3.4	1.67
	0.05	0.026		
EMU	0.1	0.059	2.0	0.0026
	0.05	0.030		
EMCl	0.1	0.074	1.5	0.0014
	0.05	0.049		
PMA[a] (Rx 6)	0.1	0.052	2.0	—
	0.05	0.026		

a) PMA is converted into PM-stearate.

administration of a Carbowax 2000 suppository containing 0.1% of each of these drugs to that containing 0.05% are designated on the bases of a ratio $C_{0.1} : C_{0.05}$ (Table Ⅳ).

The ratio $C_{0.1} : C_{0.05}$ calculated of PMA is generally higher than that of the other two drugs, and it shows a slightly wider variance during the first one to two hours after the administration being followed by a steady ratio. EMU and EMCl show low ratios with a slight variance which is individually different depending upon each water solubility.

A marked influence of water solubility of each drug on the absorption rate was observed following an increase in drug concentration in the Carbowax 2000 suppository. This finding is comformable with the result of a comparative study of $C_{0.1} : C_{0.05}$ ratio of a maximum blood concentration among these drugs (Table Ⅴ). These ratios obtained of PMA, EMU and EMCl are well in accordance with the order of water solubility of each drug. It is concluded that as far as the vaginal mucosa is concerned, the rate of absorption of mercurial compounds is related to the water solubility of the drug, and the rate of absorption is much influenced by the oil-water distribution coefficient of the drug.

Thus, it is believed that the absorption of such locally acting drugs as mercurial compounds employed in the present study may reasonably depend upon the formulation of the vehicle in view of the water solubility and oil-water partition coefficient of the drug.

The authors wish to express their heartfelt thanks to Dr. W. M. Cox, Jr., former director of Scientific Relation and Dr. W. T. Sumerford, director of Pharmaceutical Chemistry, Mead Johnson & Company for their valuable assistance and co-operation in carrying out this work.

Summary

Absorption rates of three kinds of organomercurial compounds from the rabbit's vagina were studied in refference to suppository vehicles. Several types of emulsion base and Carbowax 2000 were employed as vehicles. The compounds were labelled with isotope Hg^{203} and the blood concentration was chronologically determined after a single vaginal administration of suppository.

Modifications of the composition of emulsion vehicle resulted in some changes of an actual absorption rate for phenylmercuric acetate, because of the replacement reaction of the mercurial in the vehicle.

No significant differences were observed of the influences of the type and phase ratio of emulsion vehicle on the absorption rate.

When Carbowax 2000 was used as vehicle, phenylmercuric acetate showed a higher blood level than that of ω-ethylmercurithio-*n*-undecanoic acid or ethylmercuric chloride.

It was concluded that the rate of absorption of mercurial compounds contained in suppository vehicle through rabbit's vagina was related to the water solubility and oil-water distribution coefficient of the compounds employed.

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77. Hiroshi Fukuchi, Tsutomu Takeda, Akira Kamada, Kanjiro Kobayashi, and Masaru Aoki: The Absorption of Organomercurial Compounds from the Vaginal Route of the Rabbits. II.*1

Distribution and Excretion of ω-Ethylmercurithio-*n*-undecanoic Acid and Phenylmercuric Acetate.

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Previously a comparison was made of the vaginal absorption of mercurials, especially between PMA (phenylmercuric acetate) and EMU (ω-ethylmercurithio-*n*-undecanoic acid) administered in the form of suppository prepared with cream base Rx 6 and its modified bases.*1 The comparison which was made on blood levels revealed that modifications of the cream bases had resulted in some changes of an actual absorption rate for PMA but very few for EMU.

During the present series of experiments, care had to be taken to assure lest EMU, being a new compounds, should show any possible toxic reactions. It is understood that toxic manifestations due to the absorption of organomercurial compounds are reflected on accumulation and excretion of the compounds rather than their blood level.

According to Laug and Kunze,[1] mercury deposits mostly in the kidneys following intravaginal administration; and an appreciable amount of deposit is also found in the liver when used with a jelly base or in the form of aqueous solution. A similar deposition occured when PMA was intravenously[2] or subcutaneously[3] administered.

Thus, in the present experimentation a comparison was made of EMU with PMA which has been already in practical use. And it was attempted to pursue the results of intravaginally administered EMU pertaining to tissue distribution and excretion. Rx 6, being the least irritable and synergistically antitrichomonal, was experimentally standardized as in the previous experiment.*1

It was also attempted to study the effect of detoxicants such as α-lipoic acid and BAL on the excretion of mercurials introduced.

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*1 Part I. M. Aoki, *et al.*: This Bulletin, **12**, 540 (1964).

*2 Toneyama, Toyonaka, Osaka-fu (福地 坦, 武田 務, 鎌田 皎, 小林勘次郎, 青木 大).

1) E. P. Laug, F. M. Kunze: J. Pharmacol. Exptl. Therap., **95**, 460 (1949).
2) C. S. Prickett, E. P. Laug, F. M. Kunze: Proc. Exper. Biol. and Med., **73**, 585 (1950).
3) L. Friberg, E. Odeblad, S. Forssman: A. M. A. Arch. Indust. Health, **16**, 163 (1957).