J Anesth (2000) 14:160–163

Journal of
Anesthesia

Unexpected resistance to pancuronium in a patient with myotonic dystrophy (myotonia dystrophica)

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Key words Myotonic dystrophy · Myotonia dystrophica · Steinert's disease · Nondepolarizing muscle relaxant · Pancuronium

Introduction

Myotonic dystrophy (myotonia dystrophica, Steinert's disease) is an uncommon but serious inherited disorder that may pose substantial problems in anesthetic management [1,2]. Problems include undue sensitivity to some drugs and abnormal reactions to others [1–4].

There are conflicting reports on the response of myotonic patients to nondepolarizing muscle relaxants [1,4]. Although the nondepolarizing muscle relaxants behaved normally [5–8], exaggerated responses were also reported when dystrophic muscular changes occurred [8,9]. However, to date, there has been no report describing a myotonic patient who was resistant to the nondepolarizing muscle relaxants. In this report, we describe a patient with myotonia dystrophica undergoing general anesthesia who was unexpectedly resistant to clinical doses of pancuronium.

Case report

A 57-year-old man (weight 60 kg, height 166 cm) (ASA class III) with a diagnosis of sigmoid colon cancer was scheduled to undergo a low anterior resection of the colon. His medical history included myotonia dystrophica diagnosed about 25 years previously. He showed typical features of myotonia dystrophica, including wasting and weakness of the sternocleidomastoid muscle, grip and percussion myotonias, frontal baldness, and cataract formation. In addition, he appeared to have cardiac dysrhythmias associated with myotonia dystrophica, and he was diagnosed 7 years previously with Adam-Stokes' syndrome. However, without any cardiac medication, first-degree atrioventricular block (PQ interval, 0.28 s) was the only abnormality found in the resting electrocardiogram, and the echocardiogram was normal. Pulmonary function tests, chest X-rays, and arterial blood gas analysis were all within normal limits (NL). The patient's serum concentrations of electrolytes were all normal. However, the preoperative screening tests on the endocrine system revealed the presence of mild adrenocortical insufficiency due to pituitary dysfunction: urine 17-hydroxycorticosteroids, 0.85 to 2.465 (NL = 3.6–9.0) $mg \cdot day^{-1}$; 17-ketosteroids, 1.68 to 4.35 (NL = 3.0–13.0) $mg \cdot day^{-1}$; serum cortisol 6.2 (NL = 5.5–17.0) $\mu g \cdot dl^{-1}$; serum ACTH 13 (NL = 30–60) $pg \cdot ml^{-1}$; ACTH test, within NL. Thyroid function was, however, normal. The preoperative laboratory tests also indicated the presence of hyperlipidemia (triglycerides, 241–384 $mg \cdot dl^{-1}$; cholesterol, 255–286 $mg \cdot dl^{-1}$). Other laboratory data, including those on both hepatic and renal function, were normal. The patient had not previously undergone surgery with general anesthesia.

The patient was premedicated with intramuscular hydroxyzine hydrochloride (50 mg) and atropine sulfate (0.5 mg) 45 min prior to the induction of anesthesia. Because of the adrenocortical insufficiency, 100 mg of hydrocortisone was intravenously administered immediately before induction of anesthesia. The patient was then mildly sedated with intravenous diazepam (5 mg) and fentanyl (150 μg), and the trachea was successfully intubated without using a neuromuscular blocking agent while the patient was sedated and awake. After endotracheal intubation, the lungs were easily ventilated, and anesthesia was subsequently maintained with 67% N_2O/1–3% enflurane in oxygen and supplemented by further intravenous administration of fentanyl (total

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Received: November 12, 1999 / Accepted: April 24, 2000

dose, 300 μg). Enflurane was chosen because anesthesia using enflurane had previously been conducted successfully in three myotonic patients in our institute.

In addition to the standard anesthetic safety monitors, the degree of neuromuscular blockade was monitored in the left upper extremity with an evoked electromyograph (Anesthesia and Brain Activity Monitor, Datex-Engstrom, Helsinki, Finland). The train-of-four (TOF) stimulation (supramaximal, 2 Hz) was applied to disc electrodes placed over the distribution of the median nerve at the wrist every 1 min, and the evoked compound electromyograph (ECEMG) responses of the hypothenar muscle were recorded. The TOF stimulations did not evoke any apparent myotonic contractions in the monitored extremity. After the induction of anesthesia, 4 mg of pancuronium was intravenously administered. However, even 10 min after the administration of pancuronium, no significant reductions in either the T1 response or the TOF ratios were observed (Fig. 1a). Consistently with this, the surgeons complained of inadequate relaxation of the abdominal muscles immediately after they approached the peritoneum; however, myotonic contractions did not appear to develop in the abdominal muscles. Fortunately, increasing the inspired concentration of enflurane to 2–3% could produce some muscle relaxation, enabling them to undertake the procedure; the T1 responses were reduced to about 50% of control (Fig. 1a) and the TOF ratio to about 0.6. Following the endocrinologist's preoperative recommendation, another 100 mg of hydrocortisone was intravenously administered 2 h after induction of anesthesia. When the inspired concentration of enflurane was reduced to about 1.2% during the course of surgery, the responses to TOF stimulation returned to control; in this situation, another intravenous administration of 2 mg of pancuronium drawn from a new ampoule again failed to produce any significant muscle relaxation (Fig. 1a). However, the peritoneum was successfully closed again by increasing the enflurane concentration up to about 2% without using any muscle relaxant.

After the surgery, the patient was transferred to the intensive care unit (ICU) without extubation. His trachea was extubated about 2 h after arrival in the ICU, and the patient was transferred to the ward the next morning. The postoperative course in the ward was

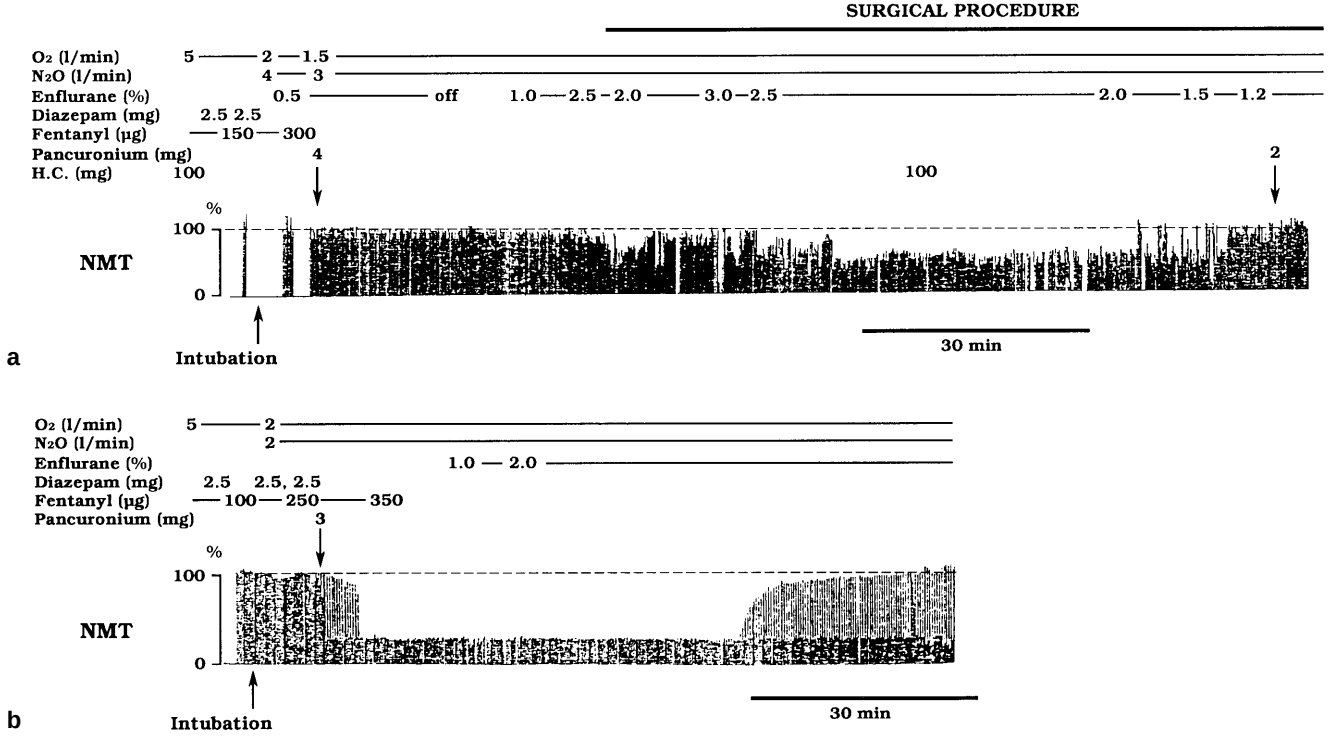

Fig. 1. Responses to train-of-four (TOF) stimulation in patients with myotonia dystrophica. **a** Intravenous administration of pancuronium (4 and 2 mg) did not cause any significant reduction in either the T1 response or the TOF ratio, whereas higher concentrations of enflurane produced significant muscle relaxation in the myotonic patient. Note intravenous administration of 100 mg of hydrocortisone (*H.C.*) prior to each administration of pancuronium. **b** Normal responses to pancuronium (reduction in both the T1 response and TOF ratio) in a 22-year-old female patient (162 cm, 55 kg) with myotonia dystrophica who underwent laparotomy with general anesthesia (O_2-N_2O-enflurane). *NMT*, neuromuscular trends

also uneventful except for left lung atelectasis on postoperative days 3 to 5, which was eventually improved by bronchoscopic suctioning and physiotherapy. The patient was discharged on the 18th postoperative day.

Discussion

One of the most important considerations for anesthesia in the myotonic patient is the abnormal response to drugs used during anesthesia [2,3]. It is generally believed that the use of deporalizing muscle relaxants should be avoided because of a higher risk of exaggerated myotonic contracture and hyperkalemia [1,4]. In contrast, nondeporalizing muscle relaxants do not appear to cause serious clinical problems in the myotonic patient as long as neuromuscular blockade is carefully antagonized and its phramacological reversal with anticholinesterase drugs, which may evoke myotonias, is avoided [2,3]. Our clinical experience in three patients with myotonia dystrophica indeed supports this idea; those myotonic patients have shown normal responses to pancuronium, as shown in Fig. 1b. However, as described above, we recently encountered an unusual situation in which a myotonic patient was totally resistant to nondeporalizing muscle relaxants.

Since the other agents administered to the patient through the same venous line as that used for administration of pancuronium had normal therapeutic effects, it is unlikely that pancuronium was administered extravenously and thus failed to exert its muscle relaxant effect. In addition, since pancuronium drawn from other ampoules in the same package (lot) was effective in other patients who underwent general anesthesia on the same day, it is also unlikely that the pancuronium used in this patient lacked the effect because of outdated or improper storage conditions. Further, it was confirmed that the device used to monitor neuromuscular blockade in this patient operated properly in other patients given muscle relaxants. It has been suggested that the response to a peripheral nerve stimulator needs to be carefully interpreted in the myotonic patient because muscle stimulation may produce myotonia, which cannot be relieved by nondepolarizing muscle relaxants [2]. However, we could not find any development of myotonia in response to TOF stimulation in the hand where the neuromuscular blockade was monitored or in the abdominal region. Indeed, no significant increases in baseline were observed in the ECEMG trace (Fig. 1). In addition, enflurane was effective in producing muscle relaxation, suggesting that myotonia was probably not present. Therefore, we do not believe that pancuronium failed to produce muscle relaxation because of the presence of myotonic contracture.

Specific pathologic states cause increased resistance to nondepolarizing muscle relaxants, e.g., upper motor neuron lesion [10], disuse atrophy [11], severe thermal injuries [12], and liver cirrhosis [13]. However, our patient was not in any of these pathologic states. In addition, several therapeutic drugs, such as anticonvulsants [14], phenytoin [15], azathioprine [16], aminophylline [17], and steroids [17–20], all have previously been shown to alter the efficacy of the nondepolarizing muscle relaxants. However, none of these drugs except corticosteroids were given to this patient. Thus, there might be a possibility that the action of pancuronium was significantly interfered with by hydrocortisone (200 mg i.v.) administered in this patient.

Meyers [18] previously observed that hydrocortisone (100 mg i.v.) partially reversed profound muscle paralysis produced by pancuronium (12 mg i.v.) in a hypophysectomized patient. Azar et al. reported an unusual resistance to pancuronium in a patient with status asthmaticus intensively treated with large doses of aminophylline and hydrocortisone (250 mg i.v., q6h) [17]. In the latter case, the authors speculated that aminophylline raised the level of cAMP and, in turn, the level of acetylcholine (ACh) at the prejunctional membrane of the neuromuscular junction and thus antagonized the blocking effect of pancuronium [17]. They further speculated that corticosteroids also might play a role in producing the resistance to pancuronium by enhancing the release of ACh and thereby facilitating neuromuscular transmission. Reddy et al. [20] also reported that a patient receiving prolonged testosterone therapy showed resistance to vecuronium. They speculated on a combination of factors that might explain the mechanism in part: increased volume of distribution secondary to salt and water retention, an increase in the number of ACh receptors from testosterone-augmented increase in skeletal muscle mass, and a possibility that testosterone might simulate adrenocorticotropic hormone and corticosteroids in enhancing neuromuscular transmission. Although the mechanism behind the corticosteroid-induced enhancement of neuromuscular transmission does not appear to have been fully clarified, it was previously suggested that corticosteroids antagonize the blocking effect of hemicholium-3 at the neuromuscular junction by facilitating choline transport at the prejunctional membrane [19].

The above-mentioned two patients had received hydrocortisone either for a long time or in large doses [17,20]. Our patient, however, received only a small dose of hydrocortisone (100 mg) shortly before administration of pancuronium. Our long clinical experience has shown that intravenous administration of 100 mg of hydrocortisone, commonly used for steroid coverage in patients with supposed adrenocortical insufficiency undergoing surgery, does not cause significant resistance

to nondepolarizing muscle relaxants. We therefore speculate that myotonic patients may be more susceptible to the enhancing action of corticosteroids on neuromuscular transmission, an effect that explains the corticosteroid-induced resistance to nondepolarizing muscle relaxants. Abnormalities in both chloride and sodium channels of the muscle membrane [21] and also in the intracellular adenosine triphosphate (ATP) system [3] have been suggested to be the pathologic mechanisms of myotonia dystrophica. Such defects in the muscle cells may render myotonic patients more sensitive to the action of steroids, which produce resistance to nondepolarizing muscle relaxants.

The present report suggests that intravenous administration of corticosteroids, even in small doses, may cause clinically significant resistance to pancuronium in patients with myotonia dystrophica. In such cases, higher concentrations of enflurane may be helpful in obtaining muscle relaxation during surgery.

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