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Pharmacokinetic Studies of the Inhibition of Glucuronization of Pentazocine by Salicylamide

NAGAHIKO YUMITA,[a] RYUICHIRO NISHIGAKI,*,[a] KOSHIRO UMEMURA,[a] TOSHIHIRO HAYASHI[b] and KAZUO KIGASAWA[b]

School of Pharmaceutical Science, Toho University,[a] 2–2–1 Funabashi, Chiba 274, Japan and Grelan Pharmaceutical Co., Ltd.,[b] 2–12–3, Sakurashinmachi Setagaya, Tokyo 154, Japan

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The serum concentrations of unchanged and glucuronized drug were determined after intravenous injection of pentazocine (PA) in rabbits. A compartment model isolating the liver from the central compartment was proposed to explain the observed time courses of the concentration, and the resulting convolution equation was $M(t)=\int_0^t D(t-\theta)G(\theta)d\theta$, where $M(t)$ and $D(t)$ are the serum concentrations of glucuronized PA and unchanged PA after intravenous injection, respectively. The weight function, $G(t)$, which represents the response for a pulse input of glucuronized PA was estimated to be $G(t)=0.00933\ (e^{-0.00818t}-e^{-0.223t})\ (\mathrm{min}^{-1})$. The simultaneous intravenous administration of salicylamide (SAM) had no effect on the glucuronization of PA in serum. The serum concentration of glucuronized PA calculated by numerical convolution of $G(t)$ and the published serum concentration of unchanged PA after oral administration represents that of glucuronide produced from the unchanged PA which escaped the first-pass effect. This calculated value was far below the published serum concentration of glucuronized PA after oral administration, and the difference represents the glucuronized PA produced by the first-pass effect. The area under the concentration-*versus*-time curve of glucuronized PA produced by the first-pass effect was 274 times larger than that of glucuronized PA produced from unchanged PA in the serum. Simultaneous oral administration of SAM only inhibits the first-pass effect.

Keywords——pentazocine; salicylamide; first-pass effect; glucuronization; convolution

Introduction

Pentazocine (PA) is a potent analgesic and is used only in injectable preparations in Japan. Oral administration of PA requires two to three times the dose necessary for an intramuscular injection.[1] The concentration of unchanged PA was reported to be related to the analgesic effect.[2] It was reported in the previous paper that after oral administration of PA, a low serum concentration of unchanged PA and a high serum concentration of glucuronized PA were observed.[3] In the same paper,[3] the simultaneous oral administration of salicylamide (SAM), which has a phenolic hydroxy group, like PA, was reported to inhibit the glucuronization of PA resulting in an increase of unchanged PA and a decrease of glucuronized PA in serum after oral administration. This report describes a pharmacokinetic study of the fate of intravenously injected PA, as well as the determination of the first-pass effect of orally administered PA and the effect of SAM on it, in rabbits.

Experimental

Materials——PA (hydrochloride salt, Grelan Pharmaceutical Co., Ltd., Tokyo, Japan) was used. SAM was purchased from Iwaki Pharmaceutical Co., Ltd., Tokyo, Japan. All other reagents were commercial products of reagent grade.

Methods——Male albino rabbits weighing 2.8—3.1 kg were fasted for 24 h before use. PA (30 mg/ml) was

injected into the ear vein at a dose of 4 mg/kg. In some experiments, SAM (240 mg/ml polyethyleneglycol 400 sol.) was injected at a dose of 160 mg/kg mixed with PA solution.

The determinations of unchanged and glucuronized PA were done fluorometrically[2,4,5] as reported previously.[3] The amount and concentration of unchanged or glucuronized PA were expressed in terms of PA base form.

Results and Discussion

The serum concentrations of unchanged and glucuronized PA after intravenous injection were determined in three rabbits with or without SAM and are shown in Figs. 1 and 2. It is clear that the simultaneous injection of SAM did not affect the serum concentration of unchanged or glucuronized PA. The time course of the serum concentration of unchanged PA (D_s) without SAM was simulated by a three-compartment open model and the parameters were estimated by a damping Gauss–Jordan nonlinear least-squares method developed in our

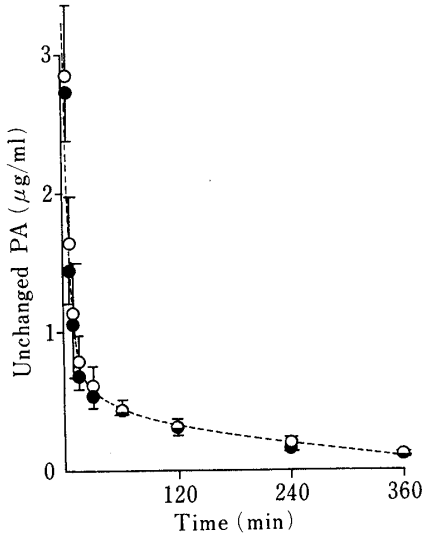

Fig. 1. Time Course of Serum Concentration of Unchanged PA after Intravenous Injection

The results are given as the means ± S.D. of three experiments.
The dashed line shows the calculated values for PA alone according to Eq. 1.
(○) PA alone, (●) with SAM.

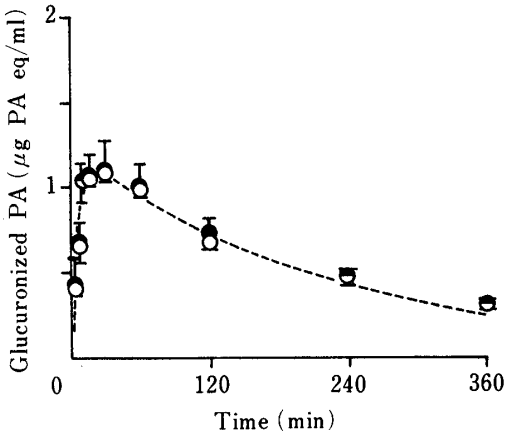

Fig. 2. Time Course of Serum Concentration of Glucuronized PA after Intravenous Injection

The results are given as the means ± S.D. of three experiments.
The concentration of glucuronized PA is given as the equivalent concentration of unchanged PA.
The dashed line shows the calculated value for PA alone according to Eq. 4.
(○) PA alone, (●) with SAM.

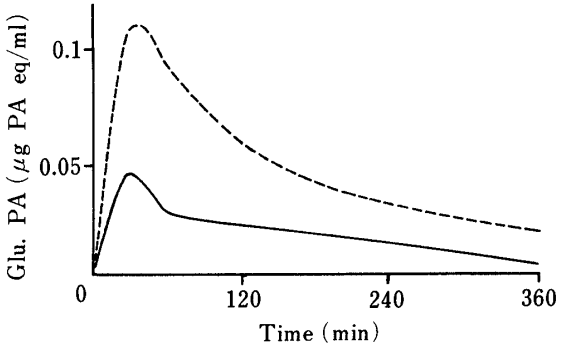

Fig. 3. Calculated Time Course of Serum Concentration of Glucuronized PA after Oral Administration

Lines were calculated by using Eq. 4 and the published data for unchanged PA according to Eq. 2.
(——) PA alone, (– – – –) with SAM.

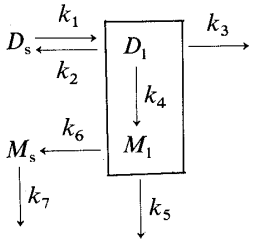

Chart 1. Compartment Model for Distribution and Disposition of PA after Intravenous Injection

D = concentration of unchanged PA.
M = concentration of glucuronized PA.
s = serum.
l = liver.
k = rate constant.

laboratory (non-weighted), resulting in Eq. 1;

$$D_s = 231.4e^{-1.998t} + 2.234e^{-0.1421t} + 0.6154e^{-0.004917t} \quad (1)$$

The results calculated according to Eq. 1 are shown in Fig. 1 and are in good agreement with the observed data.

The distribution and disposition of unchanged and glucuronized PA in the body were simulated by means of the pharmacokinetic model shown in Chart 1. The feature of this model is that the liver (where the glucuronization occurs) is isolated from the central compartment for both unchanged and glucuronized PA on the assumption that the transport rates through the liver cell membrane are relatively slow.

Under the steady-state condition for glucuronized PA in the liver, the final equation can be expressed as the following convolution form;

$$M_s(t) = \int_0^t D_s(t-\theta)G(\theta)d\theta \quad (2)$$

where the weight function, $G(t)$ is;

$$G(t) = \frac{V_{D_s}k_1k_4k_6(e^{-k_7t} - e^{-(k_2+k_3+k_4)t})}{V_{M_s}(k_5+k_6)(k_2+k_3+k_4-k_7)} \quad (3)$$

and V_{D_s} and V_{M_s} are the distribution volumes of unchanged and glucuronized PA, respectively.

$G(t)$ was estimated by the numerical deconvolution[6] of Eq. 2 with a nonlinear-least-squares method using the observed data for glucuronized PA concentrations after intravenous PA ($M_s(t)$) and Eq. 1 ($D_s(t)$);

$$G(t) = 0.00933(e^{-0.00818t} - e^{-0.223t}) \quad (\text{min}^{-1}) \quad (4)$$

The good coincidence of the calculated values of $M_s(t)$ using Eqs. 2 and 4 with the observed concentrations of glucuronized PA as shown in Fig. 2 supports the appropriateness of this model.

The serum concentrations of glucuronized PA calculated by numerical convolution of $G(t)$ and the published serum concentrations of unchanged PA after oral administration[3] (Fig. 2 of reference 3) represented those of glucuronide produced from the unchanged PA which escaped the first-pass effect. The results of calculation are shown in Fig. 3. The calculated concentrations of glucuronized PA (the peak concentrations were 0.047 and 0.111 μg/ml for PA alone and with SAM, respectively) were far smaller than the observed data after oral administration[3] (the peak concentrations were 7.3 and 5.8 μg/ml for PA alone and with SAM, respectively, Fig. 3 of reference 3). The difference between the calculated and the observed concentrations of glucuronized PA represents the glucuronide produced by the first-pass effect.

TABLE I. *AUC* of Glucuronized PA after Oral Administration

	AUC (μg min/ml)		
	Total[a]	From serum PA[b]	By first-pass[c]
PA alone	1650	6	1644
With SAM	1315	15	1300

a) Calculated from the published mean serum concentrations of glucuronized PA up to 360 min after oral administration[3] (Fig. 3 of reference 3) by a trapezoidal method. *b*) Calculated from the published mean serum concentrations of unchanged PA after oral administration[3] (Fig. 2 of reference 3). *c*) Calculated as *a*) − *b*), representing the glucuronized PA produced by the first-pass effect.

The areas under the concentration curve (AUC) of glucuronized PA are shown in Table I. It should be noted that SAM decreased the AUC of glucuronized PA produced by the first-pass effect after oral administration from 1644 to 1300 μg min/ml. The increase of the AUC relating to serum unchanged PA from 6 to 15 μg min/ml was ascribed to the increase of serum unchanged PA. The AUC values of the glucuronized PA from the first-pass effect were 274 and 87 times larger than those from unchanged PA in the serum after oral administration of PA alone and with SAM, respectively. In conclusion, the simultaneous oral administration of SAM decreased the glucuronization of PA by the first-pass effect to 80% of that of PA alone, resulting in an increase of unchanged PA in the serum.

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