BENEFITS OF A CLINICAL PHARMACOKINETIC SERVICE IN OPTIMISING PHENYTOIN USE IN THE WESTERN CAPE

P Valodia, M A Seymour, B M Kies, P I Folb

Objectives. To study the benefits of a clinical pharmacokinetic service in optimising phenytoin use in the Western Cape.

Design. Assessment of the response to treatment was based on the number of seizures during the 3 months before entering the study (first baseline period), 3 months after entering the study (second baseline period) and 3 months before the termination of the study (test period). Patients kept a seizure diary throughout the study. The Michaelis-Menten model was used to calculate doses and predict steady-state serum concentrations.

Setting. Nine epilepsy clinics.

Subjects. One hundred and ninety-five (113 black and 82 coloured) compliant people with epilepsy receiving generic phenytoin monotherapy.

Outcome measures. Reduction in seizure frequency and adverse effects.

Results. A reduction in seizure frequency (64.8% compared with pre-optimisation) was experienced by 64.9% of patients. Mean seizure frequency was reduced from 3.39 to 1.18 per month. Reductions in seizure frequency of 100% and more than 50% were reported by 39.2% and 58.7% of patients, respectively. Adverse effects of phenytoin were reduced from 20.5% at the first visit to 3.2% at the last visit.

Conclusion. The clinical pharmacokinetic dosing service for phenytoin applied in this study contributed significantly to the success of epilepsy management.

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Department of Pharmacology, University of the Western Cape, Bellville, W Cape
P N Valodia, BPharm, MPharm, PhD

Warner-Lambert Pty Ltd (South Africa), Retreat, Cape Town
M A Seymour, MB ChB, BSc Hons, FFPM (RCP)

Department of Neurology, University of Cape Town and Groote Schuur Hospital, Cape Town
B M Kies, MB ChB, FCP (SA), MRCP (UK)

Department of Pharmacology, University of Cape Town
P I Folb, MB ChB, MD, FRCP, FCP (SA)

Numerous investigators have shown the benefit of monitoring serum phenytoin concentrations in maximising efficacy and in reducing toxicity to a minimum. Optimal therapy with phenytoin requires that its administration be tailored to each patient.[1,2] Phenytoin is one of the few drugs where saturation of the metabolising enzymes occurs at therapeutic serum concentrations. Serum phenytoin concentrations do not change in proportion to dose; instead a small increase in phenytoin dose may result in a disproportionately large increase in serum phenytoin concentration.[3]

A clinical pharmacokinetic service (CPKS) can play an important role in effectively controlling epilepsy. A CPKS involves the optimisation and individualisation of a patient's dose and response. The primary objective of this study was to show the benefits of a CPKS in optimising phenytoin use in the Western Cape. Reductions in seizure frequency and adverse effects were used as the therapeutic endpoints.

METHODS

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 for the study. All the clinics were situated in the Cape Town area. The Day Hospital Organisation consists of health care centres for outpatients, providing primary health care to low-income people who are not covered by medical aid (health insurance). Patients were enlisted after confirmation of the diagnosis at and referral from a specialist neurology unit. Written informed consent was obtained in each case before entry to the study. Data were collected between August 1990 and July 1992.

Patients

All ambulant adults with epilepsy who routinely took phenytoin as a single anticonvulsant (538 in number) were screened for entry into the study. Of these, 332 were compliant, and had serum phenytoin concentrations to be expected from their daily drug dose. All 332 were included in assessment of the adverse effects. Altogether 195 patients met the entry criteria for assessing reduction in seizure frequency. In order to evaluate seizure frequency, two criteria were set for each patient. Firstly, the patient needed to have participated in the study for a minimum of 6 months, so that the baseline (control) and test periods did not overlap; and secondly s/he needed to have attended the clinic for no less than 6 consultations. All patients received phenytoin monotherapy and each one was seen individually by the pharmacokinetic consultant as an outpatient.

Compliance was assessed by means of comprehensive patient interview, tablet count,[4] checking the prescription chart, correct completion of the patient's diary, and variation between two serial serum phenytoin concentrations taken at different

times after the same dose.[5] After steady state was attained, and provided the variation between the two serum phenytoin concentrations after the same dose was less than 20%, the patient was considered to be compliant.[6,7]

Clinical pharmacokinetic service

Altogether, 2 748 consultations were conducted. The Michaelis-Menten model was used to calculate dose and to predict steady-state serum phenytoin concentrations. This model uses estimates of the maximum metabolic rate (Vm) and the Michaelis-Menten constant (Km) of phenytoin to perform its functions.[8,9] Details of the service have been described elsewhere.[10]

During the first interview demographic and medical data were obtained from the hospital folder and from the patient. This included concurrent medication, duration of therapy and dose, alcohol intake, history of other diseases, history of seizures and their frequency, description of seizures, previous admissions to hospital, and drug history, with emphasis on anticonvulsant therapy. The patient was given a diary to record seizures, adverse effects and when phenytoin was taken. Patients were seen once a month, with a few exceptions who attended more frequently.

When necessary, the Bayesian method of drug dose optimisation was used (OPT, version 4.1b, Clydesoft Statistical and Scientific Software).[11] A laptop computer was used at the clinics to run the OPT programme. The most likely estimates of Vm, Km and dose were determined, with doses calculated for two target serum phenytoin concentrations. The nearest practical dose attainable with 100 mg, 50 mg and 27 mg phenytoin sodium was used, and the corresponding target phenytoin concentration was calculated and reported. Dose recommendations were based on the judgement of the pharmacokinetic consultant.

Assessment of seizure frequency

Response to treatment was assessed over 3 months.[12] This was based on the number of seizures during the 3 months before entering the study (first baseline period), 3 months after entering the study (second baseline period) and 3 months before the termination of the study (test period). The average number of seizures occurring during the first and second baseline periods was taken as the initial frequency. To minimise the influence of non-compliance, patients in the second baseline period were given the same counselling and service as in the test period.

Assessment of adverse effects

Adverse effects of phenytoin were assessed at every visit by direct enquiry or by clinical examination. The main adverse effects looked for were dizziness, diplopia, blurred vision, nystagmus, tremor, slurred speech and ataxia. Lower limb ataxia was assessed at every visit, but upper limb ataxia was only assessed if considered necessary by the consultant. The patient and family or close friends were questioned as to whether the patient staggered or had an ataxic gait. The time of day when adverse effects occurred was noted, as was whether or not these effects occurred concurrently. Less frequent and serious adverse effects of phenytoin were recorded.

RESULTS

Table I presents the total number of seizures experienced during the first and second baseline periods and the test period. The percentage reduction in seizure frequency based on the first and second baseline periods and an average of the two are reported in Table II. No meaningful difference was found when the first or second baseline periods were compared with the test period (66.4% and 63.2%, respectively). This was surprising as patients received counselling and kept seizure diaries during the second baseline period. It is possible, however, that there was under-reporting of the number of seizures during the first baseline period. When reduction in seizure frequency was based on the average of the first and second baseline periods, reductions of 60.1% and 69.5% were obtained in black and coloured patients, respectively. In 79 patients the dose of phenytoin was adjusted within 3 months of entering the study. As seizure frequency during this period reflected the second baseline period, the reduction in seizure frequency referred to above is an underestimate.

Table I. Total number of seizures experienced during the first and second baseline periods and the test period (195 patients)*

Period	Number of seizures
First baseline period	667
Second baseline period	588
Test period	216

*Only patients who participated in the study for at least 6 months and who attended the clinic for a minimum of 6 consultations were included in the analysis.

Table II. Percentage reduction in seizure frequency (195 patients)

Period	Percentage reduction in seizures
Based on the first baseline period	66.4
Based on the second baseline period	63.2
Based on the average of the first and second baseline periods	64.8

Reduction in seizure frequency was grouped into five categories, as indicated in Table III. Of 195 patients who satisfied the inclusion criteria, 64.9% experienced a reduction in seizure frequency. The remainder (35.1%) were either seizure-free on entering the study or experienced no drop in frequency. Two patients reported an increase in number of seizures. This was attributed to severe stress and was not considered a result

of the CPKS. A 100% reduction in seizure frequency was reported by 39.2% of patients during the test period. Monthly seizure frequencies (mean and range) for the first and second baseline and test periods are reported in Table IV. The mean monthly seizure frequency was reduced from 3.39 (range 0 - 48) to 1.18 (range 0 - 16), based on comparison with the average number of seizures occurring during the first and second baseline periods.

Table III. Percentage reduction in seizure frequency grouped into various categories (195 patients)*

Reduction in seizure frequency (%)	Percentage of patients
0	35.1
1 - 24	0.5
25 - 49	5.7
50 - 74	12.3
75 - 99	7.2
100	39.2

* Patients who were already controlled on phenytoin are included in this analysis.

Table IV. Mean seizure frequency per month for specific periods before and after the initiation of the study (195 patients)

	Seizure frequency per month	
Period	Mean	Range
First baseline period	3.62	0 - 48
Second baseline period	3.15	0 - 29
Test period	1.18	0 - 16

Patients whose seizure frequency had fallen from baseline level by 50% or more in the test period were considered to have had good improvement in seizure control. Less than 50% reduction was regarded as poor to intermediate improvement.[13] According to these criteria, 58.7% had good improvement in seizure control.

At the first visit, 20.5% of patients had experienced adverse effects considered to be related to phenytoin, while at the last visit 3.2% had experienced adverse effects. The decision regarding whether or not the adverse effects were related to phenytoin was based on serum phenytoin concentration and the clinical judgement of the consultant.

Discussion

This study shows the benefits of a CPKS in the reduction of seizure frequency and adverse effects. Benefits of the service were measured by clinical response and not by the achievement of a target drug concentration as end-point. Compliance was assessed, as far as possible, by serial serum phenytoin concentrations taken at different times after the same dose. Reduction in seizure frequency can be attributed primarily to the CPKS and not to improved compliance. The second baseline period was taken into consideration in order to minimise the influence of non-compliance on the interpretation of results. The significant reduction in adverse effects of phenytoin is noteworthy; as far as possible these adverse effects were confirmed by serum phenytoin concentrations.

A number of clinicians change one anti-epileptic drug for another without ensuring that treatment is optimal. This study shows that a considerable improvement in seizure frequency can be obtained by optimising phenytoin treatment.

Conclusion

This study demonstrated the contribution of a CPKS in optimising phenytoin use in people with epilepsy in the Western Cape. CPKS effectiveness is reflected in the reduction in seizure frequency, and in the reduced adverse effects experienced. It is hoped that these findings will provide impetus for the implementation of a permanent CPKS to optimise phenytoin use in this region.

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