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# Pharmacokinetic Approaches for the Optimum Phenytoin Administration†

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= Abstract =A rapid and reliable approach in achieving an optimum individual phenytoin dosage regimen using appropriate population pharmacokinetic parameters was described. A simple graphic technique to obtain an accurate individualization of dosage regimen was also suggested.

Steady state serum phenytoin concentrations were measured in 41 patients at 3 or 4 maintenance dose levels. A rapid technique for individualization of dosage adjustment was constructed using *in vivo* $V_{max}$ and Km values based on Michaelis-Menten kinetics. Its reliability was evaluated by comparison with other reported techniques.

At dosage adjusted by the technique using steady state serum phenytoin concentration with initial maintenance dose and population $V_{max}$ based on body weight, there was highly significant correlation between observed and predicted serum concentrations($r=0.66$, $p<0.005$).

The results suggested that population $V_{max}$ based on age could be utilized in a rapid technique for optimum phenytoin dosage adjustment and that the efficiency of the adjustment will be further improved by application of the direct-linear plot technique.

Key Words: ***Phenytoin, Pharmacokinetic, Dosage adjustment, Michaelis-Menten kinetic, Direct-linear plot***

## INTRODUCTION

Phenytoin synthesized by Biltz in 1908 was first introduced by Merrit and Putnam(1938) as an anticonvulsant and has been used for management of various convulsive disorders other than petit mal seizure. Because of phenytoin's narrow therapeutic ratio, however, small changes in its dose could produce toxicity. This has been a serious difficulty in the use of empirical dosage regimen of phenytoin therapy.

Since the determination of phenytoin concentration from biological fluids was developed by Plaa and Hine (1956) and Dill et al. (1956), numerous studies have observed its concentration in blood with regard to clinical efficacy, changes in electroencephalogram pattern and incidence of toxic side effects such as nystagmus or ataxia (Loeser 1961: Kutt et al. 1964: 1966: Richens and Dunlop 1975: Reynolds et al. 1976: Myung 1981). In those studies, the proportional relationship between plasma phenytoin concentration and both clinical efficacy and incidence of toxic side effects has been shown. It has been also demonstrated that optimum therapeutic concentration of this drug was 10-20 $\mu$g/ml and that at greater than 20 $\mu$g /ml concentrations, toxic effects usually occur. Even though therapeutic and toxic plasma concentrations of phenytoin are reasonably well defined, it is still difficult to achieve the optimum therapeutic concentrations with simple empirical dosage regimen. This is due to a wide variation in steady state plasma phenytoin concentration among the individuals taking the same dose (Richens 1975). This is believed to be attributable to its characteristic pharmacokinetic behavior. The plasma concentration of this drug is known to depend mainly on

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hepatic metabolism rather than renal elimination. It has been reported that 60-70% of phenytoin adminstered is hydroxylated and elminated as glucuronide form, whereas only 1-5% is excreted in unchanged form in urine(Butler 1957; Noach et al. 1958). In the hepatic metabolism, its kinetics has been shown to follow not the first order process generally observed with most of drugs but the Michaelis-Menten process which depends on $V_{max}$, Km and concentration of phenytoin (Richens and Dunlop 1975: Arnold et al. 1970). Accordingly, the rate of metabolism fails to change in proportion to its plasma concentrations, and this kinetic characteristics can be expected to lead to non-linear relationship between dose and the resulting plasma concentration.

Based upon the pharmacokinetic characteristics of phenytoin, Richen and Dunlop(1975) proposed a nomogram for dose adjustment as a way of achieving the desirable therapeutic concentration with only one single steady state concentration. They assumed in their nomogram that the values of Km were constant in individuals. But large variation in the Michaelis-Menten parameter was reported (Ludden et al. 1977; Gibaldi 1984). Ludden et al.(1977) and Mullen(1978) developed a modified method using individual parameters that were estimated by means of a common linear-transformation of the Michaelis-Menten equation with two pairs of dose and steady state concentrations. Although this method can give a more accurate dosage adjustment, from a practical standpoint, it was found to have limitation in clincal use because the procedure takes more than 4 weeks.

The present study attempts to establish a more reliable and rapid method for dosage adjustment from single steady state serum concentation and population parameters of Michaelis-Menten kinetics and also trys to construct a practical and simple graphic approach for clinical mangement of epileptics.

## PATIENTS AND METHODS

**1. Patients and Drug administration**: Fourty-one patients diagnosed as having idiopathic grand mal seizure by clinical and EEG analysis at the Department of Neurology, Seoul National University Hospital were selected in this study. They had been treated with phenytoin either alone or concurrent with other medication having no interaction with phenytoin. Those who received the medication showing the interaction with phenytoin were excluded(Willer and Boundi 1981). In all cases any concurrent medication was held constant. The patients were between 6 to 46 years of age, weighed from 15 to 73 kg and did not show any particular abnormal finding in blood biochemistry and urinalysis.

All phenytoin tablets used were prepared uniformly at Seoul National University Hospital Pharmacy to ensure uniform bioavailability. The initial dose was from 3 to 4 mg/kg and there after the dose was increased. The drug was administered at 9:00 P.M. and at least 2 weeks were allowed between change in dose. Blood for measurement of steady state serum phenytoin concentrations were drawn at 1:00 P.M.

In 31 cases, three steady state serum phenytoin concentrations were measured at 3 different dose level and in 10 cases, 4 different dose levels. The third dose was adjusted by Michaelis Menten equation.

**2. Determination of serum phenytoin concentration**:The serum was separated by centrifugation at 3,000 rpm from each blood specimen drawn at steady state at each particular dose level. Phenytoin concentrations were determined with Syva phenytoin EMIT kit according to Booker and Dracey(1975) method.

**3. Data analysis**: *In vivo* individual $V_{max}$ and Km for phenytoin were calculated by iterative least square computer technique from phenytoin dose-steady state concentration relationship derived by 3 or 4 different steady state serum phenytoin concentration, applying Michaelis-Menten kinetic($Ro=\frac{V_{max}\cdot C_{pss}}{K_m+C_{pss}}$), where Ro is rate of administration and Cpss is steady state serum phenytoin concentration(Mawer et al. 1974).

Differences of $V_{max}$ and Km between each age group were tested by analysis of variance. The predictability of the linear transformation methods (Woolf-Augustinson-Hofstee plot, Direct-linear plot) of Michaelis-Menten equation in phenytoin therapy was analyzed by comparison of the calculated serum phenytoin concentration from estimated *in vivo* $V_{max}$ and Km in this study with determined serum phenytoin concentration.

## RESULTS

**1. Relationship between phenytoin dosage regimen and steady state serum concentration**: There was a wide individual variation in steady state serum phenytoin concentrations with daily dose based on body weight in the 41 patients(Fig.

1). Patients receiving the empirical usual daily dose of 5 mg/kg, had a steady state serum concentrations ranging from 4 μg/ml to 30 μg/ml.

The realtionship between daily dose of phenytoin and resulting steady state serum concentration in 5 representative patients showed good fit to the Michaelis-Menten equation(Fig. 2). In these cases, the individual daily doses varied by as much as twice in order to achieve the therapeutic steady state serum concentration of 10-20 μg/ml.

**2. Reliability of dosage regimen by Michaelis Menten kinetics:** A non-linear relationship between steady state serum concentration and daily maintenance dose was observed in almost all cases. In all 41 cases, individual *in vivo* $V_{max}$ and Km were calculated from steady state serum concentrations at first 2 dose levels by Michaelis-Menten equation. The reliability of phenytoin dosage regimen by Michaelis-Menten kinetics was tested by analyzing a difference between predicted concentration which was derived from calculated individual *in vivo* kinetic parameters and determined concentration.

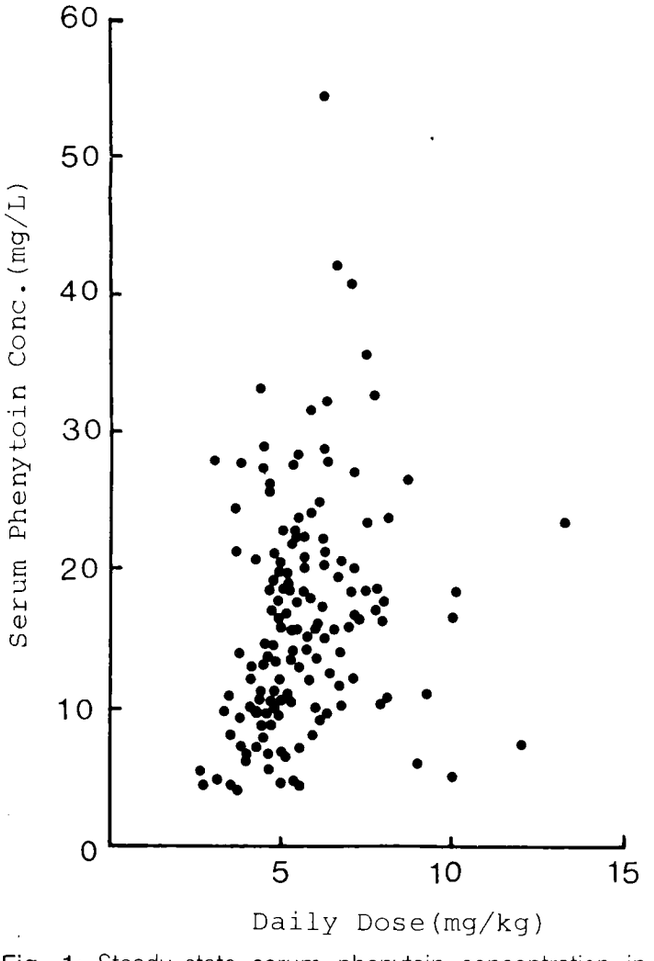


Fig. 1: Steady-state serum phenytoin concentration in relation to its daily dose in 41 patients.

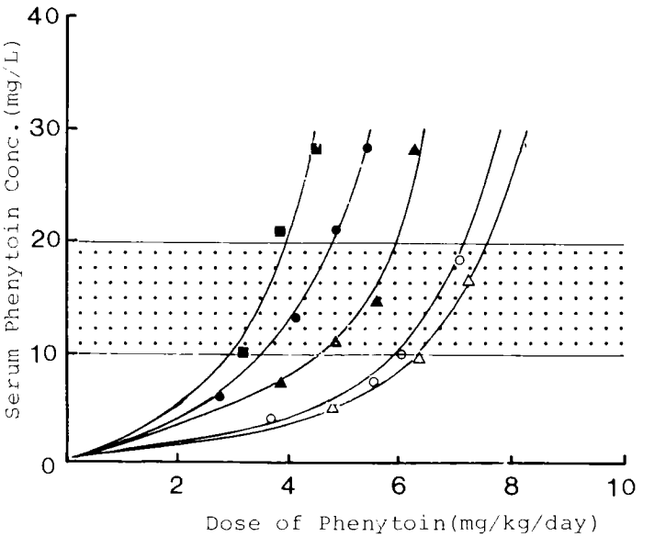


Fig. 2. Non-linear relationship between daily dose of phenytoin and resulting serum concentration in five patients on several different doses. The hatched area represents the therapeutic range of serum levels. The curves were fitted by computer using the Michaelis-Menten equation.

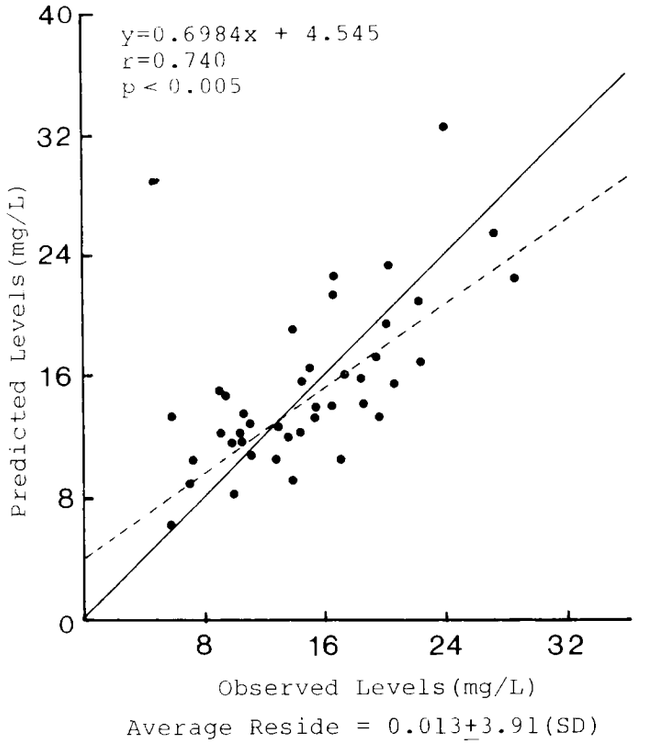


Fig. 3. Correlation of observed phenytoin serum levels with predicted levels estimated from individual Km and $V_{max}$ values derived from two steady state serum concentrations.

The observed serum concentration showed good correlation with predicted concentration($r=0.74$; $p<0.005$) and average error between those concentrations was $0.013\pm3.91$ $\mu$g/ml.

**3. Age differences of Phenytoin pharmacokinetic parameters:** Age distribution of *in vivo* $V_{max}$ and Km from the total of 41 cases calculated by iterative computer technique was shown in Table 1. Average *in vivo* value of Km in the 41 cases was $7.69\pm4.61$ mg/L. It ranged widely from 1.48 to 20.03 mg/L with no significant difference between age groups. But average *in vivo* value of $V_{max}$ based on body weight was $8.88\pm2.40$ mg/kg/day and range of $V_{max}$ was narrower than that of Km value. The $V_{max}$ value showed significant difference between age groups($p<0.005$); $V_{max}$ values of 25 adults were significantly lower than that of 5 children. The $V_{max}$ values based on body weight showed relatively good correlation with age($r=-0.592$; $p<0.005$)(Fig. 4).

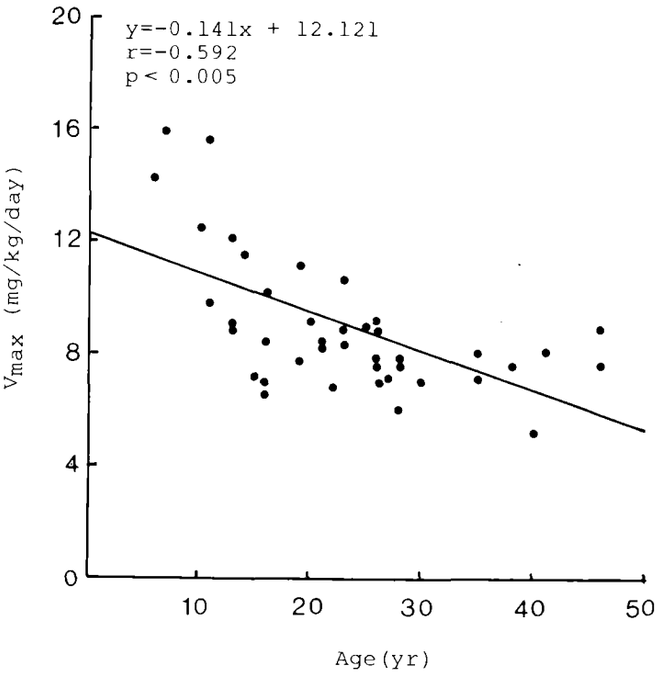


Fig. 4. Age distribution of in vivo $V_{max}$ of phenytoin. Each $V_{max}$ value was estimated from three or four steady-state serum concentrations by Michaelis--Menten equation on three or four different doses.

**4. The reliability of dosage adjustment using population $V_{max}$ and Single steady state serum phenytoin level:** Although dosage adjustment in phenytoin therapy using individual *in vivo* $V_{max}$ and Km derived from Michaelis-Menten equation showed high reliability, it required at least two steady state serum concentration at two different dose levels.

As an alternative to overcoming this disadvantage, the dosage adjustment with single steady state serum concentration was explored.

The individual Km value was estimated from steady state serum phenytoin concentration at first maintenance dose and corresponding population $V_{max}$ and then the second maintenance dose was adjusted based on these kinetic parameters.

The observed serum phenytoin concentration at this adjusted second maintenance dose was shown to be significantly correlated with predicted serum concentration in 39 out of total of 41 cases ($r=0.66$; $p<0.005$). The average difference between observed and predicted concentration was $1.77\pm8.95$ $\mu$g/ml(Fig. 5).

**5. The reliability of graphic technique for phenytoin dosage adjustment:** In search of a more reliable and simple technique of dosage adjustment by continuous serum phenytoin concentration monitoring, two graphic techniques such as W.A.H.-plot and direct linear plot base on Michaelis-Menten kinetics were examined. In 10 patients, 4 dose level serum phenytoin concentrations were obtained. The 4th maintenance dose was adjusted by means of iterative computer technique, W.A.H. plot and direct-linear plot with 3 dose level steady state serum concentrations. The

**Table 1.** Phenytoin pharmacokinetic summary (Mean±SD)

| Study Population | Km(mg/L) | $V_{max}$(mg/kg/day) |
|---|---|---|
| Total Patients | 7.69±4.61 | 8.88±2.40 |
| (Range) | (1.48~20.03) | (5.11~15.90) |
| 5 Children | 11.66±6.78 | 13.56±2.52 |
| 11 Adolescents | 8.47±4.69 | 9.01±1.96 |
| 25 Adults | 6.60±3.66 | 7.88±1.14 |
| Stat. Sign. | n.s. | $p<0.005$ |

ANOVA were performed for the statistical significance.

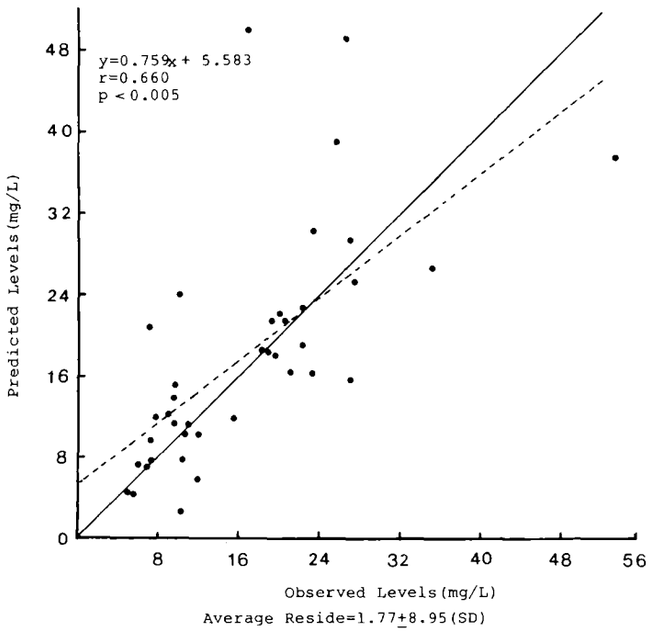


Fig. 5. Correlation of observed phenytoin serum concentrations with predicted levels estimated from single steady-state concentration and corresponding population $V_{max}$ by Michaelis-Menten equation.

variations between observed and predicted serum concentration were compared in each technique.

The graphic techniques showed a somewhat poorer correlation as compared with computer technique but there was no statistically significant difference in average resides of those thechniques (Fig. 6).

**6. Optimum phenytoin dosage adjustment by direct linear plot technique:** The two graphic techniques showed reliability comparable to the concentration were compared in each technique. ence in reliability between the two graphic techniques in this study. The direct-linear plot technique seems to be simpler and more practical in clincal phenytoin therapy. From the results of this report, rapid, reliable and simple dosage adjustment technique in phenytoin therapy was introduced as illustrated in Fig. 7. The dosage regimen(B) could be obtained by direct-liner plot of single steady state serum concentration and corresponding dose using temporary *in vivo* $V_{max}$ of each age from the population pharmacokinetic parameters of phenytoin. By direct-linear plotting of the steady state serum concentrations at adjusted dosage and initial dosage, more accurate individual *in vivo* Km and $V_{max}$ could be obtained and a more accurate optimum dosage adjustment would be available thereafter.

## DISCUSSION

It has been well known that phenytoin is one of several drugs for which there is a relatively poor correlation between dose and effect but for which there is a good correlation between the concentration of drug in serum and clinical response(Buchthal et al. 1960; Haerer and Grace 1963; Kutt et al. 1964). It is generally accepted that phenytoin

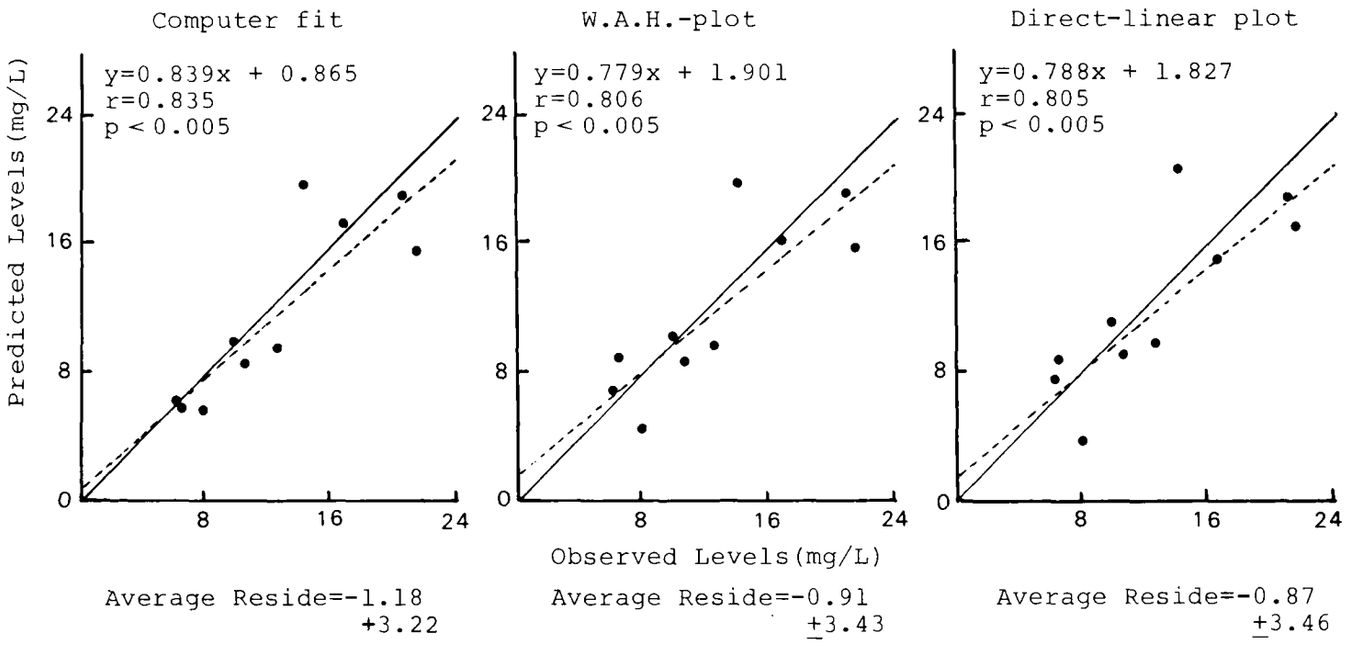


Fig. 6. The steady-state pheynytoin concentrations predicted by computer fit, direct-linear plot and W.A.H. plot techniques with serum concentration on 3 different doses compared with the actual observed concentration.

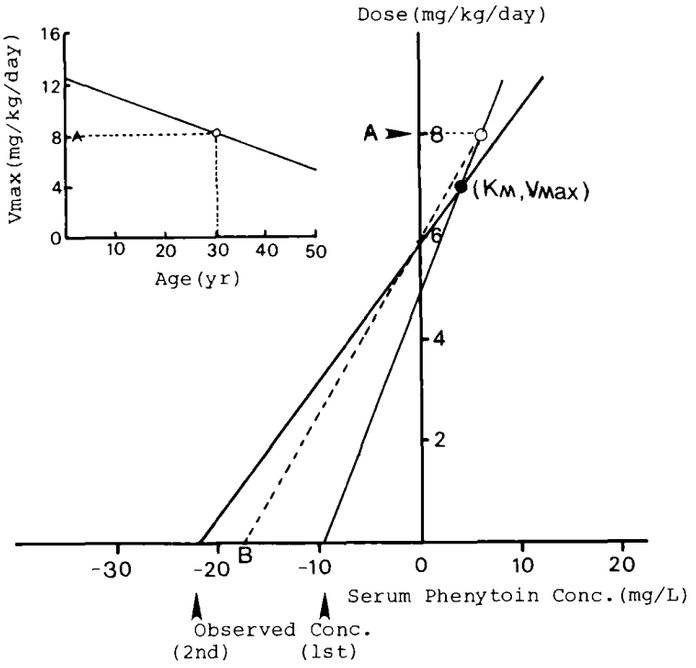


Fig. 7. The direct-linear plot for simple dosage adjustment in phenytion therapy. Single 1st steady-state phenytion serum concentration(1st conc.) is assigned arbitrarily negative value and joined to the corresponding dose by straight line which is extended into first quadrant. Adjusted dosage is obtained by connection of the intersection point (o) of A(population $V_{max}$ of each age) with desirable concentration(B). The individual *in vivo* Km and $V_{max}$ are the intersection point of the straight line which is joined the observed concentration to adjusted dosage with the straight line of 1st concentration.

has relatively narrow therapeutic range, and that the non-linear relationship between phenytoin dose and serum concentration(Richen and Dunlop 1975). Moreover, there is large individual variation in pharmacokinetic parameters(Eadie et al. 1976), the techniques for dosage adjustment using individual *in vivo* Km and $V_{max}$ have been described by various workers.

Mawer and co-workers(1974) described a method for determining a subject's apparent Km and $V_{max}$ value for phenytoin by measuring plasma phenytoin levels at various times following administration of a single large phenytoin dose. Estimation of Km and $V_{max}$ values by this technique requires relatively sophisticated computer programs for the non-linear fitting of the serum concentration of the drug.

Ludden et al.(1977) described the methods for arriving at optimum individual phenytoin dosage regimens by the estimation of individual Michaelis-Menten pharmacokinetic parameters using W.A.H. plot of reliable steady state phenytoin serum concentrations obtained from administration of different daily dose. Another simple technique for individualizing dosage has been published by Mullen(1978). This method uses a very simple direct linear plot of steady state serum phenytoin concentration and corresponding dose which was described by Eisenthal(1974). The advantage of this method is that the predicted dose can be read directly from the graph with no need of calculation. But confirmatory reports of the accuracy of this method are lacking at the present time(Gibaldi 1984).

Although the method described by Ludden and co-workers(1977) for optimum phenytoin dosage regimen has relatively high reliability, it takes at least 4 weeks after starting a given phenytoin dosage regimen before reliable two steady state phenytoin serum concentrations can be obtained.

Richens and Dunlop(1975) described a nomogram for dose adjustment in achieving the desirable therapeutic phenytoin concentration by measuring a single steady state serum concentration. But this nomogram has been found to have poor predictive value and has been criticized for use of an average Km value and a single serum concentration(Ludden et al. 1979; Gibaldi 1984). The *in vivo* phenytoin pharmacokinetic parameters reported by Eadie et al. (1976) and the results in this study (range of Km; 1,48~20,03 mg/L) also suggest the unfavorable predictive value of this nomogram techniques.

Because of phenytoin's non-linear Michaelis-Menten kinetics, the population pharmacokinetic parameters of phenytoin could be utilizable for the rapid individualization of phenytoin dosage regimen.

In this study, it was observed that the Km values were not different between age groups but $V_{max}$ values tended to decrease with age as reported by Eadie et al.(1976). The higher $V_{max}$ value in children than in adult may results from the fact that children requires larger maintenance dose than adult(Houghton et al. 1975; Myung 1981). We also found that the individual variation in $V_{max}$ was lesser than that in Km and it can be further reduced when $V_{max}$ was corrected based on body weight and age. Therefore, a technique in arriving at an optimum phenytoin dosage regimen by measuring steady state serum concentration after initial dose

and using population $V_{max}$ corrected based on body weight and age was suggested. By this technique, highly significant($p<0.005$) and reliable results were obtained. Although the results in this study showed somewhat lesser reliability compared with that of the two dose technique, it could be applied as a rapid dosage adjustment technique in clinical practice.

Furthermore, since the Mullen's direct linear plot technique was found to be comparable with W.A.H. plot technique, the graphic technique described in this report can be safely used to develop an effective and a reliable phenytoin dosage regimen.

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= 국문초록 =

# Phenytoin의 적정복용량 결정을 위한 약력학적 분석에 관한 연구

서울대학교 의과대학 약리학* 및 신경과학교실

명호진 · 박찬웅* · 신상구* · 이광우

Phenytoin은 약력학적 성상이 non-linear kinetics를 따르고 pharmacokinetic parameter가 개인차가 커, 간질 치료에 적용시 혈중농도 측정만으로 효율적인 적정용량 결정에 난점이 있다.

따라서 본 실험에서는 측정 혈청 phenytoin농도와 적절한 population pharmacokinetic parameter의 이용으로 보다 빠르고 높은 신뢰도로 적정 투여 용량을 결정하는 방안을 모색하고 이를 graphic technique에 적용하여 간편화 하고자 하였다. 총 41례를 대상으로 하여 3 또는 4 dose level의 유지용량 투여후 steady-state 혈청 농도를 측정하고 이들 *in vivo* $V_{max}$ 및 Km치를 분석하여 non-linear kinetics를 적용한 빠른 용량 결정법을 고안하고 이의 신뢰도를 기존의 제시된 방법들과 같이 평가하였다. 실험결과는 다음과 같다.

1. 연구 대상 총 41례의 평균 Km치는 7.69±4.61 mg/L 이었고 각 연령군에 따른 차이를 보이지 않았다. 이에 반해 체중 Kg당 $V_{max}$ 치는 각 연령군간에 유의한 차이를 보였으며 (평균 8.88±2.40 mg/kg/day; 성인, 7.88±1.14 mg/kg/day; 사춘기, 9.01±1.96 mg/kg/day; 소아, 13.56±2.52 mg/kg/day) $V_{max}$ 치는 연령증가에 반비례적인 역상관을 나타내었다($r=-0.59$, $p<0.005$).

2. 초기 유지용량투여후 측정한 steady-state 혈청 phenytoin 농도와 연령에 따라 보정한 population $V_{max}$치를 이용한 용량 결정 방법을 사용시 추정혈청 농도와 측정된 혈청농도 간에는 $p<0.005$ 수준의 유의한 상관성 ($r=0.66$)을 나타내었다.

3. 두 유지용량의 steady-state 혈청 phenytoin농도 측정으로 non-linenar kinetics 적용시 추정 혈청농도와 측정농도간에는 $r=0.74$의 상관성 ($p<0.005$)을 보였으며, 2회 이상의 steady state혈청 농도측정이 요구되는 기존의 제시된 방법들을 3회의 steady-state 혈청농도로부터의 추정능의 신뢰도를 비교 검정 한 바 이들간의 차이를 관찰할 수 없었다(computer fit, $r=0.84$, $p<0.005$; direct-linear plot, $r=0.81$, $p<0.005$; W.A.H.-plot, $r=0.81$, $p<0.005$).

이상의 연구결과로 간질환자에서 적정 phenytoin용량 결정에 연령 보정한 population $V_{max}$ 치를 이용한 신속한 용량 결정법과 direct-linear plot의 적용은 효율적인 약물요법이 가능케 하리라 생각된다.