Short report

4-Aminopyridine—a new drug tested in the treatment of Eaton-Lambert syndrome

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SUMMARY A 67 year old man with the myasthenic syndrome associated with small cell bronchogenic carcinoma was treated with a new drug, 4-aminopyridine. The muscle weakness showed marked improvement and electrophysiological examinations demonstrated restoration of neuromuscular transmission.

In the myasthenic syndrome sometimes associated with bronchogenic carcinoma (Eaton-Lambert syndrome) muscular weakness is caused by reduced acetylcholine release from motor nerve terminals (Elmqvist and Lambert, 1968). Guanidine is a potent drug in this condition (Lambert, 1966) but serious adverse reactions have been reported (Lambert and Howard, 1972; Cherington, 1976; Henriksson et al., 1977). We have treated a patient suffering from this syndrome with a new drug, 4-aminopyridine (4-AP). This drug powerfully increases neurally evoked transmitter release from motor nerves (Molgo et al., 1975) possibly by acting directly on the calcium channels in the nerve terminal membrane, allowing the inward calcium current during depolarisation of the nerve terminal to become regenerative (Lundh and Thesleff, 1977). The drug has recently been shown to restore neuromuscular transmission in paralysis produced by botulinum toxin in the rat (Lundh et al., 1977).

Case report

Our patient was a 67 year old man who in November 1976 began to suffer from general tiredness, weakness in his arms and legs, and haemoptysis. Radiography revealed a pulmonary tumour and sputum examination showed malignant cells from a small cell bronchogenic carcinoma. At clinical examination the patient showed proximal muscular weakness in his arms and legs. He had difficulties in raising his arms above his head and in walking, and he could not rise from a chair without the help of his arms. Muscle stretch reflexes were absent. Muscle strength was improved by intravenous injection of edrophonium. The patient also complained of dryness in his mouth.

Electrophysiological examination of the compound muscle action potential (CMAP) with surface electrodes on the thenar and hypothenar muscles demonstrated reduced CMAP amplitude, a decrement of CMAP on low frequency (1–4 Hz) nerve stimulation and an increment at high frequency stimulation (10–40 Hz) (Figure B, Table). Ten seconds of maximal voluntary contraction caused a marked (300%) increase of the CMAP amplitude.

The patient was treated with cytostatic drugs and radiotherapy. Because serious toxic effects have been reported on treatment with guanidine, we decided, together with the patient and his relatives, to try the new drug 4-AP in the treatment of his myasthenic syndrome.

Intravenous injection of 23 mg (0.33 mg/kg body weight) 4-AP chloride in several doses over a two hour time period restored the CMAP in a dose-dependent manner (Figure A, C) until it was almost normal. The decrement of muscle response at low frequency stimulation and the increment at high frequency stimulation were significantly reduced as was the potentiation after maximal voluntary contraction (Figure C).

To study whether oral administration of the drug was effective, the electrophysiological parameters described above were followed after repeated oral doses of 10 mg 4-AP chloride. This
Figure Effects of intravenous administration of 4-AP on decrement and CMAP. (A) Stimulation of right median nerve and recording by surface electrodes from the right thenar muscles. (B) Effects of repetitive nerve stimulation at indicated frequencies before treatment. Trace to the right shows responses at 2 Hz stimulation before and 5, 10, 15 seconds, etc. after a 10 s period of maximal voluntary contraction. (C) Effects of repetitive nerve stimulation at indicated frequencies after i.v. injection of 4-AP chloride. Total dose of 23 mg (0.33 mg/kg) was given.

dose of 4-AP chloride had to be given four times during a two hour time period to obtain maximal effect, and the effect disappeared during the next two to four hours.

The effects of continuous oral administration of the drug are summarised in the Table. 4-AP chloride was very hygroscopic, leading to temporary difficulties with the dosage, and this caused us to change to 4-AP sulphate which is far less hygroscopic. With a dose of 20 mg 4-AP sulphate five times a day (1.42 mg/kg and day), the CMAP and decrement became normal. The patient's muscle strength was restored and it was possible for him to rise from a chair and walk without difficulty.

The electrocardiogram and electroencephalogram were repeatedly examined and did not alter during treatment with 4-AP. The patient's blood pressure, pulse rate and body weight did not change either. Before the medication started the patient had an anaemia and leucopenia but blood values did not deteriorate further, and routine blood tests of liver and kidney functions were not influenced.
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Table  Effect of peroral administration of 4-aminopyridine on electrophysiological parameters

<table>
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<tr>
<th>Date</th>
<th>Daily dose (mg)</th>
<th>Right hypothenar CMAP (mV)</th>
<th>Decrement 4 × 2Hz (%)</th>
<th>Right thenar CMAP</th>
<th>Decrement</th>
<th>Left thenar CMAP</th>
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*4-aminopyridine-chloride—first batch.
†4-aminopyridine-chloride—second batch.
‡4-aminopyridine-sulphate.

During treatment with 4-AP the patient reported increased wakefulness with difficulty in sleeping, and with a dose of 4-AP sulphate of more than 100 mg/day the patient complained of an increased sensitivity to light which disappeared when the dosage was reduced. Neuro-ophthalmological examination and recording of the visually evoked response to pattern reversal were normal. The drug was withdrawn gradually and administration was ended after two and a half weeks. The muscle weakness then reappeared and became even more pronounced than before treatment. Concomitantly, the neurophysiological examination showed a further deterioration of the neuromuscular transmission with lower CMAPs than before treatment (Table).

Discussion

Our attempt to treat this patient with 4-AP demonstrates that the drug is efficient in the treatment of the myasthenic syndrome. The long-term toxic effects of the drug are so far unknown, which was our main reason for ending the treatment. As 4-AP is a powerful stimulant to the central nervous system (Lemeignan, 1970, 1971) it is possible that the photophobia and increased wakefulness reported by our patient are effects of the drug, although the simultaneous treatment with cytostatic drugs and radiotherapy may be of importance in this connection.

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References


