Letters

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References


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Severe sensorimotor neuropathy after cisplatin therapy

Sir: Cisplatin (Cis-dichlorodiammine platinum (II)) is a chemotherapeutic agent which is used in the treatment of head and neck, ovarian, bladder and testicular cancers. Its main toxic effects are renal, gastrointestinal and hematological. The most frequent neurological complication is neurosensory hearing loss. Some cases of sensory neuropathy have been published. However, a severe sensorimotor neuropathy, as in the case described here, is unusual.

A 48-year-old woman was operated on the 5 January 1983 for a left ovarian cystadenocarcinoma, measuring 15 × 8 cm. Chemotherapy was instituted with adriamycin (40 mg/m²), cyclophosphamide (300 mg/m²) and cisplatin (100 mg/m²). Each course was administered during 4 days, cisplatin being given on the fourth day. Six courses were given from February to September 1983, with a cumulated dose of 240 mg/m² adriamycin, 1,800 mg/m² cyclophosphamide and 600 mg/m² cisplatin. Eight days after the 5th course, the patient experienced acute pains like electric discharges in the legs. They became more severe after the 6th course and also involved the fingers. Simultaneously, the patient had paresthesia in hand and feet. She became unable to climb stairs and was admitted in November.

Physical examination revealed a proximal and distal paresis of lower limbs with amyotrophy. Muscle strength was normal in upper limbs. The pressure on muscles elicited pain but there was no sensory disturbance. Osteotendinous reflexes were all abolished. EMG revealed signs of peripheral neuropathy, with motor unit potentials firing at rapid rates in muscles of both upper and lower limbs. Motor conduction velocities were normal except in the peroneal nerve (37 m/s). A right sural nerve biopsy was performed at the level of the ankle, but the patient refused a lumbar puncture.

The treatment was interrupted after the 6th course and there was a slowly progressive improvement of clinical signs during the following months. The patient recovered a normal muscle strength and became able to climb stairs on April 1984. Pains became less severe and totally disappeared by October 1984. A new examination on November 1984 revealed neither sensory nor motor disturbances. Deep tendon reflexes had remained abolished, but there was no amyotrophy. The patient refused a new needle EMG, but measurement of motor nerve conduction by cutaneous electrodes showed values within the normal range.

The nerve biopsy specimen was studied with morphometric, optic and electron microscope methods. On morphometric studies, there was a severe loss of myelinated (2,780/mm²; normal: 5 to 9,000/mm²) and unmyelinated (15,000/mm²; normal: 18,000 to 65,000/mm²) fibres. Size fibre histogram of myelinated fibres revealed a decrease of the largest fibres (fig. 1). On optic microscope study, many myelin ovoids were seen (fig. 2). Electron microscope study revealed severe degenerative lesions of myelin sheets and axons, with Schwann cells filled with myelin debris. Some of them were invaded by macrophages.

The toxic nature of this neuropathy may

![Fig. 1 Size fibre histogram of myelinated (thick line) and unmyelinated fibres (thin lines) of the sural nerve.](http://jnnp.bmj.com/)

![Fig. 2 Semi thin section, toluidine blue. Loss of myelinated fibres; a degenerating fibre is seen on the left (arrow). Bar = 10 μm.](http://jnnp.bmj.com/)
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 Seven 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 doses 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,6 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.

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References

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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 Callaghan et al.1 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, therapeutic. 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 normal 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 or, 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