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A Bayesian graphic method for predicting individual phenytoin dosage schedule

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ABSTRACT A simple and practical graphic method based on Bayesian feedback theory for predicting individual phenytoin dosage was evaluated. Compared with the mathematical calculation, the graphic method only needs one pair of steady-state phenytoin concentration-dose data to predict individual phenytoin dosage. The observed drug levels were compared with predicted ones in 12 epileptic out-patients with a correlation coefficient of 0.94. The mean error between the observed and predicted phenytoin levels was 0.62 mg · L^{-1}. The mean kinetic parameters V_m and K_m obtained from the graph were 7.01 ± SD 0.88 mg · kg^{-1} · d^{-1} and 4.93 ± 0.91 mg · L^{-1}, respectively.

KEY WORDS forecasting; phenytoin; drug administration schedule; pharmacokinetics

Phenytoin is still considered as the drug of choice in controlling and treating epilepsy. Patients need taking the drug for a long period. Because of its narrow therapeutic index and nonlinear kinetics, it is both difficult and important to adjust phenytoin dosage regulation[1]. Presently, the most commonly used method to individualize phenytoin dosage is the mathematical calculation based on Michaelis-Menten equation[2]. But, this method requires two drug-dosage pairs and a relatively long period. So, it is not convenient both to patients and clinical rapid dosage adjustments

Sheiner *et al*[3] have presented the NONMEM (Nonlinear Mixed Effects Model) approach as a method for estimating population pharmacokinetic parameters. Vozeh *et al*[4] subsequently introduced a graphic method based on the Bayesian feedback theory for predicting individual phenytoin dosage, which only need one drug level-dosage pair. We have used the Bayesian graphic method to evaluate the validity of the method in achieving target serum phenytoin concentration in 12 epilepitic out-patients.

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MATERIALS AND METHODS

Subjects The 12 epileptic out-patients in our hospital were involved, including 6 males and 6 females. Their ages ranged from 15 to 62 yr (30 ± SD 13) and body weights from 50 to 78 kg (61 ± SD 9). The patients took original phenytoin sodium tablets according to the physician's prescription. Their hepatic and renal functions were in normal conditions.

Administration and determination of drug The original steady-state serum phenytoin concentration (C_{ss}) was monitored after patient took the drug for at least 3 wk. Then, an individual phenytoin dosage to reach a desired phenytoin level C_{ss} (pred), which was different at different individual situation, was predicted by using Bayesian graphic method. After another 3 or more than 3 wk, a second steady-state serum concentration C_{ss} (obs) was determined to evalute the validity of the graphic method.

Serum phenytoin concentrations were analyzed by fluorescence polarization immunoassay technique, which was performed with a TDx system (Abbott Laboratories Diagnostic Division, North Chicago IL, USA). The average intra-assay coefficient of variation was 4.01%, with a sensitivity of 0.5 mg · L^{-1}. The analytical recovery of phenytoin from serum averaged 101%. Drug

metabolites and commonly co-administered drugs did not affect the assay results[5].

Bayesian graphic method Vozeh *et al*[4] showed that the average values of the phenytoin Michaelis-Menten parameters and their variability within the population could form the basis of a Bayesian feedback method implemented as a graphic device (Fig 1). The shape of the contours is determined by the joint probability distribution (i.e. 0.5, 0.25 ... etc in the contours) for V_m and K_m within the population. When one C_{ss}-dosage pair is known, a line is drawn connecting the daily dose (6.8 mg · kg^{-1} · d^{-1}) to the measured C_{ss} (7.0 mg · L^{-1}) and extrapolated upwards to cross the contours. The coordinate of the line (A-B) crossing the innermost contour is the most probable value for V_m and K_m in the patient. A revised maintenance dose is determined by drawing a new line from point D to the desired C_{ss} (pred) (15 mg · L^{-1}) and reading off the point of intersection on the dose axis (8 mg · kg^{-1} · d^{-1}).

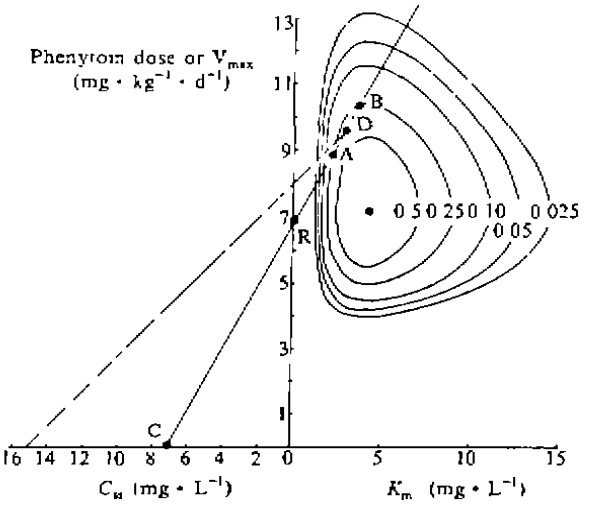

Fig 1. Graphic method based on the Bayesian feedback method to predict individual phenytoin dosage. A line is drawn connecting the daily dose of phenytoin (point R, 6.8 mg · kg^{-1} · d^{-1}) to the measured steady-state concentration (point C, 7.0 mg · L^{-1}) and extrapolated upwards so that it crosses the contours. The coordinate of the mid-point (D) of the line (A-B) crossing the innermost contour is the most probable value for V_m and K_m in a patient. A revised maintenance dose is determined by drawing a new line from this contour coordinate to the desired steady-state concentration (15 mg · L^{-1}) and reading off the intersection on the DOSE (or V_m) axis (8 mg · kg^{-1} · d^{-1}).

Evaluation of the method Validity (the ability of the method to attain a desired concentration) was assessed by determining the mean error between the predicted and observed serum phenytoin concentrations. The precision of the method was also evaluated by plotting the predicted drug levels against the observed ones. The slope, y-intercept and correlation were determined by least-squares linear regression.

RESULTS

Fourteen phenytoin C_{ss}-dosage pairs from 12 epileptic out-patients were involved in the study. The individual phenytoin kinetic parameters V_m and K_m were evaluted from the Bayesian graphic method. Then, a new individual phenytoin dosage compatible with the desired target level was predicted again from the graph. The predicted phenytoin levels were compared with the observed one by plotting the two levels. The mean error was assessed as the observed drug level minus the predicted one. The results were presented in Fig 2 and Tab 1.

Fig 2 was a plot of the predicted and observed serum phenytoin C_{ss}. The correlation equation by regression analysis was: C_{ss} (obs) = 0.93 C_{ss} (pred) + 1.51. The Bayesian graphic method resulted in a high correlation coefficient (r = 0.94) between the observed and predicted C_{ss} ($P<0.01$). The mean error from 14 phenytoin C_{ss} was 0.62 ± 1.48 mg · L^{-1}, indicating that the Bayesian graphic method is valuable in predicting phenytoin serum levels. The most probable mean kinetic parameters V_m and K_m values from graphic method were 7.01 ± 0.88 mg · kg^{-1} · d^{-1} and 4.93 ± 0.91 mg · L^{-1}.

Tab 1. Phenytoin individual kinetic parameters and predicted results in 12 epileptic patients.

No.	Sex	Age, yr	Weight, kg	Dose, mg · kg^{-1} · d^{-1}	C_{ss}, mg · L^{-1}	V_m, mg · kg^{-1} · d^{-1}	K_m, mg · L^{-1}	Dose(pred), mg · kg^{-1} · d^{-1}	C_{ss}(pred), mg · L^{-1}	C_{ss}(obs), mg · L^{-1}	Error, mg · L^{-1}
1	F	15	50	6.0	39.1	6.7	4.9	5.0	13.8	15.3	1.5
				5.0	15.3	6.6	5.0	5.5	21.2	20.8	−0.4
2	M	62	60	7.1	19.2	8.5	4.2	6.7	14.0	16.7	2.7
3	F	27	76	4.0	5.9	7.4	4.6	5.3	10.8	9.5	−1.3
4	M	24	55	5.5	21.8	6.7	5.0	4.6	10.4	12.8	2.4
5	M	28	65	3.1	2.8	7.5	4.4	5.0	6.4	7.5	1.1
6	F	22	50	6.0	26.2	7.0	4.8	5.5	16.8	15.6	−1.2
7	F	18	57	5.3	9.2	7 6	4.2	6.1	16.4	16.2	−0.2
8	F	35	63	4.8	4.9	8.3	3.6	6.3	11.4	11.3	−0.1
9	F	32	58	1.7	2.8	6.0	7.4	3.9	12.2	15.8	3.6
				3.9	15.8	5.3	5.9	2.6	11.3	10.7	−0.6
10	M	44	78	3.9	8.0	6.4	5.4	5.1	20.2	20.6	0.4
11	M	19	60	6.7	28.1	7.7	4.4	5.0	8.0	8.0	0.0
12	M	36	65	4.6	12.3	6.5	5.2	5.0	16.4	17.2	0.8
$\bar{x}$		30	61			7.01	4.93				0.62
SD		13	9			0.88	0.91				1.48

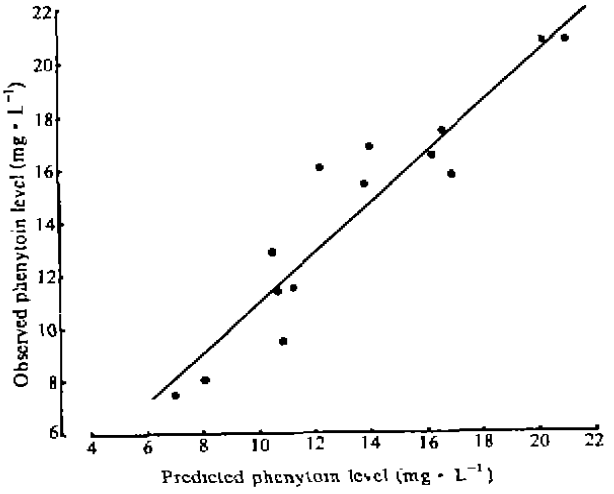

Fig 2. A comparison between the predicted and observed phenytoin levels in 12 epileptic patients

respectively. The values were similar to those predicteed by NONMEM's program (mean $V_m = 7.22 \pm 1.72$ mg · kg^{-1} · d^{-1} and mean $K_m = 4.44 \pm 2.4$ mg · L^{-1})[6]. For example, a female patient (Tab 1, No 1), aged 15 yr, originally took phenytoin sodium 250 mg · d^{-1}. The serum phenytoin level was 15.3 mg · L^{-1}. A new high dosage was needed because of incomplete seizure control. We recommended a dose of 275 mg · d^{-1} and predicted the new C_{ss} to be 21.2 mg · L^{-1}. The actual phenytoin level observed after 3 wk was 20.8 mg · L^{-1}. The patient's seizure was well controlled.

DISCUSSION

Sheiner *et al*[7] presented a general approch to predict individual pharmacokinetic parameters from population kinetic parameters and later developed a appropriate NONMEM computer software and other similar programs. These programs had some successful applications in predicting phenytoin individual kinetic parameters[8–10]. But, these methods require relatively sophisticated programs and expensive computers. So, it is difficult for them to be used in clinical situation.

The introduction of the Bayesian graphic technique is really a graphic application of the Bayesian feedback prediction based on phenytoin population pharmacokinetics.

Because the Bayesian feedback prediction uses both the individual information (C_{ss}) and phenytoin population clearance (V_m and K_m), it predicts better than do other methods that use less population information. But up to now, there were little clinical uses for the graphic method. We here reported the application of the graphic method in 12 epileptic out-patients. The correlation between the predicted and observed phenytoin serum levels was sufficiently good, and mean error was relatively small.

Theoretically, the target serum phenytoin concentration compartible with individual phenytoin adjusted dosage should be within the therapeutic range of serum level (10-20 mg · L^{-1}). But in practice, we sometimes chose the lower and higher C_{ss} because of drug toxicity or incomplete seizure control. Two patients required an additional adjustment in phenytoin dosage for the same reasons.

It was reported that the Bayesian graphic method will give some wrong information if phenytoin binding to plasma protein or metabolism is altered by factors such as pregnancy, race, malnutrition, uraemia, or co-administration of other drugs[6]. The larger error observed in patient 9 may partially resulted from the co-administration of other antiepileptic drugs. Therefore, it is necessary to consider such factors when one uses the Bayesian graphic method to avoid incorrect prediction of serum level obtained at individual phenytoin dosage. Furthermore, we believe it necessary to collect more Chinese population kinetic parameters (V_m and K_m) and form a new Bayesian graph, which is more suitable to Chinese population.

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Bayesian 图解法预测苯妥英钠个体化给药方案

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提要 本文应用基于 Bayesian 反馈理论的图解法预测临床苯妥英钠个体化给药方案，只需一点稳态苯妥英血清浓度数据即可得出病人的药物动力学参数值. 12 例癫痫病人应用本法得平均动力学参数 $V_m = 7.01 \pm SD\ 0.88$ mg · kg^{-1} · d^{-1}, $K_m = 4.93 \pm 0.91$ mg · L^{-1}. 病人预测血清浓度与实测浓度之间总体相关系数 $r = 0.94$ ($n = 14$, $P < 0.01$)，平均误差为 0.62 mg · L^{-1}，预测精度较好.

关键词 预测；苯妥英；用药计划表；药物动力学