Short report

A study of the effects of isaxonine on vincristine-induced peripheral neuropathy in man and regeneration following peripheral nerve crush in the rat

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SUMMARY Administration of isaxonine (6 mg/kg powdered diet) had no effect on regeneration following sciatic nerve crush in the rat. In 10 patients undergoing treatment with vincristine (1.4 mg/m² twice monthly) development of peripheral neuropathy was quantitated by neurological symptoms, signs and electrophysiological tests. Five also received isaxonine (1.5 g daily). All patients developed evidence of neuropathy, but in none was it severe. The three lowest disability scores were obtained in isaxonine treated patients, but the highest score was also in an isaxonine treated patient. The equivocal findings in this small study could not be amplified because the drug was withdrawn from clinical use on account of its hepatotoxicity.

The clinical use of isaxonine (N-isopropyl-amino-2-pyrimidine orthophosphate) was initiated by the experimental findings that the drug promoted sprouting of neurites in cultured mouse spinal ganglia, and enhanced the mean regeneration rate of peripheral nerve following cold injury from 1.6 to 2.3 mm per day. A number of clinical trials, some double blind, on relatively small numbers of patients with diabetic neuropathy, Bell's palsy, and vincristine induced neuropathy, suggested that isaxonine was beneficial in the prevention or treatment of peripheral nerve disease.

Between 1978 and 1982, more than 150,000 patients in France were treated with isaxonine. It then became apparent that hepatitis developed in 28 per 100,000 individuals receiving the drug, and it was withdrawn from clinical use. This occurred prior to the completion of a small double blind controlled trial of isaxonine in patients receiving vincristine in the UK. This paper reports the results of this trial, and also those of a study of the effects of the drug on peripheral nerve regeneration after crush in the rat.

Methods and results

1. Experimental study

The sciatic nerve was crushed in the thigh of 10 Sprague Dawley rats using smooth tipped watchmakers forceps applied for 10 seconds. Five animals acted as controls. One was fed a powdered diet containing 6 g/kg isaxonine (giving a daily intake of approximately 300 mg/kg body weight), and the other four received isaxonine 150 mg/kg by intraperitoneal injection five times per week from the time of crush. Serial measurements were made of amplitude and latency of the muscle action potential recorded from the first interosseus muscle through intracutaneous clip electrodes following nerve stimulation at the ankle and upper thigh at the following intervals: before crush; weekly from 3–8 weeks; every two weeks from 8–12 weeks; and every four weeks until the experiment terminated after 16–28 weeks. Two of the treated animals died, one as a result of intraperitoneal haemorrhage following injection, and the other for no obvious cause at 16 weeks.

There were no differences between the treated and untreated animals in the time of earliest detectable reinnervation (4/5 controls and 3/5 treated animals at four...
weeks), speed of maturation of nerve fibres, or degree of reinnervation at the end of the experiment (table).

2 Clinical trial

It was planned to recruit 12 patients with Hodgkin's or non-Hodgkin's lymphoma into the study prior to their receiving chemotherapy. Ten completed the trial before isaxonine was withdrawn from clinical use because of reported hepatotoxicity. Patients aged 20–70 years with Hodgkin's or non-Hodgkin's lymphoma were assessed by means of detailed clinical and neurophysiological examination prior to receiving combination chemotherapy with vincristine 1·4 mg/m², procarbazine, prednisolone and mustine ("MOPP") or lomustine ("LOPP") twice monthly. Those with diabetes, uraemia, a history of excessive alcohol consumption, or pre-existing peripheral neuropathy of any cause were excluded.

The patients were divided into two age groups (20–50 and 50–70 years) and blindly allocated to treatment with either isaxonine 750 mg bd or identical placebo capsules. Treatment was started 1–7 days prior to the first dose of cytotoxic therapy. Further clinical and electrophysiological assessments were performed 1, 3 and 4 months after the onset of chemotherapy and isaxonine or placebo was then stopped.

Patients were scored clinically on the basis of sensory symptoms, weakness, tendon reflex changes and loss of vibration sense. Electrophysiological scores were obtained from the evoked muscle action potential (MAP) amplitude from extensor digitorum brevis, the amplitude of H and tendon reflex (T) responses from soleus, and measurement of latency and amplitude of sensory nerve action potentials recorded from the median, sural and digital nerves. The score potentially ranged from 0 (normal) to 93 (most abnormal). The treatment code was broken after scoring.

All the patients developed evidence of peripheral neuropathy within one month of starting chemotherapy, although in two patients treated with isaxonine this was confined to hyporeflexia. None of the patients in either group developed severe neuropathy. Reflex loss occurred early in all of them. Sensory symptoms, consisting at worst of mild numbness or paraesthesiae in the digits with clumsiness of fine movements, occurred in all except one treated patient. The dose of vincristine was halved at 10 weeks in one control case as a result of these

Table Mean values for muscle action potential (MAP) amplitude (stimulating the tibial nerve at the ankle), latency (stimulating the sciatric nerve in the thigh), and motor nerve conduction velocity (MNCV) (thigh-ankle) in control and isaxonine treated animals after sciatric nerve crush

<table>
<thead>
<tr>
<th>Weeks</th>
<th>Number of animals</th>
<th>MAP amplitude (mV)</th>
<th>Latency (ms)</th>
<th>MNCV (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>C</td>
<td>I</td>
<td></td>
</tr>
<tr>
<td>0</td>
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<td>5</td>
<td>5</td>
<td>23-4</td>
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<td>5</td>
<td>4</td>
<td>5</td>
<td>2-0</td>
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<td>4</td>
<td>4</td>
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<td>5-4</td>
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</tr>
<tr>
<td>20</td>
<td>4</td>
<td>4</td>
<td>2</td>
<td>17-8</td>
</tr>
</tbody>
</table>

C = control, I = isaxonine.

Fig Cumulative scores of neurological abnormalities based on symptoms and clinical and electrophysiological examination during vincristine therapy.
The effects of isaxonine on vincristine-induced neuropathy

symptoms. Vibration sense was depressed at the toes in some subjects. Five patients (three placebo and two isaxonine) developed mild weakness of finger and/or wrist extension.

Cumulative scores during the trial are shown in the figure. Four out of the five cases in the treated group had consistently lower scores than those given placebo, but the difference between the two groups was not significant at the 5% level using Wilcoxon's rank sum test. The older patients had higher scores than all the younger patients except one in the treated group who scored particularly highly. There was no apparent reason for the development of severe neuropathy in this patient, who assumes importance in view of the small numbers, and it was thought that compliance was good.

Discussion

In contrast to the enhanced regeneration of peripheral nerve observed by Hugelin and colleagues in isaxonine-treated rats following cold injury, we have been unable to demonstrate a beneficial effect of isaxonine on regeneration after crush as assessed either by the number of muscle fibres reinnervated or speed of conduction. However, regeneration of healthy nerves following crush is an efficient process which may be difficult to improve. A number of neurotoxic substances delay regeneration, for example acrylamide, hexacarbons, and vincristine (a study of effects of vincristine on nerve regeneration in rats; in preparation, Shiraishi et al). It would be of interest to determine whether isaxonine influences the inhibitory effect of vincristine on regeneration following crush.

It was not possible to draw any definite conclusions about the possible role of isaxonine in reducing the severity of peripheral neuropathy in patients receiving vincristine. Such an effect would be very useful, as the dose of the drug is often limited by neurotoxicity. Vincristine neurotoxicity occurs remarkably uniformly, as was demonstrated in our patients. As none of them developed severe neuropathy, any effect of isaxonine was slight and of doubtful clinical value. This, as well as the small number of patients studied, contributed to the equivocal outcome of the trial. Since isaxonine has now been totally withdrawn from clinical use on account of its hepatotoxicity, further evaluation is not possible. If a non-toxic drug similar to isaxonine could be developed, the results of the present study, and those of others, warrant more extensive well designed clinical trials.

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