STUDY ON THE RECTAL ABSORPTION OF GENTAMICIN IV

HARUMASA TOYA and YOSHIKO KATO
Research Laboratory, Sawai Pharmaceutical Co., Ltd.

MASARU YAMAZAKI and AKIRA KAMADA
Faculty of Pharmaceutical Science, Osaka University

(Received November 4, 1983)

Gentamicin suppository containing surfactant was administered to beagle dogs (adult and aged) for 6 consecutive days, once daily, in order to examine the change of blood level of gentamicin. When polyoxyethylene (20) cetyl ether, having a rather mild effect, was used as the surfactant, the change in the blood level of gentamicin was similar in both adult and aged dogs, showing almost the same bioavailability for 6 consecutive days. However, the administration of saponin, capable of destroying the cell membrane to considerably extent, influenced the C_{max} after 4th day administration in both adult and aged dogs. So, we could not obtain constant bioavailability of GM when saponin was used as the absorption promoter.

INTRODUCTION

There are many reports concerning the rectal administration of antibiotic agents because this route is considered to be a clinically useful one[1~3].

The authors also examined basic studies on the rectal administration of the aminoglycoside antibiotic agents for past few years[4~6], and they have come up with some results. Since the aminoglycoside antibiotics are very soluble in water with poor cell membrane affinity, they are hardly able to be absorbed from the rectum. Therefore, some pharmaceutical device may be required in order to attain the effective blood level of such water soluble drugs when administered by way of the rectum. Thus, various surfactants, such as surface active agent, were added to the suppository as one of the possible pharmaceutical devices.

It was found as a result that non-ionic surfactants, which are said to be low toxic[7], accelerate the absorption in large animals. This fact may suggest that such pharmaceutical preparations as a rectal suppository containing water soluble therapeutic agent and surfactant would give effective blood levels when administered in human.

The acceleration mechanism of the rectal absorption due to the surfactants may be that the permeability of the rectal membrane is altered by the surfactants. Such a change in permeability may probably be caused by the rectal tissue lesion, and YONEZAWA[8] and AIZAWA et al[9]. have already reported on the damage of the rectal membraneous tissue by single rectal application of various surfactants. Clinically, the antibiotic agents are administered several times daily for long period for their pharmacological nature[10], and it may be the case if the rectal formula of the antibiotics are prepared for clinical purposes. Thus, damage to the rectal membrane should be throughly examined not only in the case of a single dose but also in the case of multiple daily doses.

We attempted fundamental examinations based on such a view point by administering rectal formulas of antibiotics containing surfactants for 6 consecutive days and their effect on the blood level of the antibiotic agents. In order to examine the effect of the age of animal adult and aged dogs were used as the experimental animals.

MATERIALS AND METHODS

Materials Gentamicin sulfate (GM) was obtained from Shionogi Pharmaceutical Co., Ltd. Lipophilic base, Witepsol H-15 (Dynamit Nobel

A. G., Chemishe Werke Witten, German Fedral Republic) with a melting range of 33.5~35.5℃ and congealing range of 32.5~34.5℃ was used. POE (20) cetyl ether was supplied from Nikko Chemicals and saponin was obtained from Wako Pure Chemicals.

Preparation of suppository For all experiments of rectal administration, a fixed dose of GM at 10 mg/kg and surfactant 1%(w/w) were selected. Suppositories were prepared in the same manner as described in the previous paper. The suppository were kept at 4℃ until use.

***In vivo* absorption study** Male beagle dogs were used as experimental animals. The animals were divided into two groups: 1~2 years old (adult) and 7~10 years old (aged). The study was performed between 10 a. m. and 1 p. m. Before the experiment, the animals were fasted for 12 hr. but were allowed to drink ad libitum. Blood samples were taken at 10, 30, 60, 120 and 180 min. after insertion of suppository. They were taken into 10-ml glass tubes and centrifuged at 3000 rpm for 5 min. The serum layer was taken into stoppered glass tubes and kept at 4℃ until assays were carried out.

Analytical method The antimicrobial activity of GM in serum was determined by the cup method using *Bacillus* ATCC 6633 as the test organism.

RESULTS

Serum levels of GM after administering the rectal suppository containing 1%(w/w) of POE (20) cetyl ether once daily for 6 days to adult and aged dogs are shown in Fig. 1. Kinetic parameters of the serum level of GM on the 1st, 3rd, 4th and 6th days after the administration are shown in Table 1. There was no significant difference during the 1st, 3rd, 4th and 6th day in C_{max}, T_{max}, $T_{1/2}$ and AUC, and a similar serum level pattern as in the first administration was obtained as far as POE (20) cetyl ether was administered once daily, up to the 6th day.

Serum level profile and kinetic parameters of GM, when saponin 1%(w/w) containing a suppository was administered, are shown in Fig. 2 and in Table 2. Similar serum level patterns were observed from the 1st day to the 3rd day, but C_{max} was increased after the 4th day in the adult dogs, and decreased in the aged dogs.

Leakage of the suppository was not observed in the present study, and the hardness of the feces was apparently the same in the suppository administered group and in the control group.

Table 1 Pharmacokinetic parameters of GM after 6 consecutive rectal administration of GM suppository containing POE (20) cetyl ether

Adult dogs

Day	T_{max} (min.)	C_{max} (μg/ml)	$T_{1/2}$ (min.)	AUC (μg·min/ml)
1st	30	10.2±3.8	67.2±17.9	994.5±130.7
3rd	30	9.9±3.1	72.5±14.2	985.0±180.6
4th	30	9.7±3.7	76.4±10.0	955.8± 59.7
6th	30	8.4±2.7	80.0± 7.2	838.0±118.5

Aged dogs

Day	T_{max} (min.)	C_{max} (μg/ml)	$T_{1/2}$ (min.)	AUC (μg·min/ml)
1st	30	7.7±2.4	96.2±16.3	785.5±128.0
3rd	30	8.3±2.9	85.0±16.0	985.0±180.4
4th	30	7.2±2.4	82.5±11.9	795.8± 98.4
6th	30	7.9±1.8	87.0±19.9	867.0± 94.3

Each value is the mean ± S.E. of 4 animals

Table 2 Pharmacokinetic parameters of GM after 6 consecutive rectal administration of GM suppository containing saponin

Adult dogs

Day	T_{max} (min.)	C_{max} (μg/ml)	$T_{1/2}$ (min.)	AUC (μg·min/ml)
1st	30	15.5±4.2	43.1±8.9	1273.0±207.0
3rd	30	13.4±3.9	53.1±14.8	1217.3±143.9
4th	30	18.3±4.1	70.2±14.1*	1971.0±225.8*
6th	30	22.1±3.9*	70.2±18.4*	2180.5±280.8*

Aged dogs

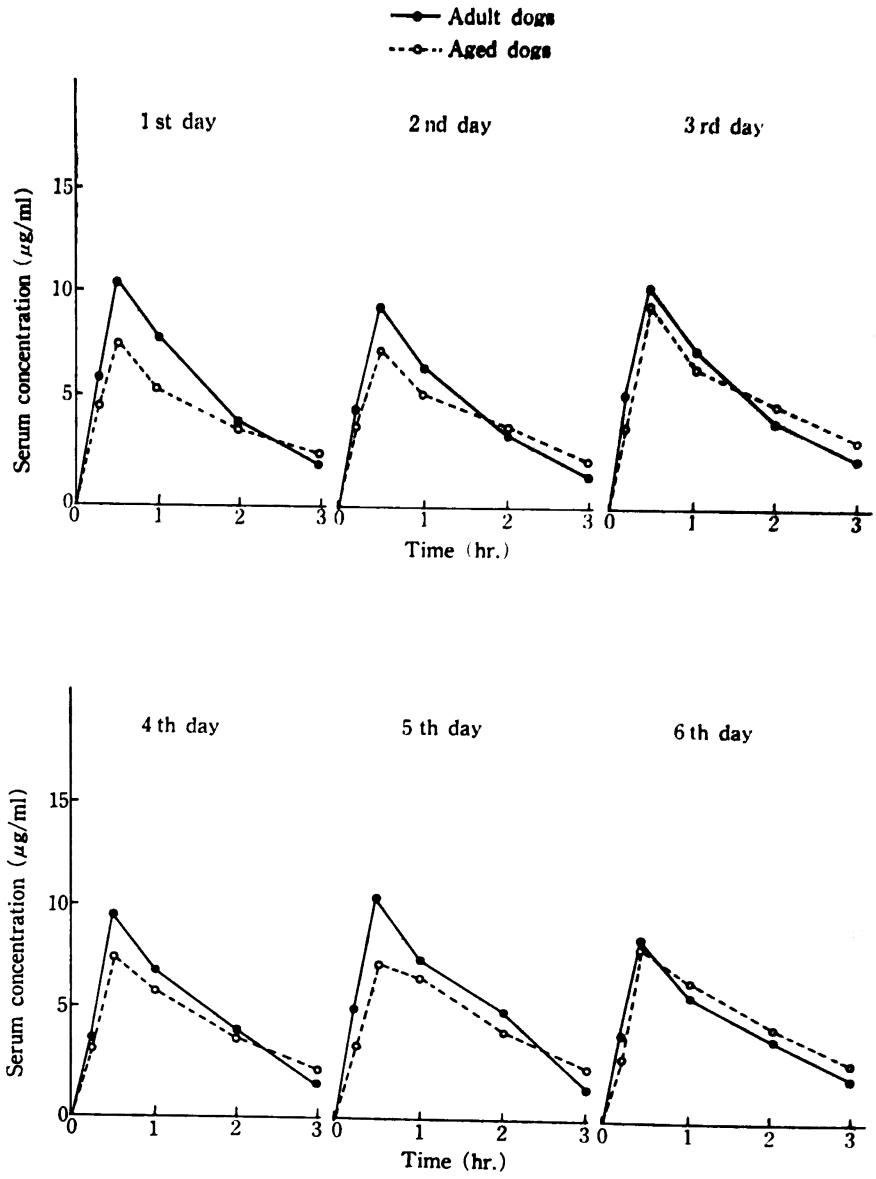
Day	T_{max} (min.)	C_{max} (μg/ml)	$T_{1/2}$ (min.)	AUC (μg·min/ml)
1st	30	12.1±3.2	60.7± 9.2	1122.0±360.1
3rd	30	12.1±3.2	70.0±11.2	1212.5±230.8
4th	30	10.8±3.2	71.3±10.9	1133.0±249.1
6th	60	7.1±2.5	130.3±19.5*	1048.3±189.5

*$P<0.05$: significant difference from 1st day. Each value is the mean ± S.E. of 4 animals

DISCUSSION

The serum level of GM was not so different in the adult and aged dogs when POE (20) cetyl ether, by which the cell membrane might be damaged to a lesser extent, was successively administered. However, when saponin, by which the cell membrane might be damaged to a greater

Fig. 1 Serum levels of GM after rectal administration of suppository containing 1%(w/w) POE (20) cetyl ether. Each value is the mean of 4 animals

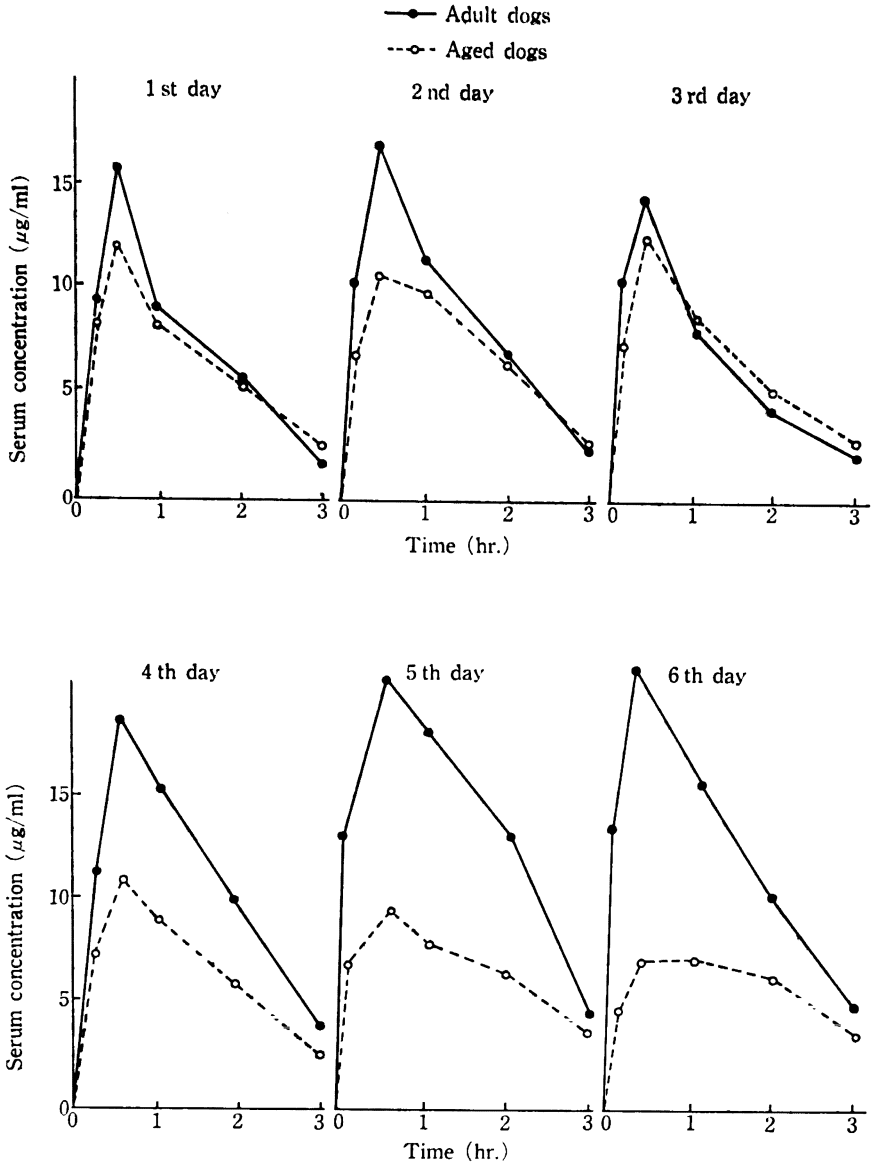


extent, was administered, the serum level pattern showed a change in both adult and aged dogs after 4 th day.

The turnover rate for the epithelial cells in the digestive organ is generally fast[11-13]. It generally takes one or two days for a turnover. Therefore, if the effect of the surfactant on the rectal tissue is mild, and if the tissue damage is within the range of spreading the space of the epithelial cells or disorientation of the cell membrane of the epithelial cells, restoration of the tissue damage may be accomplished within a short period. However, when a surfactant, by which the cell membrane is damaged to a considerable extent, is administered, the damage to the rectal tissue is not restricted to the epithelial cells but can cause damage to the muscle layer and capillary vessel. The so-called inflammation occurs in such cases.

The present experimental results might suggest

Fig. 2 Serum levels of GM after rectal administration of suppository containing 1%(w/w) saponin. Each value is the mean of 4 animals



that POE (20) cetyl ether exerted a weak effect only on the epithelial cell, and afterwards, the damage to the membrane was normalized within a short period of time.

On the other hand, saponin caused severe damage to the rectal tissue membrane inducing an inflammatory lesion. Thus, the serum level pattern in the case of saponin was complexed, and the serum levels of GM varied considerably on the 4 th, 5 th and 6 th days after the suppository administration began. In addition to tissue damage, an increase in the permeability of the capillary vessel, its occlusion, formation of granulation and other complicated factors might be related.

However, these speculations are nothing but hypothesis now, and more precise observations of the change in the tissue with microscopic pictures are going to be attempted in the near future. It might be interesting that the serum level of GM after the administration of saponin after the 4 th

day was considerably deferent in the adult and aged dogs which can be seen in Fig. 1 and 2. In other words, C_{max} increased gradually in the adult dogs, while it decreased in the aged dogs. A rational explanation for this phenomenon is not possible at present, but it might be assumed that the difference might be due to a change in the reactivity of the tissue for inflammatory degeneration due to aging[14]. The difference may be that in the regeneration of the blood vessel and in the granulation formation.

It was proven in the present experiment that a mild surfactant like POE (20) cetyl ether produced a consistent GM serum level in both the adult and aged dogs by the 6 day consecutive administration. On the other hand, such a strong surfactant as saponin, which gives severe damage to the cell membrane, does not give a consistent GM serum level during a long-term consecutive administration. However, if a certain blood level should be maintained, three or more doses daily may be required, not like the present case of once daily, and in such cases, damage to the tissue may be caused even when a mild surfactant is used. Further studies will be carried out and the results will be reported in the near future.

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ゲンタマイシンの直腸吸収に関する研究 IV

戸谷治雅*[1)]・加藤敬香[1)]・山崎 勝[2)]・鎌田 皎[2)]

* 執筆責任者

[1)] 沢井製薬研究所生物研究室

[2)] 大阪大学薬学部薬剤学教室

アミノ配糖体抗生剤であるゲンタマイシン（以下，GM と略す）の直腸吸収についてビーグル犬を用いて前報[*1~*3]にひきつづき検討した。

今回は，界面活性剤を含有した GM 坐剤を 6 日間（1 日 1 回）連続投与し，血中濃度の変動について検討した。吸収促進剤（界面活性剤）としては穏やかな膜作用を有する POE (20) cetyl ether と膜損傷作用の強いサポニンを用い，ビーグル犬は生後 1～2 年の成犬と 7～10 年の老犬を用いた。

その結果，POE(20) cetyl ether を吸収促進剤とした場合，成犬，老犬とも 6 日間を通じ GM の pharmacokinetic parameter(T_{max}, C_{max}, $T_{1/2}$, AUC) に大きな差は見られなかったが，サポニンでは 1 日目の値と比較して 4 日目から成犬の $T_{1/2}$ と AUC において有意な差 ($P<0.05$) が見られた。老犬においても C_{max} において減少傾向が見られた。このことは POE(20) cetyl ether では膜作用が弱く，組織変化がわずかであったため，短時間で直腸粘膜が修復されると考えられるのに対し，サポニンでは直腸部の組織変化が大きく，修復が充分に行なわれなかったと考えられる。さらに興味あることに，サポニン添加時では，C_{max} において老犬では，減少する傾向を示し，成犬では増加する傾向を示した。これはサポニンによる組織変化が，成犬では GM の透過性が増す方向に，逆に老犬では減少する方向であると考えられるが，詳細については今後の検討が必要である。

これらのことから，サポニンのような膜損傷作用の強い界面活性剤を吸収促進剤として用いた時は，連続投与により一定の血中濃度パターンを得ることはできないが，POE(20) cetyl ether のような穏やかな膜作用物質では少なくとも 6 日間は一定の吸収が得られることがわかった。

*1 TOYA, H. et al : Chemotherapy 31 : 634～638
*2 TOYA, H. et al : Chemotherapy in press
*3 TOYA, H. et al : Chemotherapy 投稿中