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Grey dynamic model of predicting the long-term effects of drugs and its application to pirenzepine[1]

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ABSTRACT In an attempt to approach the quantification of the dynamics of drug effects and the prediction of the long-term efffects of drugs, a grey dynamic model was proposed and it was applied to predict the long-term effects of pirenzepine on pupils and peripheral leukocytes in dogs. The inconsiderable relative errors between the predicted and observed values suggest that the model-based equations for pupil diameter, neutrophils (%) and lymphocytes (%) which, obtained by fitting the data measured before and during initial 10 wk experiment, are acceptable for predicting the effects after 20- and 24-wk treatment with the drug.

KEY WORDS pharmacodynamics; pirenzepine; pupil; leukocytes; mathematical computing

Study on the long-term effects of drugs such as adaptative tolerance, chronic toxicity, accumulative effect, circadian effect, etc. are usually carried out by long-term experimental observations. Generally speaking however, it is difficult or even impossible to perform this kind of experiments due to the limitation of conditions. A model predicting the long-term effects of drug through shorter-term experiments might therefore provide a way to achieve the goal above and enhance insight for both pharmacologist and clinician. There have been few data about this kind of model in previous reports.

On the basis of grey system theory, Deng JL[1] suggested that a time sequence of event variable in energy system allow to be characterized by differential equation. This hypothesis should be suitable for the time sequence of the drug effects in organism which is an open energy system. The purpose of this study was to present a grey dynamic model to predict the long-term effects of drug and test the fitness of the model to pirenzepine which is a selective muscarinic receptor antagonist and markedly inhibits gastric acid secretion both in animals and in man[2]

METHODS

Model A generated number sequence, which is produced by single cumulation of the initial time sequence of drug effects $X^{(0)}(1), X^{(0)}(2), \cdots, X^{(0)}(n)$, goes as following:

$$X^{(1)}(k) = \sum_{i=1}^{k} X^{(0)}(i) \quad (k = 1,2,\cdots,n) \qquad [1]$$

allows to be characterised by following differential equation:

$$dX^{(1)} / dt + aX^{(1)} = u \qquad [2]$$

where a and u are undetermined coefficients.

Let $X^{(1)}(0) = X^{(0)}(1)$, the time function of equation [2] is

$$X^{(1)}(t+1) = (X^{(0)}(1) - u / a)e^{-at} + u / a \quad (t = 1,2,\cdots,n) \qquad [3]$$

and the predicted values of the initial time sequence of drug effects can be calculated by following equation:

$$X^{(0)}(t) = X^{(1)}(t+1) - X^{(1)}(t) \qquad [4]$$

According to the definition of residual error, a residual error sequence can be produced:

$$X\varepsilon^{(0)}(k') = X^{(0)}(k) - X^{(0)}(k') \quad (k' = 1,2,\cdots,m) \qquad [5]$$

where $X\varepsilon^{(0)}(k')$ is the residual error at time k' and the relationship between k' and k de-

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pends on the time interval to be modified.

Imitating equation [1],[2] and [3], we have

$$X\varepsilon^{(1)}(t'+1)=(X\varepsilon^{(0)}(1)-u'/a')e^{-a't'}+u'/a' \quad (t'=1,2,\cdots,m) \quad [6]$$

and let $t' = t+j$, equation [6] can be expressed as:

$$X\varepsilon^{(1)}(t+j+1)=(X\varepsilon^{(0)}(1)-u'/a')e^{-a'(t+j)}+u'/a' \quad (t=1,2,\cdots,\ n;\ t+j\geqslant 0) \quad [7]$$

then the time function of the model is modified as:

$$\hat{X}^{(1)}(t+1)=X^{(1)}(t+1)+X\varepsilon^{(1)}(t+j+1) \quad [8]$$

and the predicted values of the initial time sequence of drug effects are modified by following equation:

$$\hat{X}^{(0)}(t)=\hat{X}^{(1)}(t+1)-\hat{X}^{(1)}(t) \quad [9]$$

The modification process above can be continued until r step if the fitness is not optimal.

Experiment All experiments were carried out on 5 ♂ dogs of 7.4± SD 0.6 kg. The drug used was pirenzepine kindly supplied by Yancheng Pharmaceutical Factory and all other chemicals were AR.

Pirenzepine mixed in food was administrated to dogs at dose of 104 mg / kg every morning for 24 wk while control dogs received equal amount of food as placebo. Pupil diameters were determined as described by Luduena *et al*[3]. The differential count of peripheral leukocytes was performed by the routine method. Model-based equations for pupil diameters, neutrophils (%) and lymphocytes (%) were proposed by fitting the data before and during the initial 16 wk of pirenzepine administration. Data analysis and calculation process were carried out on the IBM PC / XT computer.

Model analysis Nonlinear least square method was used for estimating the parameters of the model proposed. Statistical analysis for significance of curvilinear regression were calculated by F test[4]. Posteriori error test[5] and correlation analysis[6] were used for judging the goodness of fit. The acceptability of the long-term effects of drug predicted by model-based equations was judged by the relative error between the predicted and observed values.

RESULTS

Neutrophils (%) and lymphocytes (%) in peripheral blood and pupil diameters of pirenzepine-treated dogs were respectively shown in Fig 1. The model-based equations for the generated number sequences of pupil diameters, neutrophils (%) and lymphocytes (%) measured before and during the initial 16 wk administration of pirenzepine to dogs were equation [10],[11],[12] respectively:

$$\hat{X}^{(1)}(t/4+1)=-481.8EXP(-0.0232(t/4-0))+487.8 \quad [10]$$

$$\hat{X}^{(1)}(t/4+1)=-1453.4EXP(-0.0522(t/4-0))-6.45EXP(-0.3221(t/4-1))+1540.9 \quad [11]$$

$$\hat{X}^{(1)}(t/4+1)=277.8EXP(0.0814(t/4-0))+0.86EXP(0.3404(t/4-1))-264.4 \quad [12]$$

Tab 1 showed F test for significance of curvilinear regression and the goodness of fit of the model-based equations to the observed values.

The curves of fitting the model-based equations to the observed values and the curves of extrapolating the predicted values from the equations above were shown in Fig 1. The relative errors between the predicted and observed values of pupil diameters, neutrophils (%) and lymphocytes (%) were 0.7 %, 3.7% and 4.0 % respectively after treatment with pirenzepine for 20 wk, and were 5.8 %, 4.4%, 14.4% respectively after treatment for 24 wk.

Pupils enlarged singnificantly ($P<0.01$) but no significant alteration either in neutrophils (%) or in lymphocytes (%) appeared ($P>0.05$) during the initial 16 wk treatment with pirenzepine compared with those before treatment as shown in Fig 1. After po administration of the drug for 20 and 24 wk it was shown that the decrease of neutrophils (%) and the increase of lymphocytes (%)

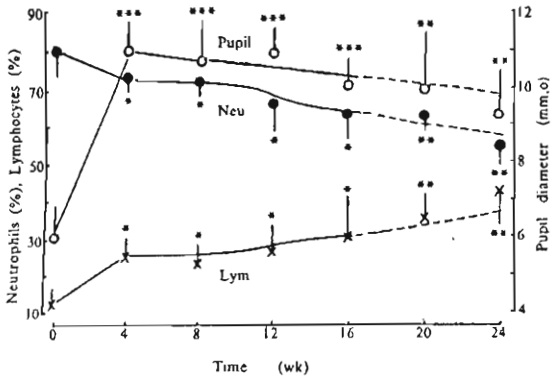

Fig 1. Pupil diameters, neutrophils (Neu) and lymphocytes (Lym) in peripheral blood after po pirenzepine 104 mg / (kg · d) to dogs. Solid lines represent the optimal fit of the model-based equations to the observed values; dotted lines represented the prediction curves extrapolated by the model-based equations. $n=5$, $\bar{x} \pm$ SD. $^{*}P>0.05$, $^{**}P<0.05$, $^{***}P<0.01$ *vs* 0 time.

Tab 1. F test for the curvilinear regression and the goodness of fit of model-based equations to the observed values. $^{**}P<0.05$, $^{***}P<0.01$ *vs* linear regression.

Curve	F values	Goodness of fit		
		p	c	R^2
Pupil diameter (mm)	140.19***	1.00	0.0833	0.9901
Neutrophils (%)	11.30**	1.00	0.0753	0.9698
Lymphocytes (%)	28.80**	1.00	0.0748	0.9717

R^2: Indexes of correlation between the predicted and observed values. p: Small error probability,

$$p = p\{|\varepsilon^{(0)}(k) - \bar{\varepsilon}| < 0.6745 S_2\},$$

where $S_2 = (1/n \sum_{k=1}^{n} (X^{(0)}(k) - \bar{X})^2)^{1/2}$.

c: Posteriori error ratio, $c = S_1 / S_2$,

where $S_1 = (1/n \sum_{k=1}^{n} (\varepsilon^{(0)}(k) - \bar{\varepsilon})^2)^{1/2}$.

became statistically significant ($P<0.05$) while pupil diameters were smaller than those measured earlier from $P<0.01$ to $P<0.05$ (Fig 1). Pupil diameters, neutrophils (%) and lymphocytes (%) of control dogs showed no significant difference from that before po placebo during 24 wk experimental observations (not shown in this paper).

DISCUSSION

In this study, we proposed a grey dynamic model to quantify the dynamics of drug effects and predict the long-term effects of drug. The present results show that the model-based equations for pupil diameters, neutrophils (%) and lymphocytes (%) fit the values measured during 16 wk treatment with pirenzepine (Fig 1, Tab 1) well and are acceptable for predicting the efffects of the drug on pupils and peripheral leukocytes after treatment for 20 and 24 wk (Fig 1), which suggest that the practical results of the model is satisfactory for pirenzepine. However, it is needed to confirm whether the model is suitable for other drugs.

In shorter-term clinical studies, blurred vision which, caused by mydriasis, was the most frequently reported side effect of pirenzepine and the incidence of it appeared to be dose dependent, and laboratory tests showed occasional deviations from the normal range in leukocytes counts[7]. What are the long-term effects of the drug on pupil and peripheral leukocytes will be an important information for further clinical study or therapeutical use. Our work has proved that the mydriasis is markedly displayed but peripheral leukocytes are not influenced by the shorter-term treatments with the drug in dogs (Fig 1). In addition, this study showed that the mydriasis tended to be weakened, and neutrophils (%) tended downwards while lymphocytes (%) upwards as the treatments continued. These results suggest that an adaptative tolerance on the mydriasis effect and a chronic effect on the differentiation of leukocytes will appear if a long-term treatment with pirenzepine is given.

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预测药物远期效应的灰色动态模型及其在哌仑西平的应用

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提要 为定量描述药物效应的动态变化和预测药物远期效应，本文建立了灰色动态模型并应用于预测给狗服用哌仑西平 104 mg / (kg · d)对瞳孔及外周白细胞的远期影响. 基于此模型，拟合给药前及给药 16 wk 期间瞳孔直径. 中性粒细胞及淋巴细胞百分比的实验数据，得到预测该药远期效应的方程式. 由此方程式计算的给药后 20 和 24 wk 的预测值与观察值之间的相对误差较小，提示预测是可行的.

关键词 药效学; 哌仑西平; 瞳孔; 白细胞; 数学计算

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Pharmacokinetics of *m*-nisoldipine in rabbits and rats

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ABSTRACT A reverse phase HPLC method was devised for determination of *m*-Nis in plasma. A mobile phase of methanol- KH_2PO_4 with a flow rate of 1 ml / min was used. Diazepam was used as the internal standard. A two-compartment model featured the pharmacokinetic process of *m*-Nis after its iv injection to rats (30 μg / kg) and rabbits (50 μg / kg). The pharmacokinetic parameters were : $T_{\frac{1}{2}\alpha}$ = 4.3 min, $T_{\frac{1}{2}\beta}$ = 63.6 min, V_d = 0.805 L / kg, Cl = 9 ml / (min · kg) in rats; $T_{\frac{1}{2}\alpha}$ = 5.0 min, $T_{\frac{1}{2}\beta}$ = 78.3 min, V_d = 1.191 L / kg, Cl = 11 ml / (min · kg) in rabbits. The pharmacokinetics for *m*-Nis after ig 200 μg / kg to rats described one-compartment model with parameters: $T_{\frac{1}{2}}$ = 84.8 min, T_{max} = 31.2 min, C_{max} = 49.97 μg / L, V_d = 0.792 L / kg and Cl = 25 ml / (min · kg).

KEY WORDS *m*-nisoldipine; pharmacokinetics; high pressure liquid chromatography

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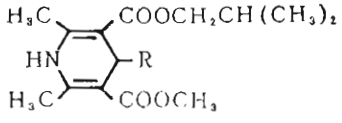
m-Nisoldipine (*m*-Nis), a new isomer of nisoldipine (Nis), was first developed in Department of Organic Chemistry, Hebei Medical College. *m*-Nis is more stable than Nis to light[1,2]. It shows active effects on the cardiovasculature and hemodynamics[1,3-5] and is a perspective agent in cardiovascular therapeutics. This paper deals with HPLC determination of *m*-Nis and its pharmacokinetics in rats and rabbits.



Nisoldipine *m*-Nisoldipine