be hypothesised because of the temporal relationship between the administration of the treatment and the course of the illness. The responsibility of cisplatin is more difficult to ascertain because this drug was associated with adriamycin and cyclophosphamide. Although adriamycin therapy may induce degeneration of dorsal root ganglia cells in rats, peripheral neuropathy has not been reported after adriamycin and cyclophosphamide treatment in man.9 Several cases of peripheral neuropathy in patients treated with cisplatin only have been published.4–6 10

The frequency of peripheral neuropathy induced by cisplatin is variously estimated, from 4-3%11 to 92% in a clinical and electrophysiological study.12 The clinical picture is that of a sensory or more rarely sensorimotor neuropathy, with paraesthesiae, dysesthesiae and pains, sensory deficit and diminution of deep tendon reflexes. The symptoms appear after cumulative dosages of cisplatin between 280 and 1,050 mg/m². Discontinuation of the therapy is followed by improvement of the neuropathy, but remaining deficits may be observed. Our case is unusual because of the predominance of motor signs and the lack of sensory deficit.

There are very few pathological data on cisplatin neuropathy. In a light microscope study, Von Hoff et al.13 noticed myelinic lesions. Roelofs et al.12 observed mixed myelin and axonal lesions. In a necropsy study, Walsh et al.14 described loss of myelinated fibres and gliosis of the dorsal columns of the spinal cord, axonal loss in the dorsal roots. In the most documented case,8 a severe axonal degeneration, mainly involving the largest myelinated fibres, but also unmyelinated fibres, was observed, as in our case. Such lesions were also noticed in animals treated with cisplatin.15

Although severe neuropathy remains a rare complication of cisplatin therapy, it must be borne in mind because of the increasing use of this treatment.

References


Accepted 12 June 1985

Matters arising

Carbamazepine, phenytoin and sodium valproate monotherapy

Sir: I was interested to read the results of a study of carbamazepine, phenytoin and sodium valproate monotherapy by Calaghans et al. and would like to make a few observations.

1. It is illogical to say that excellent control was attained with subtherapeutic levels of phenytoin. A drug level that results in excellent control of seizures is, by definition, therapeautic. In recognition of this fact the National Hospitals for Nervous Diseases have, for some years, not indicated a lower limit but only a serum antiepileptic drug (AED) level above which dose-related side effects are more likely to occur.

2. Patients received medication twice daily, at 8 am and 1 pm, and serum AED levels were assessed at an afternoon clinic. It is not stated, but presumably this was after both AED doses had been taken and so the serum levels would be peak and not trough levels. This may not be of great consequence for phenytoin, but could be for carbamazepine as peak carbamazepine levels may be twice the trough level in some patients.2 A drug was deemed to have failed if seizures continued in the face of high optimal serum levels (30–40 µmol/l for carbamazepine). At this hospital a trough carbamazepine level of 50 µmol/l is generally taken as a guideline to the top of the therapeutic range. However, in patients with continuing seizures, it would be appropriate to increase the dose gradually until further increases were precluded by side effects, irrespective of the serum drug level. Only then should it be concluded that the drug was unhelpful. These observations may explain the surprisingly poor performance of carbamazepine in patients with generalised seizures: excellent control in 39%, compared with 73% and 59% for phenytoin and sodium valproate respectively. A similar pattern was found with partial seizures.

3. For previously untreated patients a 50% reduction in seizure frequency is hardly a good one, as implied in this article, a satisfactory outcome.

4. Table 7 relates control to the duration and frequency of seizures prior to treatment. No units are given, making interpretation difficult; presumably the duration is in months and the frequency is seizures per month. If so, these figures are high. Patients achieving excellent control had a mean seizure frequency prior to treatment of 59 and...
Matters arising

- a mean duration of epilepsy of 19. Interpretation of these figures is also made difficult by there being a marked skew deviation to the distribution: of all the subgroups the highest median total number of seizures was 26.

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References


Callaghan replies:

The suggested therapeutic range of 40-80 μmol/l for phenytoin 1 2 is still widely used in clinical practice, although there is evidence that newly diagnosed patients, in particular those with a low seizure frequency prior to treatment can be controlled with serum levels less than the recommended therapeutic range. 3-6 We had hoped that our findings would help to clarify the false interpretation of the therapeutic range for phenytoin, which sometimes results in unnecessary upward dose adjustments of the drug in order to achieve a level within this range, when some patients can be adequately controlled with lower doses.

While we did not give details of the range of levels associated with excellent or good control in our paper, improved seizure control on phenytoin was associated with a wide range of serum levels, from 5-60 μmol/l for patients with generalised seizures and 6-50 μmol/l for patients with partial seizures. (In patients without improvement the serum levels ranged from 50-140 μmol/l.)

It is correct that anticonvulsant drug levels were assessed in the afternoon which enabled us to evaluate peak rather than trough levels. We found an overall range of levels associated with excellent or good control for carbamazepine, between 5-42 μmol/l for patients with generalised seizures and 10-42 μmol/l for patients with partial seizures. We feel it is unlikely that a further increase in drug levels to 50 μmol/l would have resulted in a significant further improvement. In fact, patients with poor control had a range of levels between 30-65 μmol/l. We do agree however, that some patients might have improved further if the dose of the drug had been increased to the limits of the patient's tolerance.

It is not implied in our article that a 50% reduction in seizure frequency was regarded as a good response or satisfactory outcome. A good response was regarded as a greater than 50% reduction in seizure frequency. (Thus, patients in this category had a reduction in seizure frequency within the range of greater than 50% and less than 100% seizure control.) Patients with a 50% reduction in seizure frequency or less were regarded as poor responders.

Clarification of table 7 is required. In this table the seizure frequency per unit time was not presented but rather the "total number of seizures prior to treatment" as with table 1 and table 4. The duration of seizures is presented as duration in the months prior to treatment.

The Kruskal Wallis analysis of variance is a non parametric test and does not require a normal distribution of data. We do agree that the data are considerably skewed, reflecting the variability of the seizure disorder between patients.

Finally, a mean seizure frequency per month can be calculated by dividing the total number of seizures by the mean duration of epilepsy prior to treatment. Thus, the mean seizure frequency per month for patients with excellent control was 3.1; good control 3.2-5 and poor control 6.7.

References


Thermal discrimination thresholds in normal subjects and in patients with diabetic neuropathy

SIR: We were most interested to read the report of Bertelsmann et al 1 on thermal sensation. There are, however, a number of points of principle and methodology which we would wish to raise, as we feel they have a bearing on the validity of their conclusions.

The thermal discrimination threshold, as described by the authors, is compounded of both heat and cold thresholds. 1 Reports in the literature indicate the individuality of these sensations, their receptors and fibre pathways. 2-4 In our own studies 5 we have found that heat and cold thresholds frequently vary independently and unpredictably (Jamal et al, unpublished observations), such that their combination in a single measurement is unlikely to produce an accurately quantified index of thermal sensitivity.

All of the patients studied appear to have had a clinically severe neuropathy with concomitant abnormalities on conventional electrophysiology. In terms of assessing the sensitivity of their method, it would have been informative if applied to patients with minimal, perhaps only subjective, evidence of neuropathy and no abnormality on conventional electrophysiology.

In techniques of this nature standardisation is of paramount importance. We were unhappy about Bertelsmann et al's technique in this context on three counts:

(1) There has been no attempt to standardise the temperature of the skin to which the thermal stimulus is applied. Ambient skin temperature at the time of application of the thermal stimulus is known to influence the value obtained for that threshold. 5-8 In our experience, diabetic patients as a group have a more variable and lower skin temperature than normal subjects.

(2) We have, in the past, investigated the method of standardisation of "pressure" adopted by Bertelsmann et al and found that the variation was pronounced. We, therefore, wonder whether this manual/spring assisted application of the thermode can be reproducibly quantified.

(3) It would appear from the description of their method that two stimuli are applied to the skin more or less simultaneously. There is a tactile stimulus (when the thermode is applied to the skin) and the specific thermal stimulus. It is particularly important, however, for the accurate assessment of thermosensitivity that as pure a stimulus as possible is used and that the specific stimulus is applied without tactile cues. 6-10

We feel that these are pertinent criticisms
Carbamazepine, phenytoin and sodium valproate monotherapy.

J Duncan

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