AN INDEX FOR PRESCRIBING PHENYTOIN IN CHILDHOOD

Prescribing phenytoin for the control of epilepsy is not an easy task in the adult patient (Richens & Dunlop, 1975) and can present even greater problems in childhood (Curless, Walson & Carter, 1975).

In 1973, Toseland & Albani proposed the use of the urinary hydroxyphenytoin/phenytoin ratio for the management of the epileptic patient receiving this drug. These earlier measurements were made in adults and their value was mainly demonstrated in revealing the interaction between phenytoin and other therapies. For the last 18 months the ratio had been used as a basis for prescribing phenytoin to epileptic children of all ages in the Universitäts-Kinderklinik in Göttingen. The following cases indicate the usefulness of the test.

All the patients were referred to the Neuropaediatric Department of the Universitäts-Kinderklinik and Poliklinik in Göttingen. Where phenytoin was considered to be a suitable therapeutic drug the following test was performed.

A dose of 10 mg/kg body weight of Phenhydan (diphenylhydantoin sodium from Desitin-Werke, Carle Klinke, GmbH, Hamburg) up to a dose of 100 mg per patient was given intravenously usually in the morning. The normal intravenous dose solution was used with a speed of injection of 20 mg/min or 10 mg/min for the very young children. Samples of blood were taken from the antecubital vein in the opposite arm to the injection side at intervals of 2, 4, 6, 8, and 24 h. The whole of the 24 h urine sample was collected. The urine from the very young children was collected in the usual way in a plastic bag, any spillage made the test void.

Plasma and urine phenytoin measurements were made by gas chromatography using a nitrogen sensitive detector (Toseland, Albani & Gauchel, 1975). Urine hydroxyphenytoin was measured following acid hydrolysis, essentially as the method described by Kupferberg (1970). Each patient's index is the ratio of the concentrations of the urine hydroxyphenytoin to that of the free drug.

Table 1 shows the results of the phenytoin tolerance test on six children, age range 2 days to 12 years, and their subsequent plasma phenytoin levels following a selected dose. These particular cases illustrate the main features from tests carried out on twenty-five children. Six other children tested with oral phenytoin were not included in the study, as we found that we were unable to make consistent measurements.

Table 2 demonstrates the findings in one case of a child with meningitis and septicaemia, and indicates the gross changes that can occur in the phenytoin index with altered liver function.

We have arranged the Table 1 in order of ages, for our initial results indicate that it is likely that for children the index at a particular age group may be more important than the index *per se* (e.g. patients SG, and RD, have similar indices, but the latter, younger child needs 50% more phenytoin to achieve similar plasma levels).

Various parameters have been described for the adequate control of plasma phenytoin levels.

Richens & Dunlop (1975) proposed the use of the nomogram in adult patients for the required adjustment of the phenytoin dosage, and also followed

Table 1 The results of the phenytoin tolerance test on six children

Name	Age	Weight (kg)	Phenytoin index	Dosage (mg/kg)	Plasma level* (µg/ml)
FM	2 days	3.020	5.6	8	30.5
				6	17.4
StE	5 days	2.580	177.1	**	**
SG	11 months	12.5	107.1	14.6	22.9
				8.0	2.6
				12.0	18.3
RD	3 years 9 months	15.3	122.5	22.0	37.5
				18.75	16.5
ML	5 years 5 months	24.0	11.3	9.0	32.6
				6.6	13.2
LH	11 years 11 months	50.0	160.1	10.0	12.7

* These levels refer to the steady state and were not made until at least 8 days after the last dose alteration

** Child died before reaching steady state levels

Table 2 The gross changes that can occur in the phenytoin index with altered liver function

Name	Age	Weight (kg)	Transaminases			Phenytoin index	Dosage (mg/kg)	Plasma level* ($\mu\text{g/ml}$)
			SGOT	SGPT	SyGT			
DK Septicaemia Meningitis	4 weeks	4.350	85	57	60	2.5	5.5 2.75	30.7 10.2
(<i>Klebsiella pneum.</i>)	8 weeks	4.520	10	17	—	38.7	16.5	6.7

* These levels refer to the steady state and were not made until at least 8 days after the last dose alteration

the elimination of a tracer dose of radio-labelled [^{14}C]-phenytoin in order to study plasma half-lives (Houghton & Richens, 1974). They further showed that the urine hydroxyphenytoin/phenytoin ratio correlated negatively with the plasma phenytoin level, in a group of 'steady state' patients.

Mawer, Mullen, Rodgers, Robins & Lucas (1974) gave a single large oral dose of phenytoin to a group of adult patients and followed the decay curve in serial samples over 48 h. From these results the required dose for each patient was computed.

Both Curless *et al.* (1975) and Koch-Weser (1972) emphasized the importance of studying phenytoin kinetics in children and the former stated that it would be desirable 'to measure individual kinetic parameters before beginning phenytoin therapy'.

The method we suggest makes use of the hydroxy-phenytoin/phenytoin ratio in a 24 h urine sample, a technique that we have previously shown to be reproducible in a group of adult volunteers (not epileptic) who were given an oral dose of phenytoin (100 mg) after an overnight fast. In children however we found that we were unable to obtain consistent results following oral administration, but after an intravenous dose the urine test gave reproducible results.

In this first series of tolerance tests we have also measured the plasma levels that can be conveniently obtained during the first 8 h and after 24 h. The plasma levels in fact rarely reached the recommended therapeutic ones. However no heed was paid to these actual levels and patients were assigned 'low' and 'high' according to their urine ratio. A high ratio patient requires a minimum dose of at least 10 mg/kg with higher doses for very young children. A low ratio means an initial dose of the order of 5 mg/kg.

The significant factors arising from this study are that:

1. the well known wide variation in dosage for the same phenytoin levels in children of similar ages, is consistent with their phenytoin indices, and
2. the change in drug requirement, probably resulting from an impaired liver function, correlates with the altered index in a particular patient

With regard to 1, we have two children of similar ages (RD and ML) with a three-fold difference in the phenytoin dose (18.7–6.6 mg/kg) to produce plasma levels of the same order (16.5–13.2 $\mu\text{g/ml}$), which is in keeping with the phenytoin index difference of 122.5 to 11.3.

In the case of the patient with meningitis, the phenytoin index (Table 2) was consistent with the patient becoming toxic on the initial therapy of 5.5 mg/kg, yet when the child's liver function tests showed more normal results, a repeated index correlated with a seven-fold increase in the drug dose producing only about half of the original plasma level.

Many paediatric neurologists will have seen similar case variations between matched patients and within the same patient. However in view of the narrow therapeutic range they will often err on the side of caution in altering the dose as they attempt to balance the problems of further fits and toxic side effects.

This system can never overcome the problems of the variation in bioavailability and non-compliance, but we suggest that a phenytoin index measured in a 24 h urine collected after an intravenous test dose, is a simple way to predict a particular patient's drug requirements. Instead of applying a median dose of 5 mg/kg and then gradually titrating the child against his or her plasma phenytoin levels, an index can be used to predict a more reliable dose regime.

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A RAPID METHOD FOR THE DETERMINATION OF PLASMA MEXILETINE LEVELS BY GAS CHROMATOGRAPHY

Mexiletine (Mexitil®, Boehringer Ingelheim) is a drug effective in the management of ventricular arrhythmias which has similar properties and toxic effects to lignocaine but which differs from that drug in being active orally and in having a longer half-life (Campbell, Chaturvedi, Kelly, Strong, Shanks & Pantridge, 1973; Talbot, Julian & Prescott, 1976). It is a most useful adjunct in the management of these arrhythmias and may be effective when lignocaine has failed. At this time however, it has yet to establish its place in routine therapy. Little has been published about its pharmacokinetics which seem likely to be as complex as those of lignocaine especially when the drug is used in patients with cardiac decompensation. Since the effects of mexiletine intoxication are potentially serious the monitoring of plasma levels would seem a sensible precaution at least during the early stages of drug administration. During intravenous mexiletine therapy the incidence of side-effects is reported to be around 70% (Campbell *et al.*, 1973) although it is probably much lower on long-term oral therapy (Talbot *et al.*, 1976). The therapeutic range is approximately 0.75–1.5 µg/ml (Talbot *et al.*, 1976). The nitrogen-sensitive alkali flame ionization detector is particularly useful in the rapid assay of the plasma concentration of nitrogen containing compounds since its relative insensitivity to compounds lacking nitrogen allows a shortened extraction procedure and results in a narrow solvent front on chromatography. An assay technique for mexiletine which we have used for monitoring patients in this hospital is presented in this communication.

Aliquots (1 ml) of plasma were placed in 15 ml glass stoppered round bottomed tubes and 20 µl of a 25 µg/ml solution of *p*-nitroanisole (internal standard) in methanol, 0.5 ml of 1N sodium hydroxide and 5 ml of 1% isoamyl alcohol in redistilled diethyl ether added and the whole mechanically shaken for 15 min. The tubes were then centrifuged and the ether layers transferred to 15 ml conical glass centrifuge tubes. The ether was rapidly evaporated off in a water bath at 35°C under a stream of air to leave approximately 50 µl isoamyl alcohol. 1–4 µl of this was injected directly on column. A Pye series 104 chromatograph fitted with a rubidium chloride nitrogen detector was used with a Smith model RE 541.20 servoscribe chart recorder in this work. The column was 1.5 m borosilicate glass with an internal diameter of 4 mm and packed with 2.5% OV 101 on Gas Chrom Q, 60–80 mesh. The operating conditions were: column oven temperature 150°C, detector temperature 315°C, nitrogen carrier flow 38 ml/min, hydrogen flow 46 ml/min, air flow 390 ml/min. Quantitation was achieved by use of the peak height ratio method and a calibration curve was constructed for each batch of samples using known amounts of mexiletine added to fresh human plasma carried through the entire process. Typical chromatograms are shown in Figure 1. The calibration curve is linear. Ten replicate analyses of a plasma sample to which 1.5 µg/ml mexiletine had been added yielded a mean value of 1.49 (S.D. 0.13) µg/ml. Lignocaine may be determined by the same technique but the retention time is eight times that of mexiletine at 150°C and a higher