Hospital Prescribing of Phenytoin for Epilepsy

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Phenytoin is a first-line anticonvulsant for the treatment of most forms of adult epilepsy[1]. However, it is a difficult drug to use because of its narrow therapeutic ratio; serum phenytoin concentrations below 40 μmol/litre are often ineffective while serum concentrations above 80 μmol/litre are likely to be associated with toxicity[2-4]. A curvilinear relationship between dose and serum concentration compounds the difficulties, often necessitating the use of small (25-50 mg) dosage increments to achieve maximum efficacy without toxicity[5-7]. Serum phenytoin monitoring is now widely available and should facilitate the management of epileptic patients[8] so that about 90 per cent of such individuals may be fit-free while receiving once daily treatment with phenytoin alone[9-12]. Not only should the simplicity of this regimen enhance compliance[13], often poor among epileptics[14], but it is clearly more cost effective.

The major principles underlying the optimal use of phenytoin are not new[2] and have received considerable publicity in recent years. In order to assess the impact of advances in clinical pharmacology on the care of epileptic patients we have studied the extent of deviation from 'ideal' prescribing and seizure control.

Patients and Methods

Group I

All out-patient anticonvulsant prescriptions for adults at a major Sheffield hospital from November 1977 to October 1978 inclusive were examined. Information regarding the type of anticonvulsant used, daily phenytoin dose and dosage interval was noted.

Group II

At the same hospital, laboratory records (surnames A-G inclusive) of serum phenytoin concentrations measured between October 1977 and April 1979 were examined. Note was taken of phenytoin serum concentration, daily dose and other drugs used. Where more than one serum drug measurement had been made in an individual, only the most recent concentration was used.

With the consent of consultants in charge of patients from this group, 109 case notes were reviewed to determine the diagnosis, fit frequency, drug treatment and serum phenytoin concentration at the time of blood sampling. Where possible, fit frequency and drug treatment over the previous year were also noted in order to assess any change in seizure control in relation to treatment. Frequency of fits per month was assessed retrospectively from the number of fits reported since the previous visit (usually 3-6 months). Patients were classified into 4 groups according to diagnosis:

1. Major epilepsy (tonic/clonic, temporal lobe and focal motor seizures).
2. Minor epilepsy (sensory, akinetic/myoclonic seizures).
3. Unspecified (diagnosis unclear from notes).
4. Neurosurgical (all neurosurgical patients).

Phenytoin Assay

Phenytoin was measured by gas liquid chromatography[15]. The coefficient of variation of the assay was 4 per cent, and the mean per cent deviation from the St Bartholomew's Hospital Quality Control was ± 8 per cent.

Statistical Methods

The chi-square test was used to assess differences in findings between the groups, and significance was assumed when p was <0.05.

Results

Group I

Among approximately 25,000 prescriptions there were 305 for anti-epileptic drugs. Of these, 189 were for phenytoin (Fig. 1) either prescribed as a single drug (60 per cent) or in combination with other anticonvulsants.
The daily dose of phenytoin was usually 300 mg or less (Table 1), being greater than 300 mg in only 8.9 per cent of scripts. The smallest capsule or tablet size prescribed was 100 mg in 90 per cent of scripts. Patients were advised to take their medication twice (32 per cent) thrice (57 per cent) or four times a day (6 per cent). In only 5 per cent was phenytoin prescribed on a once daily basis and many of these scripts were for a daily dose of 100 mg or less.

**Table 1. Daily dose of phenytoin prescribed.**

| mg   | Group I n = 189 | Group II n = 229 |
|------|-----------------|------------------|
| <100 | 13 (7.3%)       | 7 (3.1%)         |
| 101-200 | 55 (30.7%)      | 36 (15.7%)       |
| 201-300 | 95 (53.1%)      | 136 (59.4%)      |
| 301-400 | 15 (8.4%)       | 44 (15.7%)       |
| 401-500 | 1 (0.5%)        | 5 (2.2%)         |
| >500  | 0               | 1 (0.4%)         |

Mean dose 263 mg 303 mg*

*means dose among neurosurgical patients was 311 mg/day.

**Group II**

Subjects from Group II were receiving a slightly higher mean daily phenytoin dose than those from Group I (Table 1). This was attributable to proportionately fewer subjects taking 200 mg or less ($x^2 = 35.8$, $p<0.01$), while a greater proportion were on a dose above 300 mg ($x^2 = 50.6$, $p<0.01$). The smallest capsule or tablet size used was 100 mg in over 90 per cent but 25 mg in only 0.5 per cent.

In addition to phenytoin, 56.8 per cent of patients were receiving other anticonvulsants, phenobarbitone in 80.0 per cent. The incidence of polypharmacy was therefore significantly higher in this group than in patients in Group I ($x^2 = 26.2$, $p<0.01$) and 20 per cent of patients were prescribed three or more anticonvulsants.

Serum phenytoin concentrations were within the therapeutic range (40-80 μmol/litre) in 31.8 per cent of patients but below these levels in 58.6 per cent (Fig. 2).

**Fig. 2. Serum phenytoin concentrations in 229 outpatients.**

Patients whose case notes were examined were representative of the entire group with respect to phenytoin dose, serum concentration, evidence of polypharmacy and proportion attending medical and neurosurgical clinics. Fit frequency was clearly recorded in 100 of 109 case notes and subsequent analysis was confined to these (Table 2). Forty-seven per cent were fit-free (84 per cent of neurosurgical but only 38 per cent of medical patients). There was no correlation between fits reported and serum phenytoin concentration on attendance. Among patients with major epilepsy who were not fit-free, seizure frequency was one or more per month in 13 of 16, 12 of 15 and 4 of 5 with serum phenytoin concentrations <40, 40-79 and >80 μmol/litre, respectively. Fifty patients had attended the same clinic approximately one year earlier. At this time, 30 reported seizures but drug dose was later altered in only 12.

**Table 2. Proportion of patients reporting freedom from seizures in relation to serum phenytoin concentration.**

| Classification of epilepsy | Serum phenytoin concentration μmol/litre |
|----------------------------|------------------------------------------|
|                            | <40 | 40-79 | >80 |
| Major                      | 9/25 (36%) | 7/22 (32%) | 2/7 (29%) |
| Minor                      | 4/11 (36%) | 3/6 (50%) | - |
| Unspecified                | 2/6 (33%) | 3/3 (100%) | 1/1 (100%) |
| Neurosurgical              | 9/9 (100%) | 5/8 (63%) | 2/2 (100%) |
Discussion

Despite its use as a first-line drug, there was considerable deviation from 'ideal' phenytoin prescribing. Considering that on average a 350-400 mg daily dose is required to achieve a serum concentration of 40-80 µmol/litre [2,6,16] the mean dose used was low. Fine dose titration and once daily dosage were rare. Polypharmacy, however, was common, particularly in Group II, even though serum phenytoin concentrations were usually below 40 µmol/litre. Treatment could have been simplified if serum drug monitoring had been used as a guide to the need for an additional anticonvulsant.

A low serum phenytoin concentration may be appropriate for a patient who is free from fits. However, over half the patients studied reported having fits since their most recent visit and in most cases the attack rate was over one a month. The findings are not peculiar to Sheffield[17]. Poor control may often be due to insufficient drug in the body. The majority of patients reporting seizures had serum phenytoin concentrations below 40 µmol/litre due to an inappropriately low dose or to non-compliance with medication; the latter may have been associated with polypharmacy and the use of 3 to 4 doses a day[13,18]. However, patients in whom serum phenytoin concentrations were greater than 40 µmol/litre reported fits as often as those with a lower concentration. Large fluctuations in serum phenytoin concentrations have been reported among patients seen on several occasions at routine clinics while taking the same dose[19]. In view of the long half-life of phenytoin[11,12] this observation is likely to be due to intermittent non-compliance, which explains in part the poor correlation between serum concentrations and response.

Nevertheless, patients may vary in their response to a given serum phenytoin concentration. This is not surprising since epilepsy is a heterogeneous disorder. Resistance is most commonly seen in temporal lobe or focal motor seizures[20], while among neurological patients prophylaxis with phenytoin is highly effective. An erroneous diagnosis must be excluded as a cause of apparent resistance; such patients are likely to be labelled as suffering from akinetic or sensory epilepsy[21] and we have therefore separated this group (minor epilepsy). Our analysis is not at variance with the concept of increasing pharmacological effect with increasing serum drug concentration but emphasises the need for individualising phenytoin dosage. Richens[22] has suggested 100 µmol/litre as a guide to the upper end of the so-called therapeutic range and recommends small dose increments to achieve high concentrations where necessary; signs of toxicity such as nystagmus may be used as a guide to the maximum suitable dose for an individual. Only patients who fail to respond to this regimen may be considered resistant to monotherapy.

There may be several reasons for the apparent deviation from optimal management of epileptic patients. In some cases their regimens may have been long established and in the presence of good seizure control there could be little point in attempting to alter the management. However, at medical clinics patients with good control were in the minority. Physicians may be ignorant of the pharmacokinetics of the drugs used, the reasons for apparent resistance, and the need to simplify treatment to enhance compliance. These are unlikely to be the only explanations, since no additional treatment was given to most patients reporting fits, and we suggest that doctors may regard chronic stable epilepsy as clinically acceptable. This is particularly so because intervention in patients already receiving treatment may be less successful[23] than is optimal monotherapy in subjects presenting de novo[9]. The poor continuity of care of epileptics[24] may further account for non-intervention. We did not study continuity of care directly but, judging from the relatively small number of hospital scripts (Group I) in contrast to the potential number of patients attending hospital for epilepsy in Group II, it is certain that patient care was often shared, with most subjects receiving anticonvulsants from the general practitioners.

We have studied a selected group that may represent the more difficult epileptic patients in the community[25]. Therefore, we may have over-estimated the proportion of patients with poor control of fits. However, as the number of patients attending hospital clinics was large, the size of the problem must not be underestimated. Patients should be discharged if intervention is inappropriate. In the remainder, a simple regimen should be used aggressively in order to minimise the morbidity from this condition[26]. Continuity of care is likely to be a prerequisite to successful management.

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A Colour Atlas of Diabetes by Arnold Bloom and John Ireland. Wolfe Medical Publications Ltd, 1980. 119 pages. Price £15.

To those outside the field of diabetes, Bloom and Ireland may sound like a new novel by James Joyce; for the initiated, however, the names represent two of the doyens of diabetes. Arnold Bloom is the Chairman of the Medical and Scientific Section of the British Diabetic Association, and has recently retired as consultant physician at the Whittington Hospital in London. John Ireland is consultant physician at Southern General Hospital, Glasgow, and an authority on renal disease in diabetes. They have put together in this book a collection of nearly 300 colour pictures covering many aspects of the pathology and clinical presentation of diabetes.

The book, they say, is not designed as a manual of instruction on the management of diabetes; its purpose is to present the clinical and histological manifestations of the condition in graphic form. The target audience is stated as medical students, house physicians and general practitioners wishing to gain a better understanding of the disease.

The quality of a colour atlas must be judged on its pictures and, by this criterion, the book is an excellent one. Not surprisingly, the best sections are those showing the effects of diabetes on the skin, eye and kidney, for these are very amenable to visual representation. The photomicrographs of the kidney are particularly clear, even if, on some of the scanning E M pictures, arrows take on the camouflage of a capillary loop. The retinal photographs provide a good demonstration of the stages of diabetic retinopathy, and will provide useful learning material for students. The sections on history (a photograph of Banting and Best), aetiology, and pregnancy are not so well suited to visual representation, but other sections that adapt well to the medium are those on the vascular and nervous systems.

The text in any atlas is brief, and is best used to explain aspects of the pictures that are not self-evident. It is unfortunate that the authors have at times attempted to do more. In many places this works well, but on other occasions contentious areas of debate or complex theories are heavily condensed. The effect is to make an explanation too short to be adequate (especially in a book designed predominantly for students) or to suggest a greater consensus of opinion than in fact exists. It is not universally accepted, for example, that babies of impeccably controlled diabetic mothers are likely to be large and Cushingoid. It may be necessary in subsequent editions either to expand the text in order to outline the areas of uncertainty, or to use it merely for descriptive purposes. One other useful addition would be a section on management of diabetes; injection techniques, urine testing and blood glucose monitoring would be ideally presented in pictorial form.

Pictures are better remembered than the written word, and so represent important tools for teaching. For students wishing to learn about diabetes, this is a most valuable book. Teachers, too, will find it a useful work, despite the restrictions the publishers have placed on purloining the pictures to add to slide collections.

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