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Pharmacokinetic Study on the Polymorphs of (α-Bromoisovaleryl)urea in the Rat[1)]

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Pharmacokinetic analysis of the plasma concentration after low dose administration of (α-bromoisovaleryl)urea (mono(2-bromo-3-methylbutyryl)urea) to rats was carried out by the nonlinear least-squares curve fitting method, and the differences of bioavailability between the polymorphic forms of the drug (form I and form II) were studied. The area under the blood concentration curve (AUC) showed no significant dependence on the administration method (intravenous solution, intraduodenal solution, intraduodenal form I and intraduodenal form II). It was apparent that (α-bromoisovaleryl)urea is absorbed rapidly and completely in the intestine after the intraduodenal administration of the solution or of the crystalline forms in gelatin solution, and there was no significant difference in the extents of biogvailability. On the other hand, the absorption rate constants, obtained by pharmacokinetic analysis based on an assumed kinetic model consisting effectively of one first-order absorption process, showed significant differences between solution and crystal suspension and between the two crystalline forms. Thus, the rate of absorption of (α-bromoisovaleryl)urea appears to depend on the polymorphic form or the administration method, even though these factors do not influence the extent of bioavailability.

Keywords——(α-bromoisovaleryl)urea; polymorph; bioavailability; AUC; pharmacokinetics; least-squares analysis; absorption rate

Intrduction

(α-Bromoisovaleryl)urea has three polymorphic forms (form I, form II, and form III) which are stable at room temperature, higher temperature, and lower temperature, respectively.[2)] In the previous paper,[3)] the bioavailability of these polymorphic forms in rats after intraduodenal administration was studied by the application of a novel determination method for the concentration of the drug in plasma. The results of these studies showed no significant differences in the rate or extent of bioavailability of these three polymorphs. The results might have been due to the large variances of the terminal concentration (C_z) and of the ultimate elimination rate constant (λ_z).[3)]

However, the dissolution of the crystals must be the rate-limiting process in the absorption of this drug, because the increases in the initial region of the plasma concentration curves were different among the polymorphs, and the maximum plasma concentration time (T_{max}) after the administration of the solution was significantly ($p<0.05$) smaller than those for any of the crystals, as shown in the previous report.[3)] Furthermore, differences of the dissolution rate of the polymorphs *in vitro* have been observed.[4)]

Therefore, for the purpose of the present study, the dissolution and absorption processes are combined, and a pharmacokinetic model having one first order absorption process after the administration of the crystals is presented. Nonlinear least-squares curve fitting analyses were carried out on this model. In order to obtain the pharmacokonetic parameters of *in vivo* behavior of the drug, the dose was decreased to 20 mg/kg for intravenous administration. Only form I and form II were investigated as polymorphic forms, because of their large differences of dissolution properties.[4)] The bioavalability of the polymorphic forms of (α-bromoisovaleryl)urea is discussed in termes of the absorption rate constants and the area under the

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blood concentration curves (AUC) obtained by the pharmacokinetic analysis.

Experimental

Preparation and Identification of (α-Bromoisovaleryl)urea Polymorphs——(α-Bromoisovaleryl)urea polymorphs (form I and form II) were prepared and identified as described in the previous paper.[2]

Animal Experiments——Wistar male rats, weighting 180—220 g, were treated as described in the previous paper.[3] Four mg of powdered (α-bromoisovaleryl)urea (100—170 mesh) was suspended in 0.25 ml of 5% gelatin solution in order to prevent the transformation[4] of crystalline form and immediately administered into the duodenum of the rat (200 g body weight) through the cannula with a syringe. After the administration, the remaining suspension was washed into the duodenum with 2.0 ml of water. In the case of administration of aqueous solution, the drug was dissolved in isotonic saline solution at the concentration of 2.0 mg/ml, and 2.0 ml of the solution was administered intraduodenally or intravenously. The samples were collected and the plasma concentration was determined as in the previous study.[3]

Computation——Computation was carried out on a digital computer (HITAC M-200H) at the Computer Center of the University of Tokyo, and an IBM 3031 machine at the Science University of Tokyo. The library program in the center, SALS (statistical analysis with least-squares fitting, by T. Nakagawa and Y. Koyanagi), was used for nonlinear least-squares analysis. Other programs were written by the authors in Fortran. AUCs were calculated by the linear trapezoidal method.[3,4]

Results and Discussion

Figure 1 shows semi-logarithmic plots of the plasma concentration-time course after intravenous administration of (α-bromoisovaleryl)urea to rats. As these plots show a biphasic decrease, a two-compartment model was used to describe the *in vivo* behavior of the drug in rats as shown in Fig. 2, as the simplest reasonable pharmacokinetic model for evaluating the bioavailability. The plasma concentration curve was fitted by the nonlinear least-squares method (SALS program) on the model. The initial values of the pharmacokinetic parameters for the fitting were obtained by the peeling-off method[6] on semi-logarithmic plots shown in Fig. 1. The first converged parameter set obtained by analysis of the mean data after intravenous administration was used as initial values, and each data set after intravenous administration was analyzed by SALS. The results are shown in Table I. The *in vivo* half-life of this drug calculated from the elimination rate constant (K_{el}) was 27 min. This half-life is fairly short for a hypnotic.

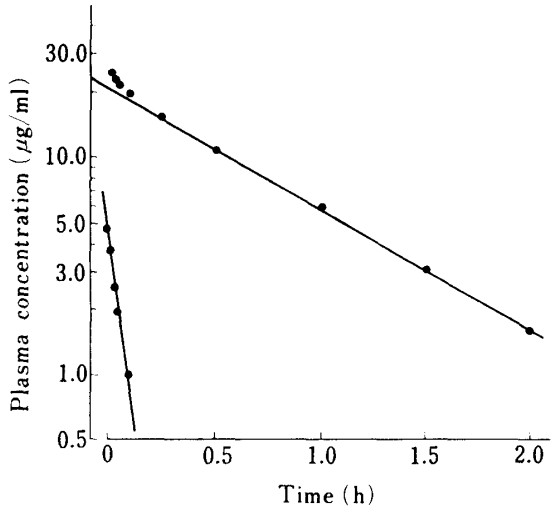

Fig. 1. Semi-logarithmic Plots of Plasma Concentrations of (α-Bromoisovaleryl)urea after Intravenous Administration

Points are means of four experiments.

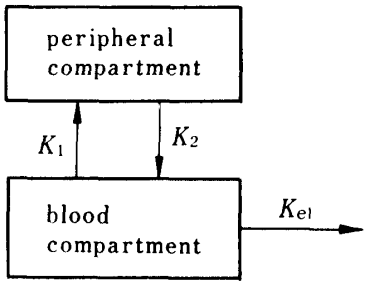

Fig. 2. Pharmacokinetic Model for *in Vivo* Behavior of (α-Bromoisovaleryl) urea after Intravenous Injection

K_1, K_2 and K_{el}: First-order rate constants for transfer of drug.

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The plasma concentration data sets after the intraduodenal administration of solution and crystals of (α-bromoisovaryl)urea were also analyzed in the same manner on the model shown in Fig. 3. As the initial values for the fate of the drug *in vivo*, the same values as in the intravenous experiments described above were used. The initial values of the absorption rate constants (k_a) were obtained by the peeling-off method from semi-logarithmic plots of the plasma concentration data after the administration of the solution and the crystals, respectively, assuming that the *in vivo* behavior of the drug after absorption follows a one-compartment model.

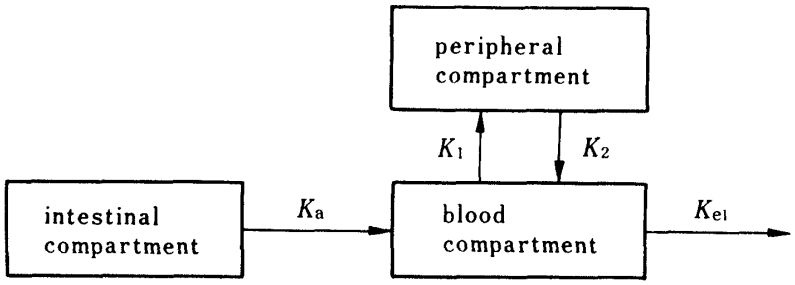

Fig. 3. Pharmacokinetic Model for *in Vivo* Behavior of (α-Bromoisovaleryl)urea after Intraduodenal Administration of Crystals

K_a; First-order rate constant for absorption. Other expressions are the same as in Fig. 2.

The fitting by SALS in the analysis is carried out as follows; the parameters after the absorption are given 10% flexibility in the fitting processes for the experimental error, and the absorption rate constant is free with no restraint. The results obtained are shown in Table I. The absorption rate constants showed significant differences ($p<0.05$) between the solution and the crystalline suspension, and between the polymorphic forms. On the other hand, other pharmacokinetic parameters and AUCs showed no significant difference ($p>0.05$) among the experiments. The half lives of absorption calculated from the absorption rate constants were 0.973, 17.37, and 7.73 min for solution, form I, and form II, respectively. The absorption half-life of the solution is extremely short. These results show that the dissolution of crystals is the rate-limiting step of the dissolution-absorption process, and support the suitability of the pharmacokinetic model having one first-order rate process in the dissolution–absorption process of the crystals as the rate limiting process, as discussed in this study.

TABLE I. Pharmacokinetic Parameters[a] after Intravenous or Intraduodenal Administration of (α-Bromoisovaleryl)urea Solution or Polymorphs at a Dose of 4.0 mg/head

	K_a (min^{-1}) $\times10^{-1}$	K_1 (min^{-1}) $\times10^{-2}$	K_2 (min^{-1}) $\times10^{-1}$	K_{el} (min^{-1}) $\times10^{-2}$	V (ml)	AUC ($min\cdot mg\cdot ml^{-1}$)
IV		4.016±0.053	1.828±0.012	2.562±0.224	155.0±11.4	1.055±0.087
SOL	7.123±0.933	4.116±0.026	1.758±0.015	2.495±0.225	163.8± 6.9	0.999±0.146
Form I	0.399±0.064	4.039±0.018	1.811±0.014	2.636±0.108	168.3± 7.4	0.926±0.136
Form II	0.897±0.157	4.466±0.070	1.493±0.075	1.777±0.080	194.7± 6.2	1.118±0.081

a) Parameters are means ± S.D. of four experiments.
IV : intravenous administration of solution.
SOL : intraduodenal administration of solution.
Form I : intraduodenal administration of form I suspension.
Form II : intraduodenal administration of form II suspension.

Figure 4 shows the experimental data and the calculated blood concentration curves obtained by using parameters values in Table I; there is good agreement between the experi-

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mental data and the calculated curves.

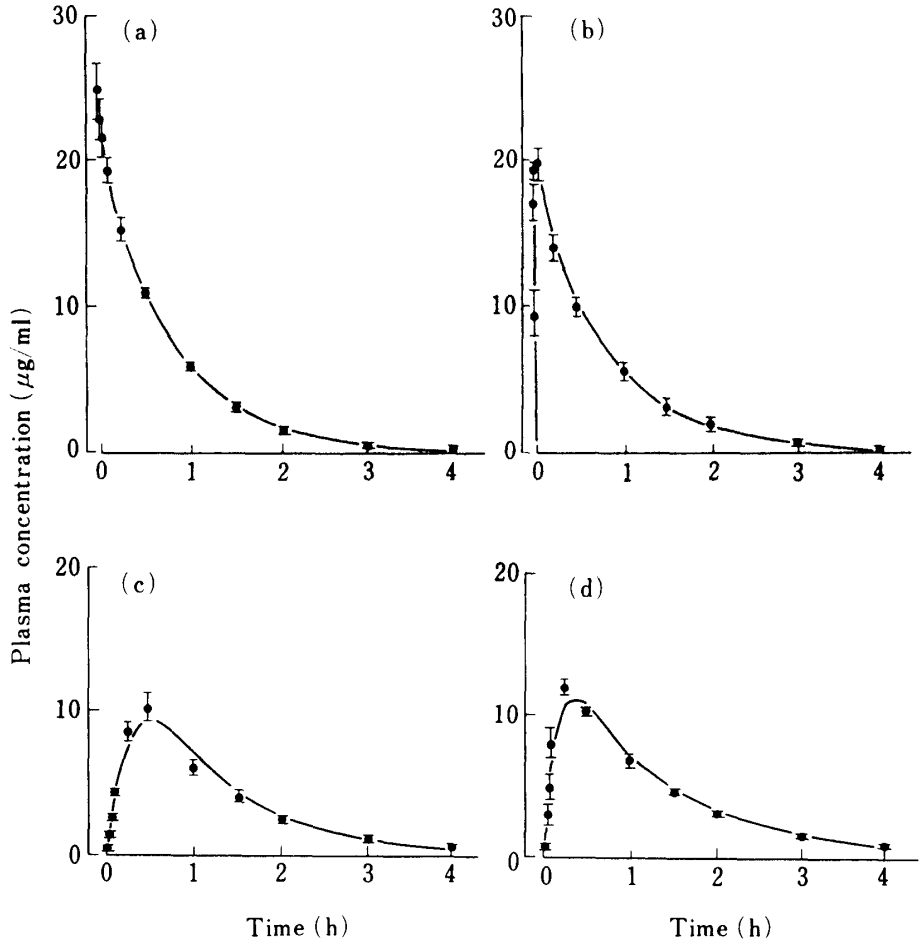

Fig. 4. Plasma Concentration of (α-Bromoisovaleryl)urea after Administration of 20 mg/kg to Rats

(a): Intravenous administration of solution.
(b): Intraduodenal administration of solution.
(c): Intraduodenal administration of form I suspension.
(d): Intraduodenal administration of form II suspension.
Points are means ± S.E. of four experiments. The continuous lines are those computed by the SALS program for the model shown in Fig. 2 or Fig. 3.

The AUCs, which indicate the extent of bioavailability, showed no significant dependence on the administration methods, as was previously found at high dose.[3] It is suggested that the (α-bromoisovaleryl)urea was completely absorbed after the intraduodenal administration of the solution and also the crystalline suspension of the drug. However, the absorption rate constants, which indicate the rate of bioavailability, showed a significant difference between the polymorphic forms (form I and form II), and also between the solution and the crystalline suspensions. In the previous paper,[3] we tried to detect differences in the rate of bioavailability among the polymorphic forms by using the statistical moment theory.[5,7] However, MRTs (mean resident time) showed no significant differences among the polymorphic forms, and no differences in the rates of bioavailability were detected, because of the wide variances of the terminal blood concentration (C_z) and ultimate elimination rate constants (λ_z).[3]

In the present experiments, a significant difference of the rate of bioavailability between form I and form II was detected, that is, form II (which has a higher dissolution rate at 37°C

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than form I)[4] showed a significantly larger absorption rate constant in pharmacokinetic analysis assuming one first order absorption process as described above. It is considered that this simple model is the most suitable for the evaluation of the rate of bioavailability of the polymorphic forms of this drug. However, more detailed kinetic studies are needed on the actual dissolution-absorption properties of this drug, and these are being carried out in our laboratory.

The results obtained in this experiment seem to be inconsistent with the relationship of difference of free energy (ΔG) and bioavailability assumed by Aguiar *et al.*[8] However, they referred only to the extent of bioavailability, and not the rate of bioavailability. Therefore, it has become apparent that differences in the rate of bioavailability may be observed even between two polymorphic forms having a small difference of free energy and both being absorbed completely, if the method of administration and/or data analysis is selected appropriately, as shown in this study. This view is partially supported by the works of Kuroda *et al.*[9] using the sulfathiazole polymorphs, which have a small difference of free energy. They reported that the polymorphic forms of the compound show a difference of bioavailability after intraduodenal administration to rabbits.

References and Notes

1) A part of this work was presented at the 102nd Annual Meeting of the Pharmaceutical Society of Japan, Osaka, April, 1982.
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