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Nonlinear Pharmacokinetics of Aprindine in Guinea Pigs

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Summary: After intravenous bolus administration of aprindine (AP) to conscious guinea pigs, the semilogarithmic plasma concentration versus time curve was linear at a dose of 2 mg/kg, but convex at doses of 5 and 10 mg/kg. AP concentrations immediately after administration (Cp0) were almost identical, irrespective of the dose received. The areas under the plasma concentration-time curves (AUCs) were proportional to the AP doses. At 2 mg/kg, the plasma total clearance (CLtot) of AP was high (279 ± 80 mL/h), and its volume of distribution (Vdss) was large (245 ± 99 mL). Total blood clearance and time-averaged blood clearance (CLave) values for AP were similar to those for R(+) propranolol (PL) after intravenous coadministration of R(+) PL (0.25 mg/kg) and AP (2 or 10 mg/kg). An in vitro serum protein binding study showed that the unbound fraction of AP was concentration-dependent. In guinea pigs pretreated with turpentine oil (2 mL/kg/day), the elimination of AP after intravenous doses of 2 and 5 mg/kg closely followed first-order kinetics, while Cp0 and AUC increased in proportion to the AP doses. The bound fraction of AP in the serum was larger after turpentine oil pretreatment than in normal guinea pig serum in vitro. From these observations, the nonlinear pharmacokinetics of AP observed in guinea pigs can be attributed to nonlinear serum protein binding.

Key words: aprindine; guinea pigs; nonlinear pharmacokinetics; nonlinear protein binding; α1-acid glycoprotein

Introduction

Aprindine (AP) hydrochloride is an antiarrhythmic drug which belongs to class 1B of the Vaughan-Williams classification system and is effective in the treatment of supraventricular and ventricular arrhythmias.1–3) Its pharmacokinetics have been reported to show nonlinear behavior in humans.4,5) Because AP is predominantly eliminated via hepatic metabolism,6–8) it has been suggested that this nonlinearity is due to nonlinear metabolism in the liver. Similar nonlinear behavior has also been observed in dogs.9)

During a preliminary investigation of the pharmacokinetics of AP in various animal species (unpublished data), linear pharmacokinetics were observed in rats after intravenous doses of 2 to 10 mg/kg, whereas nonlinear pharmacokinetics were observed in guinea pigs. The purpose of this study was to clarify the mechanisms responsible for the nonlinear pharmacokinetics of AP in guinea pigs.

Materials and Methods

Materials: AP hydrochloride was kindly supplied by Mitsui Pharmaceuticals Co. (Tokyo, Japan). Pentobarbital (NEMBUTAL®) was obtained from Abbott Laboratories (Chicago, IL, USA). Amitriptyline hydrochloride, bovine serum albumin (BSA, fraction V, fatty acid-free) and R(+) propranolol were purchased from Sigma Chemical Co. (St. Louis, MO, USA). Quinidine sulfate was obtained from Nakarai Tesque Inc. (Kyoto, Japan). Turpentine oil, n-hexane 1,000 and diethylether 300 were purchased from Wako Pure Chemical Industries Ltd. (Osaka, Japan). Other chemicals were of reagent grade.

Animals: Male Hartley guinea pigs weighing 230–330 g (Tokyo Laboratory Animals Science Co., Ltd., Tokyo) were used. They were fasted for about 18 h prior to the experiment, but allowed free access to water.

Comparison of the pharmacokinetics of AP in the conscious and anesthetized states: Guinea pigs were fixed on their backs on boards in either the conscious state or after anesthesia with intraperitoneal pentobarbital (30 mg/kg). AP hydrochloride (2, 5 or 10 mg/kg, calculated as AP base) was dissolved in 0.9% NaCl solution and injected as a bolus via the left jugular vein. Blood samples (about 0.5 mL) were withdrawn from the right jugular vein at 0.03, 0.08, 0.17, 0.5, 1, 1.5, 2, 3, 4
and 5 h after administration, collected in sample tubes containing 10 μL heparin (100 units/mL) and centrifuged. The resulting plasma samples were stored at −80°C until required for assay.

Influence of hepatic blood flow on the pharmacokinetics of AP: R(+) propranolol (PL; 0.25 mg/kg) or a mixture of AP hydrochloride (2 or 10 mg/kg, calculated as AP base) and R(+) PL (0.25 mg/kg) was dissolved in 0.9% NaCl solution and injected as a bolus via the left jugular vein of conscious guinea pigs. Blood (about 0.6 mL) was withdrawn from the right jugular vein at 0.03, 0.17, 0.5, 1, 2, 3, and 4 h after administration and collected in sample tubes containing 10 μL heparin (100 units/mL). To 0.3 mL blood, 0.6 mL water was added, and the resulting blood samples were stored at −80°C until required for analysis.

In vitro protein binding study: Whole blood was taken from the abdominal aorta of fasted, conscious guinea pigs and the serum was separated. The serum protein binding of AP was determined at 37°C using an equilibrium dialyzer (Spectrum®, Medical Industries, Inc., Houston, Texas, U.S.A.) with a Spectra/Por® 2 dialysis membrane (M.W. 12-14,000; Medical Industries, Inc.). AP was added to the serum to a final concentration of 1, 2, 3, 5 or 10 μg/mL. After incubation at 37°C for 5 min, 1 mL aliquots were dialyzed against 1 mL phosphate-buffered isotonic saline (PBS; pH 7.4) for 2.5 h at 37°C.

Influence of treatment with turpentine oil on the pharmacokinetics of AP: Guinea pigs were treated with turpentine oil (2 mL/kg/day by intramuscular injection into the thigh) for three successive days prior to AP dosing. An in vivo pharmacokinetic study and in vitro protein binding study were then performed as described for conscious guinea pigs (see above).

Analytical methods: Concentrations of AP in plasma or blood were measured by high-performance liquid chromatography (HPLC). As an internal standard, amitriptyline (ATP) was dissolved in the HPLC mobile chromatography (HPLC). As an internal standard, quinidine (QD) was dissolved in the HPLC mobile phase to produce a 4.05 μg/mL solution and used as an internal standard. QD solution (0.1 mL) was added to 0.3 mL of blood sample together with 0.3 mL 1 N sodium hydroxide and 6 mL diethylether 300. After shaking for 10 min and centrifuging for 10 min at 1000 × g, 4 mL of the organic layer was removed and evaporated to dryness at 40°C. The residue was dissolved in 0.1 mL of the HPLC mobile phase, and a 50 μL aliquot of this solution was injected into the HPLC system. The mobile phase was a mixture of 0.1 M sodium phosphate buffer (pH 3.0) and acetonitrile (62/38, v/v). PL concentrations were monitored using a fluorescence detector (RF-535, Shimadzu Co.) with excitation at 295 nm and emission at 340 nm. A reverse-phase column (Bensil CN; i.d., 4.6×150 mm; Bentech Ltd.) with a guard filter (Waters Associates) was also included. The flow rate was kept at 1.0 mL/min and the column temperature was maintained at 30°C.

For the analysis of α1-acid glycoprotein (AGP) concentrations, 0.2 mL plasma or serum was diluted to 50 mL with buffer A (0.01M citrate-sodium phosphate buffer, pH 4.0) and the solution was loaded onto a Toyopak DEAE M anion-exchange column (Tosoh Co., Tokyo). After washing with 5 mL buffer A, AGP was eluted with 0.5 mL buffer B (0.50 M citrate-sodium phosphate buffer, pH 4.0), then 100 μL of the eluate was injected into an HPLC system comprising a pump (HRLC gradient module, Nihon Bio-Rad, Tokyo), an integrator (HRLC software system, Nihon Bio-Rad) and a detector (Model 1760 UV/VIS monitor, Nihon Bio-Rad). A hydroxyapatite column (A-7610; i.d., 7.6×100 mm; Koken Co., Tokyo) with a guard column (HCA cartridge, C-3201; i.d., 3.2×15 mm; Koken Co.) was also incorporated. The column was maintained at room temperature. A linear gradient mobile phase sys-
tem, which changed from 100% mobile phase A (0.01 M potassium phosphate buffer, pH 6.2) to 100% mobile phase B (0.35 M potassium phosphate buffer, pH 6.2) over 20 min, was used. The flow rate was maintained at 1.0 mL/min, and the eluate was monitored at 280 nm.

Pharmacokinetic analysis: The pharmacokinetic parameters of AP and PL were estimated using a non-compartmental method.10) The apparent terminal phase elimination rate constant (β) was calculated using a nonlinear least-squares regression method. The initial plasma concentrations of AP present immediately after administration (Cp0) were obtained from the intercept on the y-axis of a straight line in the distribution phase. The area under the plasma concentration-time curve (AUC) from time 0 to the last sampling time (tn), AUC0-tn, was determined using the trapezoidal rule, while AUC from 0 to infinity (AUC0-∞) was calculated according to the equation:

\[
AUC_{0-\infty} = AUC_{0-tn} + \frac{C_{ptn}}{\beta}
\]

where \(C_{ptn}\) was the observed plasma concentration at tn.

The total clearance (CLtot) was determined from the following equation:

\[
CL_{tot} = \frac{Dose}{AUC_{0-\infty}}
\]

The time-averaged total clearance (CLave)11) of AP at the higher doses used was determined from the equation:

\[
CL_{ave} = \frac{Dose}{AUC_{0-\infty}}
\]

The mean residence time (MRT0-∞) was determined from the equation:

\[
MRT_{0-\infty} = \frac{AUMC_{0-\infty}}{AUC_{0-\infty}}
\]

where AUMC0-∞ was the area under the first order moment curve; AUMC from 0 to tn was calculated using the linear trapezoidal rule, and AUMC tn to infinity (AUMCtn-∞) was calculated from the following equation:

\[
AUMC_{tn-\infty} = tn \cdot \frac{C_{ptn}}{\beta} + \frac{C_{ptn}}{\beta^2}
\]

The apparent volume of distribution at steady state (Vdss) after intravenous administration was estimated from the following equation:

\[
V_{dss} = CL_{tot} \cdot MRT_{0-\infty}
\]

Calculation of binding parameters: The unbound fraction (fu) of AP was calculated from the following equation:

\[
f_u(%) = \frac{C_t}{(C_t - C_f) \cdot (V/V_o) + C_f} \cdot 100
\]

where \(C_t\) was the total drug concentration in the serum at equilibrium, \(C_f\) was the drug concentration in the buffer at equilibrium, \(V\) was the volume of serum at equilibrium and \(V_o\) was the volume of serum before dialysis.

The index of volume shift, \(V/V_o\), was obtained from the protein concentrations before dialysis and at equilibrium. The protein concentrations in the serum were determined by the method of Lowry et al.12

The binding parameters were calculated according to the following equation:

\[
C_b = \frac{n \cdot p \cdot K_d \cdot C_f}{K_d + C_f} + \beta \cdot C_f
\]

where \(n\) is the number of binding sites per protein molecule, \(p\) is the molar concentration of total protein, \(K_d\) is the dissociation constant and \(\beta\) is the proportional constant for non-specific binding. The data were analyzed using a nonlinear least-squares regression analysis program, NLS,13) in which the errors for \(C_t\) and \(C_f\) were assumed to be 5%.

Statistical analysis: All pharmacokinetic parameters were expressed as the mean ± S.D. Pharmacokinetic parameters were compared between two treatments using the unpaired t test or the Aspen Welch procedure after performing the F test. In addition, the pharmacokinetic parameters were compared between the three dose levels using ANOVA or the Kruskal Wallis test after performing Bartlett’s test. Scheffe’s multiple comparison procedure was also used when necessary. Differences were considered to be statistically significant when \(P < 0.05\).

Results

Comparison of the pharmacokinetics of AP in the conscious state: Fig. 1 shows the semilogarithmic plasma concentration-time curves for AP obtained after intravenous administration to conscious guinea pigs. The elimination of AP was linear at a dose of 2 mg/kg, but tended to deviate from first-order kinetics, producing convex elimination curves on the semilogarithmic plots, at doses of 5 and 10 mg/kg. Elimination also became slower as the dose was increased.

Fig. 2 illustrates the pharmacokinetic parameters obtained after intravenous administration of AP. Cp0 values did not increase in proportion to AP doses of 2, 5 and 10 mg/kg, whereas AUC0-∞ values increased almost linearly in accordance with the dose. At 2 mg/kg, the Vdss of AP was fairly large (245 ± 99 mL) in comparison to the plasma volume of the guinea pigs (38.6 mL/kg).14) The plasma CLave observed at 2 mg/kg of AP was high (279 ± 80 mL/h).

Influence of hepatic blood flow on the pharmacokinetics of AP: The blood CLtot of AP (2 mg/kg) and the blood CLave of AP (10 mg/kg) were determined directly from the blood concentrations achieved after
intravenous administration. In contrast, the blood CL tot of \( R(+) \) PL was determined as an index relative to hepatic blood flow because \( R(+) \) PL is approximately 100 times less potent than \( S(-) \) PL as a beta-adrenergic antagonist,\( ^{15} \) and its CL tot has been reported to be flow-limited in humans.\( ^{16,17} \)

Table 1 shows blood CL tot values for \( R(+) \) PL after intravenous administration with or without AP (2 or 10 mg/kg) to conscious guinea pigs. The blood CL tot of \( R(+) \) PL was about 750 mL/h, which is consistent with reported hepatic blood flow values in guinea pigs (810 mL/h).\( ^{18,19} \) Blood CL tot values for \( R(+) \) PL were not significantly affected by the coadministration of AP; the blood CL tot of \( R(+) \) PL and the blood CL tot (CL ave) of AP were similar (Fig. 3), although there was no significant correlation between them (\( r = 0.698 \)).

**In vitro protein binding study:** Scatchard plots of AP binding showed a biphasic profile, with a linear phase at lower \( C_b \) and a plateau at higher \( C_b \) (data not shown). Models representing a single specific binding site and nonspecific binding were therefore fitted to the observed data. The resulting binding parameter estimates are shown in Table 2. The open circles in Fig. 4 illustrate the unbound fractions of AP observed at the various concentrations of AP added to normal guinea pig serum, and the solid line represents the curve calculated from the estimated binding parameters. The unbound fraction of AP increased dramatically at total AP concentrations above 2.5 \( \mu g/mL \).

**Influence of pretreatment with turpentine oil on the pharmacokinetics of AP:** AP has been reported to bind with high affinity to AGP in human serum.\( ^{20} \) Moreover, the free fraction of AP in the serum has been found to show negative correlation with AGP levels in patients with certain medical conditions as well as in healthy volunteers.\( ^{20,21} \) However, the binding of drugs to AGP varies widely between species.\( ^{22-24} \) We were therefore interested in clarifying the contribution of AGP to the total serum protein binding of AP in guinea pigs. Since turpentine oil has been reported to induce

### Table 1. Blood clearance of \( R(+) \) PL after intravenous administration of \( R(+) \) PL with (2, 10 mg/kg) or without AP to conscious male guinea pigs (\( n = 3 \))

<table>
<thead>
<tr>
<th>Dose of AP (mg/kg)</th>
<th>Blood clearance of ( R(+) ) PL (mL/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>777.6 ± 112.2</td>
</tr>
<tr>
<td>2.0</td>
<td>732.9 ± 68.4</td>
</tr>
<tr>
<td>10.0</td>
<td>720.3 ± 119.2</td>
</tr>
</tbody>
</table>

Each point represents mean ± S.D.

### Table 2. In vitro binding parameters of AP to serum protein of guinea pig

<table>
<thead>
<tr>
<th>Untreated</th>
<th>Pretreated with turpentine oil</th>
</tr>
</thead>
<tbody>
<tr>
<td>( n_p ) (( \mu M ))</td>
<td>7.85 ± 0.81</td>
</tr>
<tr>
<td>( K_d ) (( \mu M ))</td>
<td>0.0084 ± 0.0023</td>
</tr>
<tr>
<td>( \beta )</td>
<td>2.66 ± 0.63</td>
</tr>
</tbody>
</table>

Data show estimated value ± asymptotic S.D.
Fig. 3. Relationship between the blood CL_{tot} (or CL_{ave}) of AP and the CL_{tot} of R(+)-PL after intravenous coadministration to conscious male guinea pigs.
AP i.v. dose: ○: 2 mg/kg, ●: 10 mg/kg

Fig. 4. Unbound fraction of AP in male guinea pig serum.
○: Serum from unpretreated guinea pigs, ●: Serum from guinea pigs pretreated with turpentine oil (2 mg/kg x 3 days). The solid and dotted lines represent the simulation curves for unpretreated and turpentine oil-treated animals, respectively, based on the binding parameters derived from the in vitro protein binding study.

Fig. 5. Concentrations of AP in plasma after intravenous administration to male guinea pigs pretreated with turpentine oil (2 mg/kg x 3 days).
AP i.v. dose: ○: 2 mg/kg, ●: 5 mg/kg, △: 10 mg/kg. Each point represents the mean ± S.D. (n = 3).

acute inflammation and increase plasma AGP concentrations, guinea pigs were treated with turpentine oil (2 mL/kg/day by intramuscular injection into the thigh) for three successive days prior to AP dosing. The serum concentration of AGP measured after pretreatment with turpentine oil was 0.904 mg/mL, almost three times higher than that in untreated serum (0.306 mg/mL). In contrast, the unbound fraction of AP was lower in the serum obtained after turpentine oil treatment than in normal guinea pig serum (Fig. 4, solid circles), and the critical AP concentration, above which the unbound fraction increased dramatically, was found to be 4 μg/mL. The dotted line represents the binding curve simulated from the estimated binding parameters. Fig. 5 shows the semilogarithmic concentration-time profile of AP after intravenous administration to guinea pigs pretreated with turpentine oil. The AGP serum concentration measured at 0.03 h after intravenous administration of AP (0.465 ± 0.172 mg/mL) was significantly larger than that in unpretreated guinea pigs (0.269 ± 0.023 mg/mL; P < 0.05). After an AP dose of 10 mg/kg, the elimination phase appeared as a convex curve on the semilogarithmic concentration versus time plot, whereas the elimination phase plots after 2 and 5 mg/kg doses followed a straight line. C_{p0} values for AP showed a dose-dependent increase, with a significant difference (P < 0.05) between the 2 mg/kg and 10 mg/kg doses (Fig. 6). Furthermore, as shown in Fig. 4 (solid circles), the C_{p0} values for AP doses of 2 mg/kg (2.93 ± 0.21 μg/mL) and 5 mg/kg (3.48 ± 0.44 μg/mL) were within the linear binding region range identified by the in vitro study (<4 μg/mL), while the C_{p0} for the 10 mg/kg dose (4.83 ± 0.58 μg/mL) was on the borderline between the linear and nonlinear binding regions. The fact that the serum AP binding capacity was increased by pretreatment with turpentine oil suggests that AP exhibits linear pharmacokinetics under these conditions.

Discussion
We investigated the mechanisms underlying the nonlinear pharmacokinetics of AP observed in guinea pigs. In general, in vivo pharmacokinetic and pharmacodynamic studies have been performed on anesthetized animals. However, since anesthetics such as pentobarbital may affect hepatic blood flow and the serum protein binding of drugs, we carried out a preliminary comparison of the pharmacokinetics of AP in conscious and anesthetized guinea pigs. In the anesthetized guinea pigs, plots of the elimination phase...
produced almost straight lines for all the doses studied, although elimination was prolonged as the dose was increased. C\textsubscript{p0} values for AP showed a dose-dependent increase, with a significant difference (P < 0.05) between the 2 mg/kg and 10 mg/kg doses, while AUC\textsubscript{0-\infty} increased almost linearly in accordance with the dose (data not shown). Since the pharmacokinetic profiles in anesthetized guinea pigs differed considerably from those in conscious guinea pigs, the pharmacokinetic study of AP was performed in conscious animals.

After intravenous administration of a 100 mg dose to humans, AP was found to have a large V\textsubscript{dss} (109 L) and a small blood CL\textsubscript{tot} (165 mL/min).\textsuperscript{28} Furthermore, after multiple dosing with AP 30 or 60 mg/day, the elimination phase produced a convex curve on the semilogarithmic plasma concentration versus time plot, and the elimination half-time was slower than after a single 100 mg dose.\textsuperscript{5} These characteristics are similar to those observed in guinea pigs during the present study. However, the bound fraction of AP in human serum remained constant (94–97%) throughout the therapeutic concentration range (0.2–2 \mu g/mL).\textsuperscript{20,29} and the nonlinear pharmacokinetics of AP observed in human subjects may thus be attributed to nonlinear hepatic metabolism.

In guinea pigs, which also exhibit nonlinear AP pharmacokinetics, the C\textsubscript{p0} values did not show dose-dependency, and AUC\textsubscript{0-\infty} increased almost linearly when the AP dose was increased from 2.0 mg/kg to 10.0 mg/kg (Fig. 2), although a tendency to overestimate AUC\textsubscript{1-\infty} (C\textsubscript{p0}/\beta) at the 5 and 10 mg/kg doses cannot be discounted because of insufficient plasma sampling during the terminal phase. These data suggest that the nonlinear pharmacokinetics of AP observed in guinea pigs are related to V\textsubscript{dss}, not to CL\textsubscript{tot}.

As parameters such as CL\textsubscript{tot} and V\textsubscript{dss} cannot be estimated accurately using AUC and MRT values because of the nonlinear pharmacokinetics of AP,\textsuperscript{11} we estimated these parameters only for a low dose of AP (2 mg/kg). We also estimated CL\textsubscript{ave} using the AUC value. The V\textsubscript{dss} of AP at 2 mg/kg was fairly large (245 ± 99 mL) compared with the total body water volume reported for guinea pigs (38.6 mL/kg),\textsuperscript{14} and V\textsubscript{dss} at this low dose can therefore be approximated as follows:

$$V_{dss} = (f_{ub}/f_{ut}) \cdot VT$$

where f\textsubscript{ub} and f\textsubscript{ut} are the unbound fractions of AP in the plasma and tissue, respectively, and VT is the volume of distribution in the tissue.

Since the unbound fraction of AP depended on the plasma concentration (Fig. 4), the apparent dose-dependency of V\textsubscript{dss} at higher doses can reasonably be attributed to nonlinear plasma protein binding. On the other hand, CL\textsubscript{tot} would not be expected to change significantly with the dose because AUC\textsubscript{0-\infty} increased almost linearly as the AP dose was increased from 2.0 mg/kg to 10.0 mg/kg. As only a small amount of AP was excreted in the urine after oral administration to guinea pigs (data not shown), CL\textsubscript{tot} is approximately the same as the hepatic clearance (CL\textsubscript{H}). The CL\textsubscript{tot} of AP at the 2 mg/kg dose was high (279 ± 80 mL/h), and both the blood CL\textsubscript{tot} at 2 mg/kg and the blood CL\textsubscript{ave} at 10 mg/kg were very similar to the values obtained with R(+) PL (Fig. 3), suggesting that the clearance of AP must be hepatic blood-flow-dependent. These observations explain why the AUC values increased linearly with the AP dose. Taken together, our results indicate that the nonlinearity of AP pharmacokinetics in guinea pigs are attributable to nonlinear plasma protein binding, resulting in a nonlinear volume of distribution, and not to the features of its hepatic metabolism. This situation is quite different from that observed in humans.

AP has been reported to bind to AGP in human serum, and its affinity constant for binding to AGP was about 100 times greater than that for human serum albumin.\textsuperscript{20} The free fraction of AP in serum has also been reported to correlate negatively with AGP levels in patients suffering from rheumatoid arthritis and renal
failure, as well as in healthy volunteers. In contrast, the binding of drugs to AGP has been shown to vary widely between animal species. Although our results did not directly identify the main plasma protein responsible for the nonlinear binding of AP in guinea pigs, the data obtained after pretreatment with turpentine oil strongly suggest that AGP contributes to its total serum protein binding. To the best of our knowledge, this study is the first to indicate that AP exhibits low-capacity binding to AGP in guinea pigs.

In this study, during the early phase after intravenous injection of AP to conscious guinea pigs, the apparent elimination rate constant tended to decrease as the dose was increased, producing a convex curve on the semilogarithmic plasma concentration-time plots (Fig. 1). This is consistent with the results of a simulation study reported by Oie et al., in which a drug with high intrinsic clearance and a large volume of distribution was shown to produce a convex elimination curve under saturable serum protein binding conditions.

The potential clinical significance of the nonlinear total plasma concentration of AP observed in guinea pigs needs to be considered in terms of the free concentration of AP in blood. The free concentration present immediately after AP dosing under steady state conditions (C_{pof}) can be represented as follows:

$$C_{pof} = D / (V_{ds}/f_{ub}) = D / (VT/f_{at})$$

From this equation, the free concentration of AP (C_{pof}) would be expected to increase linearly in proportion to the dose, irrespective of any change in f_{ub} although the total concentration of AP (C_{pbo}) would not increase at all. In addition, the area under the free concentration-time curve (AUC_{f}) after intravenous administration of AP can be represented by the following equation:

$$AUC_{f} = D / (CL_{tot}/f_{ub}) = D / (QH/f_{ub})$$

where \(QH\) is hepatic blood flow. The AUC_{f} of AP would be expected to form a concave curve as the dose increased, since f_{ub} increases dose-dependently, although the AUC of the total concentration increases linearly irrespective of any change in f_{ub}. Therefore, nonlinear protein binding, such as that shown by AP in this study, would be expected to have great clinical significance if it occurs with drugs that show similar pharmacokinetic characteristics to AP (i.e., a large Vd and high CL) in humans.

References


