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TOXICOKINETIC PARAMETERS IN THE MANAGEMENT OF POISONING: AN EXAMPLE OF PODOPHYLLOTOXIN INTOXICATION

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In clinical setting, from kinetic point of view, to minimize the absorption and maximize the elimination of toxin involved are the two major principles in poisoning management. Based on this principle, such as emetics, gastric lavage, forced diuresis, hemodialysis, and even hemoperfusion are used in many occasions of clinical poisonings. The kinetic parameters are usually required in the process of decision making for choosing the appropriate procedure to achieve the purpose of decontamination and enhancement of toxin elimination. However, in daily practice, more frequently, one may get across the condition of either the kinetic parameters is missing or unfavorable of any particular action. We hereby using Podophyllotoxin (Px) to illustrate the role of kinetic parameters and its difficulty in the management of poisoning.

Six years ago, a clinical syndrome of diarrhea, abdominal pain, abnormal liver functions, leukopenia, thrombocytopenia, and neurological disturbance was observed among patients of herbal poisoning incidentally resulted from consuming rhizome blend of *Dysosma pleianthum*. The major active ingredient of the plant rhizome involved was Px. The clinical syndrome developed within a few hours after oral exposure of the plant rhizome. It resulted in significant neurological sequel such as vegetative status, unstable gait and even death in some severe cases. Since more than a dozen of patients with severe intoxication were identified within a few years, we were challenged by the question "was there any action can be taken to prevent the development of severe toxicity?". Upon that time, unlike many other therapeutic drugs, there was no kinetic information available about Px. We therefore designed a rabbit model to evaluate the kinetic parameters of Px. Our study showed that the $T_{1/2\beta}$: 1.80 ± 0.66 min; V_d : 0.146 ± 0.071 L/Kg; K_{12} : 0.174 ± 0.085 ; K_{21} : 0.0738 ± 0.0168 ; K_e : 0.181 ± 0.060 ; $T_{1/2}$: 20.3 ± 6.51 min. The kinetic pattern was

well described with a two compartment Pk model. Podophyllotoxin was extremely rapidly distributed to the extra-vascular tissue. The observed Pk pattern and clinical syndrome suggests that the developed toxicity of Px may be related with the rapid tissue distribution and the ensuing immediate action of Px and/or its metabolite. This finding strongly suggests that practically elimination enhancement of Px such as using the procedure of hemodialysis or hemoperfusion is unlikely to be useful in treating acute Px intoxication.

INTRODUCTION

In clinical setting, in addition to the procedure of identification, the management of poisoning also usually contains the following procedures: (1) stabilize the vital signs; (2) minimize the continuous absorption; (3) enhance the elimination; (4) specific treatment (e.g. antidotes application). During the whole process, the understanding about the properties and characters of the substance involved and the timing of medical attention are critical in determining the prognosis.

As well as in therapeutic condition, kinetic parameters (volume distribution, absorption half-life, elimination half-life, protein binding, etc.) is also considered to be essential in treating poisoning. However, clinically, there have been many situations that the kinetic parameters required in the decision making for treatment selection were either absent or incomplete. Under these circumstances, designed research in animal model or simple clinical model to find some key parameters will be very useful in risk assessment for clinical management. The followings are examples which we have encountered in the last few years clinically.

Example

The dried roots and rhizome of *Dysosma pleianthum* (Mayapple, also known as Bajiaolian in

China) have been widely used as a lay medicine in Chinese society as well as western cultures. A clinical syndrome of herbal poisoning incidentally resulted from consuming Bajiaolian blend for various medical purposes have been observed in last few years. The most prominent and serious consequence of the poisoning was related to neurological disturbances. Aside from neurological disturbances, patients also exhibited clinical signs and symptoms such as severe diarrhea, abdominal pain, abnormal hepatic functions, leukopenia and thrombocytopenia. Fatality of significant neurological sequelae may develop in severe cases of poisoning. Podophyllotoxin (Px) is the main toxic ingredient for Bajiaolian herbal. The pathological effects of podophyllotoxin on the organ system and the biochemical effects on the cellular level in animals have been documented recently. However, the kinetic information of podophyllotoxin is unclear but essential in the clinical management of poisoning. Under this consideration, we designed a rabbit model to evaluate the toxicokinetics of podophyllotoxin.

MATERIALS AND METHODS

Blood sampling for podophyllotoxin determination

Podophyllotoxin was intravenously administered in a dose of 3 mg/Kg onto the margin vein of 6 rabbits ear and sequential plasma concentrations of this compound were detected by a method of HPLC. "Two step approach" to Pk analyses was applied to examine the Pk parameters (V_d , K_{12} , K_{21} , and K_e).

Pharmacokinetic Analysis

We fitted the plasma concentrations of podophyl-

Fig. 1. The two-compartment model for fitting Px plasma concentrations.

lotoxin (Px) after i.v. injections with a one- or two-compartment model (Fig. 1.) using a nonlinear regression program, PCNONLIN⁽¹⁾. Initial values of pharmacokinetic (PK) parameters were obtained from the back-stripping method⁽²⁾ using a program, BOOMER⁽³⁾. A two-exponential terms is used for the back-stripping method (Equation 1). Total clearance (Cl) of Px in the plasma was calculated by the equation 2. The distribution half-life ($T_{1/2\alpha}$) and elimination half-life ($T_{1/2\beta}$) are calculated with the equation 3 and 4⁽⁴⁾.

where Dose is the amount of Px being injected into the rat (i.e., 3 mg/kg) and the area under plasma concentrations (AUC_0^∞) was calculated using the trapezoidal integration. In addition, we used a popu-

$$C_p = A \cdot e^{-\alpha t} + B \cdot e^{-\beta t} \quad (1)$$

$$Cl = \frac{\text{Dose}}{AUC_0^\infty} \quad (2)$$

$$T_{1/2\alpha} = \frac{\ln(2)}{\alpha} \quad (3)$$

$$T_{1/2\beta} = \frac{\ln(2)}{\beta} \quad (4)$$

Fig. 2. The plasma concentration of Px after i.v. injection. Each dot (■) represents the mean concentrations obtained from 6 rats at each sampling time. The error bar is one standard deviation from the mean. The line represents the calculated values from the mean values of PK parameters.

lation PK program, NONMEM⁽⁵⁾ (ADVAN3), to fit all plasma concentrations of Px. The power function model is chosen for the random error.

RESULTS AND DISCUSSION

We found that the Px plasma concentrations one hour after i.v. injection with a dose of 3 mg/kg were undetectable. The plasma concentrations of Px after i.v. injection were declined biexponentially (Fig. 2.). It indicates that Px exhibits a significant peripheral distribution in the rats. Table1 summarizes the results from compartmental data analysis. The central volume of distribution(Vd) is calculated as 146 ± 71 mL/kg. A very short distribution half-life ($T_{1/2\alpha}$) was detected in this study (1.80 ± 0.66 min), which may imply that Px distributes into the peripheral compartment very rapidly after i.v. injection. The microconstants(k_{12} and k_{21}) between the central and the peripheral compartment are 0.174 ± 0.085 min⁻¹ and 0.0738 ± 0.0168 min⁻¹, respectively. We therefore can predict that the volume of distribution of Px in the peripheral compartment be twice more than Vd in the central compartment. The mean value of AUC_0^∞ is

117 ± 21 min· μ g/mL. The terminal half-life of Px in the plasma was 20.3 ± 6.51 min although its elimination pathway still remains unclear. Total clearance of Px is 26.4 ± 4.3 mL/min (Table 1).

Figure 3 shows the results of using NONMEM to fit all measured plasma Px concentrations. Parameter values obtained from NONMEM fitting is summarized in Table 2. The results obtained from NONMEM fitting are very comparable to those of individual fitting (Table 1) described previously.

In conclusion, we have presented pharmacokinetics of Px in six rats. In this study, we found that Px plasma concentrations in rats can be well described using a two-compartment, open PK model. The results from this PK study may not be able to explain the sustained toxicity one hour after an i.v. injection with a dose of 3 mg/kg. We found that the rats did not recover from intoxication and were found to be cyanotic and dyspnea at the end of each study. However, the present study did find that Px had a significantly peripheral or extra-vascular distribution in the plasma. These kinetic finding has concluded that neither hemodialysis nor hemoperfusion will be helpful in the treatment of acute Px intoxication.

Table 1. Pharmacokinetic parameters of podophyllotoxin in rats (n = 6).

Parameters	Mean $\pm$ S.D.
Vd, mL/kg	146 ± 71
k_{12} , min ⁻¹	0.174 ± 0.085
k_{21} , min ⁻¹	0.0738 ± 0.0168
k_e , min ⁻¹	0.181 ± 0.060
AUC_0^∞ , μ g·mL/min	117 ± 21
Cl, mL/min	26.4 ± 4.3
$T_{1/2\alpha}$, min	1.80 ± 0.66
$T_{1/2\beta}$, min	20.3 ± 6.51

Table 2. Summaries of population PK parameters from NONMEM fitting.

Parameters	Value (95% C.I.)	ω^2
Vd, mL/kg	122 (121.9~122.1)	.0786
k_{12} , min ⁻¹	0.166 (0.0483~0.284)	.0070
k_{21} , min ⁻¹	0.0766 (0.0525~0.101)	.0174
k_e , min ⁻¹	0.187 (0.139~0.234)	.0592
σ^2		.0223

Fig. 3. Calculated data (the bold line) obtained from NONMEM Fitting. The scatter dots are the observation data from six rats.

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