PRACTICAL MANAGEMENT OF THERAPEUTIC DIPHENYLHYDANTOIN CONCENTRATIONS IN CHILDREN

A Smit, J F Schoeman, H I Seifart, D P Parkin

Objective. Development of easy, practical methods for the management and optimisation of therapeutic diphenylhydantoin (DPH) concentrations in children.

Design. Investigation of DPH concentration profiles and pharmacokinetic parameters in children with poorly controlled epilepsy. Subsequent determination of individual-specific DPH maintenance dosage and volume of distribution data suitable for use in routine therapeutic concentration management procedures.

Setting. Department of Paediatrics and Child Health and Department of Pharmacology, University of Stellenbosch, Tygerberg Hospital.

Subjects. Children of both sexes between the ages of 4 and 12 years with poorly controlled epilepsy receiving DPH as sole medication.

Results. In all subjects evaluated epilepsy was unsatisfactorily controlled because of inadequate DPH dosage regimens. Individual-specific maintenance dosage and volume of distribution data could be calculated for all individuals participating in the trial. The calculated data were suitable for use in routine management procedures and in no instance was it necessary to recalculate parameters in a 12-month follow-up period subsequent to evaluation.

Conclusions. Therapeutic DPH concentration profiles can be managed satisfactorily in children if individual-specific DPH pharmacokinetic parameters are derived and skilfully applied.

Table I. Derived data from population parameters for larger children and adults in respect of DPH, assuming Vm = 9.22 ml/kg/d; Km = 5.7 mg/l and a Vd = 0.64 l/kg

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<th>[DPH] (mg/l)</th>
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<th>t1/2</th>
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Diphenylhydantoin (DPH, phenytoin) is widely used in paediatric patients for the treatment of generalised tonic/ clonic seizures, tonic seizures, partial seizures, secondarily generalised seizures and status epilepticus. Although DPH is an excellent drug when indicated, less effective alternatives are perhaps often used in preference because of the pharmacokinetic difficulties generally encountered in accurately controlling therapeutic concentrations in the therapeutic range (10 - 20 mg/l).1

The rate of DPH elimination is governed by metabolic processes that are saturated at relatively low concentrations since the Michaelis constant is low (Km = 5.7 ± 2.9 mg/l in adults) relative to optimal therapeutic steady-state concentrations. Consequently, the rate conditions governing DPH elimination change from essentially first-order in the subtherapeutic range, to essentially zero-order in the therapeutic and higher ranges. As indicated by the data in Table I, derived from population parameters, the change is a continuum.

Therapy with a drug such as DPH, which is subject to zero-order elimination rate phenomena, is not easily controlled and requires special techniques, since, in contrast to true first-order rate processes, dosage and steady concentrations are not linearly related; a modest increase in the maintenance dosage in excess of the maximum concentration; a maximal elimination rate exists and a modest increase in the maintenance dosage may cause an extensive increase in the steady-state concentration; a maximal elimination rate exists and if a maintenance dosage in excess of the maximum is administered, concentrations will never stabilise but will increase.
continuously and inexorably to toxic levels; and the elimination half-life is directly proportional to concentration and increases as concentration increases. These aspects are well illustrated in the data derived from population parameters and are indicated in Table I.

Although a number of methods have been devised to optimise DPH maintenance dosage, they do not address the practical, hands-on DPH dosage and concentration management skills required for routine application in environments with less sophisticated health care infrastructures. The methods described here address these issues and involve three clear objectives: (i) careful estimation of the maximal elimination rate of DPH for the purpose of calculating an appropriate daily maintenance dosage; (ii) estimation of the volume of distribution for the purpose of calculation of adjustment dosages that are inevitably required from time to time; and (iii) adjustment measures, not involving alterations to the maintenance dosage, for appropriate upward or downward displacement of the DPH concentration-time ([DPH]-time) profile applicable to the dosage interval.

The methods presented here are an aid to, but do not replace, the need for ongoing therapeutic concentration monitoring. It is important that the clinician has a clear understanding of the [DPH]-time profile that needs to be achieved, and how best to achieve it.

METHODS

Patients

Ten children of both sexes between 4 and 12 years of age being treated with DPH for seizure control, but in whom therapeutic results were unsatisfactory, were admitted to the study provided that they were receiving no medication other than DPH. The demographic data are shown in Table II. Approval for the study was obtained from the Institutional Ethics Authority and consent for inclusion of a child in the trial was obtained from a parent or guardian.

Dosage and sampling

All the children had been treated with DPH for at least 2 weeks before admission to hospital. DPH concentrations were determined on admission to evaluate therapeutic drug level status as a first step in determining the cause of unsatisfactory seizure control. A single oral best-estimate DPH dose was then administered by the attending paediatrician in an attempt to elevate DPH concentrations to within the therapeutic range. On the following day, the trial day, extending over 24 hours, a baseline blood sample ([DPH]ₘ) was drawn immediately before the time of administration of an intravenous test dose of DPH (approximately 5 mg/kg body weight) by slow bolus intravenous injection, i.e. at a rate less than 0.75 mg/kg/min. ²³

<table>
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<tr>
<th>Patient No.</th>
<th>Mass (kg)</th>
<th>Age (yrs)</th>
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<th>[DPH]ₘ (mg/l)</th>
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[DPH]ₘ = the baseline DPH concentration immediately before administration of the IV test dose; [DPH]ₘ = the peak concentration measured at the intercept of the best-fit linear concentration-time graph with the ordinate; [DPH]ₘ = the concentration 24 hours after completion of the administration of the test dose.

Blood samples (1 ml) for the determination of DPH concentrations were then drawn 6, 16 and 24 hours after completion of the injection. In no instance had a patient received DPH in the 12-hour period before the time the test dose was given.

Analytical methods

Blood samples (1 ml) were collected into 1.5 ml Eppendorf tubes and allowed to clot, after which they were centrifuged at 5 000 g for 5 minutes to sediment fibrin in suspension. The serum was then analysed in triplicate for DPH content using an Abbott AXSYM Phenytoin II System (Abbott Laboratories, Diagnostic Division, USA), which is an immunoassay utilising fluorescence polarisation technology.

Precision was determined as described in the National Committee for Clinical Laboratory Standards (NCCLS) protocol by the addition of known quantities of phenytoin to recalcified drug-free plasma. The intra-run and inter-run coefficients of variation at DPH concentrations of 7.5, 15.0 and 30.0 mg/l were 1.94, 2.07 and 2.46% and 3.94, 3.52 and 2.84%, respectively. The coefficient of variation for DPH analyses in our laboratory falls well within the specifications indicated by the manufacturer.

Recovery of assay procedure was performed by comparison of spiked plasma samples with spiked buffer samples. An overall recovery rate of 99.88 ± 1.96% was found within the concentration range of 2.5 - 20.0 mg/l. At concentrations of below 0.5 mg/l both recovery and the coefficient of variation were found to be outside the 95% confidence interval (CI); the sensitivity was therefore defined as 0.50 mg/l, representing the lowest measurable concentration that can be distinguished from zero with 95% confidence.
**Calculations**

Graphic representation of measured concentration versus time data. Least squares linear regression was performed on the plasma [DPPH]-time data of each patient and the resulting graph was back-extrapolated to time zero \((t = 0)\). Time zero, indicating the origin of the ordinate, was taken as the time at which the baseline sample \([\text{[DPPH]}_b]\) was collected and the DPH test dose was administered, in the same order, in rapid succession.

**Peak concentration.** The peak concentration \([\text{[DPPH]}_p]\), at time zero, was determined from the intercept of the \([\text{[DPPH]}]-\text{time}\) graph and the ordinate.

**Volume of distribution (Vd).** The apparent Vd was calculated from \([\text{[DPPH]}]_b\) \([\text{[DPPH]}]_p\) and the magnitude of the DPH test dose \((D)\), as follows:

\[
\text{Vd} = \frac{D}{(\text{[DPPH]}_b - \text{[DPPH]}_p)} \quad (1)
\]

**Elimination rate or rate out (Ro, mg/l/h).** Ro was calculated directly from the slope of the best-fit linear graph of the \([\text{[DPPH]}]-\text{time}\) data, as per Fig. 1. Ro was also calculated from the two most distal \([\text{[DPPH]}]-\text{time}\) data points using the equation:

\[
\text{Ro} = \frac{(\text{[DPPH]}_u - \text{[DPPH]}_d)}{(t_2 - t_1)} \quad \text{mg/l/h} \quad (2)
\]

in which \([\text{[DPPH]}]_u\) and \([\text{[DPPH]}]_d\) are DPH concentrations applicable to times \(t_1\) and \(t_2\) in the post-distribution phase.

**Maintenance dose (MD, mg/d).** The daily maintenance dose was calculated as:

\[
\text{MD} = \text{Ro} \times \text{Vd} \times \tau, \quad \text{(mg/d)} \quad (3)
\]

in which \(\tau\) is the dosage interval in hours, with 24 hours in the trial.

**Trough concentration ([DPPH]_{trough}).** The optimal trough concentration was calculated from the optimal therapeutic concentration, set at 15 mg/l for larger children and adults, and the calculated MD expressed in terms of mg/l/d, as follows:

\[
\text{[DPPH]_{trough}} = (15 - \frac{(\text{MD})}{2}) \text{mg/l} \quad (4)
\]

**Loading or adjustment dose (LD, AD).** The most appropriate loading or adjustment (upward) dose can be calculated from the target \([\text{[DPPH]}_{trough}]\) value and the measured situational DPH trough concentration \([\text{[DPPH]}_{measured}]\), as follows:

\[
\text{LD or AD} = \text{Vd} \times ([\text{[DPPH]}_{measured}] - [\text{[DPPH]}_{trough}]) \quad \text{mg} \quad (5)
\]

**RESULTS**

The baseline \([\text{[DPPH]}_b]\), peak \([\text{[DPPH]}_p]\) and 24-hour post-dose \([\text{[DPPH]}_{24h}]\) concentrations of each individual, generated on the trial day, are shown in Table II. The apparent volume of distribution of DPH \((Vd, l/kg)\), the apparent maximal DPH elimination rate \((v = Ro, mg/l/h)\), the optimal daily maintenance dose, in both volume and mass terms \((MD: mg/kg/d; mg/l/d)\), and the optimal target trough concentration \([\text{[DPPH]}_{trough}]\), were calculated for each of the children. The results are shown in Table III.
for our children, MD = 5.78 (± 0.97) mg/kg/d, closely approximated the elimination Vm data reported for adults, i.e. Vm = 5.9 (± 1.2) mg/kg/d. What our data do show is that notwithstanding similarities, population data applicable to adults are of only limited use in planning a dosage regimen for an individual child.

**DISCUSSION**

DPH concentrations were subtherapeutic in all our children, and in the final analysis poor seizure control could be ascribed directly to inadequate dosage in all instances. The consistent trend in the direction of subtherapeutic DPH concentrations probably reflects awareness of the zero-order pharmacokinetic profile of DPH concentrations in the therapeutic range and the desire of the clinician not to overdose the patient.

For decades DPH pharmacokinetics have been used as a model for the study of saturable *in vivo* xenobiotic elimination phenomena. Useful data have been generated and a variety of methods of varying degrees of sophistication have been derived with which to maintain DPH concentrations within therapeutic limits. The unsophisticated but eminently practical methods presented here have the advantage of being intuitively easy to understand and, once learnt, extremely user-friendly. They are also immediately applicable to any circumstance at all stages of therapy, i.e. from initiation of a DPH-containing regimen through to long-term maintenance therapy, almost inevitably complicated from time to time by aberrations in dosage, absorption or compliance.

As practical 'hands-on' skills develop, the careful clinician with some experience should not find it difficult to manage therapy involving DPH provided that high-quality DPH analytical services are available for routine monitoring purposes. In this regard a method for the quantitation of DPH with an SD of less than 5% is required. A rapid specimen delivery-analytical result turnaround time also does much to facilitate efficient correction of aberrant DPH-time profiles.

Since IV injection of DPH ensures absolute and immediate bio-availability, the time to the linear elimination phase is decreased considerably, allowing sufficient time within a 24-hour dosage interval for the collection of the requisite well- and widely-spaced samples. Consequently, it is practically easy to estimate graphically, or to determine by least-squares linear regression, the slope of the [DPH]-time graph from 3 appropriately spaced accurately measured [DPH]-time data points within a 24-hour dosage interval. The elimination rate (Ro, mg/l/h) calculated (as per equation 2) from [DPH]-time data 6 and 24 hours after the test dose did not differ significantly (data not shown) from the values calculated directly from the best-fit linear graph.

Whenever possible the DPH elimination characteristics of the individual should be determined over a 24-hour period in order to minimise the impact of distribution/redistribution phenomena on elimination rate (v) parameters. Once the daily MD most appropriate to the individual has been determined, the required total daily dosage may be subdivided, if necessary, to accommodate the needs of a 12-hourly dosage regimen.

It is clear that a MD calculated from the slope of the best-fit linear graph will approximate, but not overestimate, the maximal permissible MD of DPH since the slope of the [DPH]-time graph will approach, but never attain, a maximum; at maximum slope the maximal elimination rate, i.e. the V•• component in Michaelis-Menten concepts, applies. Although occasional minor upward displacement of [DPH]-time profiles, by means of a single adjustment dose, was necessary in all our patients in the 12-month post-trial follow-up period, in no instance was the MD excessive, and consequently in no instance did DPH concentrations show a tendency to rise inexcogably to toxic levels as shown hypothetically in trace D of Fig. 2.

![Fig. 2. Hypothetical concentration-time profiles](image-url)

For the reasons discussed above, in the chronically underdosed patient or the patient who has not previously received but is now to be treated with DPH, an IV test dose for the purpose of computation of specific pharmacokinetic parameters is advisable in order to circumvent complications related to the rate and/or extent of DPH absorption and distribution. On the other hand, [DPH]-time data required for the calculation of the DPH elimination rate can easily be determined directly in the patient presenting with
supratherapeutic concentrations by the simple expedient of obtaining a set of samples over the time-course of the decline of DPH to the lower range of therapeutic concentrations (10 mg/l). Each such untoward event should be utilised to determine, confirm or improve information in respect of the most appropriate maintenance dosage.

An additional advantage of an IV test dose of DPH is that it allows approximation of the apparent Vd of the individual from data generated, as described, by extrapolation of the linear section of the [DPH]-time graph to the time of completion of administration of the test dose, marked by the location of the ordinate. The volume of distribution is required for efficient upward or downward displacement of the therapeutic [DPH] profiles since occasional one-off adjustments should be seen as an integral part of DPH maintenance concentration management. As shown in Table III, at the outset of therapy individuals may have a Vd that differs significantly from, or which falls in the extremes of, the quoted range; these individual-specific values should be taken into account whenever adjustment procedures become necessary. As therapeutic DPH steady-state concentrations are approached and deep tissue compartments become saturated the apparent Vd values tend, theoretically, to decrease to a stable minimum.

If Vd is not calculated, as is often not possible in routine therapeutic monitoring situations, it should be estimated from populations parameters, e.g.: 

\[ Vd = \text{mass (kg)} \times 0.64 (l/kg) \times 0.64 \pm 0.04 l/kg \]

If [DPH] is subtherapeutic, condition A in Fig. 2 applies.

If [DPH] is supratherapeutic, condition C or condition D in Fig. 2 applies.

2. Withhold therapy and repeat [DPH] determinations 12-hourly until [DPH] approaches 10 mg/l.

3. From the slope of the linear graph of the [DPH]-time data determine the correct MD.

4. Having determined, or confirmed, the correct MD, continue with maintenance therapy using the correct MD after administering a LD/AD to elevate trough [DPH]s appropriately.

Flowchart indicating procedures to be followed in the management of aberrant therapeutic diphenylhydantoin concentrations

If the therapeutic control of the patient being treated with DPH for epilepsy is unsatisfactory, determine the trough [DPH] as a priority in the initial clinical evaluation.

1. If [DPH] is supratherapeutic, either condition C or condition D in Fig. 2 applies.

2. If [DPH] is subtherapeutic, condition A in Fig. 2 applies.

3. Administer a LD of DPH calculated to approach a [DPH] of 20 mg/l by slow IV injection; effect [DPH] determinations 12-hourly until [DPH] approaches 10 mg/l.

4. From the slope of the linear graph of the [DPH]-time data determine the correct MD.

5. Having determined, or confirmed, the correct MD, continue with maintenance therapy using the correct MD after administering a LD/AD to elevate trough [DPH]s appropriately.
Compliance of the respiratory system as a predictor for successful extubation in very-low-birth-weight infants recovering from respiratory distress syndrome

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Objective. To develop additional criteria to predict for successful extubation of very-low-birth-weight infants recovering from respiratory distress syndrome.

Design. Prospective study.

Setting. Neonatal intensive care unit at a university teaching hospital.

Interventions. Infants ready for extubation according to clinical, ventilatory and blood gas criteria were studied. Before extubation, tidal volume (VT), minute ventilation, respiratory rate/VT and mean inspiratory flow were measured during two different ventilatory settings: (i) during intermittent mandatory ventilation (IMV); and (ii) while breathing spontaneously with endotracheal continuous positive airway pressure (CPAP). Tidal volume was obtained through electronically integrated flow measured by a hot-wire anemometer. Total respiratory compliance (Crs) was determined during IMV and was derived from the formula Vt/PIp-PEEP, where the difference between peak inspiratory pressure (PIP) and positive end-expiratory pressure (PEEP) represented the ventilator inflation pressure.

Measurements and main results. Each of 49 infants was studied once before extubation. 33 infants (67%) were successfully extubated and 16 (32.6%) required reintubation. Infants in the success and failure groups were matched for gestation, post-conceptional age, study weight and methylxanthine therapy at the time of study. Successful extubation was associated with a higher mean absolute Crs value (ml/cm H2O) specific Crs value (standardised for body length; ml/cm H2O/cm) compared with infants in whom extubation failed (0.67 v. 0.46; P = 0.01 and 0.018 v. 0.014; 0.46).

References


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