PHARMACOKINETIC－PHARMACODYNAMIC ANALYSIS OF CHANGROLIN IN DOGS WITH ARRHYTHMIA

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ABSTRACT The pharmacokinetics and pharmacodynamics of changrolin (CRL) were studied in 7 dogs with arrhythmia induced by coronary artery ligature. The ECG and the percentage of reduction ratio of ventricular premature were used to evaluate the effect of CRL, and an HPLC method was used to determine the serum drug concentration. A pharmacokinetic program was used to fit concentration－time (C－T) data and a combined pharmacokinetic-pharmacodynamic model was used to analyze effect－time (E－T) data in individual dogs. After infusion with CRL 83.33 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 60 min, it was found that K_{10}, $T_{1/2}$, Vd, Cl and Ce were 0.0087 min^{-1}, 78.03 min, 40.55 $ml \cdot kg^{-1}$, 0.42 $ml \cdot kg^{-1} \cdot min^{-1}$, and 2.01 $\mu g \cdot ml^{-1}$, respectively.

Key words Changrolin; Pharmacokinetics; Pharmacodynamics; Antiarrhythmia agent

Changrolin (CRL, 4-[4-(quinazolinyl) amino-2, 6-bis (-pyrrolidinyl) methyl] phenol) was reported to have antiarrhythmic activity[1]. Clinical trials revealed its therapeutic effects in relieving ventricular beats, auricular premature beats, and paroxysmal ventricular tachycardia[2].

For researching new antiarrhythmic drugs to obtain more potent antiarrhythmic activity and to overcome unwanted side effects of CRL, modification of the molecular structure of CRL was carried out. To compare pharmacological activity and pharmacokinetics of the new compounds with that of CRL, the pharmacodynamics and pharmacokinetics of CRL were studied.

The pharmacokinetics of CRL was studied in normal experimental animals and arrhythmic patients[3～5], but the relationship of the concentration－time process and the effect－time process were not reported. The present investigation was to study the relationship between drug concentration and antiarrhythmic activity of CRL by using a combined pharmacokinetic－pharmacodynamic model in dogs with experimentally induced arrhythmia.

MATERIALS AND METHODS

Changrolin injection (4 $mg \cdot ml^{-1}$) was produced by the Shanghai Institute of Materia Medica.

Experimentally induced arrhythmias were produced in 7 ♂ dogs (11.7±2.6 kg) by ligating the left anterior descending branch of the coronary artery (LDA) under pentobarbital (30 $mg \cdot kg^{-1}$, iv)

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anesthesia[6]. After 24 h, the dogs with experimentally induced arrhythmia received pentobarbital (30 mg·kg^{-1}, iv) again. The brachial vein of the foreleg was catheterized for blood sampling. The ECG was recorded in the dogs. Blood samples were collected while ECG was recorded. The serum was separated and stored in the dark at −10℃ until analysis.

Analysis of drug concentration Serum 1 ml was made alkaline with 1 ml of 1 mol·L^{-1} NaOH, and extracted with 5 ml of CH_2Cl_2. The extract was evaporated to dryness under a stream of nitrogen at 40℃. The residue was dissolved in the mobile phase (perchloric acid 0.01 mol·L^{-1}: methanol 20: 80, v/v), and 10 μl of the solution was injected onto the column of an HPLC system (Hitachi LC-638 HPLC). Column: 25 cm × 4.6 mm (id) packed with Hitachi gel 3010. Flow rate: 0.8 ml·min^{-1}. UV Detector: 230 nm. Standard curves were prepared by assaying known quantities of CRL in serum of normal dogs. The recovery was 84.5%～91.7% at the range of 0.1～4 μg·ml^{-1}. The precision was acceptable with a maximum coefficient of variation of 10%. The sensitivity of the assay was 0.1 μg·ml^{-1} of serum.

Antiarrhythmic effect One hour before iv CRL, the dog was infused with the drug at constant rate (83.33 μg·kg^{-1}·min^{-1}) for 60 min. During infusion the ECG was recorded for 20 s every 10 min until 60 min, then the ECG was recorded at 10, 20, 40, 60, 90, 120, 150 and 180 min after stopping infusion. From the 20 s ECG recording, the number of ventricular extrasystole (VE) was counted and expressed as the epm. The reduction ratio of VE was calculated and expressed in percentage as follows:

$$\text{Reduction ratio of VE (\%)} = \frac{VE(0) - VE(t)}{VE(0)} \times 100\% \quad (1)$$

The percentage was used as a measure of the anti-arrhythmic effect.

Pharmacokinetic－pharmacodynamic model The one compartment open model with an effect compartment was used to calculate the kinetic parameters (Fig 1).

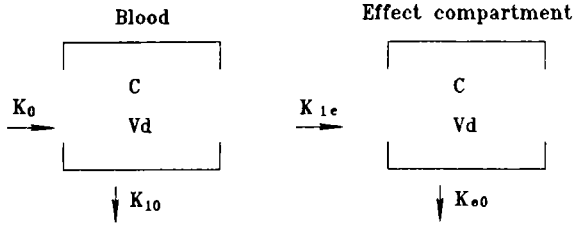

Fig 1 Pharmacokinetic-pharmacodynamic model for analysis of serum CRL concentration and antiarrhythmic effect.

The exponential function (Eq 2) was fitted to the serum drug C－T data by a computer program using weighted nonlinear methods for parameter estimates[7].

$$C = \frac{K_0}{VK_{10}}(1 - e^{-K_{10}T})e^{-K_{10}t} \quad (2)$$

where T is the time that infusion stops, and t is the time after infusion.

The pharmacodynamic model (E－T model) was combined with the pharmacokinetic model. In this model, response can be modeled as a function of the drug concentration (Ce) in the hypothetical effect compartment "E" (Eq 3), whose kinetics can be related to the serum drug concentrations (C)

by a first order process[8].

$$Ce=\frac{K_{10}\cdot K_0}{K_{e0}(K_{10}-K_{e0})V}(1-e^{-K_{10}T})e^{-K_{10}t}+\frac{K_{1e}\cdot K_0}{K_{e0}(K_{10}-K_{e0})V}(1-e^{-K_{e0}T})e^{-K_{e0}t} \quad (3)$$

The measured pharmacological effect is related to the drug concentrations in the effect compartment (Ce) by Hill equation (Eq 4).

$$E=\frac{E_{max}\,Ce^{r}}{Ce^{r}+Ce(50)} \quad (4)$$

where E is the intensity of the pharmacological effect, expressed as VE reduction ratio (%), E_{max} is the maximal effect, $Ce(50)$ is a constant, i. e., the value of Ce at 50% effect, and r is Hill parameter that allows sigmoidicity of the Ce to effect relationship.

The pharmacological effect is independent of the transfer rate constant (K_{1e}). The hypothetical concnetration (Ce) is simply a function of pharmacokinetic profile and the rate constant for elimination of the concentration in the effect compartment (K_{e0}). From this model, the effect data were fitted to the Hill equation with pharmacokinetic parameters as input, using nonlinear least square regression to obtain Hill parameter (r) and $Ce(50)$, a measure of the sensitivity of the site of action of CRL in the heart.

Statistical analysis of data were represented as arithmetic means and standard deviations ($\bar{x}\pm s$).

RESULTS

Pharmacokinetics

The experimental data on serum concentrations and antiarrhythmic activity of CRL were given in Tab 1. The pharmacodynamic and pharmacokinetic parameters during and after stopping infusion of CRL in dogs with arrhythmia were listed in Tab 2.

The pharmacokinetic parameters calculated from the one compartment open model, elimination half-life $T_{1/2}=78.03$ min, elimination rate constant $K_{10}=0.0087\ min^{-1}$, volume of distribution $Vd=40.55\ ml\cdot kg^{-1}$, and clearance $Cl=0.42\ ml\cdot kg^{-1}\cdot min^{-1}$.

Tab 1 Experimental data of serum concentration (C) and antiarrhythmic effect (E) of CRL during infusion and after stopping infusion with the dose of 83.33 mg·kg^{-1}·min^{-1} in arrhythmic dogs ($\bar{x}\pm s$, $n=7$)

Time (min)	Serum concentrations ($\mu g\cdot ml^{-1}$)	Antiarrhythmic effect (E) VE (epm)
0	0	183.4±31.7
10	0.32±0.09	158.0±41.3
20	0.54±0.05	152.8±46.5
30	0.86±0.42	141.0±50.9
40	1.43±0.58	105.6±56.9
60	1.97±0.50	102.2±48.3
70	1.40±0.51	63.8±49.8
80	1.35±0.43	73.4±49.7
100	1.11±0.28	120.4±21.2
120	0.96±0.40	124.6±40.5
150	0.73±0.23	145.2±21.2
180	0.50±0.18	126.4±35.0
210	0.37±0.10	143.0±45.2
240	0.21±0.09	149.8±35.8

Tab 2 Pharmacokinetic and pharmacodynamic parameters of CRL after infusion with the dose of 83.33 mg·kg^{-1}·min^{-1} in arrhythmic dogs ($\bar{x} \pm s$, $n = 7$)

Parameter	Value
A (μg·ml^{-1})	4.16 ± 3.36
K_0(μg·kg^{-1}·min^{-1})	83.33
K_{10}(min^{-1})	0.0087 ± 0.0026
$T_{1/2}$(min)	78.03 ± 12.68
Vd (ml·kg^{-1})	40.55 ± 30.70
Cl (ml·kg^{-1}·min^{-1})	0.42 ± 0.39
K_{e0}(min^{-1})	0.0048 ± 0.0014
E_{max}(%)	42.91 ± 11.65
T_{max}(min)	72.09 ± 11.71
Ce(50) (μg·ml^{-1})	2.01 ± 1.27
r	0.8338 ± 0.2477

Pharmacodynamics

The reduction ratio of VE calculated by using equation (1) and the concentrations in effect compartment (Ce) by using equation (3) are listed in Tab 3. The pharmacological response of CRL varied considerably in these dogs. The mean VE was 183.4 epm before infusion. As shown in Tab 3, the reduction ratio of VE was 65.2% at 70 min after infusion. The mean $Ce(50)$, the elimination rate constant (K_{e0}) and the Hill parameter (r) were 2.01 μg·ml^{-1}, 0.0048 min^{-1}, and 0.8338, respectively.

As shown in Tab 3, the pharmacological effect (E) was parallel to the drug concentrations in the effect compartment (Ce) by comparing the $Ce-T$ data with $E-T$ data. The maximum effect and the maximum Ce all appeared at 70 min after infusion. The maximum Ce is very close to $Ce(50)$.

Comparison of C with Ce indicates that the time reaching Ce peak lagged about 10 min than the time reaching C peak (Fig 2). This time lag may be related to the rate of CRL transferring from blood into the effect compartment(K_{1e}).

Tab 3 Comparision of calculated concentration in effect compartment (Ce) with antiarrhythmic effect (E) of CRL after infusion with dose of 83.33 mg·kg^{-1}·min^{-1} in arrhythmic dogs ($\bar{x} \pm s$, $n = 7$)

Time (min)	Calculated Ce (μg·ml^{-1})	Antiarrhythmic effect (E) Reduction ratio of VE (VE%)
0	0	0
10	0.38 ± 0.05	13.6 ± 3.5
20	0.56 ± 0.17	16.7 ± 5.1
30	0.78 ± 0.28	23.1 ± 8.3
40	1.42 ± 0.35	42.2 ± 12.7
60	1.58 ± 0.41	44.5 ± 11.6
70	2.09 ± 0.57	65.2 ± 17.7
80	1.93 ± 0.52	60.0 ± 16.2
100	1.37 ± 0.16	34.4 ± 4.0
120	1.26 ± 0.27	32.1 ± 7.1
150	1.17 ± 0.14	20.8 ± 2.5
180	1.12 ± 0.22	31.1 ± 6.0
210	0.78 ± 0.19	22.0 ± 5.4
240	0.58 ± 0.11	18.3 ± 3.6

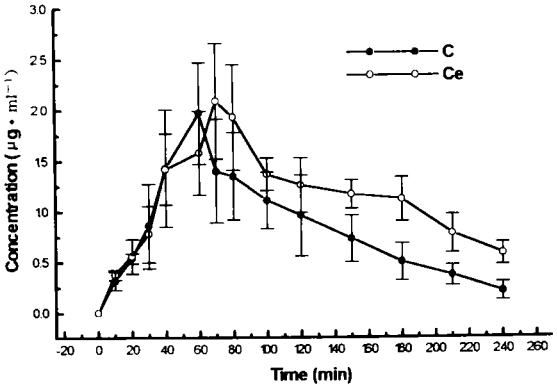

Fig 2 Comparison of serum CRL concentrations (C) with calculated concentrations(Ce) of CRL in the effect compartment in dogs during infusion of CRL at dose of 83.33 mg·kg^{-1}·min^{-1} and after stopping infusion ($\bar{x} \pm s$, $n = 7$).

DISCUSSION

Chen *et al*[4] reported that the effective serum concentration of CRL was 2.6 $\mu g \cdot ml^{-1}$ in arrhythmic patients. This value was similar to *Ce*. Therefore, we presume that serum drug level may be used as a measurement of the therapeutic effect. In clinical therapy, determination of blood drug concentration can be used to predict drug effect and to control infusion speed during therapy.

In this present study, the pharmacological response was measured as the percentage of VE reduction, thus, the response was a direct measurement of antiarrhythmic activity of CRL. An arrhythmic model induced by the Harris method may allow quantitative assessment of the kinetics of pharmacological response. The simplest model, one-compartment open model with an effect compartment, is adequate to describe the experimental data in dogs with arrhythmia. The combined pharmacokinetic-pharmacodynamic model gives some insight into the relationship between pharmacological response and serum levels of CRL that might be present at the site of action.

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常咯啉在实验性心律失常狗的药代动力学—药效动力学分析

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摘要　用 Harris 冠脉结扎法诱发的心律失常狗研究常咯啉药代动力学—药效动力学。7 只狗按 83.33 $\mu g \cdot kg^{-1} \cdot min^{-1}$ 静脉滴注 60 min，在给药期间和停药后不同时间记录 ECG 及测定血药浓度。C－T 数据用药代程序计算药代参数；药效数据用药代—药效同步分析模型计算药效动力学参数，K_{10}，$T_{1/2}$，*Vd*，Cl 分别为 0.0087 min^{-1}，78.03 min，40.55 $ml \cdot kg^{-1}$ 和 0.421 $ml \cdot kg^{-1} \cdot min^{-1}$；$K_{e0}$ 和 *Ce*(50) 分别为 0.0048 min^{-1} 和 2.01 $\mu g \cdot ml^{-1}$.

关键词　常咯啉；抗心律失常药；药代动力学；药效动力学