Acute motor axonal polyneuropathy after a cisatracurium infusion and concomitant corticosteroid therapy


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A 40-yr-old male was admitted to the intensive care unit following blunt chest trauma. He had multiple rib fractures, bilateral pneumothoraces, and acute respiratory failure requiring mechanical ventilation. Sedation was achieved with midazolam and morphine, and later with propofol. The patient was paralysed with a continuous infusion of cisatracurium 1.42–5.75 μg kg⁻¹ min⁻¹. Methylprednisolone 125 mg i.v. every 12 h was also started. After discontinuation of the cisatracurium infusion 7 days later, the patient manifested a flaccid quadriplegia with absence of deep-tendon reflexes. No sensory deficits were observed. Electromyography (EMG), repetitive nerve stimulation testing, and single fibre EMG (SFEMG) were performed at regular intervals after stopping cisatracurium. Clinical symptoms and electrophysiological examinations supported the diagnosis of acute motor axonal polyneuropathy related to concomitant administration of cisatracurium and corticosteroid therapy.

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Critical illness polyneuropathy (CIP) may occur in intensive care patients and is usually related to sepsis or systemic inflammatory response syndrome.1,2 A primary axonal neuropathy, considered a variant of CIP, has been described in mechanically ventilated patients after discontinuation of non-depolarizing neuromuscular blocking drugs and concomitant steroid therapy.2–7

No case of polyneuropathy related to a continuous infusion of cisatracurium has been described. Only prolonged weakness after discontinuation of a continuous infusion of cisatracurium and concomitant high-dose corticosteroids because of myopathy has been reported in a critically ill patient.8 We present a case of acute motor axonal polyneuropathy with flaccid quadriplegia after discontinuation of a 7-day cisatracurium infusion. The patients who had had chest trauma, also received concomitant corticosteroid therapy.

Case report

A 40-yr-old male was admitted to our intensive care unit (ICU) with respiratory failure following blunt chest trauma. He presented with rib fractures and bilateral pneumothoraces. Chest X-ray revealed changes characteristic of pulmonary contusion. Neurological examination was normal.

The patient required tracheal intubation with mechanical ventilation. Arterial blood gas values were: pH 7.35, P açO₂ 6.4 kPa, P açO₂ 9.1 kPa, S açO₂ 90.6%. Sedation was achieved with midazolam and morphine, and later with propofol. To minimize barotrauma, the patient was paralysed with a continuous infusion of cisatracurium starting at 1.42 μg kg⁻¹ min⁻¹, titrated according to clinical evaluation. No other neuromuscular blocking drug was used. The paralysed limbs and trunk were moved passively to maintain a full range of movement three times a day. Correct posture was maintained through orthoses and changing the patient position every 3 h. The aim was to prevent movement of the diaphragm and respiratory muscles. First cisatracurium and then the sedation were stopped every 24 h until the patient was awake and able to move his upper and lower limbs, as suggested by Haenel and colleagues,9 and until the diaphragm and respiratory muscles were contracting. In addition, serum creatine phosphokinase (CPK) concentration was routinely monitored.

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and 203 U litre±1 (normal range less than 210 U litre ±1). Subsequently, CPK ranged from between 62 and 1126 U litre ±1 on the day of ICU admission, and 1126 U litre ±1 the following day. CPK ranged from between 62 and 203 U litre ±1 (normal range less than 210 U litre ±1). A muscle biopsy was recommended, but it was refused by the patient.

Electrophysiological studies
The results of electrophysiological studies performed repeatedly after discontinuation of cisatracurium are detailed in Table 2.

Concurrent administration of methylprednisolone 125 mg i.v. every 12 h was also started to reduce lung dysfunction, because of its beneficial effects in severe chest trauma.10–13 Other medication included ambroxol, enoxaparin, ranitidine, furosemide, meropenem, and teicoplanin.

One week later, the required infusion rate of cisatracurium had reached 5.75 μg kg⁻¹ min⁻¹. Respiratory conditions had improved (arterial blood gases: pH 7.40, \(P_aCO_2\) 4.5 kPa, \(P_aO_2\) 11.0 kPa, \(S_aO_2\) 98.6%). First the neuromuscular blocking drug and then the sedative infusions were stopped. After developing the tetraplegia, methylprednisolone was discontinued. The patient’s clinical course after discontinuation of cisatracurium is detailed in Table 1.

Twelve days after discontinuing cisatracurium, the patient was transferred to the Neurological Rehabilitation Section of our department for intensive physical rehabilitation. Computed tomography, magnetic resonance imaging of the head and neck, and electroencephalography recordings were repeatedly performed with normal results. Cerebral spinal fluid (CSF) examination, performed after discontinuation of cisatracurium and 3 weeks later, was unremarkable. Serum CPK concentrations were 2177 U litre⁻¹ on the day of ICU admission, and 1126 U litre⁻¹ the following day. Subsequently, CPK ranged from between 62 and 203 U litre⁻¹ (normal range less than 210 U litre⁻¹). A muscle biopsy was recommended, but it was refused by the patient.

Diagostic investigations during the period of ICU admission excluded the presence of sepsis, SIRS, multiple organ dysfunction syndrome (MODS), renal and hepatic failure, acid–base and electrolyte disorders, hyperosmolality, diabetes, alcoholism, porphyria, myoglobinuria, or hyperpyrexia.

Electromyography (EMG) demonstrated significant numbers of positive sharp waves and fibrillation potentials in all muscles particularly in the distal groups. These potentials indicate muscle membrane instability even if they do not prove a neurogenic lesion. A reduced amplitude of compound motor action potentials (CMAPs) with a normal motor latency is compatible with either intrinsic muscle disease or an axonal neuropathy, as might occur in a disease of the anterior horn cell or neuromuscular junction. In our patient, the course of the disease and the EMG findings were not consistent with anterior horn cell disease. To make a firm diagnosis of CIP, electrophysiological studies are necessary and it is important to demonstrate depression of sensory nerve action potentials.14 Sensory conduction studies in our patient were always normal. Repetitive nerve stimulation (RNS) and stimulated single fibre EMG, which are electrophysiological techniques evaluating neuromuscular transmission, failed to reveal any disorder of the neuromuscular junction. Furthermore, early recruitment, low amplitude, and short duration of motor unit action potentials (MUAPs), which are EMG signs of a primary myopathy, were not present. Demonstration of low amplitude CMAPs accompanied by positive sharp waves and fibrillation potentials and long duration polyphasic MUAPs located preferentially in the distal muscle groups, with the lower extremities more affected than the upper extremities, was compatible with axonal neuropathy affecting almost exclusively motor fibres. The relatively rapid recovery of CMAP amplitude, on the EMG (Table 2) findings could be a result of distally located motor nerve fibre lesions requiring a shorter time for reinnervation. The co-existence of conduction blocks in the distal part of the motor axons because of a change in the myelin or ion channel dysfunction, which both recover quickly, cannot be excluded.

Discussion
We administered a continuous infusion of cisatracurium and concomitant corticosteroid therapy for a week in a sedated patient with chest trauma. Cisatracurium was selected because, in ICU patients, it provides a satisfactory level of neuromuscular block, has minimal haemodynamic effects, only releases minimal amount of histamine, and produces

<table>
<thead>
<tr>
<th>Day</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Patient awake. Flaccid quadriplegia with absence of deep-tendon reflexes. No sensory deficits.</td>
</tr>
<tr>
<td>10</td>
<td>Weaning from mechanical ventilator. Able to move fingertips of right hand.</td>
</tr>
<tr>
<td>20</td>
<td>Patient transferred to the Neurological Rehabilitation Section for intensive physical rehabilitation. Quadriplegia persisted, except for mild flexion and extension movements of the right hand.</td>
</tr>
<tr>
<td>45</td>
<td>More severe paralysis in the lower than upper limbs and unable to stand.</td>
</tr>
<tr>
<td>60</td>
<td>Patient could stand with unilateral support. Able to walk using a walker with forearm support.</td>
</tr>
<tr>
<td>90</td>
<td>Patient could walk without help. Stepping gait more evident on the right side. Slight paresis of the upper right limb and a moderate paresis of the upper left limb. Deep-tendon reflexes reduced in the upper right limb but absent in other limbs.</td>
</tr>
</tbody>
</table>

Table 1 Patient’s clinical course after stopping cisatracurium
using a titration algorithm. Our patient had hyperglycaemia of 9.9 mmol litre⁻¹ on admission, but normoglycaemia was reached after 9 h, within the 24 h safety margin.20 It was demonstrated recently that lower blood glucose levels reduce the incidence of CIP by 44%.19 It is feasible and safe to maintain blood glucose levels at less than 6.1 mmol litre⁻¹ by using a titration algorithm.20 Our patient had hyperglycaemia of 9.9 mmol litre⁻¹ on admission, but normoglycaemia was reached after 9 h, within the 24 h safety margin.20 It was maintained during his intensive care by using insulin titration guidelines. Nutritional insufficiency has also been implicated in the genesis of CIP.21 The feeding regimen used in our patient was glutamate-enriched enteral nutrition increasing from 500 to 1600 kcal day⁻¹ during the first 7 days of intensive care (the period of severe illness).

Nevertheless, after discontinuation of the cisatracurium infusion, the patient manifested a flaccid quadriplegia and areflexia, without sensory loss. Clinical and electrophysiological findings supported the diagnosis of acute motor axonal polyneuropathy. In addition, there were no risk factors for classic CIP, such as: long stay in ICU; MODS or sepsis; acid–base and electrolyte disorders or hyperosmolarity; hypoxia or hyperpyrexia; or diabetes, renal failure, alcoholism, or porphyria.18 In particular, it has been demonstrated recently that lower blood glucose levels reduce the incidence of CIP by 44%.19 It is feasible and safe to maintain blood glucose levels at less than 6.1 mmol litre⁻¹ by using a titration algorithm.20 Our patient had hyperglycaemia of 9.9 mmol litre⁻¹ on admission, but normoglycaemia was reached after 9 h, within the 24 h safety margin.20 It was maintained during his intensive care by using insulin titration guidelines. Nutritional insufficiency has also been implicated in the genesis of CIP.21 The feeding regimen used in our patient was glutamate-enriched enteral nutrition increasing from 500 to 1600 kcal day⁻¹ during the first 7 days of intensive care (the period of severe illness).

Similarly, muscle biopsy was refused by the patient, an intrinsic muscle disease is unlikely on the basis of the clinical and electrophysiological data. CPK levels were normal (with the exception of the first 2 days because of the acute trauma) whereas they should be elevated in thick filament myopathy and in acute necrotizing myopathy, when myoglobinuria may also occur.2 Lack of an increased protein concentration with a normal cell count on repeated CSF examination did not support the diagnosis of an immune-mediated neuropathy. Moreover, several case reports of acute motor axonal neuropathy have described rapid neurological recovery within a month.22 Other neuropathic causes of rapidly progressive generalized weakness or paralysis, such as Guillan–Barré syndrome or Acute Motor Axonal Neuropathy, were incompatible with the clinical features of this case. Thus, in our patient, co-administration of cisatracurium and corticosteroids was the sole risk factor for acute motor axonal polyneuropathy.

In critically ill patients, neuromuscular blocking drugs and concomitant corticosteroid therapy favour the development of a polyneuropathy.2–7 The mechanisms by which they may contribute to this iatrogenic complication are still not completely understood; nevertheless sepsis and SIRS are important underlying factors.18

The critical illness per se is unrelated to the development of a neuropathy and sepsis does not induce a neuromuscular transmission defect.23 24 Sepsis does induce early changes in the microvasculature associated with impaired perfusion of peripheral nerves and increased permeability of capillaries.24 25 This process may be accentuated by the administration of corticosteroids or neuromuscular blocking drugs.26 What is more, neuromuscular blocking drugs and corticosteroids could gain entry to nerves and have toxic effects on peripheral nerve axons.18 25 27 Thus, neuromuscular blocking drugs can favour the development of or increase the severity of a neuropathy.3 24

<table>
<thead>
<tr>
<th>Day</th>
<th>Motor nerve conduction studies</th>
<th>Sensory nerve conduction studies</th>
<th>RNS and s-SFEMG</th>
<th>Concentric Needle EMG</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Reduction in CMAP amplitudes for all nerves studied (more than 50% of the lower limit of normal).</td>
<td>Normal</td>
<td>Normal</td>
<td>No spontaneous activity. Sporadic normal MUAPs in all muscles examined.</td>
</tr>
<tr>
<td>14</td>
<td>CMAP not recordable in lower limbs. Further reduction of CMAP amplitudes in upper limbs.</td>
<td>Normal</td>
<td>Normal</td>
<td>Positive sharp waves and fibrillation potentials in all muscles, especially in distal muscles. Occasional normal MUAPs in upper limb muscles. No MUAPs in lower limb muscles.</td>
</tr>
<tr>
<td>30</td>
<td>Widespread increase in CMAP amplitudes for all nerves studied.</td>
<td>Normal</td>
<td>Normal</td>
<td>Positive sharp waves and fibrillation potentials in all muscles, especially distal. Polyphasic, long duration, normal amplitude MUAPs in all muscles with a single oscillation full effort pattern in lower limb muscles and transitional pattern in upper limb muscles.</td>
</tr>
<tr>
<td>50</td>
<td>CMAP amplitudes reached lower limit of normal range.</td>
<td>Normal</td>
<td>Normal</td>
<td>Sporadic positive sharp waves and fibrillation potentials in all muscles. MUAPs features similar to day 30, but with the full effort pattern in all muscles.</td>
</tr>
</tbody>
</table>
Cases of acute axonal neuropathy or polynuropathy associated with the use of neuromuscular blocking drugs and corticosteroids have been reported. Gorson and Ropper described four critically ill patients with paralysis, acute respiratory failure and continued ventilator dependency following relaxant administration. Electrophysiological studies supported a severe acute axonal motor neuropathy, considered to be a variant of CIP. Isner-Horobeti and colleagues described three cases of polyneuropathy associated with corticosteroids and/or muscle relaxants, and some studies reported vecuronium-associated axonal motor neuropathy in paediatric patients. As with myopathy in critically ill patients, early reports of neuropathy or polynuropathy associated with the use of muscle relaxants and corticosteroids implicated steroid-based agents (e.g. pancuronium and vecuronium) rather than benzylisoquinolinium-based drugs (e.g. atracurium, cisatracurium, doxacurium). Nevertheless, in the same way that subsequent reports also associated myopathy with benzylisoquinolinium agents, it is likely that these agents will be implicated in critical illness neuropathy. Neuromuscular blocking drugs are now often avoided in the critically ill, having been replaced by new i.v. sedatives such as propofol. This has reduced the incidence of NMB-related critical illness neuropathy.

There are no reports of polynuropathy after discontinuation of cisatracurium. Davis and colleagues described a woman with respiratory distress syndrome who underwent mechanical ventilation and was paralysed with a continuous infusion of cisatracurium for 2 weeks, and developed prolonged weakness. The authors ascribe the weakness to a myopathy. This report and our own share several clinical features. Both patients presented were paralysed without sensory loss and with normal CPK levels, and both patients were able to move their fingertips 10 days after cisatracurium discontinuation. Both patients received the same daily dose of methylprednisolone during the 2 days preceding the onset of paralysis. Nevertheless, in the case reported by Davis and colleagues, the cisatracurium infusion was stopped after 13 days, approximately 1 week longer than in our patient, and the infusion rates were higher, ranging from 6.3 to 10.5 μg kg⁻¹ min⁻¹. EMG was not performed. In fact, in the case report of Davis and colleagues, the diagnosis of myopathy was based only on clinical findings and no electrophysiological data were provided which could help to distinguish a myopathy from a polynuropathy. Moreover, we were not able to ascertain if the patient described by Davis and colleagues had as rapid a neurological recovery as our patient.

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