药效学模型 R 969.1

卢建丰，陈 刚，相秉仁[1]，安登魁[1]
(南京军区总医院临床药理科，南京 210002；[1]中国药科大学药物分析研究室，南京 210009，中国)

摘要 本文分析了8位中国健康男性血清咪达唑仑浓度-脑电效应的定量关系，采用 12—30 Hz 之间的每秒总波数 (TNW_{12-30})作为脑电效应指标. 由药物动力学-药效学软件所计算的药效学参数为：$T_{\frac{1}{2}ke0}=1.3\pm0.9\ min^{-1}$，$EC_{50}=254\pm54\ \mu g\cdot L^{-1}$，$N=2.9\pm0.6$. 实验证明了由脑电分析得出的参数 TNW_{12-30} 可用于浓度-效应关系的研究.

关键词 咪达唑仑；药物动力学；药效学；脑电描记术

药代动力学

BIBLID: ISSN 0253-9756 Acta Pharmacologica Sinica 中国药理学报 1994 Sep; 15 (5): 403—407

Microprocessor-programmed infusion of theophylline rapidly attained expected steady-state level in rabbit plasma[1]

DUAN Shi-Ming, XU Xun, YE Miao, FU Ying (*Department of Pharmacology, Faculty of Anesthesiology, Xuzhou Medical College, Xuzhou 221002, China*)

ABSTRACT A self-made microprocessor-programmed (two-compartmental model) infusion controller was connected with an infusion pump, which achieved an expected steady-state plasma concentration (C_{pss}) rapidly (5 $T_{\frac{1}{2}\alpha}$) and maintained the level. Theophylline was selected as an example, and its pharmacokinetic parameters of rabbits, expected C_{pss}, body weight (wt), and infusion time (t) were inputted. The programmed infusion rate (K_r) was determined by the following equation: $(K_r)=C_{pss}\cdot K_{10}\cdot V_c\cdot wt\ \{1+[(K_{21}-\beta)/\beta]EXP(-K_{21}t)\}$ and the predicted value was calculated by the formula: $C_{(t)}=C_{pss}\times[1-EXP(-\alpha t)]$. The needed concentration and total volume of drug were automatically shown on the screen. The drug was automatically infused after pumping, and the plasma concentration of theophylline was measured by colorimetric method. The results showed that the median absolute value of the performance error (MAVPE) was 8.3 %. Although $T_{\frac{1}{2}\beta}$ of theophylline was 6.08 h, the expected C_{pss} was attained in only 30 min (5 $T_{\frac{1}{2}\alpha}$) after start of infusion and then well maintained.

KEY WORDS theophylline; pharmacokinetics; computer-assisted drug therapy; drug administration schedule

Received 1993-07-14 Accepted 1994-06-06
[1] Project supported by the Natural Science Foundation of Jiangsu Education Committee, № 8865.

Since 1981 computer-assisted continuous infusion system (CACI) has been gradually developing in clinical drug therapy. The microprocessor-controlled infusion is a convenient way to optimize application schemes in some area of drug treatment. In a CACI of a linear open (2 or 3)-compartment model, many investigators used a bolus loading dose so as to rapidly reach an expected C_{pss} and then maintained this level by the automated continuous infusion system[1,2]. Since some drugs could not be given in a bolus loading way, we

devised a single exponentially declining infusion model and developed a microprocessor-programmed infusion controller to make CACI miniaturization and integralization.

MATERIALS AND METHODS

Rabbits White ♀ rabbits weighing 2.5±*s* 0.4 kg (Laboratory Animal Center, Xuzhou Medical College, China) were used.

Chemicals and reagents Aminophylline contains 80.02 % theophylline (Changzhou Pharmaceutical Factory, ChP 1990), chloroform (Wuxi Dongfeng Chemical Factory) and isopropanol (Shanghai First Reagent Factory) were AR.

Determination of plasma theophylline The concentration of plasma theophylline was assayed colorimetrically[3]. The linear range was 0.125—10 $\mu g \cdot ml^{-1}$, recovery rate was 82 ± *s* 3 %. Standard curve: $\Delta A = 0.0002 + 0.0589\,C$ ($\mu g \cdot ml^{-1}$) ($n=5$, $r=0.9999$). CV=2.17 %.

Pharmacokinetic study Rabbits were anesthetized with iv urethane 1 $g \cdot kg^{-1}$. The blood samples were collected from carotid artery at 3, 6, 9, 12, 18, 24, 30, 60, 120, 180, 240, and 360 min after theophylline 10 $mg \cdot kg^{-1}$ was injected into posterior auricular vein. The plasma was used to measure the concentration of theophylline[3]. The data were analyzed by PKBP-N1 program in IBM-PC computer[4].

Programmed infusion Microprocessor-programmed infusion controller was connected with a DYB-2A Electron Infusion Pump (Haimen Electronic Machinery, Jiangsu). The pharmacokinetic parameters (V_c, K_{10}, K_{21}, and β), C_{pss}, wt and t were inputted into the microprocessor-programmed infusion controller. Drug solutions were prepared according to the concentration and volume of the tested drug shown on the screen. Then, the prepared drug solutions were infused automatically. During the infusion, the blood was taken and the plasma theophylline concentration was assayed at 5, 10, 15, 30, 60, 120, 180, and 240 min.

Analysis of data The percent performance error (%PE) and the median absolute value of the performance error (MAVPE) were calculated[5,6].

$$\%PE = [(\text{measured} - \text{predicted})/\text{predicted}] \times 100$$

$$MAVPE = \text{median}\ |PE|$$

RESULTS

Selection of compartment model The disposition exhibited a two-compartment model after iv theophylline 10 $mg \cdot kg^{-1}$:

$$C_t = 24.6\ EXP(-0.1496t) + 19.4\ EXP(-0.0019t)$$

The changes of plasma drug concentration *vs* time are shown in Fig 1.

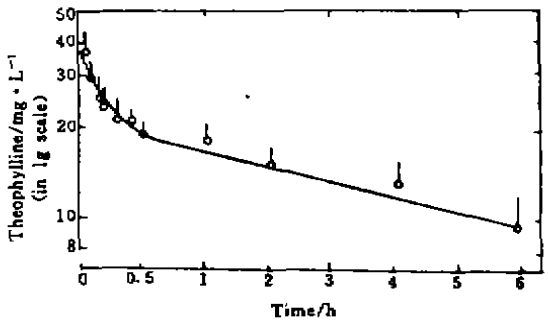

Fig 1. Theophylline concentrations in plasma after iv bolus 10 $mg \cdot kg^{-1}$ in 7 rabbits. $\bar{x} \pm s$.

The pharmacokinetic parameters obtained were: $\beta = 0.0019\ min^{-1}$, $K_{10} = 0.0043\ min^{-1}$, $K_{21} = 0.0670\ min^{-1}$ and $V_c = 0.2279\ L \cdot kg^{-1}$ (Tab 1).

Tab 1. Pharmacokinetic parameters after iv theophylline 10 $mg \cdot kg^{-1}$ in 7 rabbits. $\bar{x} \pm s$.

A	23.3±7.3 $mg \cdot L^{-1}$	V_c	0.246±0.058 $L \cdot kg^{-1}$
B	19.3±3.3 $mg \cdot L^{-1}$	K_{10}	0.248±0.079 h^{-1}
α	9.1±3.9 h^{-1}	β	0.114±0.034 h^{-1}
K_{12}	4.76±2.41 h^{-1}	K_{21}	4.22 ±1.76 h^{-1}

Rate of programmed infusion The equation for rate of programmed infusion (K_i) is:

$$K_i = C_{pss} K_{10} V_c\ wt\ \{1 + [(K_{21} - \beta)/\beta]\ EXP(-K_{21}t)\}$$

The pharmacokinetic parameters, C_{pss} (40 $\mu g \cdot ml^{-1}$), wt (2 kg) and t (240 min) were inputted into the microprocessor-programmed infusion controller. K_i ($mg \cdot min^{-1}$) = 0.0784 + 2.6862×EXP(−0.0670t). The change of

drug efflux *vs* time was shown in Fig 2.

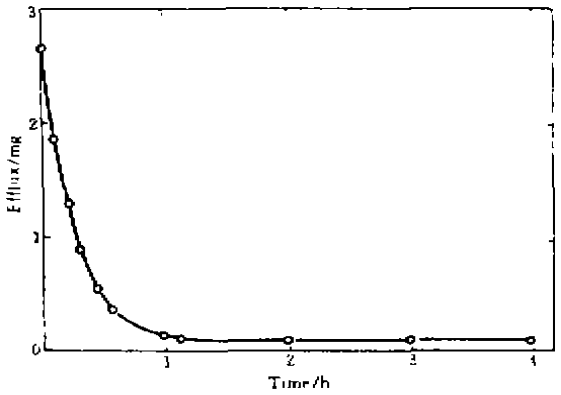

Fig 2. Theoretical values of the programmed infusion.

Accuracy of programmed infusion The effluent solutions from programmed infusion pump were collected at different intervals, and compared with predicted volumes (Tab 2).

Tab 2. Efflux values of microprocessor-programmed infusion pump. $n=4$, $\bar{x}\pm s$.

t/min	predicted/ml	measured/ml
0—5	37.6	37.5 ±0.4
10—15	19.9	20.50±0.1
20—30	18.8	19.75±0.1
40—50	6.8	7.1 ±0.3
70—80	3.1	3.18±0.2
90—100	2.6	2.58±0.1

The volumes (ml) were calculated as follow:

$$\int_{t_1}^{t_2} [0.25+8.57\ \mathrm{EXP}(-0.067t)]dt$$

The dispersion of measured and predicted plasma theophylline concentration was shown in Fig 3.

Theophylline concentration in plasma during programmed infusion

The predicted value was calculated by the formula:

$$C_{(t)}=C_{ss}\times[1-\mathrm{EXP}(-\alpha t)]$$

The predicted *vs* measured drug concentration was shown in Tab 3.

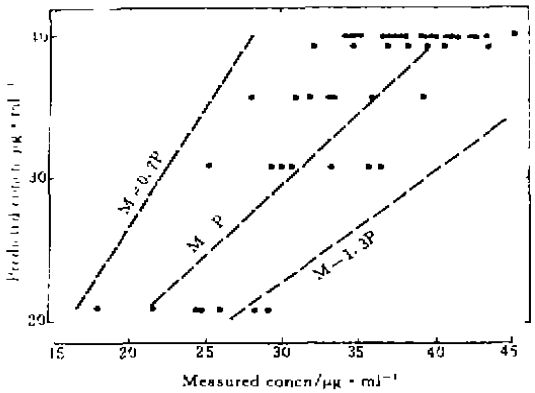

Fig 3. Predicted (P) *vs* measured (M) theophyline concentration in 55 plasma samples. Dashed lines = delineates measured samples at ±30 % of predicted.

Tab 3. Theophylline concentration in plasma during programmed infusion in 7 rabbits. $\bar{x}\pm s$.

Time /min	Concentration/μg·ml^{-1} predicted	measured
5	21.1	24±4
10	31.0	31±4
15	35.8	33±4
30	39.6	38±4
60	40.0	38±3
120	40.0	38±2
180	40.0	38±3
240	40.0	40±3

DISCUSSION

In the present study, the standard curve, recovery rate and CV% of plasma theophylline assay were consistent with those in others[5]. The plasma theophylline concentration reached 31±s 4 μg·ml^{-1} (78 % of C_{ss}) in 10 min and 94 % of C_{ss} in 30 min after the initiation of the programmed infusion. With the way of constant iv drip and the same pharmacokinetic parameters (to attain the same C_{ss}), the plasma theophylline concentration was only 14.9±s 1.3 μg·ml^{-1} 4 h after the start of infusion[7]. According to this result, it would

take 30.4 h ($5T_{1/2\beta}$) to achieve the C_{pss}. It was acceptable that PE of assayed plasma concentration ranged from ±20 to ±30 %, never exceeding ±50—±60 % in computer-assisted infusion[5]. In our study, 96 % (53/55) of the measured values were within ±30 % of those predicted and MAVPE was only 8.3 %. The results indicate that the programmed infusion used in this study is very reliable. It is also shown that the individual programmed infusion with population pharmacokinetic parameters is practical and useful.

The single programmed infusion devised in the present study could also be used for the drugs, which could not be given in a bolus loading way, to achieve a required expected C_{pss} rapidly and then maintain this level.

In general, a CACI system consists of a computer (IBM-PC or Apple II), an interface and an infusion pump. We have developed a programmed infusion pump which can make the CACI system miniaturization and integralization for clinical drug therapeutics.

However, our programmed infusion pump lacks the ability of feedback regulation on the concentration of drug and therefore remains to be further improved.

APPENDIX

We are concerned with a general, linear two-compartment model shown as Fig 4.

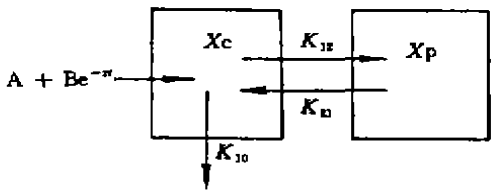

Fig 4. Linear two-compartment model.

We assume that the infusion rate (mg·min^{-1}) is

$$K_{(t)}=A+Be^{-\gamma t} \quad (1)$$

The amount of drug obtained by Eq (1) is infused into the central compartment, eliminated from the central compartment and redistributed to peripheral compartment.

Let $Xi(t)$ be the amount of drug in compartment i at time t. The variation of $Xi(t)$ with time is described by

$$\begin{cases} dXc/dt=A+Be^{-\gamma t}+K_{21}X_p-(K_{10}+K_{12})Xc & (2) \\ dXp/dt=K_{12}Xc-K_{21}Xp & (3) \end{cases}$$

where K_{ij} are the first-order rate constants (min^{-1}).

The solution, obtained by Laplace transformation, is

$$Xc=\frac{AK_{21}}{\alpha\cdot\beta}-\left[\frac{A(\alpha-K_{21})}{\alpha(\alpha-\beta)}+\frac{B(K_{21}-\alpha)}{(\alpha-\beta)(\gamma-\alpha)}\right]e^{-\alpha t}-\left[\frac{A(\beta-K_{21})}{\beta(\beta-\alpha)}+\frac{B(K_{21}-\beta)}{(\alpha-\beta)(\beta-\gamma)}\right]e^{-\beta t}-\frac{B(K_{21}-\gamma)}{(\gamma-\alpha)(\beta-\gamma)}e^{-\gamma t} \quad (4)$$

The concentration-time equation is

$$C_{(t)}=(AK_{21}/V_c\alpha\beta)-Le^{-\alpha t}-Me^{-\beta t}-Ne^{-\alpha t} \quad (5)$$

where V_c is the apparent volume of the central compartment and L, M and N are coefficients. Let M, N be zero, solving the values of A, B and γ

$$\gamma=K_{21},\ B=A(K_{21}-\beta)/\beta$$

When $t\to\infty$, the equation (5) may be written as

$$\lim_{t\to\infty}=C_{pss}=A\,K_{21}/V_c\alpha\beta$$

or $A=C_{pss}V_c\alpha\beta/K_{21}=C_{pss}V_cK_{10}$

Substituting the values of A, B, and γ in Eq (1), and solving the equation for the single exponentially declining infusion yields

$$K_i=C_{pss}V_cK_{10}+C_{pss}V_cK_{10}[(K_{21}-\beta)/\beta]\,EXP(-K_{21}t)$$
$$=C_{pss}V_cK_{10}\{1+[(K_{21}-\beta)/\beta]\,EXP(-K_{21}t)\}$$

Substituting the values of A, B, and γ in Eq (5), and solving the equation for the concentration-time yields

$$C_{(t)}=C_{pss}(1-e^{-\alpha t})$$

REFERENCES

1 Schwilden H. A general method for calculating the dosage

403－407

scheme in linear pharmacokinetics.
Eur J Clin Pharmacol 1981; 20: 379－86.
2 Hill HF, Saeger L, Bjurstrom R, Donaldson G, Chapman CR, Jacobson R. Steady-state infusions of opioids in human volunteers. 1. Pharmacokinetic tailoring.
Pain 1990; 43: 57－67.
3 Chen G. Therapeutic drug monitoring, principle and practice. Beijing: Ren-Min Military Medical Publ, 1988: 355－63.
4 Yang YC, Chen G, Yuan L. A non-linear method and its program for calculating pharmacokinetic parameters.
Acta Pharmacol Sin 1983; 4: 217－20.
5 Glass PSA, Jacobs JR, Smith LR, Ginsberg B, Quill TJ, Bai SA, *et al*. Pharmacokinetic model-driven infusion of fentanyl: assessment of accuracy.
Anesthesiology 1990; 73: 1082－90.
6 Raemer DB, Buschman A, Varvel JR, Philip BK, Johnson MD, Stein DA, *et al*. The prospective use of population pharmacokinetics in a computer-driven infusion system for alfentanil.
Anesthesiology 1990; 73: 66－72.
7 Duan SM, Huang HF, Fu Y. The study on exponentially declining intravenous infusion of a linear two-compartment model drug.
Acta Acad Med Xuzhou 1991; 11: 42－5.

茶碱经微处理机程序输注迅速达到期望兔血浆稳态水平

R965.2

段世明，徐 迅，叶 妙，傅 英（徐州医学院麻醉学系药理教研室，徐州221002，中国）

摘要 自制二室模型药物程序输液泵．向控制器输入兔茶碱药物动力学参数，期望血浆稳态浓度(C_{pss})，体重及时间．输注速率(K_r)＝$C_{pss}K_{10}V_c$ wt$\{1+[(K_{21}-\beta)/\beta]EXP(-K_{21}t)\}$，血药浓度预报式为$C_{(t)}=C_{pss}(1-e^{-\alpha t})$，依据显示配药液，自动输注．比色法测定血药浓度．96 %的执行百分误小于±30 %，其绝对值的中位数为8.3 %．虽然$T_{\frac{1}{2}\beta}$＝6.08 h，但输注后30 min ($5T_{\frac{1}{2}\alpha}$)，血药浓度达期望C_{pss}．

关键词 茶碱；药物动力学；计算机辅助药物治疗；用药计划表

BIBLID: ISSN 0253-9756 Acta Pharmacologica Sinica 中国药理学报 1994 Sep; 15 (5): 407－410

Protective effect of tetramethylpyrazine against damages of aortic endothelial cells elicited by low-density lipoproteins[1]

LI Yu-Jie, LI Yuan-Jian, WU Jin-Xiang, YU Xian-Jie, YAN You-Fang[2]
(*Department of Pharmacology, Hu-nan Medical University, Changsha 410078, China*)

ABSTRACT Effects of tetramethylpyrazine (TMP) on endothelial cells damaged by low-density lipoproteins (LDL) were investigated. When endothelial cells were incubated with LDL (1.5 mg protein·ml^{-1}) the level of malondialdehyde (MDA) was increased and the activity of superoxide dismutase (SOD) was inhibited, and levels of cGMP and epoprostenol were decreased. TMP at concentrations of both 20 and 150 mg·L^{-1} nullified the inhibition of SOD activity and the reduction of cGMP and epoprostenol content elicited by LDL. However, the elevation of MDA content induced by LDL was negated by TMP only at 150 mg·L^{-1}. TMP also caused a reduction in MDA content and an increase of epoprostenol level in normal endothelial cells. This study suggests that TMP protects endothelial cells against damages elicited by LDL

Received 1993-09-13 Accepted 1994-05-04
[1] Project supported by the National Natural Science Foundation of China, № 3880737.
[2] Correspondence to Prof YAN You-Fang.