SERUM-PHENYTOIN LEVELS IN MANAGEMENT OF EPILEPSY

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Summary Steady-state serum-phenytoin levels were measured in five patients whose phenytoin dosage was changed three or more times for therapeutic purposes. Data from four of these patients and from fifteen others have been used to construct a nomogram which permits the clinician, given a single, accurate, steady-state phenytoin level, to adjust the dosage to achieve the desirable therapeutic concentration of 60 or 80 μmol per litre (15 or 20 μg. per ml.).

Introduction

ALTHOUGH phenytoin is a drug of first choice in the treatment of major epilepsy, it has several important disadvantages. It has a narrow therapeutic ratio; it produces a characteristic syndrome of intoxication, manifested by signs of cerebellar dysfunction; and with chronic use it produces a wide variety of adverse effects.[1] Furthermore, its kinetics in man make it a difficult drug to use in practice, because its hydroxylation by hepatic microsomal enzymes is a saturable process; the rate of metabolism fails to increase in proportion to the serum concentration of the drug, leading to a non-linear relationship between dose and the resulting serum level.[2-4] This is an important cause of the wide variation in serum levels seen in epileptic patients, and monitoring drug levels has consequently proved to be of great value in the management of phenytoin therapy.[4-7]

We have examined further the relation between dose and serum level, and have devised a practical scheme for making increments in dosage in order to achieve a serum level within the therapeutic range of 40–100 μmol per litre (10–25 μg. per ml.).

Patients and Methods

Five patients at the National Hospitals-Chalfont Centre for Epilepsy were selected for study because their dose of phenytoin needed to be changed for therapeutic purposes. Steady-state serum-phenytoin levels were measured by gas chromatography [8] at three or more different maintenance doses of the drug. At least 4 weeks was allowed between changes in dose and subsequent re-estimation of the serum level in order that equilibrium with respect to the drug could be reached. Specimens were drawn at 7 a.m., before the patients' first dose of drugs for that day. Although each patient was receiving at least one other drug in addition to phenytoin, the dose remained constant throughout the study.

Results

The relationship between serum-phenytoin level and daily dose of phenytoin administered to the five patients is illustrated in fig. 1. A good fit was found between the observed data and the values predicted by the Michaelis-Menten equation. In each patient

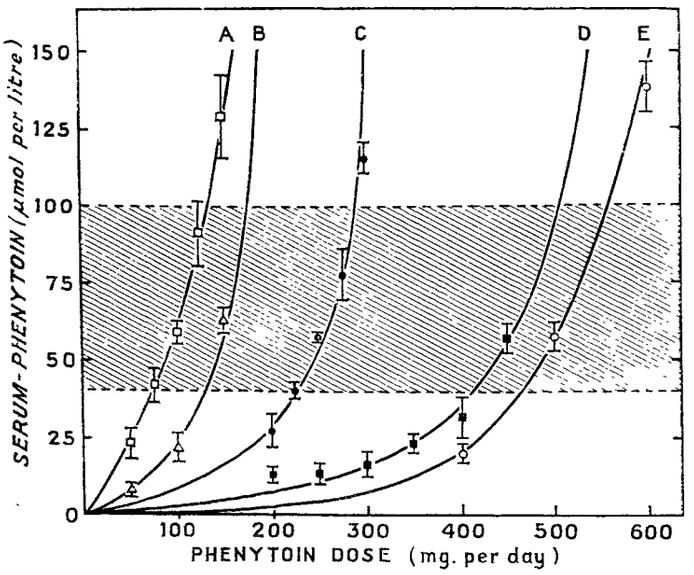

Fig. 1—Relation between daily dose of phenytoin and resulting serum level in five patients on several different doses of the drug.

Each point represents the mean of 3-8 separate estimations in the steady state. The bars represent 1 S.E.M. The hatched area represents the therapeutic range of serum levels. The curves were fitted by computer, using the Michaelis-Menten equation. (1 μmol/l. = 0·25 μg./ml.)

a dose increment of only 50–100 mg. would be required to raise the serum level from the lower to the upper limit of the therapeutic range used in our laboratory—namely from 40 to 100 μmol per litre (10–25 μg. per ml.).

From these computer plots, K_m values (i.e., the serum level at which metabolism is 50% saturated) were derived for each patient. Values for patients B–E varied between 12 and 23 μmol per litre. Patient A had a somewhat higher K_m (90 μmol per litre). Mawer et al.[3] reported an average K_m of 15·2 μmol per litre in fifteen patients who were given large single doses of phenytoin. We have therefore taken the average K_m value of these fifteen patients and our own four, excluding patient A (who was a very slow metaboliser of phenytoin and who might conceivably have an atypical hydroxylation mechanism), and have constructed a nomogram * (fig. 2) which enables the clinician to estimate the dose of phenytoin required to produce a serum level within the therapeutic range.

Discussion

The saturable nature of phenytoin metabolism has been confirmed in this study. The steepness of the relationship between dose and serum level within the therapeutic range has a number of important implications in clinical practice:

(1) Therapeutic levels are likely to be unstable because small changes in daily intake of the drug will greatly alter the serum level. Drug intake is never completely under the control of the supervising physician because differences in biological availability,[9,10] fluctuations in absorption, and unreliable drug intake [11] can occur without the physician's knowledge.

(2) If serum-phenytoin levels are used as a guide to

* Copies of the nomogram may be had from A. R.

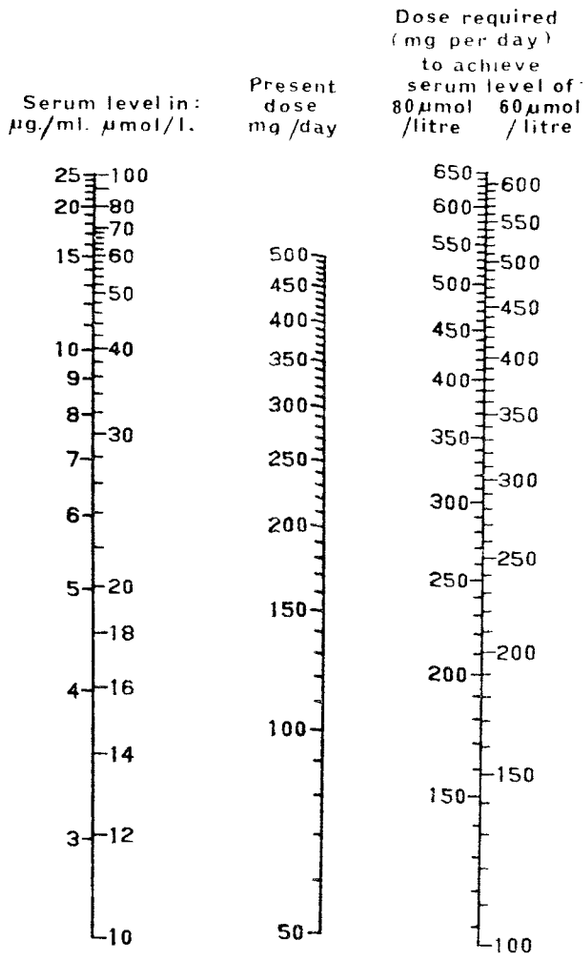

Fig. 2—Nomogram for adjusting phenytoin dosage.

Given a single reliable serum level on a given daily dose of the drug, the dose required to achieve a serum level of 60 µmol/l. (15 µg./ml.) or 80 µmol/l. (20 µg./ml.) can be predicted. A line is drawn connecting the measured serum level (left-hand scale) with the dose administered (centre scale), and then by extending this line to the right-hand scale the dose required to produce a therapeutic level of the drug can be read off.

This nomogram will give misleading predictions if the serum-level measurement is inaccurate, if the patient's compliance is in doubt, or if a change in concurrent treatment has been made since the measurement of the serum level. Since the nomogram has been constructed on the data of nineteen patients, predictions will on average be correct, but individual predictions may slightly overestimate or underestimate the final dose required to produce a therapeutic level. The minimum information needed is one accurate serum-level estimation in steady-state (i.e., after at least 2 weeks on a constant intake of the drug). A prediction based on an uncertain drug intake in a non-compliant patient is likely to be highly misleading. Very low serum-levels of phenytoin (below 10 µmol/l., 2·5 µg./ml.) are rarely measured precisely enough to allow predictions involving an increment of greater than 200 mg. to be made, and these low values have not been taken into account in the nomogram.

phenytoin dosage, increments in dose should become smaller as the therapeutic range is approached. Intoxication will almost certainly result if the dose is increased by 100 mg. or more in a patient whose serum level is approaching, or is just within, the therapeutic range. At most, 50 mg. should be added and the serum level re-estimated 2–4 weeks later. In some patients, a 25 mg. dose unit would be useful. The nomogram in fig. 2 will provide a more accurate guide to dosage.

(3) Because the enzyme which metabolises phenytoin may be close to saturation, interactions with this drug are common and sometimes potentially hazardous to the patient. For example, sulthiame is a potent inhibitor of phenytoin metabolism, and the incidence of phenytoin intoxication in patients on combined therapy is high.[12] Many other drugs can inhibit phenytoin metabolism.[13]

(4) Because of the instability of phenytoin levels within the therapeutic range, the validity of the range needs reappraisal. Although the recent work of Lund[14] has supported the earlier claim[15] that a level of at least 40 µmol per litre (10 µg. per ml.) is necessary to achieve adequate control, the patients included in both these studies had frequent seizures. It is possible that many patients with mild epilepsy will be fully controlled at lower, and more stable, serum-phenytoin levels.

(5) Monitoring serum-phenytoin levels allows a much safer and more effective management of the epileptic patient.

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C1-BYPASS COMPLEMENT-ACTIVATION PATHWAY IN PATIENTS WITH CHRONIC URTICARIA AND ANGIO-ŒDEMA

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Summary During the routine screening of 152 patients with urticaria or angio-œdema for hypocomplementæmia, 4 patients were found to have low serum levels of the third component of complement (C). These patients were noteworthy and differed from previous reports of patients with urticaria-like skin lesions and hypocomplementæmia because of the absence of immune-complex disease.

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