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Optimization of phenytoin therapy in adults with epilepsy in the Western Cape, South Africa

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SUMMARY

Objective: To assess the extent to which adults with epilepsy were optimized and individualized on phenytoin monotherapy in the Western Cape, South Africa and to estimate the average optimized dose and serum phenytoin concentration, and the therapeutic range for this patient group.

Methods: Patients were considered to be optimized on phenytoin if they were seizure-free or the best compromise was achieved between seizure reduction and side-effects.

Results: 538 (233 black and 305 coloured) adult people with epilepsy were treated at nine epilepsy clinics as outpatients. Of these patients, 332 (226 male and 106 female, 149 black and 183 coloured) were included in the data analysis as they were considered to have reliable phenytoin levels. Phenytoin doses and steady-state serum concentrations were predicted using the Michaelis–Menten equation. Patients attended a clinical pharmacokinetic service for 7·7 ± 5·3 (range 1–22) months. The average optimized dose was 305·8 (range 100–500) mg/day and the average optimized level was 62·7 ± 23·9 (range 15–133) μmol/l. Most patients (61·9%) were optimized in the therapeutic range 40–79 μmol/l; 21·1% were optimized above and 17% below this range. In 1·6% of patients serum concentrations above 120 μmol/l were required. Dosage adjustments were made in 47·0% of patients, increased in 31·9% and reduced in 15·1%.

Conclusion: These findings indicate that many patients (47%) attending outpatient clinics were not optimized on phenytoin therapy.

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INTRODUCTION

Due to the nonlinear pharmacokinetics of phenytoin, the serum concentration of phenytoin is difficult to interpret pharmacokinetically (1). This justifies the optimization and individualization of phenytoin therapy (2). Patients were considered to be optimized on phenytoin if they experienced not more than one seizure in 3 months. The objective of the study was to determine the extent to which adults with epilepsy attending outpatient clinics in the Western Cape, South Africa were optimized and individualized on phenytoin monotherapy. These results should help to determine whether there was a need for a clinical pharmacokientic service. Information on the optimized dose and the therapeutic range for this patient group should also provide useful information when offering such a service.

A clinical pharmacokinetic service (CPKS) provides support for the optimization and individualization of a patient's response to drug therapy. This can be achieved by dosage regimen analysis, design, modification and calculation, based on pharmacokinetic data and serum drug concentrations. It is primarily about interpreting serum drug concentrations to make clinical decisions. Clinical pharmacokinetic services are introduced for two main reasons: to improve the quality of health care and to decrease costs. The cost-effectiveness of such a service has been demonstrated (3). Because of the national cost-containment pressures on hospitals in South Africa, this service is likely to become increasingly important.

METHOD

Patients

A total of 538 (233 black and 305 coloured) adult people with epilepsy was treated by the CPKS. Of

these patients, 332 (226 male and 106 female, 149 black and 183 coloured) were included in the data analysis as they were considered to have reliable phenytoin levels. All patients were treated on an outpatient basis, were on phenytoin monotherapy and were registered after confirmation of the diagnosis by and referral from a neurology department of the local teaching hospitals.

Six day-hospitals, a neurology outpatient clinic, the South African National Epilepsy League (SANEL) protective workshop and a school for people with epilepsy were chosen. All of the clinics are situated in the Western Cape, South Africa.

Inclusion critera

All patients satisfied the following inclusion criteria: compliant with drug therapy and able to understand the instructions; above 16 years of age; no hepatic or renal disease; no evidence or history of alcohol or drug abuse; no major depressive or psychiatric diseases; no intake of medicines that might interfere with phenytoin serum levels within two weeks of entering the study; taking phenytoin routinely as the only anticonvulsant; taking phenytoin by oral administration only; and not pregnant or breastfeeding.

Pharmacokinetic consultations

In order to assess the extent to which patients were optimized and individualized on phenytoin monotherapy, each patient was seen personally by a pharmacokinetic consultant. The main purpose of the first interview was to gather information about the patient and to establish a baseline regarding seizure frequency and adverse effects. During the first interview, demographic and medical data were collected which included the patient's age, mass, height, frame size, concurrent medication, duration of therapy and dosages, alcohol intake, history of seizure duration, frequency and clinical features, and drug history with emphasis on the history of anticonvulsant therapy. The hospital folder was carefully examined for information such as the seizure type, the cause of the seizures and adverse effects.

The patient was given a diary and asked to record seizures and any side-effects or comments corresponding with the date when the events occurred. An explanation was given as to what to do in the event of missing a dose/s when the patient was on a once-, twice- or thrice-a-day dosage regimen. Patients were usually reviewed once a month. Poorly controlled patients were seen more frequently, either to obtain a duplicate blood sample for phenytoin concentration or to adjust the dose. The patient was counselled about phenytoin use and this advice was reinforced by written instructions. The patient was also informed that the full therapeutic response of phenytoin might only be obtained 4 weeks after the initiation of therapy or following a change in dose. Patients and their families were informed about epilepsy, the signs and symptoms of phenytoin toxicity and the importance of drug compliance was stressed.

Blood sample collection and assay

If the patient was compliant and at steady state at the second and subsequent consultations, a blood sample for serum phenytoin concentration was collected. The times of the last dose and when the blood sample was collected were documented. For the purpose of dose evaluation the first blood sample for the measurement of serum phenytoin concentration was taken after a minimum of 4 weeks (4–6) on a constant maintenance dose. Subsequent samples were taken after intervals of 2–4 weeks, provided the dosage regimen was the same and compliance was optimal (7). When necessary the time to reach steady-state was calculated. A few days to a week were allowed between the calculated time taken to reach steady state (8) and the blood collection to ensure that a steady state had been achieved. Total serum phenytoin concentrations were measured with a fluorescent polarization immunoassay using an automated TDxFLx^{R} system (Abbott Laboratories, Diagnostic Division, North Chicago).

Dose calculation

If the serum phenytoin level was below the therapeutic range and the patient was seizure-free, no adjustment was made. Phenytoin doses were modified according to clinical response. If the serum phenytoin level was subtherapeutic, as indicated by inadequate seizure control and an absence of toxicity, there was a need to adjust the dose. If a reliable feedback serum level was available, this was used in the calculation of a

new dose (9). The Michaelis–Menten equation (2) was used. A Michaelis–Menten constant (Km) of 4·4 mg/l (17·4 μmol/l) was assumed and the Vm (maximum metabolic rate) was calculated.

If at least two reliable steady-state serum phenytoin levels on different daily doses were available, the patients individual Vm and Km were calculated (2, 10). These individual parameter estimates were used to estimate a new dose, using the Michaelis–Menten equation. When more than two dose: serum concentration pairs were available, the Bayesian technique of drug dose optimization was employed using OPT^{R}, version 4·1 b (Clydesoft Statistical and Scientific Software, Lanarkshire, U.K.) (11). A laptop computer was used at the clinics to run OPT^{R}. The most likely estimates of Vm, Km and dose were derived. Doses were often calculated for two target serum phenytoin concentrations. Dosing recommendations based on the pharmacokinetic calculations were decided on by the clinical judgement of the consultant.

Doses were often adjusted empirically without pharmacokinetic calculations. A modification of the recommendations of Mawer *et al.* (12) and Aronson *et al.* (13) was used. The daily dose was usually prescribed as a single dose (14). Epanutin Infatabs^{R} (phenytoin acid) were used for small increments or decrements of dose.

Compliance was assessed by an extensive patient interview, tablet counts (15), correct completion of the patient's diary and variation between two measured serial serum phenytoin concentrations taken at different times on the same dose (16). After steady state was attained and if the variation between two serum phenytoin concentrations on the same dose was less than 20%, the patient was considered compliant (17, 18).

Treatment optimization

Patients were considered to be optimized on phenytoin if they were seizure-free or the best compromise was achieved between seizure reduction and side-effects.

RESULTS AND DISCUSSION

Patient data

Of the 538 patients who entered the CPKS, 206 (38·3%) defaulted by not attending the clinic regularly. Of these, only 22·8% had been optimized on phenytoin or did not require treatment and the remainder defaulted on attendance, even though they were not ideally controlled. 49·7% of the patients smoked cigarettes. Smoking has been shown to influence the Vm of phenytoin significantly (19).

The demographic characteristics of the patients are shown in Table 1. Two hundred and sixty-five dosage adjustments were made during the CPKS in 156 patients. Some spent as many as 14 months in the service without producing a reliable serum phenytoin level for dosage adjustment. Dose adjustments were made in 47·0% of patients (Table 2). When considering only the patients in whom dosage adjustments were made, one, two or three dosage adjustments were made in 69·8, 24·4 and 5·8% of patients, respectively. If only patients optimized on phenytoin were considered, the results showed little difference. Patients attended the CPKS for 7·7 ± 5·3 (range 1–22) months. The average optimized dose of phenytoin was 305·8 mg/day, range 100–500 mg/day. This value may be skewed as the calculation did not take into account the lowest dose necessary to control the seizures. Many patients were started on 300 mg/day phenytoin and the small increments and decrements in doses made were probably overshadowed by the large number of patients on 300 mg/day phenytoin. In our outpatient clinics the standard dose of phenytoin 300 mg/day as an initial dose is acceptable if this is compared to an average optimized dose of 305·8 mg/day as found in the present study. The number of prescriptions for 50 mg phenytoin sodium and 25 mg phenytoin acid (half an Epanutin Infatab^{R}) increased from 20 to 116 and from 0 to 51, respectively. The following doses of phenytoin sodium (mg/day) were prescribed: 100, 150, 177, 200, 227, 250, 277, 286, 300, 307, 314, 327, 334, 341, 350, 364, 377, 384, 400, 414, 427, 450 and 500. Note that 25 mg phenytoin acid is equivalent to 27 mg phenytoin sodium. These doses were attained with 100, 50 and 27 mg (i.e. half an Epanutin Infatab^{R}) phenytoin sodium. Even an increase of 27 mg/day phenytoin sodium in a few instances was too large and it was necessary to prescribe, e.g. 400 and 427 mg on alternate days. An extra 50 mg phenytoin twice a week was occasionally recommended.

The relationship between the therapeutic concentration range of phenytoin and the number of patients optimized in the specific range is given in Table 3. Most (61·9%) were optimized in the therapeutic

Table 1. Demographic characteristics of patients regularly attending the clinical pharmacokinetic service

	$n=332$ Mean (SD)	Range
Age (y)	36·4 (14·1)	15·0–82·0
Height (cm)	166·2 (9·4)	142·5–197·0
Mass (kg)	64·0 (12·7)	36·9–135·0
Body surface area (m^2)	1·7 (0·2)	1·2–2·6
Duration in study (months)	7·7 (5·3)	1·0–22·0
Duration of epilepsy (y)	11·3 (8·8)	1·0–48·0
Phenytoin dose at start of study (mg/d)	299·1 (53·4)	100·0–500·0
Phenytoin dose at end of study (mg/d)	310·4 (64·9)	100·0–500·0
Optimized phenytoin dose (mg/d)	305·8 (60·7)	100·0–500·0
Optimized phenytoin level (μmol/l)	62·7 (23·9)	15·0–133·0

Table 2. Percentage of patients in whom the phenytoin dose was either increased, decreased or unchanged

	Percentage of patients $n=332$
Dose increased	31·9
Dose decreased	15·1
No change in dose	53
Dose adjusted	47

Table 3. Relationship between therapeutic concentration of phenytoin and the percentage of patients optimized at that concentration range

Therapeutic concentration (μmol/l)	Percentage of patients $n=171$
0·0–19	0
20–39	17
40–59	31·2
60–79	30·7
80–99	10·9
100–119	8·6
120–139	1·6

range 40–79 μmol/l. This therapeutic range for phenytoin is the same as that reported in literature (10). A significant number of patients (21·1%) was optimized on phenytoin at serum concentrations above that, and 1·6% required serum concentrations above 120 μmol/l. On the other hand, 17% were optimized at serum levels below 40 μmol/l.

In conclusion, only 47% of patients were optimized on phenytoin. There is undoubtedly a need for a CPKS in these hospitals. The optimization and individualization of phenytoin therapy reduced seizure frequency by 64·8% and adverse effects by 84·4%. As it is not within the scope of this paper, the benefits of our CPKS have been discussed in detail elsewhere (20). This CPKS was offered for a period of 22 months as a result of a generous sponsorship from a pharmaceutical company. It is hoped that the Department of Health in South Africa will consider establishing posts so that this service to optimize phenytoin therapy could be offered. A pharmacokinetic consultant working at various centres on a rotational basis will serve the needs of our patients. The data described in this paper provide support for a service to optimize phenytoin therapy.

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