FUTURE PROSPECTS FOR TOXICOKINETICS: ITS ABILITY TO PREDICT DRUG ADVERSE EVENTS IN HUMANS

Yuichi SUGIYAMA, Kiyomi ITO, Mitsuhiro TSUDA* and Ikuo HORII**

Department of Pharmaceutics, Faculty of Pharmaceutical Sciences, University of Tokyo,
7-3-1 Hongo, Bunkyo-ku, Tokyo 113, Japan
*Division of Pharmacology, Biological Safety Research Center,
National Institute of Health Sciences,
1-18-1 Kamiyoga, Setagaya-ku, Tokyo 158, Japan
**Department of Toxicology and Pathology,
Nippon Roche Research Center,
200 Kajiwara, Kamakura-shi, Kanagawa Pref., 247 Japan

INTRODUCTION
Toxicokinetics (TK) has recently become indispensable in performing the toxicity test. Moreover, “Note for guidance on toxicokinetics: reassessment of systemic exposure in toxicity studies” has been proposed for ICH, confirming the necessity of a flexible and stepwise approach in association with a case-by-case response. The ultimate goal of TK studies is to avoid adverse events in humans and, hence, it is important to establish appropriate methodology for predicting adverse events in humans based on TK data obtained from animal studies. What kind of information and/or analyses are required to improve the power of such predictions?

1. Which TK parameters reflect adverse events?
The occurrence of toxic effects may be related to AUC, Cmax, or mean residence time (MRT), depending on the type of drug involved (Fig. 1). However, few studies have been done to examine which is an important parameter to be considered. In association with the pharmacological mechanism of action, it is important to determine whether the pharmacological effect depends on AUC, Cmax, or MRT (Horii et al., 1995). This may, in future, enable mechanism-based evaluation of important parameters in TK studies. For this purpose, it is absolutely necessary for relevant people in industry, government, and academia to collaborate in allowing data to be collected on the relationship between the occurrence of adverse events (including those in humans) and various TK parameters.

Anticancer drugs can be classified into two groups, Type 1 and Type 2, based on their cell-killing kinetics (pharmacodynamic features) using in vitro human cultured tumor cells. The cell-killing effects of Type 1 drugs, including antitumor antibiotics, alkylating agents, platinum derivatives and topoisomerase-II inhibitors, are AUC-dependent. On the other hand, Type 2 drugs, typified by antimetabolites and vinca alkaloids, exhibit time-dependent cell-killing effects. If a similar classification can be applied to drug toxicity, we need to consider the difference between humans and animals not only in terms of AUC but also other parameters such as the residence time in plasma and/or tissues.
Fig. 1. Relationships among drug dose, free drug concentration, and pharmacological or toxic effect. Pharmacokinetics, toxicokinetics, pharmacodynamics, and toxicodynamics are all highly variable depending on the species, individuals, disease state, age, etc.

For most drugs, the half-life is smaller and the initial plasma concentrations are higher after intravenous administration to small animals, such as mice, than to large animals including humans, even if different doses are given to both small and large animals to obtain the same AUC value. Thus, the exposure time is shorter for mice than for humans even when the AUC of mice and humans is equal [Skipper Concept (Collins et al., 1986; Skipper et al., 1970), Fig. 2]. Therefore, the activity and toxicity for humans is predicted to be greater than for mice in the case of Type 2 drugs, following administration of the dose needed to produce the same AUC (Fuse et al., 1995).

Although anticancer drugs cause various kinds of toxic effects in different tissues, cells with high proliferative activity like tumor cells, such as bone marrow cells and gastrointestinal cells, are more susceptible to toxicity. Investigation of the literature has revealed that anticancer drugs may also be classified into two groups according to their toxicodynamics: those with a constant total LD_{10} showing no schedule-dependence and those with a decreasing LD_{10} at short dosing intervals. This classification agrees well with the pharmacodynamic classification mentioned above, indicating the danger of making a clinical safety assessment based only on the total exposure, using the AUC in the case of time-dependent Type 2 drugs (Sugiyama et al., 1993; Fuse et al., 1995). Indeed, only in the case of Type 1 anticancer drugs, has it been demonstrated that the mouse AUC at the LD_{10} equals the human AUC at the maximal tolerated dose (MTD) (Fig. 3).

If drug-induced toxicity is proved by these analyses to be AUC-dependent, the human AUC at which the adverse event may be induced can be estimated from TK parameters in animals.

Fig. 2. Skipper Concept (Collins et al., 1986; Skipper et al., 1970). Typical plasma concentrations in mice and humans following equal bolus doses (mg/m^3). Assumes that the volume of distribution (l/kg) and clearance (ml/min/m^3) are similar in both species.
Therefore, by combining in vitro metabolic data using human tissues and prediction of renal clearance by animal scale-up methods etc, it may become possible to predict human optimal doses and the therapeutic index in clinical situations (Sugiyama et al., 1993; Sugiyama et al., 1986; Iwatsubo et al., 1996).

2. Time of blood sampling.

A lot of animal scale-up studies have demonstrated that total clearance per unit body weight is lower in animals with larger body weights (Sugiyama et al., 1993; Sugiyama et al., 1986; Iwatsubo et al., 1996). For example, renal clearances of many drugs have been shown to correlate with body weight with power coefficient of about 0.75. Because the interspecies difference in the volume of distribution per unit body weight does not seem to be very large, the “equivalent time” in drug elimination can be defined in each species according to its body weight. Table 1 lists the equivalent times for various species, which have been calculated based on the fact that the power coefficient in equation (1) is close to 0.25 for many drugs.

\[
\text{Half-life} = 0.693 \frac{V_d/CL_{tot}}{CL_{tot}} = 0.693A (BW)^{1.00}/B (BW)^{0.75} = 0.693C (BW)^{0.25}
\]  

(1)

![Fig. 3. AUC at MTD in humans vs AUC at the LD10 in mice for (a) Type 1 and (b) Type 2 drugs (Sugiyama et al., 1993; Fuse et al., 1995). Type 1: Log (human AUC) = 0.886 \times \log (\text{mouse AUC}) + 0.216 (r=0.898, n=8) Type 2: Log (human AUC) = 0.788 \times \log (\text{mouse AUC}) - 0.080 (r=0.677, n=14) LogSS/N : \text{Sum of } [\text{human value} - \text{mouse value}]^2/\text{number of drugs.}]

<table>
<thead>
<tr>
<th>Animal</th>
<th>Mean Body Weight (g)</th>
<th>(Body weight)$^{1/4}$</th>
<th>Equivalent Time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse</td>
<td>22</td>
<td>2.16</td>
<td>0.13</td>
</tr>
<tr>
<td>Rat</td>
<td>160</td>
<td>3.56</td>
<td>0.22</td>
</tr>
<tr>
<td>Monkey</td>
<td>4,000</td>
<td>7.95</td>
<td>0.49</td>
</tr>
<tr>
<td>Dog</td>
<td>5,000</td>
<td>8.42</td>
<td>0.52</td>
</tr>
<tr>
<td>Humans</td>
<td>70,000</td>
<td>16.3</td>
<td>1.00</td>
</tr>
</tbody>
</table>
where Vd_β is the volume of distribution in the β phase, Cl_total is the total clearance, BW is the body weight, and A, B, and C are constants. This suggests the need to change the time of blood sampling in planning TK studies, depending on the animal species used. For example, in the case of blood sampling in humans from 5 min to 5 hrs after drug administration, the corresponding sampling period in dogs is from 2.6 min to 2.6 hrs, and that for mice is 0.65 min to 0.65 hrs. Therefore, analyses should not be based on the same sampling times for all species since this may lead to incorrect results.

3. Is it sufficient to measure only blood concentrations?

1) Need to measure free drug concentrations in blood

Many of the PK/PD studies have so far emphasized the need to measure concentrations of free drug, i.e. not bound to plasma proteins. As the interspecies and interindividual variability in protein binding is large, this is especially important for drugs which are highly protein bound (more than 80–90%).

For example, the β-blocking activity of propranolol was decreased in rats after laparotomy when it was evaluated in terms of total plasma concentrations of propranolol (Fig. 4) (Yasuhara et al., 1985). In contrast, when the β-blocking activity was evaluated using unbound plasma concentrations there was no difference between control and laparotomized rats, suggesting that the pharmacological activity of propranolol depends on its unbound concentration in plasma. The laparotomy-induced reduction in the β-blocking activity of propranolol could be considered largely due to an increase in its binding to α_1-acid glycoprotein in plasma, which was found to have markedly increased after laparotomy.

2) Drugs with adverse effects on the gastrointestinal tract and liver

As mentioned above, AUC, Cmax and MRT based on blood concentrations have usually been used as TK parameters. However, in the case of a drug which is orally administered and taken up by the gastrointestinal epithelial cells and/or hepatocytes exhibiting an extensive first-pass effect, it is clear that the AUC of the blood concentrations never reflects the gastrointestinal or liver concentrations. The same is true in the case of a drug with efficient enterohepatic circulation.

For example, the accumulated biliary secretion of indomethacin and its conjugates, based upon biliary clearances and areas under portal and peripheral plasma profile, was found to vary approximately 30-fold among five laboratory spe-

![Graph](image-url)

**Fig. 4.** Relationship between the concentration and β-blocking effect of propranolol in control and laparotomized rats after intravenous administration of propranolol at a dose of 0.5 mg/kg (Yasuhara et al., 1985). Propranolol concentration is shown as the total plasma concentration (○, ●) or unbound drug concentration in plasma (□, ▲).
cies, and provided a quantitative correlation with wide species variation in sensitivity to indomethacin-related intestinal lesions (Fig. 5) (Duggan et al., 1975). This finding suggests that the species difference in the intestinal toxicity of indomethacin can be reasonably predicted from that in cumulative biliary excretion, which may be mainly attributed to the species variation in the ability of biliary excretion of indomethacin.

In these cases, it is necessary to predict tissue concentration profiles based on pharmacokinetic models and this is possible by combining animal experiments using different administration routes and different sampling sites.

3) Drugs with blood-tissue transport barriers and active transport systems

If the distribution of a drug from blood to tissue is relatively rapid and the degree of distribution in the tissue is dependent on the plasma protein binding and nonspecific binding to tissue macromolecules, the tissue distribution in humans (reflected by the volume of distribution) can be predicted from animal data by correcting for species differences in plasma protein binding (Fig. 6) (Sawada et al., 1985). However, when

\[
\sum \% \text{ bile} = \frac{\text{CL}_{\text{bile}} \times \text{AUC} \times 100}{\text{Dose}}
\]

(containing the molecules in the enterohepatic circulation)

where \(\text{CL}_{\text{bile}}\) represents the biliary clearance of ulcerogenic substances (parent + conjugates), and \(\text{AUCP}\) represents the area under plasma concentration profile of indomethacin (plasma concentrations of indomethacin conjugates are negligibly small in all species).

**Fig. 5.** Correlation of total biliary secretion of indomethacin with sensitivity to intestinal lesions (Duggan et al., 1975).

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\text{Fig. 6.} \text{ Correlation between volumes of distribution of various drugs in rats and humans (Sawada et al., 1985). (a) Volume of distribution for total drug concentration (V). (b) Unbound volume of distribution } [V_T (distributive tissue volume)/f_{u_T} (fraction of drug in tissue unbound)].
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1) phenytoin; 2) hexobarbital; 3) pentobarbital; 4) phenylbutazone; 5) warfarin; 6) tolbutamide; 7) valproate; 8) phenobarbital; 9) amobarbital; 10) quinidine; 11) chlorpromazine; 12) propranolol; 13) pentazocin; 14) diazepam; 15) antipyrine.
the distribution between blood and tissue does not rapidly reach equilibrium, as represented by transport through the blood-brain barrier, and when the drug distribution is regulated by an active transport system found in tissues such as liver, kidney and small intestine (Yamazaki et al., 1996), predicting what happens in humans is difficult because little information is available about species differences in transfer function connecting blood and organs. Further basic research is also needed in this area.

References


