EFFECT OF AGE, HEIGHT, WEIGHT AND SEX ON SERUM PHENYTOIN CONCENTRATION IN EPILEPTIC PATIENTS

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- 1 Steady-state serum phenytoin concentrations were measured in adult epileptic patients receiving a maintenance dose of phenytoin (300 mg daily).
- 2 Serum phenytoin concentration showed a positive correlation with age.
- 3 Serum phenytoin concentration showed a negative correlation with body weight and with height. Multiple correlation analysis indicated that body weight influenced the concentration to a much greater degree than height.
- 4 When corrected for body weight and height, the serum phenytoin concentrations in women were lower than those in men, although the difference was not statistically significant.
- 5 Although each of these factors contributes to the interindividual variation in serum phenytoin concentrations, the contribution of each is small. Other factors, such as genetic differences and the effect of saturation kinetics, are much more important in determining steady-state concentrations. Adjusting the dose according to the age, weight and height of a patient would achieve only a marginal improvement in therapy.

Introduction

An increase in the incidence of drug interactions with increasing age has been reported by Hurwitz (1969). O'Malley, Crooks, Duke & Stevenson (1971) showed that the half-life of antipyrine was significantly longer in healthy geriatric patients than in younger controls. One possible explanation for these results is an age-related change in the ability to metabolize drugs.

Svensmark & Buchthal (1964) found that children metabolized phenytoin at a faster rate than adults. They related this finding to the higher basal metabolic rate per kg found in children. Jalling, Barrens, Rane & Sjöqvist (1970) and Dawson & Jamieson (1971) both confirmed that young children required a larger dose of phenytoin/kg of body weight in order to achieve therapeutic concentrations. There is, however, no published evidence in adults of any relationship between the serum concentration of phenytoin and age.

Many drugs which are eliminated largely by hepatic metabolism show different disappearance rates in males and females. In the rat, metabolism is often faster in male animals. Hexobarbitone (Quinn, Axelrod & Brodie, 1958) morphine, methadone and meperidine (Axelrod, 1956) and pentobarbitone (Kuntzman, Mark, Brand,

Jacobson, Levin & Conney, 1966) are all metabolized at a faster rate in male rats. In humans, the serum half-life of antipyrine is longer in men than in women of a comparable age. Travers, Reynolds & Gallagher (1972) showed that women receiving the same daily dose of phenytoin had a lower mean serum phenytoin concentration than did men. However, Eadie, Tyrer & Hooper (1973) failed to find such an effect and suggested that sex itself did not alter the relation between plasma phenytoin concentration and dose in either adults or children.

The effects of increasing weight and height on serum phenytoin concentrations have not been investigated. It is, however, generally accepted that for many drugs dosage on a mg/kg basis leads to more accurate control of therapy. In order to assess the contribution of these factors to the interindividual variation in serum phenytoin concentrations, we have studied a large number of patients receiving long-term phenytoin therapy for epilepsy.

Methods

Serum phenytoin concentration was estimated for routine clinical purposes in most of the residential

Figure 1 Relationship between age and serum phenytoin concentration in 170 patients receiving phenytoin (300 mg/daily). A linear regression was assumed and a regression line fitted by the method of least squares. Multiple correlation = 0.31, log serum concentration = $1.471 + 0.0046 \text{ age} + \text{residual error}$. $t = 4.1$, $P < 0.001$.

patients at the National Hospitals-Chalfont Centre for Epilepsy, Chalfont St. Peter, Buckinghamshire. Most, but not all, of these patients were supervised in taking their tablets and therefore the drug intake was probably closer to what was actually prescribed than is usual in hospital outpatients. All patients were receiving phenytoin sodium either in tablet form (Boots) or as Epanutin and Pheno-barbitone capsules (Parke-Davis). Blood samples were taken at 07.00-08.00 h, before the morning dose of anticonvulsant drugs. Serum phenytoin was estimated by a gas-chromatographic method involving flash-methylation (Houghton & Richens, 1974a), which has been shown to produce consistent and accurate results in an inter-laboratory quality control scheme (Richens, 1975).

Many of the patients studied had severe epilepsy and almost all were receiving multiple drug therapy. Analysis has been restricted to those who were receiving phenytoin (300 mg daily), but those who were receiving the known inhibitors of phenytoin metabolism, sulthiame (Houghton & Richens, 1974b) or pheneturide (Huisman, van Heycop Ten Ham & van Zijl, 1970), were excluded. Most of the patients included in the analysis were therefore receiving phenobarbitone or primidone in addition to phenytoin, and some were receiving a variety of other drugs for epilepsy or for general medical purposes.

Age, sex, height and weight were recorded at the time of blood sampling in order to assess the influence of these physiological factors on serum phenytoin concentration. As the distribution of serum phenytoin concentrations was log normal, statistical analysis has been performed on logged data. Concentration has been plotted on a logarithmic scale against age, height and weight, and a regression line fitted by the method of least squares assuming a linear relationship.

Results

Correlation of age with serum phenytoin concentration

Serum phenytoin concentration was plotted on a logarithmic scale against age in 170 patients (Figure 1). A positive correlation was found and this was significantly different from zero ($P < 0.001$). There were no important differences in drug therapy or in other relevant physiological factors between different age groups which could have explained this result.

There was no indication that a nonlinear model would have fitted the data better. However, the multiple correlation coefficient was low, which meant that only a small proportion of the variation in the serum concentration was explained

Figure 2 Relationship between weight and serum phenytoin concentration in (a) 48 women and (b) 91 men. For men, multiple correlation = 0.29, log serum concentration = $2.091 - 0.00679 \text{ weight} + \text{residual error}$. $t = -2.8$, $P < 0.01$. For women, multiple correlation = 0.36, log serum concentration = $2.174 - 0.00906 \text{ weight} + \text{residual error}$. $t = -2.7$, $P < 0.01$.

by the regression line. This suggests that variables other than age are more important in determining the serum concentration of phenytoin.

Correlation of height and weight with serum phenytoin concentration

Serum phenytoin concentration was estimated in 91 males and 48 females. For each sex, concentration was plotted on a logarithmic scale against height and weight. The negative slope of the least squares regression line of log concentration against weight (Figure 2) was significantly different from zero ($P < 0.01$) for both sexes. There was no evidence that a nonlinear model would have fitted the data better. Again, the multiple correlation coefficients were small, suggesting that body weight only partly accounted

Figure 3 Relationship between height and serum phenytoin concentration in (a) 48 women and (b) 91 men. For men, multiple correlation = 0.20, log serum concentration = $2.714 - 0.00635 \text{ height} + \text{residual error}$. $t = 1.9$, $P < 0.1$. For women, multiple correlation = 0.34, log serum concentration = $3.544 - 0.01191 \text{ height} + \text{residual error}$. $t = -2.5$, $P < 0.02$.

for the interindividual variation in serum phenytoin concentrations.

The slope of the least squares regression line of log serum concentration against height was also negative for both sexes (Figure 3). For women the slope was significantly different from zero ($P < 0.02$), but for men it was not.

There was no marked difference in concurrent therapy between patients of differing height and weight. As expected, however, an increase in weight was linked to an increase in height in both sexes. It is possible that the negative correlation

Table 1 Geometric mean serum phenytoin concentrations calculated separately in men and women. All patients were receiving phenytoin (300 mg daily).

<i>Patients</i>	<i>Mean age, height and weight</i>	<i>Number of patients</i>	<i>Geometric mean serum phenytoin concentration (μM)</i>	<i>67% confidence limits</i>	<i>Significance of difference between means*</i>
Men	36.0 years 174 cm 69.4 kg	134	42.8	83.7 21.9	NS
Women	36.6 years 158 cm 56.4 kg	84	44.3	73.6 26.7	

* Student's *t* test on logarithmically transformed data

found between log serum phenytoin concentration and height could be completely explained by the obvious relationship between height and weight.

In order to investigate this further, log serum phenytoin concentration was regressed against height and weight together. Men and women were analysed separately. The multiple correlation coefficients for these models were only slightly larger than those of the regressions on weight alone, but considerably larger than those of the regressions on height alone. These results suggest that body weight is more important than height in determining serum phenytoin concentration. The positive correlation between height and weight probably explains the small difference between the multiple correlation coefficients of the height and weight model and that of the model for weight alone.

Effect of sex on serum phenytoin concentration

Serum phenytoin concentration was estimated in 134 males and 84 females receiving phenytoin (300 mg) daily. There was no significant difference between the mean concentration in men and women (Table 1), but this did not take into account the differing average heights and weights of the two sexes. In order to take this important difference into account, the mean height (H) and the mean weight (W) of the epileptic population under study was calculated, and the corrected serum phenytoin concentration of each patient, had he or she been of weight (W) and height (H) was estimated from the multiple regression models. The estimate of the corrected mean concentration for women was $35.6 \mu\text{M}$, and that for the men was $44.9 \mu\text{M}$. This just failed to reach significance at the 5% level. There was a difference between the means of logged data of 0.1011 with a standard error of the difference between the mean of the logs being ± 0.0624 , and a *t* value of 1.63 using a one tailed test.

Discussion

In agreement with the observations of other workers (e.g. Lascelles, Kocen & Reynolds, 1970; Kutt, 1971) we have found a wide interindividual variation in the serum phenytoin concentration produced by a standard dose of 300 mg daily. Possible explanations for this variation include differences in absorption of the drug, age and weight related differences between patients, a variable degree of hepatic microsomal enzyme induction by other drugs given concurrently, genetically determined differences in the rate of metabolism of phenytoin, or simply unreliable drug taking.

Although we have shown that serum phenytoin concentration is positively correlated with patients' age, and negatively correlated with body weight, the magnitude of the multiple correlation coefficients indicate that these factors account for only a small part of the variation between patients. This suggests that dosing on a mg/kg basis or adjusting the dose for the age of the patient is likely to achieve only a marginal improvement in drug management. Indeed, several authors have previously shown that the wide variation in serum phenytoin concentrations is still seen after correcting the dose for body weight (Lascelles *et al.*, 1970; Lund, 1973; Eadie & Tyrer, 1974).

The negative correlation with weight is entirely predictable because the apparent volume of distribution of the drug will increase in proportion to body weight. A positive correlation with the age might also have been predicted from published evidence with other drugs, although this is scant. O'Malley *et al.* (1971) showed that geriatric patients had longer plasma antipyrine half-lives than younger control subjects. The most likely explanation of this finding, and of our observations with phenytoin, is that the metabolizing capacity of hepatic enzymes was reduced in the

aged, although the contribution of other factors such as a change in distribution volume, plasma binding and liver blood flow have not been assessed.

Travers *et al.* (1972) reported that women had a lower mean serum phenytoin concentration than men treated with an identical dose/kg of body weight although the difference was not statistically significant. Eadie *et al.* (1973), however, failed to find a sex-related difference in either adults or children. Although we observed no appreciable difference in the mean concentration in men and women treated with the same dose of phenytoin, when adjustment was made for the difference in height and weight between the two sexes, it was found that, in general, women had lower concentrations than men, although statistical significance was not reached. Thus it can be concluded that if a real difference exists between the sexes, it is a small one and of little practical importance in the day to day management of epilepsy.

Phenytoin has been shown to exhibit saturation

kinetics (Atkinson & Shaw, 1973; Houghton & Richens, 1974c). The dose at which enzyme saturation occurs was shown to vary considerably between patients by Mawer, Mullen, Rodgers, Robins & Lucas (1974), who successfully used the integrated form of the Michaelis-Menten equation described by Gerber & Wagner (1972) to predict steady-state serum phenytoin concentrations. Presumably the interindividual variation in saturability of the enzyme is genetically determined.

It seems likely that genetic differences, exaggerated by enzyme saturation, are far more important in determining a patient's steady state plasma phenytoin concentration than are the effects of age, weight and height. An understanding of the kinetics of phenytoin will help the clinician to adjust the dose of the drug more precisely to the patient's requirements.

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References

- ATKINSON, A.J. & SHAW, J.M. (1973). Pharmacokinetic study of a patient with diphenylhydantoin toxicity. *Clin. Pharmac. Ther.*, **14**, 521-528.
- AXELROD, J. (1956). The enzymatic N-demethylation of narcotic drugs. *J. Pharmac. exp. Ther.*, **117**, 322-330.
- DAWSON, K.P. & JAMIESON, A. (1971). Value of blood diphenylhydantoin estimation in the management of childhood epilepsy. *Arch. Dis. Child.*, **46**, 386-388.
- EADIE, M.J., TYRER, J.H. & HOOPER, W.D. (1973). Diphenylhydantoin dosage. *Proc. Aust. Assoc. Neurol.*, **10**, 53-59.
- EADIE, M.J. & TYRER, J.H. (1974). *Anticonvulsant Therapy. Pharmacological Basis and Practice*. Edinburgh and London: Churchill Livingstone.
- GERBER, N. & WAGNER, J.G. (1972). Explanation of dose dependent decline of diphenylhydantoin plasma levels by fitting to the integrated form of the Michaelis-Menten equation. *Res. Comm. Chem. Path. Pharmac.*, **3**, 455-466.
- HOUGHTON, G.W. & RICHENS, A. (1974a). Inhibition of phenytoin metabolism by sulthiame in epileptic patients. *Br. J. clin. Pharmac.*, **1**, 59-66.
- HOUGHTON, G.W. & RICHENS, A. (1974b). Phenytoin intoxication induced by sulthiame in epileptic patients. *J. Neurol. Neurosurg. Psychiat.*, **37**, 275-281.
- HOUGHTON, G.W. & RICHENS, A. (1974c). Rate of elimination of tracer doses of phenytoin at different steady-state serum phenytoin concentrations in epileptic patients. *Br. J. clin. Pharmac.*, **1**, 155-161.
- HUISMAN, J.W., VAN HEYCOP TEN HAM, M.W. & VAN ZIJL, C.H.W. (1970). Influence of ethylphenacetamide on the serum levels of other antiepileptic drugs. *Epilepsia*, **11**, 207-215.
- HURWITZ, N. (1969). Predisposing factors in adverse drug reactions. *Br. med. J.*, **1**, 536-539.
- JALLING, B., BARENS, L.O., RANE, A. & SJOQVIST, F. (1970). Plasma concentrations of diphenylhydantoin in young infants. *Pharmac. Clin. (Berl.)*, **2**, 200-202.
- KUNTZMAN, R., MARK, L.C., BRAND, L., JACOBSON, M., LEVIN, W. & CONNEY, A.H. (1966). Metabolism of drugs and carcinogens by human liver enzymes. *J. Pharmac. exp. Ther.*, **152**, 151-156.
- KUTT, H. (1971). Biochemical and genetic factors regulating Dilantin metabolism in man. *Ann. N.Y. Acad. Sci.*, **179**, 704-722.
- LASCELLES, P.T., KOCEN, R.S. & REYNOLDS, E.H. (1970). The distribution of plasma phenytoin levels in epileptic patients. *J. Neurol. Neurosurg. Psychiat.*, **33**, 501-505.
- LUND, L. (1973). Effects of phenytoin in patients with epilepsy in relation to its plasma concentration. In *Biological Effects of Drugs in Relation to their Plasma Concentration*. Ed. Davies, D.S. and Pritchard, B.N.C., pp. 227-238. London: Macmillan.
- MAWER, G.E., MULLEN, P.W., RODGERS, M. ROBINS, A.J. & LUCAS, S.B. (1974). Phenytoin dose adjustment in epileptic patients. *Br. J. clin. Pharmac.*, **1**, 163-168.
- O'MALLEY, K., CROOKS, J., DUKE, E. & STEVENSON, I.H. (1971). Effect of age and sex on human drug metabolism. *Br. med. J.*, **3**, 607-609.
- QUINN, G.P., AXELROD, J. & BRODIE, B.B. (1958). Species, strain and sex differences in metabolism of hexobarbitone, amidopyrine, antipyrine and aniline. *Biochem. Pharmac.*, **1**, 152-159.
- RICHENS, A. (1975). Results of phenytoin quality

control scheme. In *Clinical Pharmacology of Anti-Epileptic Drugs*, Springer-Verlag, Heidelberg (In press).
SVENSMARK, O. & BUCHTHAL, F. (1964): Diphenylhydantoin and phenobarbital serum levels in children. *Am. J. Dis. Child*, **108**, 82-87.

TRAVERS, R., REYNOLDS, E.H. & GALLAGHER, B. (1972). Variation in response to anticonvulsants in a group of epileptic patients. *Arch. Neurol.*, **27**, 29-33.

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