INDIVIDUAL VARIATION IN DAILY DOSAGE REQUIREMENTS FOR PHENYTOIN SODIUM IN PATIENTS WITH EPILEPSY

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1 Ninety adult patients receiving phenytoin sodium were studied prospectively in an epileptic centre. Serum concentrations of phenytoin under steady state conditions were measured by gas liquid chromatography. When clinically indicated the daily dosage rate was adjusted by 50 mg steps until a serum concentration of 10–20 mg/l was produced.

2 Concentrations within the above range were obtained in 50 patients; the required dosage rate varied from 200–500 mg/day. Twenty-five clinical, biochemical and haematological attributes were recorded for each patient and tested for correlation with dosage requirement.

3 The dosage requirement correlated most strongly ($r=0.57$, $P<0.001$) with body surface area. This relationship (approximately 200 mg/day per m^2) accounted however for only one third of the total dosage variance.

4 Amongst 18 patients receiving simultaneous treatment with phenobarbitone, the effective plasma clearance of this drug taken in conjunction with body surface area accounted for a significantly greater proportion of the total dosage variance. Multiple regression analysis failed to reveal other, more widely applicable predictors of individual phenytoin dosage requirements.

Introduction

Phenytoin is one of the most useful drugs in the treatment of the epilepsies apart from myoclonic seizures and petit mal absences (Sutherland & Eadie, 1974). The recent report from Reynolds, Chadwick & Galbraith (1976) on the effectiveness of phenytoin alone in the treatment of epilepsy emphasises the importance of obtaining adequate serum concentrations of the drug before pronouncing it ineffective. Seizure control may not be obtained until concentrations of 10–20 mg/l have been reached (Buchthal, Svensmark & Schiller, 1960).

In the individual case however it can be difficult to produce steady state serum concentrations within this range because even at relatively low concentrations phenytoin exhibits dose dependent kinetics (Bochner, Hooper, Tyrer & Eadie, 1972). To facilitate dosage adjustment nomograms have been constructed (Richens & Dunlop, 1975; Martin, Tozer, Sheiner & Riegelman, 1976) which require at least one reliable estimate of the steady state serum concentration whilst the patient is receiving a provisional daily dose. With either method the probability of accurately predicting the ideal dose is greatest when the provisional dose gives serum concentrations close to the desired level. It

would therefore be useful if individual phenytoin dosage requirements could be predicted to within narrow limits (for example ± 50 mg) from the patient's age, sex and body weight or other relevant and easily measured attributes. This paper gives the results of a search for such attributes and the corresponding predictive relationships in a group of epileptic patients.

Methods

Ninety adult patients resident at the David Lewis Centre were studied prospectively. Most had a long history of anticonvulsant treatment and all were receiving phenytoin sodium (Epanutin, Parke Davis & Co.) as two or three divided doses daily, alone or in combination with other drugs; none was receiving sulthiame.

The patients were seen at a special clinic set up for this purpose. At the first visit age, sex, weight, height and dosages of all medications received by each patient were recorded. At each visit the patient was questioned and examined for clinical evidence of drug intoxication. Venous blood samples were collected at

approximately the same time on each visit for the measurement of serum phenytoin concentration, indicators of liver and kidney function and blood cell counts. The first sample for the measurement of serum phenytoin concentration in the steady state was taken after a minimum of 4 weeks on a particular dosage schedule. Subsequent samples were taken after intervals of 2–4 weeks.

Blood was kept at 4°C overnight; serum was then separated, frozen and stored at –20°C until the day of assay. Concentrations of phenytoin and phenobarbitone were measured by the method of MacGee (1970) which gave coefficients of variation of 4% and 3% respectively. Gas-liquid chromatography was carried out on the Perkin-Elmer F 30 with temperature programming to shorten the retention time of phenytoin. The internal standards, 5-(*p*-methylphenyl)-5-phenylhydantoin and 5-ethyl-5-*p*-tolylbarbituric acid were obtained from Aldrich Chemical Co. Ltd.

The mean concentration derived from two or more samples was taken as the steady state serum phenytoin concentration corresponding with a particular daily dose. When this lay outside the range 10–20 mg/l and there was clinical justification, the daily dosage rate was adjusted by 50 mg steps.

Biochemical and haematological determinations were made on blood from each patient in the clinical laboratories of the Manchester Royal Infirmary. The former included serum albumin, alkaline phosphatase, bilirubin, creatinine and urea. The latter included haemoglobin, mean corpuscular haemoglobin con-

centration, red and white cell counts. Body surface area was estimated from height and weight using the equation of Du Bois & Du Bois (1916). Creatinine clearance was estimated from age, sex, weight and serum creatinine concentration using the nomogram of Siersbaek-Nielsen, Hansen, Kampmann & Kristensen (1971).

The exposure of each patient to potential inducers of phenytoin hydroxylation was roughly quantitated by a scoring method (Hunter, Maxwell, Carella, Stewart & Williams, 1971). The induction score was the total sum of inducing units prescribed daily excluding phenytoin itself. The following were assumed to be approximately equipotent and one each represented one inducing unit: carbamazepine 200 mg, ethosuximide 250 mg, phenobarbitone 30 mg and primidone 100 mg. Benzodiazepines, chlorpromazine and sodium valproate were assumed not to induce the hydroxylation of phenytoin.

Urinary excretion of D-glucaric acid was measured in 6 h samples (9.00–15.00 h) obtained from seven healthy male volunteers and fourteen male patients chosen to represent the full range of phenytoin dosage requirements. The method involved preliminary purification by ion exchange chromatography, then oxidation and spectrophotometry (Ishidate, Matsui & Okada, 1965). Recovery of standard D-glucaric acid added to blank urine varied from 60 to 90%. The creatinine content of the urine samples was measured by the standard Technicon Auto-analyser method to provide a check on the completeness of urine collection.

Table 1 Correlations between individual dosage requirements for phenytoin (mg/day) and selected attributes of 50 epileptic patients.

Attribute	Mean $\pm$ s.e. mean	Range	r*	100 r ² **
<i>P</i> < 0.001				
Surface area m ²	1.70 $\pm$ 0.18	1.18–2.26	0.57	33
Height cm	164 $\pm$ 9	139–183	0.56	31
Weight (kg)	65 $\pm$ 12	33–104	0.50	25
<i>P</i> < 0.01				
Sex (33m, 17f)			0.34	12
<i>P</i> > 0.10				
Haemoglobin (g/l)	137 $\pm$ 10	116–159	0.25	6
Creatinine clearance (ml/min)	113 $\pm$ 32	52–150	0.18	3
Duration of epilepsy (years)	30 $\pm$ 13	10–61	–0.16	3
Age (years)	40 $\pm$ 16	16–73	–0.15	2
Red cell count ($\times 10^{12}$ /l)	4.4 $\pm$ 0.3	3.6–5.3	0.15	2
Serum albumin (g/l)	43 $\pm$ 3	38–50	0.13	2
Induction score***	6.7 $\pm$ 4.0	0–16	0.06	<1
Serum bilirubin (mg/l)	4.0 $\pm$ 1.3	1–6	–0.05	<1

*Coefficient of linear correlation between dosage requirement and attribute

**Percentage of total dosage variance explained by correlation with attribute

***Sum of arbitrary induction units (Hunter *et al.*, 1971) excluding phenytoin

Figure 1 Distribution of dosage requirements for phenytoin sodium in male □ and female ■ patients separated into groups according to estimated body surface area (a) greater than 1.8 m² (b) between 1.6 and 1.8 m² and (c) less than 1.6 m².

Having produced steady state serum phenytoin concentrations within the range 10–20 mg/l in a group of the patients the required daily dosage rates were compared with single recorded patient attributes by least squares linear regression analysis and with sets of attributes by stepwise multiple linear regression. Single and multiple correlation coefficients (r) were calculated and assessed by the corresponding probability (P) and by the percentage of the total variance explained ($100 r^2$).

Results

The daily dosage rate required to produce a steady state serum phenytoin concentration within the range of 10–20 mg/l was determined in 50 patients. The ranges of selected individual patient attributes of

possible relevance to phenytoin dosage requirements are shown in Table 1. The complete data matrix is available for study in the postgraduate thesis of the first author (Maheendran, 1976). The patient group varied widely in age and size but seldom gave any abnormal biochemical findings. All but three of the patients were receiving one or two other anticonvulsant drugs. Eighteen were receiving phenobarbitone, 25 primidone and one was receiving both.

Individual dosage requirements varied from 200–500 mg/day. Linear regression analysis revealed significant correlations between dosage requirements and body surface area, height, weight and sex (Table 1). The strongest relationship was with surface area rather than weight but this relationship accounted for only 33% of the total variance of phenytoin dosage requirements. The least squares regression line relating dosage requirement (Q mg/day) to body surface area (BSA m²) was described by the expression:-

$$Q = -102 + (251 \pm 52 \text{ s.e. mean}) \text{ BSA} \\ \text{Equation 1}$$

Since the intercept was within error limits of zero it was considered legitimate to force the line through the origin giving a dosage requirement of 192 mg/day per square metre.

Multiple regression analysis failed to reveal a second patient attribute which taken in conjunction with surface area would significantly increase the proportion of the total variance explained. In particular, age, duration of epilepsy, serum concentrations of albumin or bilirubin, induction score and the doses of individual anticonvulsant drugs were of no value in this respect. The only exception to this generalisation was observed in the subgroup of 18 patients who were receiving phenobarbitone with phenytoin. Amongst these patients the ratio of the phenobarbitone dose (A mg/day) to its serum concentration (B mg/l), which is in effect the phenobarbitone clearance (A/B l/day) proved a useful second attribute (Table 2). Neither dose nor concentration alone made a significant contribution

Table 2 Correlation of individual dosage requirements for phenytoin (mg/day) with body surface area and phenobarbitone clearance in 18 epileptic patients receiving concurrent treatment with both drugs.

Attribute	r^*	$100 r^2$	P^{**}
Surface area	0.71	51	<0.001
Phenobarbitone clearance***	0.80	65	<0.05

*Coefficient of multiple correlation

**Significance of contribution made by the addition of each succeeding item

***Daily dose (mg/day) per unit serum concentration (mg/l)

however. The least squares regression line was described by the expression:-

$$Q = -170 + (220 \pm 66 \text{ s.e. mean}) \text{ BSA} + (23 \pm 9 \text{ s.e. mean}) \text{ A/B Equation 2}$$

The urinary excretion of D-glucaric acid (mg/6 h or mg/mg of creatinine) was substantially increased in the patients compared with the volunteers (Table 3). Three of the patients excreted a very small amount of creatinine; this was attributed to incomplete collection. The remaining patients showed no significant correlation ($P > 0.38$) between phenytoin dosage requirement (mg/day or mg/day per m^2) and D-glucaric acid excretion. Nor was there a significant correlation ($P > 0.10$) amongst the total group of 14 patients with the excretion of D-glucaric acid per mg creatinine.

Discussion

This study has confirmed that body surface area estimated from height and weight is a better guide to individual dosage requirements of phenytoin than body weight (Sherwin, Loynd, Bock & Sokolowski, 1974). The sex difference (Table 1) was entirely explained by surface area differences (Figure 1). The majority of females had surface areas below 1.6 m^2 ; in this group the commonest dose requirement was 250 mg/day, whereas the group with surface areas above 1.8 m^2 was almost exclusively male and most commonly required 400 mg/day. Half the patients had surface areas between 1.6 and 1.8 m^2 and this group included almost every level of dosage requirement.

Substitution of surface area into equation 1 gave estimated dosage requirements within 50 mg of the observed values in 30 out of 50 patients. This level of success in the selection of a provisional dose is however only a little better than the common practice of prescribing 300 mg daily to all adult patients; this would have come within 50 mg of the observed dosage requirement in 26 patients.

The failure to make a substantial improvement in the prediction of individual dosage requirements may be due to several factors. Clearly no generally applicable second patient attribute has been identified which has useful predictive potential when taken in conjunction with body surface area. The results obtained from the subgroup of patients receiving phenobarbitone suggest parallelism between individual capacities to metabolise this drug and phenytoin. Substitution into equation 2 gave estimated dosage requirements within 50 mg of the observed values in 13 out of the 18 patients. The usefulness of this relationship is however inevitably restricted to the small and decreasing number of patients stabilised on phenobarbitone treatment before starting phenytoin. The results obtained from the subgroup of patients in which the urinary excretion of D-glucaric acid was measured do not suggest that this will assist in the prediction of phenytoin dosage requirements.

It is possible that relationships between phenytoin dosage requirements and patient attributes were concealed by the presence of other drugs. Simultaneous induction and inhibition of phenytoin hydroxylation may have produced complex, biphasic interactions which were not detected. The work of Reynolds and his colleagues (Reynolds *et al.*, 1976;

Table 3 Urinary excretion of D-glucaric acid in 14 male patients and 7 healthy male volunteers.

	Phenytoin dose (mg/day)	Serum concentration (mg/l)	Induction units*	Creatinine (mg/6 h)	D-glucaric acid (mg/6 h)
1	200	12.9	8.0	0.10**	10.4
2	200	12.2	6.0	0.06**	6.1
3	300	10.4	16.0	0.46	17.1
4	300	13.6	13.5	0.21	29.0
5	300	12.3	12.5	0.22	23.8
6	300	15.6	22.0	0.14**	14.9
7	350	14.6	15.0	0.30	44.0
8	350	10.0	13.0	0.25	24.8
9	400	12.2	8.0	0.36	21.8
10	400	12.7	10.0	0.35	20.3
11	400	10.0	20.5	0.31	46.5
12	400	10.0	17.0	0.66	49.0
13	500	16.0	20.5	0.37	26.9
14	500	20.6	18.0	0.45	26.1
		Mean $\pm$ s.e. mean patients		0.36 $\pm$ 0.04	25.8 $\pm$ 3.5
		volunteers		0.43 $\pm$ 0.05	4.1 $\pm$ 0.9

*Sum of arbitrary induction units (Hunter *et al.*, 1971) including phenytoin

**Urine collections suspected of being incomplete

Shorvon & Reynolds, 1977), has weakened ethical objections to the study of large numbers of epileptic patients receiving only phenytoin. In such a population it may be possible to identify further patient attributes which will assist in the prediction of individual phenytoin dosage requirements.

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