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HAZARDS OF NEOSTIGMINE IN PATIENTS WITH NEUROMUSCULAR DISORDERS

Report of two cases

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SUMMARY

In a 57-yr-old female with dystrophia myotonica, attempts to reverse residual non-depolarizing block with neostigmine 1.0 mg were only partially effective and the administration of a further dose (0.5 mg) produced long-lasting muscle weakness. The train-of-four response of this patient resembled that of a depolarizing block and suggested an alteration in the electrical properties of the muscle membrane A 50-yr-old male with a 30-yr history of progressive muscle dystrophy, exhibited a tonic response to neostigmine in the evoked mechanomyogram during recovery from partial neuromuscular block. It is concluded that the type of reaction to neostigmine in patients with neuromuscular disease is unpredictable.

On account of their tonic response to depolarizing neuromuscular blocking drugs, various types of myotonia represent a source of potential hazard during general anaesthesia (Örndahl, 1962a; Paterson, 1962; Thiel, 1967; Mitchell, Ali and Savarese, 1978; Ellis, 1980). By facilitating depolarization of the motor end-plate, anticholinesterase drugs may cause contracture (Ellis, 1980). Since we are not aware of clinical reports on the effects of these drugs in myotonic patients, a report on adverse reactions to neostigmine in two patients with different neuromuscular disorders may be of interest.

CASE REPORTS

Dystrophia myotonica

The patient

A 57-yr-old female (65 kg) was admitted to another hospital for cholecystectomy. She was known to suffer from dystrophia myotonica with a prevailing dystrophic component. The first symptoms dated back to childhood, with predominant involvement of the muscles of her face and neck. During adolescence, she complained of contractures of her hands during milking. The diagnosis had been established 15 yr before the present admission, by both clinical signs and electromyography. During the past 5 yr, the patient was unable to lift her head and exhibited a typical myopathic face. Her sternocleidomastoid muscles were atrophic, and the muscles of her hands and forearms were much weaker than those of her upper arms. She had diplopia, cataracts, respiratory insufficiency and coronary heart disease. However, cardiomyopathy, a manifestation typical of dystrophia myotonica, was not present.

The anaesthetic procedure is illustrated in figure 1. The course of anaesthesia was uneventful during the 35-min operation and, in particular, no adverse effects of suxamethonium were reported. However, neuromuscular transmission was not monitored. The patient regained consciousness promptly, but severe respiratory insufficiency persisted during the following 1 h. The patient received neostigmine 1.0 mg with atropine 0.5 mg i.v. Her neuromuscular performance improved and the endotracheal tube was removed. Since head lifting was still impossible another neostigmine 0.5 mg was administered. A few minutes later inadequate breathing and cyanosis necessitated reintubation of the trachea and the patient was transferred to our intensive care unit. Several attempts to resume spontaneous ventilation failed and long-term mechanical ventilation was instituted.

On the 2nd and 3rd days after her operation it became increasingly difficult to synchronize the patient with the ventilator. As a result of this and because of her unstable arterial pressure, it was decided to use temporary myoneural blockade with pancuronium rather than larger doses of sedatives

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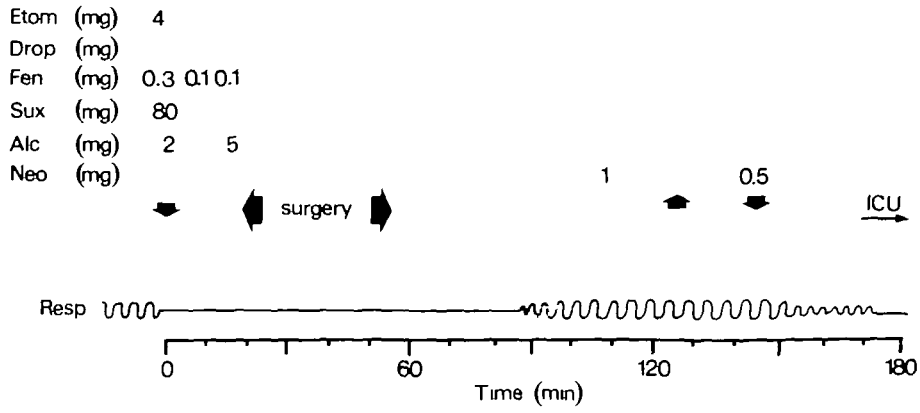

FIG. 1 Dystrophia myotonica (female patient, 56 yr, 65 kg). Premedication: atropine 0.5 mg, fentanyl 0.05 mg, droperidol 2.5 mg 30 min before induction of anaesthesia. Mechanical ventilation with 50% nitrous oxide in oxygen. ▼ = intubation, ▲ = extubation. Ventilation (Resp.) spontaneous (wavy line) or mechanical (——).

and narcotics to facilitate the mechanical ventilation. Furthermore, myoneural blockade during prolonged mechanical ventilation provided the opportunity to re-examine the patient's adverse response to neostigmine under controlled conditions including the monitoring of evoked twitch tension.

For this purpose the patient's forearm was secured by an appropriate splint, and a force displacement transducer was adjusted to her thumb with a preload providing maximum twitch response. Supramaximal train-of-four stimuli (2 Hz, 0.2 ms) were delivered to the ulnar nerve at the wrist 30–60 s apart. After a total of pancuronium 3.0 mg, given in incremental doses of 0.5 mg, twitch tension decreased to 16% of control (fig. 2). The train-of-four pattern showed the typical fade of a non-depolarizing block. At 45% recovery (57th min), neostigmine 1.0 mg was given with atropine 0.8 mg. No significant effect was observed, except on train-of-four fade. After another dose of neostigmine 0.5 mg with atropine 0.3 mg, complete neuromuscular block developed without concomitant increase of train-of-four fade. The block gradually assumed the characteristics of a depolarizing block. No muscarinic side-effects were observed after the injection of neostigmine and atropine. Spontaneous recovery of neuromuscular transmission commenced about 1 h later (160th min; not shown in figure 2). After almost 7 h, recovery was still incomplete (80% at 412th min).

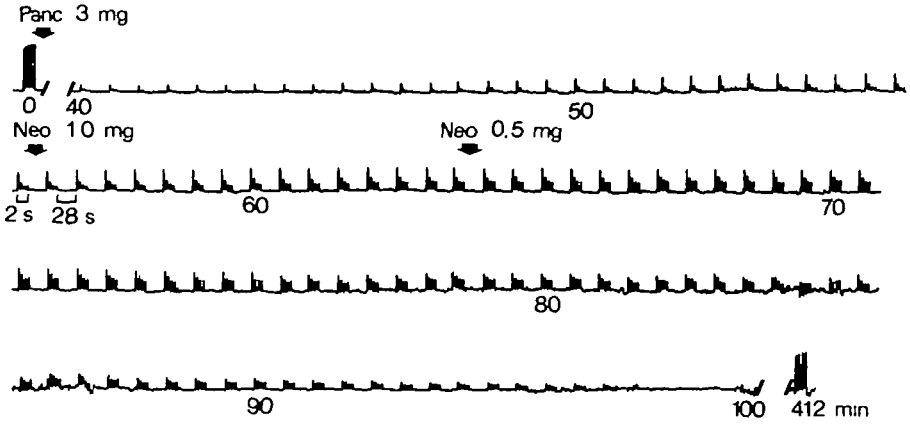

FIG. 2. Same patient as in figure 1. Twitch tension of right adductor pollicis muscle under repetitive train-of-four stimulation every 30 s. Normal response to a total of pancuronium (Panc) 3 mg given in six divided doses of 0.5 mg, partial recovery of neuromuscular transmission after neostigmine (Neo) 1.0 mg and recurrent long-lasting muscle weakness after a further administration of neostigmine 0.5 mg.

Pulmonary gas exchange improved subsequently, and the endotracheal tube was removed on the 5th day after operation. However, 12 h later recurrent respiratory failure and bronchial hypersecretion required reintubation of the trachea, and mechanical ventilation was resumed. The patient died on the 29th day following operation, as a result of intractable bronchopneumonia and severe hypoxaemia, hypercapnia and recurrent bradyarrhythmia.

Discussion

This patient was subject to four events: (i) apparently normal neuromuscular blockade after suxamethonium, (ii) normal sensitivity to pancuronium (and certainly to alcuronium), (iii) muscle weakness secondary to neostigmine which had been given to reverse residual alcuronium and pancuronium blockade, and (iv) inadequate use of the head-lift test in the recovery room, because head lifting had been impossible for 5 yr.

Dystrophia myotonica is a tonic muscle disease, and accordingly the patient had a history of tonic attacks. Hence one would have expected muscle contractures in association with suxamethonium. However, these were not reported by the attending anaesthetist. This may be because muscle atrophy is the progressive component of the disease rather than muscle contracture (Ellis, 1981). Muscle atrophy was also the predominant symptom in this patient and may have prevented the muscle contractures. This interpretation is supported by the fact that neostigmine was found to aggravate muscle paralysis rather than to reverse the block or to give rise to contractures. However, it cannot be excluded that some moderate tonic response to suxamethonium might have been detected if evoked twitch tension had been monitored (see patient with progressive muscle dystrophy, figure 3).

Impaired neuromuscular transmission secondary to the administration of neostigmine was observed both at the end of anaesthesia and during intensive care. However, this phenomenon is not only observed in muscle disease. In the absence of both neuromuscular disorder and neuromuscular blocking agents, Churchill-Davidson and Christie (1959) reported that during tetanic (25–50 Hz) stimulation the tension output was not maintained after the administration of neostigmine 1.25–2.5 mg. Larger doses (2.5–5 mg) caused a partial neuromuscular blockade, with decreases in the e.m.g. potentials, even at slow (2.5 Hz) rates of stimulation. Recently Hughes and Payne (1977) and Payne, Hughes and Al Azawi (1980) studied the effect of neostigmine on peak tetanic tension and tetanic fade (50 Hz) both without and after previous administration of non-depolarizing neuromuscular blocking drugs. The occurrence of muscle weakness depended on the fractional administration of neostigmine rather than on its total dose. The type of block created by neostigmine was always curariform in terms of decreased peak tetanic tension and marked tetanic fade. Concomitant decreases in single twitch tension were not a constant observation. Although the authors did not use train-of-four stimulation, the findings with stimulation at 2.5 Hz (Churchill-Davidson and Christie, 1959) make it reasonable to assume that train-of-four fade would have occurred when tetanic fade was present. The mechanism of neostigmine-induced muscle weakness is not yet completely understood.

In our patient with dystrophia myotonica, muscle weakness also developed after the second dose of neostigmine in the presence of residual non-depolarizing blockade. However, in terms of train-of-four response the characteristics were those of a partial depolarizing block (fig. 2). Furthermore, the

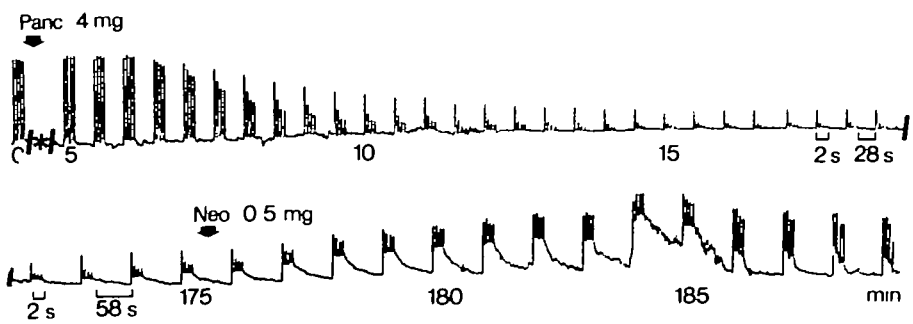

FIG. 3. Progressive muscle dystrophy (male patient, 50 yr, 59 kg). Twitch tension of left adductor pollicis muscle under repetitive train-of-four stimuli 30 s (upper tracing) and 60 s (lower tracing) apart. Normal response to pancuronium (Panc.), tonic response to neostigmine (Neo.).

amount of block was greater and the duration was much longer than in previous studies (Churchill-Davidson and Christie, 1959; Hughes and Payne, 1977; Payne, Hughes and Al Azawi, 1980).

Apparently, while interfering with partial non-depolarizing neuromuscular blockade, neostigmine may impair neuromuscular transmission by different mechanisms, depending on the presence or absence of neuromuscular disease. We do not believe that in the latter case the increase in blockade with concomitant reversal of train-of-four fade (fig. 2) was simply attributable to cholinesterase inhibition and excess acetylcholine at the motor end-plate. This view is supported by two unpublished observations we have made in more than 50 patients without neuromuscular disease: (i) neostigmine $0.015\,mg\,kg^{-1}$ given to reverse partial non-depolarizing blockade always counteracted both depression of twitch and train-of-four fade. Reversal of train-of-four fade with a concomitant decrease in twitch tension was never observed. (ii) If suxamethonium was given in a dose sufficient to increase partial non-depolarizing block (0.5 mg kg), the decrease of tension output was always associated with increasing train-of-four fade, that is under these conditions suxamethonium never produced a "depolarizing block". The tracings from this patient with dystropia myotonica fit neither into these findings nor into those of Hughes and Payne (1977), and Payne, Hughes and Al Azawi (1980). Therefore, it is most likely that the particular pathology of the muscle fibre in terms of altered electrical properties of the muscle membrane or dysfunction of the sarcoplasmic reticulum are responsible for this type of adverse reaction since electrolyte imbalance and hypothermia can be excluded.

Progressive muscle dystrophy

The patient

A 50-yr-old man (59 kg) had a history of progressive muscle dystrophy. The diagnosis had been established 30 yr earlier and confirmed by biopsy. The disease involved the muscles of the shoulders, arms, lower spine, pelvis and legs. He had difficulty in maintaining an upright posture and his gait was short-stepped. The patient was admitted to hospital for surgical treatment of a non-malignant prepyloric stenosis. After premedication with atropine 0.5 mg, pethidine 50 mg and flupromazine 10 mg, anaesthesia was induced with thiopentone 300 mg, fentanyl 0.5 mg and droperidol 12.5 mg. Pancuronium 4 mg was given to produce neuromuscular blockade before endotracheal intubation. Anaesthesia was maintained with 67% nitrous oxide in oxygen and ventilation was controlled mechanically. Fentanyl 0.85 mg in fractional doses and pancuronium 1.0 mg were administered during surgery. Neuromuscular transmission was not monitored. The courses of surgery and anaesthesia were uneventful. At the end of anaesthesia the residual neuromuscular block was not reversed because the patient had been scheduled for prophylactic postoperative mechanical ventilation until the following day.

Alerted by the case of dystrophia myotonica and in consideration of the possibility that the patient might require further anaesthesia and surgery in the future, we took advantage of the mechanical ventilation which was in progress to investigate his response to pancuronium and neostigmine. Two-and-a-half hours after the end of anaesthesia and under sedation with droperidol and fentanyl a total of pancuronium 4 mg (approximately $0.07\,mg\,kg^{-1}$) was administered in divided doses of 0.5, 0.5 and 3.0 mg while the evoked twitch tension was monitored (fig. 3). The maximum effect (24% residual transmission) was obtained within 15 min. Increments of pancuronium 1.0 and 0.5 mg were given after 1 and 2 h at 46 and 38% recovery respectively (not depicted in figure 3). From the 172nd min spontaneous recovery of neuromuscular transmission was associated with a moderate, but increasing, elevation of the base-line during each train-of-four response. A test-dose of neostigmine (0.5 mg) given at 40% recovery (176th min) produced almost immediate cessation of the train-of-four fade and a prompt increase of twitch tension to 84% of control within 9 min. The reversal of neuromuscular block was associated with an increase in the base-line to 70% of the peak tension output (184th min). The base-line returned to normal between the 10th and 15th min after neostigmine and, concomitantly, twitch tension decreased to 77% of control (187th min). Four hours after the first dose of pancuronium, neuromuscular transmission was restored completely (train-of-four ratio = 1.0). On the 1st day after operation spontaneous ventilation was restored and the endotracheal tube removed. The further clinical course was uneventful.

Discussion

Since pancuronium 4 mg did not provide total neuromuscular blockade it would appear that the

sensitivity of this patient to pancuronium was normal and although the duration of neuromuscular blockade was prolonged we have observed similar recovery periods in healthy individuals. The administration of neostigmine to reverse the residual non-depolarizing blockade gave rise to a tonic response in the indirectly stimulated muscle. This finding was surprising because progressive muscle dystrophy is not typically a tonic disease and the patient gave no history of tonic attacks.

Basically, in the evoked mechanomyogram the tonic response of skeletal muscle to indirect electrical stimulation is reflected by an increase in the base-line, because the electrical activity of the muscle fibres diminishes more rapidly than the mechanical contraction (Örndahl, 1962b). In severe cases this type of reaction may occur after any kind of stimulation and may cause acute peripheral respiratory failure. It has been suggested that this phenomenon might be a result of the presence of several end-plates on a single muscle fibre (Örndahl, 1962b). However, this view is challenged by the observation that non-depolarizing myoneural blockers or spinal anaesthesia may not prevent, or reverse, contractures caused by direct surgical stimulation (Ellis, 1980). More recent investigation indicates that the underlying pathology of myotonia is related to the sarcotubular system, rather than to the neuromuscular junction (Buxton, 1980). In particular, the tonic response of our patient is explained on the basis of an increased agonistic potential acting on muscle fibres with electromechanical imbalance. So far this mechanomyographic finding does not appear to be of major clinical relevance, since there were no visible muscle contractures. However, neostigmine 0.5 mg was a small dose, and the response to the higher doses usually given for reversal of non-depolarizing block or in the treatment of ileus remains open to question.

GENERAL COMMENT

In addition to the problems peculiar to these two entirely different types of muscle disease, which have been discussed above, there are several aspects of this topic which relate to clinical anaesthesia in general.

(i) Although these are rare diseases, the management of patients with muscle disease is not restricted to specialized centres. Any anaesthetist may encounter such patients and will have to manage them without having particular experience in this field.

(ii) It is impossible to predict the individual sensitivity to non-depolarizing neuromuscular blocking drugs, the type of response and the individual sensitivity to depolarizing neuromuscular blocking drugs, and the type and degree of the response to neostigmine. Therefore it is of clinical interest to obtain reliable information on a particular patient's response to these drugs under controlled conditions to delineate any future requirement for myoneural blocker and neostigmine. The results of a neostigmine test may be important if the use of this drug is considered for the treatment of ileus.

(iii) In anaesthesia for patients with neuromuscular disease, attempts should be made to avoid the use of myoneural blocking drugs in favour of regional analgesia alone or in combination with general anaesthesia.

(iv) If the use of neuromuscular blocking drugs is mandatory their administration should be subject to meticulous monitoring with the aid of a peripheral nerve stimulator to avert the need for reversal agents. The new short-acting drugs like Org NC 45 (Bowman and Norman, 1980) and atracurium (Payne and Hughes, 1981) may be more advantageous than the relatively long-acting agents in current use.

(v) Despite various reports on successful reversal of residual non-depolarizing neuromuscular blockade by anticholinesterase agents in myotonic patients (Coleham and Davies, 1964; Dalal et al., 1972), this technique is ill-advised because of the neuromuscular and systemic complications of the disease. Because of the cardiac pathology frequently present in patients with muscle disease, anticholinesterase agents may precipitate severe bradyarrhythmias (Church, 1967; Kilburn, Eagen and Heyman, 1959). Residual curarization should only be treated by mechanical ventilation.

(vi) It is most likely that the untoward reactions observed with neostigmine may occur with any anticholinesterase agent.

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LES RISQUES DE LA NEOSTIGMINE CHEZ LES PATIENTS ATTEINTS D'ANOMALIES NEUROMUSCULAIRES

A propos de deux cas

RESUME

Chez une femme de 57 ans atteinte de *dystrophie myotonique*, les tentatives d'antagonisation d'un bloc non dépolarisant résiduel par 1 mg de néostigmine n'ont été que partiellement efficaces et l'administration d'une dose supplémentaire (0,5 mg) a entraîné une faiblesse musculaire prolongée. La réponse au train de quatre chez cette patiente ressemblait à celle d'un bloc dépolarisant et évoquait une altération des propriétés électriques de la membrane musculaire. Un homme de 50 ans avec une histoire longue de 30 ans de *dystrophie musculaire* progressive, a objectivé une réponse tonique à la néostimine sur le mécanomyogramme évoqué au cours de la récupération d'un bloc neuromusculaire partiel. Nous en concluons que le type de réaction à la néostigmine chez les patients atteints de maladies neuromusculaires est imprévisible.

GEFAHREN DER ANWENDUNG VON NEOSTIGMIN BEI PATIENTEN MIT NEUROMUSKULÄREN ERKRANKUNGEN

Bericht über zwei klinische Fälle

ZUSAMMENFASSUNG

Bei einer 57 Jahre alten Patientin mit nahezu lebenslanger Anamnese einer Dystrophia myotonica wurde nach Cholecystektomie die Aufhebung des Überhangs einer nicht depolarisierenden neuromuskulären Blockade mit Neostigmin versucht. Eine Dosis von 1,0 mg war nahezu wirkungslos, während auf eine zweite Dosis von 0,5 mg eine über mehrere Stunden anhaltende neuerliche neuromuskuläre Blockade erfolgte. Bei dieser Patientin bot die Vierfachreizantwort das Bild eines Depolarisationsblocks. Dies läßt daran denken, daß die elektrischen Eigenschaften der Muskelmembran verändert waren. Bei einem 50 Jahre alten Patienten mit einer 30 Jahre zurückreichenden Anamnese einer progressiven Muskeldystrophie führte Neostigmin während der Erholung von einem partiellen Pancuroniumblock zu einer tonischen Reaktion im evozierten Mechanomyogramm. Die Reaktion von Patienten mit neuromuskulären Erkrankungen auf Neostigmin ist dem-nach unvorhersehbar.

PELIGROS DE LA NEOSTIGMINA EN PACIENTES CON DESORDENES NEUROMUSCULARES

INFORME DE DOS CASOS

SUMARIO

Los intentos efectuados para invertir el bloqueo no despolarizante y remanente con 1,0 mg de neostigmina, en una paciente de 57 años de edad con *distrofia miotónica*, fueron certeros tan sólo parcialmente y la administración de una dosis complementaria de 0,5 mg produjo una prolongada debilidad muscular La respuesta-de-cuatro impulsos de este paciente asemejó la de un bloqueo despolarizante y sugirió una alteración en las propiedades eléctricas del músculo Un paciente masculino de 50 años de edad, con un historial de 30 años de *distrofia muscular progresiva*, mostró una respuesta tónica a la neostigmina en el mecanomiograma evocado, durante la recuperación del bloque neuromuscular parcial La conclusión es que el tipo de reacción a la neostigmina por parte de pacientes con enfermedades neuromusculares es impredecible.