

## Bayesian Feedback Method for Optimum Phenytoin Dosing<sup>1</sup>

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= Abstract = The accuracy of Bayesian feedback method for predicting phenytoin dosage was assessed and compared to conventional predictive methods such as the Richens & Dunlop method and Ludden method from 57 patients who took phenytoin for the treatment of grandmal epilepsy. For the comparison of absolute predictability of each method, correlation coefficient between predicted and actual dosage, mean error (ME) and root mean squared error (RMSE) were calculated. For a single data pair, the Bayesian method showed a higher correlation coefficient (0.915) and less ME & RMSE values (-2.0% & 8.8%) than the Richens & Dunlop method, and there was a statistically significant difference between these two methods ( $p < 0.05$ ). For multiple data pairs, the Bayesian method also showed a higher correlation coefficient (0.93) and less ME & RMSE values (0.69% & 7.2%), though there was no significant difference. It is suggested that the Bayesian method has better predictability and can be used conveniently even with single Cpss-dose data pair for optimum phenytoin dosage prediction.

Key words: **Phenytoin, Dosage prediction, Bayesian method, Ludden method, Richens & Dunlop method**

### INTRODUCTION

Phenytoin has been used in the treatment of seizure disorders for several decades. The therapeutic and toxic effects of phenytoin have been reported to correlate well with its serum concentration (Buchthal *et al.* 1960; Kutt *et al.* 1964). The therapeutic range of serum concentrations is usually recognized to be approximately 10 to 20  $\mu\text{g/ml}$  (Lund 1974), though some patients may require lower or higher concentrations. However, its pharmacology and pharmacokinetics make the determination of an appropriate maintenance dose difficult because phenytoin is eliminated by metabolic processes, which exhibit

Michaelis-Menten kinetic characteristics (Arnold and Gerber 1970; Perucca *et al.* 1978). The clinical implication of Michaelis-Menten kinetics is that there is a nonlinear relationship, and nonproportional changes, between maintenance dose levels and steady-state phenytoin concentrations (Garrettson and Jusko 1975).

For prediction of optimum maintenance dose, several methods have been proposed, which use steady-state concentration data (Richens and Dunlop 1975; Ludden *et al.* 1977; Mullen 1978). Recently, Vozeh and Coworkers (1981) have described a method using Bayesian forecasting to adjust phenytoin dosing. The Bayesian method uses the conditional probability of obtaining the measured concentrations or dosing rates, given a set of parameter values and the independent probability of the parameter themselves, to obtain the most likely set of parameters for the individual patient (Sheiner and

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Beal 1982).

Since the Bayesian method relies upon previous estimates of population parameter distributions, it might be necessary to obtain population values for different groups of patients, such as different age groups. Thus, the purpose of this study was to evaluate the Bayesian method which incorporated population pharmacokinetic parameters described by vozeh *et al.* (1981) before clinical application of this method to our therapeutic drug monitoring system in Seoul National University Hospital and to compare its predictive power with conventional dose predicting methods. Conventional methods included the Richens & Dunlop (1975) and Ludden methods (1977), the former method using one set of steady-state phenytoin concentration with fixed parameter of  $K_m$  to  $4.0 \mu\text{g/ml}$  for optimum dose prediction and the latter method requiring more than two sets of  $C_{\text{pss}}$ -dose pairs under two different steady-state conditions. The Richens & Dunlop method is compared to a one-point Bayesian method which use only one set of  $C_{\text{pss}}$ -dose pairs for the prediction of phenytoin dose, and the Ludden method is compared to two-point Bayesian method.

### MATERIALS AND METHODS

Fifty-seven patients with grandmal epilepsy on the basis of clinical diagnosis and EEG patterns were selected for this study in the outpatient clinic of neurology, Seoul National University Hospital. Patients who had not previously been treated were preferred for this study, however, patients who had been treated with phenytoin were also included. The following patients were excluded in our study; a) pregnant women b) patients with rapid progressing hepatic and/or renal dysfunction c) patients receiving drugs which may interact with phenytoin (ethanol, disulfiram, chloramphenicol, salicylate, benzodiazepines, carbamazepine, phenobaribital, valproate, isoniazid, phenothiazines, phenylbutazone, sulfonamide, methylphenidate). The average age and weight of subjects were 26.91 yr (range; 11 to 66 yr) and 55.4 kg (range 14.0 to 74.0 kg), respectively. Thirty-one patients were male.

Initial daily dose of 3 to 4 mg/kg/day of phenytoin, 30 to 50 mg Tablet produced by pharmacy Department of SNUH, was recommended for

the patients who had not been previously treated. Phenytoin was administered as a single daily dose in 22 patients. For the other patients, dosage was twice daily. The method of administration in an individual patient was fixed until steady-state plasma samples were drawn. At least two weeks were allowed between changes in dose and subsequent reestimation of the serum level in order that equilibrium with respect to the drug could be reached.

Serum levels of phenytoin were determined by the fluorescence polarizing immunoassay method (TDx: Abott Co.), and the coefficient of variance of this method in the range of 7.5 to  $30 \mu\text{g/ml}$  was below 5 percent.

The reliability of patient compliance of drug intake and steady-state phenytoin levels was evaluated by an extensive patient interview regarding compliance with the prescribed dosage regimen; by the variation in phenytoin serum levels during a period in which no change in the prescribed dosage regimen; by comparing the results of the phenytoin assay by TDx.

Three methods were used to estimate optimum phenytoin dosage.

Method 1. The following equation is the mathematical expression for the nomogram published by Richens & Dunlop (1975), where  $k_m$  was set equal to  $4 \mu\text{g/ml}$ .

Dose (predicted)

$$= \frac{C_{\text{pss}}(\text{desired})[k_m + C_{\text{pss}}(\text{observed})]}{C_{\text{pss}}(\text{observed})[k_m + C_{\text{pss}}(\text{desired})]} \times \text{Dose}(\text{observed})$$

this method uses a single observed  $C_{\text{pss}}$ -dose pair. From this method, 57 single-point predictions were made in our study.

Method 2: When two or more  $C_{\text{pss}}$ -dose pairs are available, the method of Ludden and Coworkers may be used (Ludden *et al.* 1977). This method uses essentially no population parameters, and estimates the values of  $V_{\text{max}}$  and  $k_m$  directly from the two data points as shown in the following equations.

$$\text{Dose 1} = -k_m \frac{\text{Dose 1}}{C_{\text{pss 1}}} + V_{\text{max}}$$

$$\text{Dose 2} = -k_m \frac{\text{Dose 2}}{C_{\text{pss 2}}} + V_{\text{max}}$$

From the estimated parameters, one can predict a new maintenance dose. In our study, 28 predictions were made by this method. However, in 6 cases of 34 subjects reasonable parameters could not be obtained by Ludden method because the calculated parameter  $km$  resulted in a negative value:

Method 3: The Bayesian method of Vozech *et al.* (1981) minimizes the following objective function;

$$OBJ = \frac{(V_{max} - \hat{V}_{max})^2}{\sigma_{V_{max}}^2} + \frac{(km - \hat{km})^2}{\sigma_{km}^2} + \sum_{i=1}^n \frac{(Dose_i - \hat{Dose}_i)^2}{\sigma_D^2}$$

where,  $V_{max}$  and  $km$  are the population mean values (6.642 mg/kg/day and 4.44  $\mu$ g/ml, respectively),  $\hat{V}_{max}$  and  $\hat{km}$  are the individual parameter estimates with respect to which the above objective function is to be minimized:  $\hat{Dose}_i$  is the predictive dosage for  $i$ th observed Cpss-dose pair:  $Dose_i$  is the actual dosage associated with the  $i$ th of the pairs;  $\sigma_{V_{max}}$  and  $\sigma_{km}$  are the interindividual standard deviation of  $V_{max}$  and  $km$  (1.72 and 2.4), respectively; and  $\sigma_D$  is the standard deviation of the combined intraindividual and model misspecification residual error (0.25). New dose prediction for the appropriate steady-state phenytoin concentration is performed by the approximation of the parameter estimates at convergence with a personal computer. This method can be used for obtaining most probable pharmacokinetic parameter without restriction of the member of Cpss-dose pairs, even with only one Cpss-dose pair. Fifty-seven optimum dose predictions were made from initial one Cpss-dose pair, and 34 dose predictions from multiple data pairs by this method.

The precision of various methods were evaluated by correlating predicted phenytoin dosages against actual dosage for all three methods. The correlation coefficient between predicted and actual dosage was determined by least-squares linear regression. For more precise comparison, we assessed absolute predictability of the three dosing methods by measures of bias and precision, ie, mean error (ME) and root mean squared error (RMSE), respectively. ME and RMSE expressed as a percentage of the actual dose:

$$ME = \frac{1}{N} \sum_{i=1}^n \frac{Predicted\ dose - Actual\ dose}{Actual\ dose} \times 100\%$$

$$RMSE = \frac{1}{N} \sum_{i=1}^n \sqrt{\left( \frac{Predicted\ dose - Actual\ dose}{Actual\ dose} \right)^2 \times 100\%}$$

Statistical difference between Richens & Dunlop method and one-point Bayesian method and between Ludden and two-point Bayesian method was tested by paired t-test.

The percentage of predictions that yielded errors > 100% were also calculated to compare the performances of each method and were expressed as a percentage of the total predictions for that method.

## RESULTS

Figures 1 to 4 show the scatter plots for the predicted dosages against actual dosages for each method.

One-point Bayesian method (Fig. 3) showed higher correlation coefficient ( $r=0.915$ ) than Richens & Dunlop method ( $r=0.893$ ) when the method used a single set of Cpss-dose pair for the dosage predictions compared. Likewise, the two-point Bayesian method also showed higher correlation ( $r=0.93$ ) than the Ludden method ( $r=0.873$ ) for multiple data pairs. In general, linear regression curves of Bayesian methods were close to unity and are compared to the curves of conventional methods.

Table 1. Summarizes the percentage of predictions with error > 10% for each method. The two-point Bayesian method had the lowest percentage of underpredictions, 8.85, as well as the lowest percentage of total error > 10% in relative magnitude. The Richens & Dunlop method had the largest percentage of total error > 10%, 43.8%.

The one-point Bayesian method gave lower ME & RMSE values than the Richens & Dunlop method (Table 2), and there was a significant difference between these two methods ( $p < 0.05$ ) by paired t-test.

In addition the two-point Bayesian method gave a lower ME & RMSE values than the Ludden method, but there was no significant difference between these methods statistically ( $0.05 < p < 0.01$ ) by paired t-test for 28 cases.

Where, we excluded 6 case of 34 predictions in two-point Bayesian method for the statistical analysis because they were unmatched with the predictions by Ludden method.

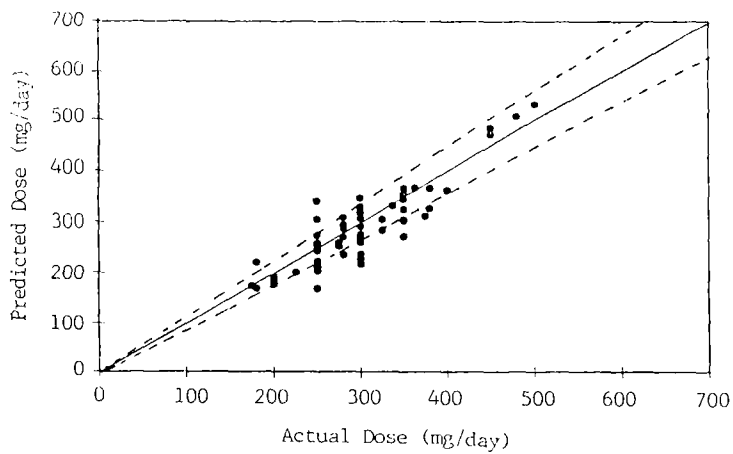


Fig. 1. Dosage predicted by Richens & Dunlop method vs. the actual dosage to achieve various plasma concentrations within therapeutic range ( $r = 0.893$ ). The solid line represents the line of the unity and the dashed line represent  $\pm 10\%$  deviation from the unity.

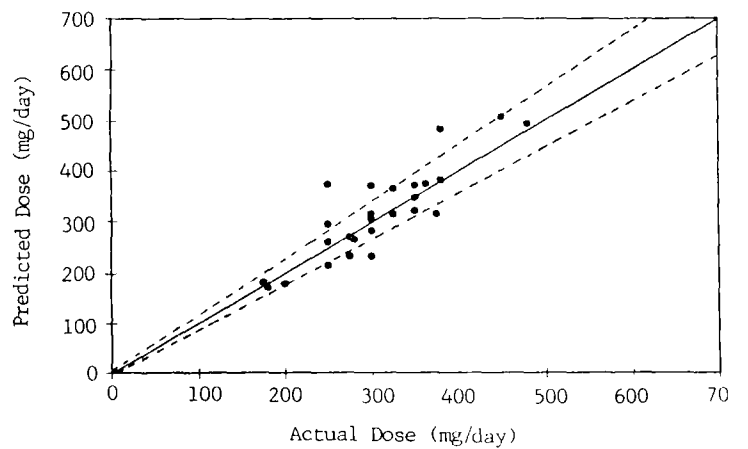


Fig. 2. Dosage predicted by Ludden method vs. the actual dosage to achieve various plasma concentrations within therapeutic range ( $r=0.873$ ). The solid line represents the line of the unity and the dashed lines represent  $\pm 10\%$  deviation from the unity.

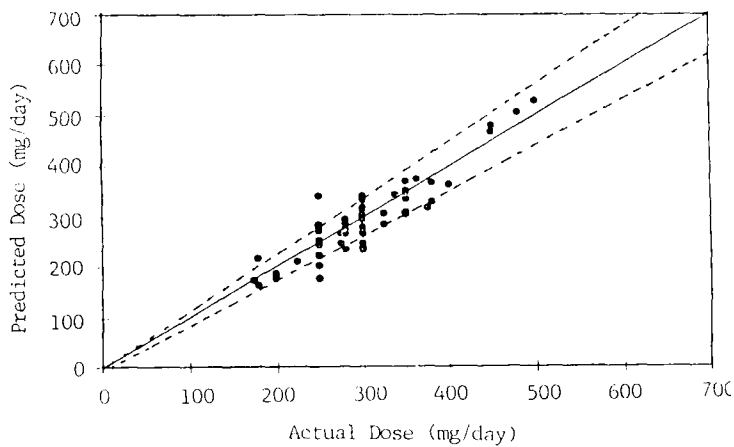


Fig. 3. Dosage predicted by one-point Bayesian method vs. the actual dosage to achieve various plasma concentrations within therapeutic range ( $r=0.915$ ). The solid line represents the line of the unity and the dashed lines represent  $\pm 10\%$  deviation from the unity.

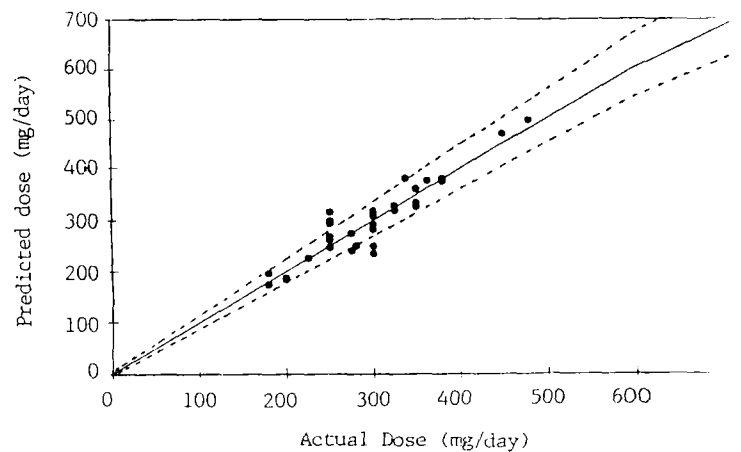


Fig. 4. Dosage predicted by two-point Bayesian method vs. the actual dosage to achieve various plasma concentrations within therapeutic range ( $r=0.930$ ). The solid line represents the line of the unity and the dashed lines represent  $\pm 10\%$  deviation from the unity.

Table 1. Percentage of predictions with error  $> 10\%$

	Richens & Dunlop (%)	Ludden (%)	One-point Bayesian (%)	Two-point Bayesian (%)
over-prediction	31.6	21.4	10.5	11.8
under-prediction	12.2	17.9	24.6	8.8
total	43.8	39.4	35.1	20.6
n	57	28*	57	34

\*Negative parameter (km) in 6 subjects

Table 2. Bias and precision of dosage prediction methods

	Rechens & Dunlop (%)	Ludden (%)	One-point Bayesian (%)	Two-point Bayesian (%)
ME	-3.21 ± 12.44	2.17 ± 14.29	-1.96 ± 11.49 <sup>a</sup>	0.69 ± 9.65
RMSE	10.02 ± 8.05	10.35 ± 10.59	8.77 ± 7.19 <sup>a</sup>	7.17 ± 6.59
n	57	28*	57	34

\*Six subjects were omitted due to negative values of calculated parameter km.

a: Statistically significant difference to Richens & Dunlop method (p < 0.05). Each values of this table indicate mean ± SD.

### DISCUSSION

Phenytoin is one of several drugs for which there is relatively poor correlation between dose and effect, but for which there is a good correlation between plasma level and clinical response (Buchthal *et al.* 1960; Lund 1974). The monitoring of phenytoin plasma levels has therefore become a useful tool for evaluating the efficacy of phenytoin dose regimens in individual patients (Koch-Weser 1975). However, optimum dose prediction of phenytoin is difficult even with monitoring of plasma drug level because this drug exhibits a nonlinear elimination process. Therefore a 10% or greater error in phenytoin dosage can produce a much larger error in the resulting steady-state concentration in certain individuals (Mawer *et al.* 1977). A 10% error in dosing rate is not as significant in most drugs. Thus, there has been considerable interest in the accurate prediction of phenytoin dosing rates to achieve therapeutic, nontoxic concentrations. Numerous investigators have reported various degrees of success from several dosing methods (Schumacker 1980; Murphy *et al.* 1981; Robinson *et al.* 1981).

Regardless of which dosing technique is used, however, some individuals may receive an inappropriate regimen and subtherapeutic or toxic steady-state phenytoin levels may be noted occasionally after changing dose regimen. Thus, it is always important to monitor phenytoin concentrations and clinical status at appropriate interval after alteration of phenytoin regimen. It is acknowledged, however, that all these predictive techniques provide generally good guidance when dosage adjustment is necessary.

Since introduction of Bayesian theorem in dosage prediction by Sheiner and Coworkers (1979), this principle has been applied to optimum dose

prediction for various drugs (Burton *et al.* 1975; Vozeh *et al.* 1975). Vozeh *et al.* (1981) described a Bayesian population parameter distribution of phenytoin, which can be used with Bayesian theorem for optimum phenytoin dose prediction.

In the current study, we incorporated Vozeh's phenytoin population parameter for Bayesian prediction. The Bayesian method showed better predictability than conventional dosage prediction methods on the basis of both percentage of significant over- and under-prediction (> ± 10%), bias and precision. For estimation using single data pair, there was a significant difference between one-point Bayesian and Richens & Dunlop method (Table 1 & 2). One-point Bayesian method also showed similar or slightly better results than Ludden method which used two set of data pairs.

For estimations using two data pairs, the two-point Bayesian method showed a lower percentage of predictions with error > over 10% and less ME and RMSE values than the Ludden method, though there was no significant difference between these methods. However, it should be emphasized that Ludden method could not be applied in 18% of cases in our study.

From the current results, it is suggested that the Bayesian method is superior to the conventional method in dosage prediction with the same number of Cpss-dose pairs. Above all, the Bayesian method conveniently provides a single method applicable to the use of either single or multiple data pairs because it combines individual and population data in a statistically optimum manner.

Clinically, it is important to rapidly and accurately predict the optimum phenytoin maintenance dosage within 2 weeks. The Bayesian

method may offer greater accuracy in predicting the optimum dosage regimen which will achieve therapeutic steady-state plasma level, as early as possible.

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= 국문초록 =

## Phenytoin 용량적정화를 위한 Bayesian Feedback법

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Phenytoin 적정용량 예측을 위한 Bayesian Feedback법의 정확도 및 예측능을 기존의 용량예측법인 Richens & Dunlop법 및 Ludden법과 비교하고자 하였다. 각 방법의 절대예측능을 비교하기 위해 대발작 치료를 위해 phenytoin을 복용하는 남녀 57명의 환자로 부터 예측용량과 실제 용량 사이의 상관계수, 평균오차(mean error: ME) 및 자승근 평균오차(root mean squared error: RMSE)를 각각 측정하였다.

한개의 steady-state혈장농도(Cpss)-용량(dose)데이터를 이용하는 방법에 있어서 Bayesian법이 Richens & Dunlop법에 비해 높은 상관관계( $r=0.915$ )를 보였다. 또한 Bayesian법의 ME 및 RMSE는 각각  $-2.05$  및  $8.8\%$ 로 Richens & Dunlop법에 비해 적었으며 통계적으로 유의한 차를 보였다( $P < 0.05$ ). 두개의 Cpss-dose 데이터를 이용한 경우 더높은 상관관계 ( $r=0.93$ )를 보였고 ME 및 RMSE치도  $0.69\%$  및  $7.2\%$ 로 Ludden법에 비해 적은 것으로 나타났으나 두 방법간에 통계적으로 유의한 차이는 없었다( $0.05 < p < 0.01$ ).

이상의 연구결과에서 Bayesian법이 기존의 phenytoin용량예측법에 비해 예측능이 더 뛰어난 것을 알 수 있으며 또한 이 방법은 한개의 Cpss-dose데이터 만으로도 적정 phenytoin용량을 예측할 수 있다는 점에서 임상적으로 유용하게 이용될 수 있을것으로 기대된다.