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Influence of Macrogol Bases on the Bioavailability of Bacampicillin after Rectal Administration in Rabbits¹⁾

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Rectal administration of bacampicillin hydrochloride (BAPC) in Witepsol H-15 base suppository provided a fairly good absorption in rabbits; the extent of bioavailability was 44%. Since BAPC has high lipophilicity compared to the parent compound (ampicillin, ABPC), rectal absorption from hydrophilic bases (macrogol 1000 and/or 4000) was examined. The highest bioavailability (88%) was obtained with macrogol 1000 base, but the bioavailability decreased with the increase of macrogol 4000 base addition. It is known that macrogol bases increase the secretion of rectal fluid while oleaginous bases do not change the amount of the fluid. The solubility of BAPC, however, was constant regardless of the amount and kind of the macrogol bases. In contrast, the partition coefficients (toluene/water) were reduced by the addition of both kinds of macrogol bases. Furthermore, the release rates of BAPC from the suppositories were little affected by the addition of the bases. Therefore, macrogol 1000 base seems to improve the bioavailability by prolonging absorption with an increase of the distribution area in the rectum. On the other hand, macrogol 4000 base is assumed to reduce the bioavailability by taking up secreted rectal fluid to dissolve and/or by forming a highly viscous solution.

Keywords—bacampicillin; rectal absorption; bioavailability; Witepsol H-15 base; macrogol base; mean residence time; solubility; partition coefficient; ampicillin; rectal fluid secretion

In the previous paper,²⁾ it was proved that bacampicillin hydrochloride (BAPC) was absorbed fairly well from the rectum by using a suppository formulated with Witepsol H-15 base. The absolute bioavailability was about 44% and its bioavailability was 80% of that of oral absorption. However, investigation of other suppository bases seemed worthwhile to improve the bioavailability. Since BAPC, a prodrug of ampicillin (ABPC), is more lipophilic than the parent drug, the release rate of the drug from the base should be promoted and fast absorption may be obtained by using hydrophilic bases.

The purpose of this study was to investigate the effect of macrogol bases on the rectal absorption of BAPC in rabbits.

Experimental

Materials—BAPC (659 µg/mg) was a gift from Yoshitomi Pharmaceutical Ind., Ltd. (Osaka, Japan), ABPC Na was purchased from Meiji Seika Kaisha Ltd. (Tokyo, Japan), and macrogols and polyoxyethylene sorbitan monooleate (Tween 80) were supplied by Wako Pure Chemical Ind., Ltd. (Osaka, Japan). All other chemicals were of the highest reagent grade and were used without further purification.

Preparation of Suppositories—Physical mixtures of macrogol bases as shown in Table I were heated at 60°C in a thermostated bath. Then, BAPC was mixed in the melted base, followed by sonification with an ultrasonic cleaner (Branson, 220J) for 5 min at 60°C. The mixtures were quickly poured into steel molds and allowed to solidify at room temperature.

The formulae of suppositories prepared in this work are listed in Table I. All suppositories were stored in stoppered flasks at 4°C, and were administered within a week after preparation.

Drug Release Test—The release test was carried out as previously reported.²⁾ Normal saline (300 ml) was used

TABLE I. Bacampicillin Suppository Preparations

| Suppository | Base component (%) | | BAPC content (mg/g) ^{a)} |
|-------------|--------------------|-----|-----------------------------------|
| PEG | Macrogol 1000 | 100 | 99.1 ± 0.9 |
| PEG I | Macrogol 1000 | 96 | 101.2 ± 1.1 |
| | Macrogol 4000 | 4 | |
| PEG II | Macrogol 1000 | 81 | 100.3 ± 1.1 |
| | Macrogol 4000 | 9 | |
| PEG III | Macrogol 1000 | 75 | 98.9 ± 0.8 |
| | Macrogol 4000 | 25 | |

a) Each value represents the mean ± S.D. (n = 10) determined by I₂-colorimetry.

for the dissolution test. Each suppository, together with 7 ml of the test solution, was placed in a cylindrical plastic cell equipped with an artificial membrane (Millipore filter, 0.45 μm). The inner test solution of the cell was stirred at 50 rpm, while the outer solution was stirred at 100 rpm at 37°C. Aliquots of 5 ml of the releasing fluid were removed and the same volumes of normal saline were added to the vessel to maintain the original volume. The BAPC concentration was assayed by I₂-colorimetry³⁾.

Analytical Methods—a) I₂-colorimetry. This spectrophotometric analysis was reported in a previous paper.³⁾ b) High-performance liquid chromatography (HPLC). A reversed-phase column (TSK gel ODS 80-TM, Toyo Soda Manufacturing Co., Ltd.) with a 0.02 M phosphate buffer (pH 6.0)–MeOH (75:25) mixture for ABPC or 0.02 M phosphate buffer (pH 5.0)–MeOH (30:70) mixture for BAPC as the mobile phase, was employed. HPLC apparatus (Shimadzu, LC-5A) equipped with a detector (Shimadzu, SPD-2A) was used. Other conditions for analysis were as follows: flow rate, 0.8 ml/min; wavelength, 225 nm; sensitivity, 0.02 a.u.f.s.

Animal Experiments—Intravenous administration. White male rabbits weighing from 2.5 to 3.5 kg were used. BAPC or ABPC Na (100 mg/ml) dissolved in sterile purified water was intravenously injected into the marginal ear vein at a dose of 17 or 12.6 mg/kg, respectively. Rectal administration. White male rabbits weighing from 2.5 to 3.5 kg were fasted for 24 h prior to the experiments, but were given water freely. The suppositories were positioned 3 cm into the rectum. In order to prevent expulsion of the suppository, a clamp was used to keep the anus closed for 4 h after dosing. After the administration, 1–2 ml blood samples were collected at appropriate intervals from an ear vein of rabbits after administration of heparin (100 unit/kg). The plasma samples were stored at 0°C until assay, and total ABPC (bound + unbound plasma protein) concentration in the plasma was determined by diluting the plasma 5- to 10-fold with water,²⁾ followed by HPLC analysis.

Determination of Solubility of BAPC—A suitable amount of BAPC was suspended in 0.15 M phosphate buffer (pH 6.00, μ = 0.5), which contained various concentrations of macrogols, at 0°C. To obtain a good suspension, 0.1% Tween 80 was added to the solution and the suspension was stirred at about 50 rpm by using a magnetic stirrer. The concentration of BAPC in aqueous solution decreases with time due to the precipitation of nonionic species of BAPC.⁴⁾ Thus, when the BAPC suspension reached to the equilibrium state (about 96 h), a sample was taken out and filtered immediately through a filter (pore size, 0.45 μm), followed by the determination of BAPC by HPLC assay.

Apparent Partition Coefficient—The apparent partition coefficients of BAPC were measured as follows. BAPC was dissolved in 0.15 M phosphate buffer (μ = 0.5), which contained various concentrations of macrogol 1000 or 4000, at pH 5.00 and 6.00. Ten (at pH 5.00) or twenty (at pH 6.00) milliliters of the solution was transferred into a separatory funnel together with 10 (at pH 5.00) or 2 (at pH 6.00) ml of toluene. The funnel was shaken vigorously for 10 min at 25°C. When equilibrium had been achieved, the aqueous layer was separated, and the concentration of BAPC in aqueous layer was measured by HPLC.

The apparent partition coefficients of BAPC in toluene/water were calculated from the observed concentration of BAPC in the aqueous layer before and after the extraction with toluene.

Results and Discussion

Stability of BAPC in Macrogol 1000

The time course of the content of BAPC, which was mechanically dispersed in the melted macrogol 1000, was investigated at 60°C (Table II). The determination was done after dissolving 0.1 g of the above BAPC suspension in water to make 50 ml, and the concentrations of BAPC and its degradation product, ABPC, were measured simultaneously by HPLC

TABLE II. Stability of Bacampicillin in Macrolog 1000 at 60 °C

| Time (h) | BAPC content (mg/g) | ABPC content (mg/g) |
|----------|---------------------|---------------------|
| 0 | 101.6 | N.D. |
| 1 | 99.3 | N.D. |
| 3 | 100.2 | 0.04 |
| 5 | 99.5 | 0.07 |
| 8 | 98.8 | 0.10 |

N.D.: Not detected. Each value represents the mean of two experiments.

TABLE III. Stability of Bacampicillin in Macrolog 1000 at 4 °C

| Time (d) | BAPC content (mg/g) | ABPC content (mg/g) |
|----------|---------------------|---------------------|
| 0 | 102.0 | N.D. |
| 1 | 101.5 | N.D. |
| 7 | 101.7 | N.D. |
| 14 | 99.6 | 0.02 |
| 21 | 98.5 | 0.02 |

N.D.: Not detected. Each value represents the mean of two experiments.

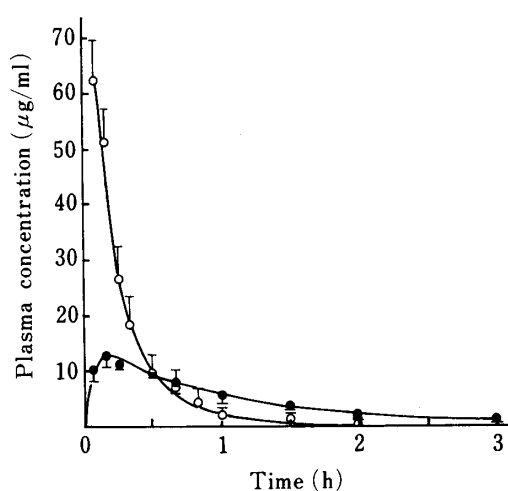


Fig. 1. Ampicillin Concentration in the Plasma of Rabbits after Intravenous Administration of Ampicillin or Bacampicillin

○, ampicillin, dose 12.6 mg/kg; ●, bacampicillin, dose 17.0 mg/kg. Each solid line was generated by the least-squares method from the equations (see Appendix) derived based on the scheme in Chart 1. Each point represents the mean \pm S.D. of three rabbits.

analysis. As shown in Table II, BAPC was quite stable in this base during the preparation of the suppository. Further, a storage test of suppositories prepared with the same content was carried out at 4 °C. The BAPC content remains unchanged during 7 d (Table III). Thus, all the suppositories were used for experiments within one week after preparation.

Pharmacokinetic Analysis of Intravenous Administration of BAPC and ABPC

In order to estimate the absolute bioavailability of BAPC for rectal absorption, intravenous administration (i.v.) of BAPC should be examined. However, BAPC was not detected in the blood after BAPC oral administration; only ABPC was present in the blood.⁵⁾ Further, we found previously²⁾ that BAPC was not detectable in the plasma after rectal administration. This seems to be because BAPC is hydrolyzed by esterases in the blood, or during the absorption from the intestinal tract and the rectum. Therefore, ABPC i.v. administration was examined to assess of the bioavailability.

Average ABPC plasma concentrations after i.v. administration of 12.6 mg/kg of ABPC Na are shown in Fig. 1. The average ABPC level *versus* time curve was fitted to one-compartment and two-compartment models using the computer program MULTI.⁶⁾ As shown in Fig. 1, based on Akaike's information criterion (AIC),⁷⁾ slightly better fits were obtained when a one-compartment open model was used (AIC: 19.2 for the one-compartment model, 25.7 for the two-compartment model). Thus, the kinetics of ABPC after i.v. administration in the present study can be adequately characterized by the one-compartment open model, though Yata *et al.*⁸⁾ preferred a two-compartment model for i.v. administration of 15 mg/kg of ABPC in rabbits. By using the computer-generated parameters for ABPC plasma data, the overall first-order elimination rate constant (k_e) and the area under the plasma concentration *versus* time curve ($[AUC]_0^\infty$) were obtained as $4.64 \pm 0.26 \text{ h}^{-1}$ and

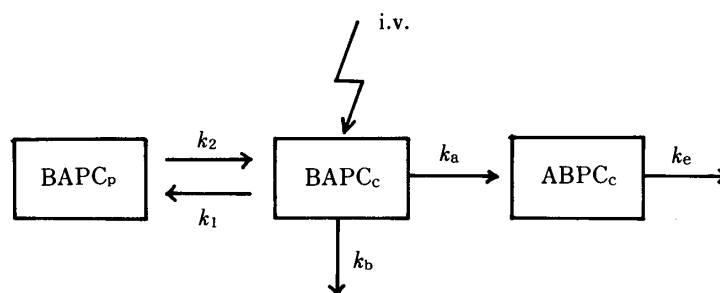


Chart 1

$18.08 \pm 4.17 \mu\text{g} \cdot \text{h}/\text{ml}$, respectively.

On the contrary, following single bolus doses (17 mg/kg) of BAPC, the plasma concentration of ABPC declined in a triexponential fashion, as shown in Fig. 1. Its mean maximum plasma concentration (C_{max}) level was very low compared with that of ABPC i.v. administration and the time to peak (t_{max}) was about 10 min after administration. This plasma concentration *versus* time curve is very similar to that of oral absorption of BAPC. Since the disposition of ABPC was in good agreement with a one-compartment model as described above, and assuming that the time course of BAPC i.v. administration can be approximated by a two-compartment model (Chart 1), the following equation was obtained:

$$C_p^t = Ae^{-\alpha t} + Be^{-\beta t} - Ce^{-k_e t}$$

where C_p^t is the plasma concentration of ABPC, the hybrid parameters, A, B and C are the intercepts obtained from the semilogarithmic plot of C_p^t versus t , α and β are the first-order disposition rate constants (see Appendix), and the microscopic parameter (k_e) is the overall first-order elimination rate constant obtained from the result of ABPC i.v. administration. These exponential parameters in the above equation were obtained by using the non-linear regression analysis program MULTI.⁶⁾ Initial parameters for MULTI were calculated by using a computer adaptation of the classical residual, peeling-off technique.⁹⁾ Fitting the data into the two-compartment model yielded a random scatter of the data points about the regression line, and the parameters A, B, C, α , β and k_e were 2.93 ± 0.46 ($\mu\text{g}/\text{ml}$), 18.11 ± 1.74 ($\mu\text{g}/\text{ml}$), 11.73 ± 1.09 ($\mu\text{g}/\text{ml}$), 3.21 ± 0.50 (h^{-1}), 1.11 ± 0.13 (h^{-1}) and 4.65 ± 0.31 (h^{-1}), respectively. Then, $[\text{AUC}]_0^\infty$ of BAPC i.v. administration was calculated to be $14.7 \pm 3.43 \mu\text{g} \cdot \text{h}/\text{ml}$ from these parameters. As mentioned above, the time course of ABPC disappearance from the blood and the $[\text{AUC}]_0^\infty$ level following ABPC i.v. administration were significantly different from those of BAPC i.v. administration. These results indicate that if BAPC itself could be absorbed from the rectum without hydrolysis to ABPC, the plasma ABPC levels would be further prolonged compared to ABPC administration. In this study, however, no BAPC was detected in the plasma after rectal administration of BAPC. Therefore, $[\text{AUC}]_0^\infty$ obtained from ABPC i.v. administration should be used to calculate the extent of the bioavailability (EBA) due to BAPC rectal administration.

Rectal Absorption of BAPC from Macrogol Suppositories

A preliminary study was carried out to assess the absorption behavior of BAPC following rectal administration. This antibiotic was given in the form of a suppository, which was formulated with Witepsol H-15 base, to rabbits at a dose of 17 mg/kg, equimolar to 12.6 mg/kg of ABPC Na. The result is shown in Fig. 2, where C_{max} is $6.95 \pm 0.25 \mu\text{g}/\text{ml}$ at 17.1 ± 4.1 min (t_{max}), as listed in Table IV. The $[\text{AUC}]_0^\infty$ was estimated by means of the trapezoidal rule and was $8.00 \pm 0.74 \mu\text{g} \cdot \text{h}/\text{ml}$. The last determined plasma concentration was extrapolated to infinite time by using the terminal slope of the log-time disposition curve. Then, the rectal absorptions of BAPC from four macrogol suppository bases, as well as

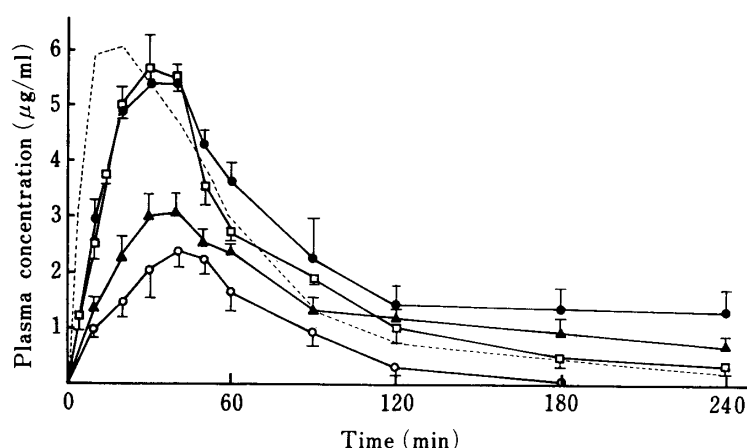


Fig. 2. Plasma Concentration *versus* Time Curves of Ampicillin after Rectal Administration of Bacampicillin in Various Kinds of Macrogol Base Suppositories in Rabbits

●, PEG; □, PEG I; ▲, PEG II; ○, PEG III. Each point represents the mean \pm S.D. (vertical bar) of four rabbits. The dotted curve represents BAPC rectal administration with Witepsol H-15 base suppository.

TABLE IV. Bioavailability Parameters of Bacampicillin (Dose 17.0 mg/kg) in Rabbits after Rectal Administration of Suppository

| Suppository | C_{\max} ($\mu\text{g/ml}$) ^{a)} | t_{\max} (min) ^{a)} | MRT (h) ^{a)} | $[\text{AUC}]_0^\infty$ ($\text{h} \cdot \mu\text{g/ml}$) ^{a)} | EBA ^{b)} (%) |
|--------------------|---|--------------------------------|-----------------------|---|-----------------------|
| PEG | 5.07 ± 0.31 | 36.7 ± 3.8 | 8.02 ± 2.22 | 15.90 ± 1.90 | 87.9 |
| PEG I | 6.03 ± 1.93 | 27.5 ± 9.6 | 2.23 ± 0.81 | 6.61 ± 1.83 | 36.6 |
| PEG II | 2.97 ± 0.52 | 40.0 ± 0.0 | 3.70 ± 1.10 | 6.82 ± 0.52 | 37.7 |
| PEG III | 2.40 ± 1.01 | 30.0 ± 9.7 | 1.60 ± 0.51 | 2.75 ± 1.53 | 15.2 |
| Witepsol H-15 | 6.95 ± 0.25 | 17.1 ± 4.1 | 1.42 ± 0.35 | 8.00 ± 0.74 | 44.2 |
| Oral ^{c)} | 6.33 ± 0.37 | 33.3 ± 9.4 | 1.77 ± 0.78 | 10.10 ± 2.70 | 55.9 |

a) Each value represents the mean \pm S.D. of four rabbits. b) Extent of bioavailability: $\frac{[\text{AUC}]_0^\infty \text{ supp.}}{[\text{AUC}]_0^\infty \text{ i.v.}}$, $\frac{[\text{AUC}]_0^\infty \text{ oral}}{[\text{AUC}]_0^\infty \text{ i.v.}}$.

c) These data were taken from ref. 2.

Witepsol H-15 base, were examined. The rectal profiles of absorption were compared based on the plasma concentration data of ABPC shown in Fig. 2. In each case, BAPC showed good rectal absorption from the macrogol bases, as with Witepsol H-15 base. However, no detectable absorption was observed following ABPC rectal was administration (data not shown), which corresponds to previous findings in a rectal absorption study from Witepsol H-15 base suppository.²⁾

Various bioavailability parameters obtained from these results are summarized in Table IV. The C_{\max} values obtained from the suppository bases (PEG and PEG I) were similar to that of Witepsol H-15 base and that of oral administration. However, t_{\max} values of the four macrogol suppositories were all apparently larger than that of Witepsol H-15, which may be due to the prolonged absorption (see also the mean residence time (MRT) in Table IV). By comparing the $[\text{AUC}]_0^\infty$ of BAPC rectal administration with that of ABPC i.v. administration, EBA values were calculated to be 15.2–87.9%. The lowest EBA of PEG III may be due to its low C_{\max} level, while that of PEG II was similar to that of PEG I, where the C_{\max} level was fairly high. The EBA of PEG II seems to be high because of the prolonged absorption, as shown by the MRT. PEG suppository consisting of macrogol 1000 alone showed the best

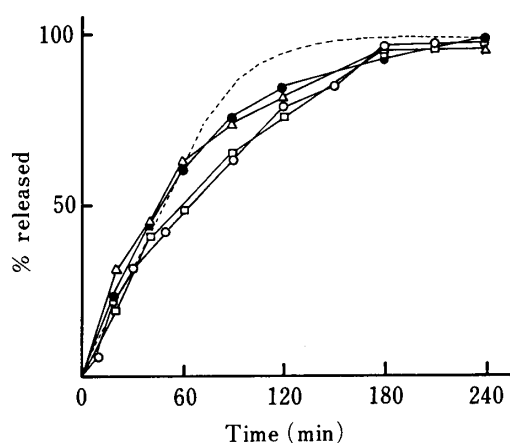


Fig. 3. Dissolution Percentages of Bacampicillin from Suppositories in Normal Saline at 37°C

●, PEG; △, PEG I; □, PEG II; ○, PEG III. All points represent the mean values of two experiments. The dotted curve represents the dissolution curve of BAPC from Witepsol H-15 base suppository.

TABLE V. Solubility of Bacampicillin in Various Concentrations of Macrogol Solution at pH 6.00 and 0°C

| Macrogol content (w/v%) | BAPC concentration (M) | |
|-------------------------|------------------------|---------------|
| | Macrogol 4000 | Macrogol 1000 |
| 0 | 0.0211 | 0.0207 |
| 5 | 0.0230 | 0.0199 |
| 10 | 0.0198 | 0.0196 |
| 20 | 0.0201 | 0.0203 |

Each solubility was determined at 120 h after suspending 1 g of BAPC in 20 ml of buffered solution which contained various amounts of macrogols, and represents the mean of two experiments.

effect on EBA, which was almost twice that in the case of Witepsol H-15 and was superior to that of oral administration, in four suppository bases as shown in Table IV. This is evidently due to the extremely prolonged rectal absorption of BAPC as indicated by the MRT.

The ability of BAPC to be absorbed, in contrast to ABPC, may most likely be ascribed to the much higher lipophilicity of BAPC. Furthermore, macrogol 1000 has a strong affinity for the membrane of the rectum. No differences of the release rate of BAPC from the suppositories were observed among the four suppositories as discussed below (Fig. 3).

Interrelation of BAPC Solubility and Release Rate

Figure 3 shows the effect of macrogol content on the release behavior of BAPC from suppositories. The release rates of BAPC from PEG and PEG I were high, but those from PEG II and PEG III were a little low, especially up to 2 h. The release behavior of BAPC from PEG and PEG I, however, was similar to that of Witepsol H-15 base suppository, as shown in Fig. 3. Thus, the decrease C_{\max} values seen with PEG II and III suppositories may be due to the change of the solubility of BAPC resulting from the addition of macrogol 4000. Kakemi *et al.*¹⁰⁾ reported the solubility behavior of unionized sulfonamides in buffered solutions, indicating a linear relation between the logarithm of their solubilities and the concentrations of macrogol 4000, and they suggested that macrogol 4000 influences the polarity of the sulfonamide solution. However, the solubilities of BAPC in various concentrations of macrogol 4000 were constant at pH 6.00, where BAPC is almost wholly ionized,⁴⁾ regardless of the base concentration, and further they were in good agreement with those of BAPC in macrogol 1000 solution at the same pH and the same concentration, as shown in Table V. Therefore, the low C_{\max} with macrogol 4000 addition should not be considered to be due to a change of the solubility of BAPC.

Release of BAPC (water-soluble) from macrogol bases occurs simply by dissolution of the base, and macrogol bases dissolve readily in an aqueous medium. The decreased release rates of BAPC from PEG II and III are thought to be due to the slower dissolution rate of macrogol 4000 than that of macrogol 1000.¹⁰⁾

Effect of Macrogol Bases on Partition Coefficient

When the drug is administered into the rectum as a water-soluble base suppository, the

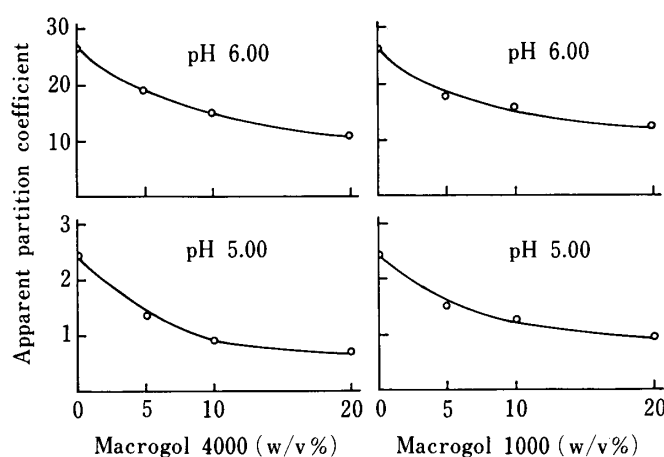


Fig. 4. Influence of the Concentration of Macrogol on the Partition Coefficient of Bacampicillin

Each point represents the mean of two experiments.

suppository is dissolved rapidly by rectal secreting fluid, and then the drug is absorbed from this aqueous solution. The drug absorption from the rectum has been explained in terms of partition to and diffusion through the lumen lipid.¹¹⁾ Kakemi *et al.*¹⁰⁾ suggested that macrogol 4000 affects the partition of sulfonamides to the rectal membrane in the absorption process from the vehicle, resulting in a reduced rectal absorption rate of sulfonamides due to the decrease of partition coefficients. Therefore, macrogols might influence the partition of BAPC to rectal membrane lipid, decreasing the polarity of the fluid. To test this possibility, the apparent partition coefficients were measured at various concentrations of macrogol 1000 and 4000 using toluene as the organic solvent. The aqueous phases in this experiments were the buffered solutions (pH 5.00 and 6.00).

Figure 4 shows that the apparent partition coefficients of BAPC are reduced with increase of the concentrations of both macrogol 1000 and 4000 bases. From these results, the partition of BAPC between the lipoidal phase and the aqueous phase seems to depend mainly upon the polarities of both phases, and since the polarity of the aqueous phase is decreasing with the addition of macrogols, the partition of BAPC must be decreased. The partition coefficients of BAPC, however, decreased regardless of the kind of macrogol, and therefore, the mechanism of the decreased bioavailability with macrogol 4000 is not thought to be due to the reduced partition coefficient.

Witepsol H-15 base melts at body temperature to release the drug. Since BAPC is not soluble in the base, the partitioning of the drug into the rectal fluid is rapid. On the other hand, the rate-limiting step in drug absorption from the macrogol formulations is the dissolution of the vehicle in the rectal fluid. If the amount of secreted fluid is altered by the amount or kind of base, both the absorption area and the concentration of drug and base should differ greatly, that is, the distribution area of the drug in the rectum should vary.

It has been reported that rectal fluid is increased by macrogol base, and that the concentration of macrogol in the rectal fluid is about 30%, independent of the base volume. In contrast, there was no detectable amount of the fluid after administration of oleaginous base.¹²⁾ Since the concentration of macrogol was constant in this study and BAPC solubility was also constant with the addition of macrogol, the concentration of BAPC should apparently be constant, but the amount of the BAPC dissolved was thought to increase depending on the amount of rectal fluid, resulting in an increase of distribution area of BAPC in the rectum. The t_{\max} values with the macrogol bases were significantly larger than that with Witepsol H-15, and the resulting $[AUC]_0^\infty$, especially in PEG, was extremely large compared to that in the case of Witepsol H-15. This can be explained in terms of an increase of the distribution area of BAPC in the rectum. C_{\max} value, however, was almost equal to that of Witepsol H-15 regardless of the increase of rectal fluid by PEG. This is thought to be because

that the increase of rectal secreting fluid and the reduction of partition coefficient by the addition of macrogol base effectively cancel each other out.

Consequently, the decrease of the bioavailability with PEG II and III can be explained as follows: macrogol 4000 base requires a large amount of secreting fluid to dissolve compared to macrogol 1000 base, and/or the viscosity of the fluid after dissolution of macrogol 4000 is higher than that in the case of macrogol 1000.¹³⁾

Appendix

If the time course of BAPC i.v. administration can be approximated by a two-compartment model as shown in Chart 1, the mass-balances of the drug in the body at any time t are given by:

$$\frac{d}{dt}[\text{BAPC}_c] = k_2[\text{BAPC}_p] - (k_1 + k_a + k_b)[\text{BAPC}_c] \quad (1)$$

$$\frac{d}{dt}[\text{ABPC}_c] = k_a[\text{BAPC}_c] - k_e[\text{ABPC}_c] \quad (2)$$

$$\frac{d}{dt}[\text{BAPC}_p] = k_1[\text{BAPC}_c] - k_2[\text{BAPC}_p] \quad (3)$$

where $[\text{BAPC}_c]$, $[\text{BAPC}_p]$ and $[\text{ABPC}_c]$ are the concentrations of BAPC in the central compartment and in the peripheral compartment, and the concentration of ABPC in the central compartment, respectively, k_e is the overall first-order elimination rate constant of ABPC, k_b is the overall first-order elimination (excluding the metabolic rate constant from BAPC to ABPC) rate constant, k_a is the first-order hydrolysis rate constant from BAPC to ABPC, and k_1 and k_2 are the microscopic rate constants associated with movements of BAPC between central compartment and peripheral compartment. At time $t=0$, the initial concentration of BAPC is $[B]_0$ and that of ABPC is zero. Integration of Eqs. 1, 2 and 3 gives the following equation.

$$C_p^t = k_a[B]_0 \left\{ \frac{k_2 - \alpha}{(\alpha - k_e)(\alpha - \beta)} e^{-\alpha t} + \frac{k_1 - \beta}{(\beta - \alpha)(\beta - k_e)} e^{-\beta t} - \frac{k_e - k_1}{(\alpha - k_e)(\beta - k_e)} e^{-k_e t} \right\} \quad (4)$$

where $\alpha + \beta = k_1 + k_2 + k_a + k_b$, $\alpha\beta = k_2(k_a + k_b)$. By using the hybrid constants, this equation can be simplified to Eq. 5.

$$C_p^t = Ae^{-\alpha t} + Be^{-\beta t} - Ce^{-k_e t} \quad (5)$$

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