PRACTICAL MANAGEMENT OF THERAPEUTIC DIPHENYLHYDANTOIN CONCENTRATIONS IN CHILDREN

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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.

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Diphenylhydantion (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.[1-4] 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).[5]

The rate of DPH elimination is governed by metabolic processes that are saturated at relatively low concentrations since the Michaelis constant is low ($K_m = 5.7 \pm 2.9$ mg/l in adults[6]) 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,[6] 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 dose (MD) 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

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

[DPH] (mg/l)	v = Ro (mg/l/d)	k (l/d)	Cl (l/kg/d)	$t^1/_2$ (d)	MD (mg/l/d)	MD (mg/kg/d)
2	2.39	1.195	0.765	0.580	2.39	1.53
4	3.80	0.950	0.608	0.730	3.80	2.43
6	4.72	0.786	0.503	0.882	4.72	3.02
8	5.38	0.672	0.430	1.031	5.38	3.44
10	**5.87**	**0.587**	**0.376**	**1.181**	**5.87**	**3.76**
12	6.25	0.521	0.333	1.330	6.25	4.00
14	6.55	0.468	0.300	1.481	6.55	4.19
15	**6.68**	**0.445**	**0.285**	**1.557**	**6.68**	**4.28**
16	6.79	0.424	0.271	1.634	6.79	4.35
18	7.00	0.389	0.249	1.782	7.00	4.48
20	**7.17**	**0.358**	**0.229**	**1.936**	**7.17**	**4.60**
22	7.32	0.333	0.213	2.081	7.32	4.69
24	7.50	0.312	0.200	2.221	7.50	4.80
26	7.56	0.291	0.186	2.381	7.56	4.84

[DPH] = diphenylhydantoin (DPH) steady-state concentration; v = Ro = elimination velocity or rate out; k = first-order elimination rate constant; Cl = clearance; $t^1/_2$ = elimination half-life; MD = maintenance dose.
A quick plot of the data will show that: (*i*) a maintenance dose equal to the biotransformation or elimination rate (v) is not linearly related to the DPH steady concentration that will ensue; (*ii*) the first-order elimination rate constant (k, l/d) and clearance (Cl) = kVd, l/kg/d are not linearly related to [DPH]; and (*iii*) the elimination or biotransformation half-life, in contrast to k, is indeed linearly related to [DPH].

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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[6] and are indicated in Table I.

Although a number of methods have been devised to optimise DPH maintenance dosage,[7-11] 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 ($[DPH]_b$) 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.[12-14]

Table II. DPH concentration versus time data following administration of a test dose of DPH by slow IV injection

Patient No.	Mass (kg)	Age (yrs)	Dose (mg/kg)	$[DPH]_b$ (mg/l)	$[DPH]_p$ (mg/l)	$[DPH]_{24}$ (mg/l)
1	22.7	9	5.00	5.50	13.87	5.48
2	32.0	7	5.00	1.90	7.09	1.30
3	25.3	8	5.14	3.00	8.66	2.21
4	20.6	6	4.85	1.10	6.58	0.98
5	20.0	8	5.00	3.00	7.66	1.36
6	18.5	9	5.00	3.60	9.82	3.48
7	30.0	11	5.00	2.60	8.77	1.60
8	16.1	4	4.97	1.00	6.23	1.17
9	20.0	8	7.50	2.57	10.44	1.89
10	30.4	12	4.93	3.97	9.67	3.10

$[DPH]_b$ = the baseline DPH concentration immediately before administration of the IV test dose; $[DPH]_p$ = the peak concentration measured at the intercept of the best-fit linear concentration-time graph with the ordinate; $[DPH]_{24}$ = 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 [DPH]-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 ($[DPH]_b$) was collected and the DPH test dose was administered, in the same order, in rapid succession.

Peak concentration. The peak concentration ($[DPH]_p$), at time zero, was determined from the intercept of the [DPH]-time graph and the ordinate.

Volume of distribution (Vd). The apparent Vd was calculated from $[DPH]_b$, $[DPH]_p$ and the magnitude of the DPH test dose (D), as follows:

$$Vd = D / ([DPH]_p - [DPH]_b)\ l \quad (1)$$

Elimination rate or rate out (Ro, mg/l/h). Ro was calculated directly from the slope of the best-fit linear graph of the [DPH]-time data, as per Fig. 1.[15] Ro was also calculated from the two most distal [DPH]-time data points using the equation:

$$Ro = ([DPH]_{t1} - [DPH]_{t2}) / (t_2 - t_1)\ mg/l/h \quad (2)$$

in which $[DPH]_{t1}$ and $[DPH]_{t2}$ are DPH concentrations applicable to times t_1 and t_2 in the post-distribution phase. DPH concentrations measured at 6 and 24 hours after the test dose were used in the digital calculations.

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

$$MD = Ro \times Vd \times \tau,\ (mg/d) \quad (3)$$

in which τ is the dosage interval in hours, with 24 hours in the trial.

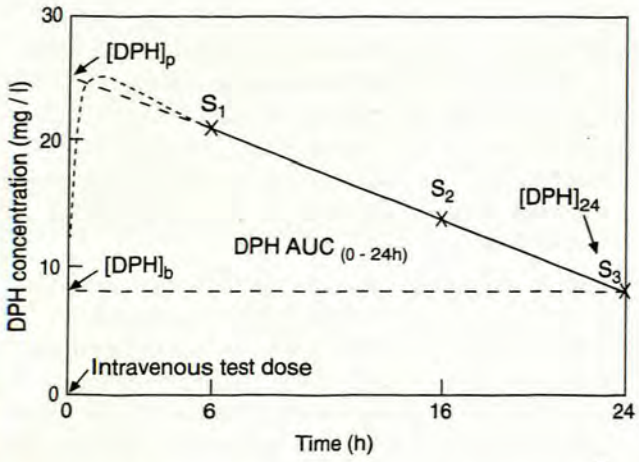

Fig. 1. Origins of concentration factors required for the determination of the DPH elimination velocity or rate out (Ro = v, mg/l/h) and volume of distribution (Vd, l). ($[DPH]_b$ = baseline concentration; $[DPH]_p$ = post-dose peak concentration following an IV test dose; S_1, S_2, S_3 = sampling times.)

Trough concentration ($[DPH]_{trough}$). The optimal trough concentration was calculated from the optimal therapeutic concentration, set at 15 mg/l for larger children and adults,[16] and the calculated MD expressed in terms of mg/l/d, as follows:

$$[DPH]_{trough} = (15 - (MD/2))\ mg/l \quad (4)$$

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

$$LD \text{ or } AD = Vd\ ([DPH_{trough} - [DPH]_{measured}),\ mg \quad (5)$$

RESULTS

The baseline ($[DPH]_b$), peak ($[DPH]_p$) and 24-hour post-dose ($[DPH]_{24}$) 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 ($[DPH]_{trough}$ mg/l), were calculated for each of the children. The results are shown in Table III.

Table III. Pharmacokinetic parameters of trial subjects following administration of an IV test dose of DPH

Patient No.	Mass (kg)	Vd (l/kg)	v = Ro (mg/l/h)	MD (mg/kg/d)	MD (mg/l/d)	$[DPH]_{trough}$ (mg/l)
1	22.7	0.597	0.350	5.02	8.40	10.80
2	32.0	0.963	0.241	5.57	5.78	12.11
3	25.3	0.908	0.270	5.88	6.48	11.76
4	20.6	0.885	0.233	4.95	5.59	12.21
5	20.0	1.073	0.263	6.77	6.31	11.85
6	18.5	0.804	0.265	5.11	6.36	11.82
7	30.0	0.810	0.298	5.79	7.15	11.43
8	16.1	0.950	0.211	4.81	5.06	12.47
9	20.0	0.953	0.357	8.17	8.57	10.72
10	30.4	0.865	0.278	5.77	6.67	11.67
Mean		0.8808	0.2766	5.7840	6.6370	
(± SD)		(0.1208)	(0.0449)	(0.9696)	(1.0786)	

Vd = apparent volume of distribution of DPH; v = Ro = DPH elimination velocity or rate out; MD = DPH maintenance dose; $[DPH]_{trough}$ = optimal target trough DPH concentration.

There was considerable inter-individual variation in our patients both in terms of the volume of distribution and the required daily maintenance dosage, as was to be expected among children of widely differing age, with means (± standard deviations) of 0.88 (± 0.12) l/kg for Vd and 5.78 (± 0.97) mg/kg/d for MD. The Vd of 0.88 (± 0.12) l/kg was considerably higher than that reported for adults, i.e. 0.64 (± 0.04) l/kg,[6] notwithstanding the fact that the Vd values were not determined under proper steady-state conditions. On the other hand, the mean (SD) of the required maintenance dosage

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.[7-11] 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.[17]

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_{max} 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 inexorably to toxic levels as shown hypothetically in trace D of Fig. 2.

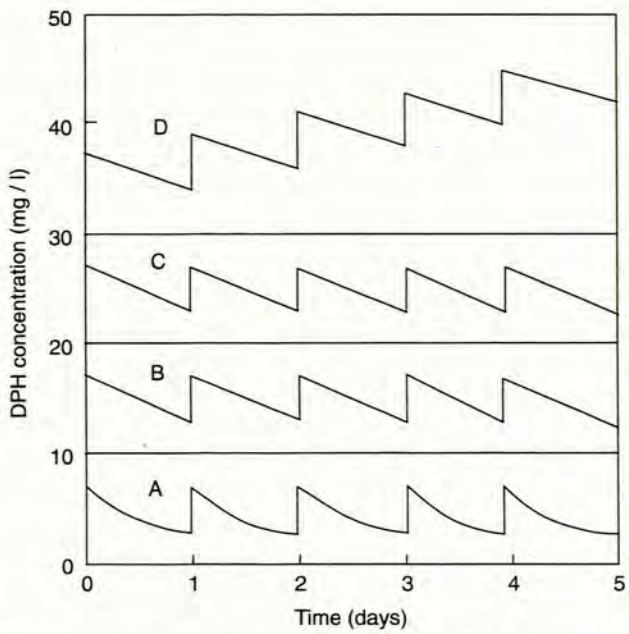

Fig. 2. Hypothetical concentration-time profiles (trace A = maintenance dose too low; trace B = maintenance dose optimal and concentration-time profile optimally located within the therapeutic range; trace C = maintenance dose correct but concentration-time profile inappropriately high; trace D = maintenance dose too high).

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.[18] 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.:

$$Vd = \text{mass (kg)} \times 0.64\ (l/kg)\ l, \quad (6)$$

0.64 ± 0.04 l/kg being the mean population parameter for children older than 12 years and adults (when concentrations are within the therapeutic range and at steady state). Population parameters for children vary considerably from those of adults and true steady-state conditions rarely apply; in difficult cases pro-active determination of the volume of distribution by the methods described are justifiable.

The impact of variation of DPH elimination characteristics from essentially first-order at lower concentrations to essentially zero-order at therapeutic and higher concentrations is shown graphically in sequence in Fig. 2. The usual distortions to the essentially linear [DPH]-time graph, caused by delays or lag-times in absorption and systemic distribution, have been ignored for the purposes of simplicity since they are essentially irrelevant in the therapeutic setting. The dosage-dependent [DPH]-time profile can generally be described by one of the four traces A to D constituting Fig. 2. Trace A: the MD, and consequently the therapeutic [DPH]-time profile, are too low; the correct MD should be determined and an adjustment dose of appropriate magnitude should be given to displace the [DPH]-time profile upwards into the therapeutic range. Trace B: the MD is optimal and the therapeutic [DPH]-time profile is satisfactorily located within the therapeutic range; no intervention is necessary. Trace C: MD is optimal but the [DPH]-time profile is located in the supratherapeutic region; the location of the profile should be displaced downward into the therapeutic range by withholding a DPH dose, or fraction of a dose, as appropriate. Trace D: MD is in excess of the maximal permissible MD (V_{max} in classic Michaelis-Menten concepts) and the [DPH]-time data indicate excessive and ever-increasing concentrations; DPH dosage should be withheld until concentrations fall within the therapeutic range, and an appropriate MD should be determined directly from appropriately spaced [DPH]-time data as concentrations decline.

It is clear from Fig. 2 that allowance must be made for any dose of DPH that the patient neglects to take or any additional dose that the patient accidentally takes, by appropriately adding a dose or withholding a dose as the situation demands. An adjustment dose may be administered at any time but large doses should be subdivided and administered at appropriate intervals, e.g. the larger portion should be administered at bedtime. A constant and meticulous record of DPH dosage should be kept in order to be able to balance dosage excesses and deficits weekly. It should be borne in mind that if a patient takes one MD extra, or neglects to take a single MD, he or she will effectively be and remain overdosed or underdosed,

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.	If [DPH] is subtherapeutic condition A in Fig. 2 applies.
2.	Withhold therapy and repeat [DPH] determinations 12-hourly until [DPH] approaches 10 mg/l.	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.
3.	From the slope of the linear graph of the [DPH]-time data determine the correct MD.	From the slope of the linear graph of the [DPH]-time data determine the correct MD and the Vd.

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.

[DPH], mg/l = DPH concentration; IV injection should proceed at a rate not exceeding 0.75 mg/kg/min;[12-14] MD, mg/l/d — calculate the maintenance dose using equation 3, consulting Fig. 1 and the text for clarification; LD or AD, mg — calculate the most appropriate loading dose or adjustment dose using equation 5; use the individual-specific volume of distribution, *vide infra*, if known, and population parameters if not; Vd, l — calculate the volume of distribution using equation 1, consulting Fig. 1 and the text for clarification; Trough concentration ($[DPH]_{trough}$), mg/l — calculate the most appropriate $[DPH]_{trough}$ value using equation 4 and consulting the text for clarification.

respectively, until such time as appropriate adjustment is made.

A flowchart summarising the steps that should be followed when managing aberrant DPH concentrations is shown in order to fix concepts, as well as for convenience. It is helpful, initially, to pay particular attention to the units being used in a particular equation; as familiarity with procedures develops interconversion between units presents no real difficulties.

To obtain a true steady-state concentration in the therapeutic range in a patient receiving treatment with oral DPH requires meticulous compliance with a precisely determined and correct MD, constant absolute bio-availability characteristics of the DPH formulation being administered and constant absorption from the gut over a sufficiently long period of time. In the practical therapeutic setting such a condition, not requiring ongoing therapeutic monitoring, adjustment and correction, is the very rare exception rather than the rule. The only workable way in which to ensure acceptable, if not optimal, therapeutic results in less sophisticated populations is to encourage full co-operation between physician and patient in an attempt to ensure compliance; use of high-quality DPH formulations; and skilful application of adjustment and correction techniques based on high-quality routinely generated analytical [DPH] data.

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