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## Resistance to Muscle Relaxants in a Patient Receiving Prolonged Testosterone Therapy

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To date, there are no published data describing the interaction between androgenic hormones and muscle relaxants. We recently encountered an unusual situation of a transsexual receiving prolonged testosterone therapy who was resistant to the effects of both depolarizing and nondepolarizing muscle relaxants while undergoing a total abdominal hysterectomy and bilateral salpingo-oophorectomy as part of a sexual reassignment procedure.

### CASE REPORT

A 35-yr-old woman was admitted for a total abdominal hysterectomy and bilateral salpingo-oophorectomy as part of a sexual reassignment procedure. Her past medical history was unremarkable. She had undergone an uneventful bilateral mastectomy under general anesthesia 5 yr earlier as the initial phase of sexual reassignment. The patient had no known history of drug allergy. She stated that she had regularly used testosterone enanthate (Delatesteryl®, Squibb) 200 mg intramuscularly twice monthly for 10 yr. Physical examination revealed a muscular female 5'1" tall weighing 150 lb with signs of virilization including hoarseness, hirsutism, acne, male pattern baldness, and clitoromegaly. She stated that she had received the last dose of testosterone enanthate 2 wk prior to this admission. The patient denied using any other medications. The patient stated she had smoked one pack of cigarettes per day for 2 yr prior to admission. All preoperative laboratory data including liver and kidney functions were normal. Chest radiograph and ECG were normal.

Intraoperative monitoring included ECG, noninvasive blood pressure, pulse oximetry, end-tidal CO<sub>2</sub>, body temperature, and neuromuscular blockade monitor. The stimulating electrode was placed over the ulnar nerve at the wrist and a supramaximal stimulus using 0.1 Hz frequency was established prior to administration of the muscle relaxant. The patient received meperidine 50 mg, hydroxyzine 50 mg, and atropine 0.4 mg im 1 h prior to surgery. Vital signs before induction were as follows: blood pressure 130/70 mmHg; heart rate 90 beats/min; respiratory rate 18 breaths/min; and skin temperature 36.5° C.

The patient breathed oxygen and was given vecuronium 1 mg iv. Three minutes later, anesthesia was induced with sodium thiamylal 400 mg and succinylcholine 100 mg iv. The lungs were easily ventilated by mask. Approximately 2 min later an attempt to insert an orotracheal tube was unsuccessful because of rigidity of the jaw. An oral airway was inserted and ventilation by mask continued without difficulty. Visual

assessment revealed reduction in the size of the baseline single twitch response. Vecuronium 0.1 mg/kg iv and fentanyl 250 µg iv were then given. Over the next 3 min we noted an apparent depression in the twitch response by approximately 50%. A second attempt to insert the orotracheal tube was successful. Anesthesia was maintained with 60% N<sub>2</sub>O in oxygen and isoflurane 1%. The end-tidal CO<sub>2</sub> was in the range of 32-35 mmHg, with a minute ventilation of 6 l/min. Skin temperature remained constant at 36° C. Fifteen minutes later surgery started; however, the surgeon complained of inadequate relaxation of the abdominal muscles. Train-of-four stimulation evoked four equal twitches without fade. The response to tetanic stimulation at 50 and 100 Hz was also sustained. Inspired isoflurane concentration was increased to 2% and additional vecuronium 0.08 mg/kg drawn from a new vial was administered iv. Four minutes later, the fourth response of the train-of-four disappeared, only to reappear approximately 10 min later. The response to 50 Hz and 100 Hz tetanic stimulation was still sustained. Additional doses of freshly dissolved vecuronium from different batches were administered iv in 2-mg boluses 10 min apart, but the train-of-four response remained unaltered. A total dose of 22 mg of vecuronium was administered over a 50-min period. At the completion of surgery approximately 100 min later, the patient breathed spontaneously with a tidal volume of 500-600 ml. Edrophonium 0.5 mg/kg and atropine 0.6 mg were given iv and 5 min later the trachea was extubated. The postoperative course was uneventful.

### DISCUSSION

Testosterone enanthate is a derivative of the primary endogenous androgen testosterone. In its active form it contains a 17-beta-hydroxy group, esterification of which increases its duration of action. In plasma, testosterone is 98% bound to a specific testosterone-estradiol binding globulin. Both testosterone enanthate and vecuronium possess a steroid nucleus, but the steroid in the latter is devoid of any hormonal activity. Androgenic hormones serve different functions at different stages of life. Apart from its potent virilizing effects, the anabolic steroid testosterone is known to enhance skeletal muscle growth and cause an increase in body weight secondary to retention of sodium and water.

All possible causes that could account for such an unusual failure of effect of a muscle relaxant, such as outdated vecuronium, improper storage conditions, and loss of potency, were carefully assessed before being excluded as the likely cause. There was no infiltration of the iv infusion at any time during the procedure. We subsequently used the same batches of succinylcholine and vecuronium for a variety of other procedures with normal therapeutic effect. We checked the placement of the stimulating electrode along the ulnar nerve at the wrist during the procedure and excluded the possibility of inadvertent

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direct muscle stimulation. The neuromuscular blockade monitor used was thoroughly checked and found to be functioning adequately.

There are specific pathologic states such as upper motor neuron lesions,<sup>1,2</sup> severe thermal injuries,<sup>3,4</sup> liver disease,<sup>5</sup> renal failure, and disuse atrophy,<sup>6</sup> all of which show an increased resistance to the therapeutic effects of nondepolarizing muscle relaxants. Some of the mechanisms in the aforementioned states are purely speculative and include increased extrajunctional sensitivity to acetylcholine<sup>7</sup>; increased availability of acetylcholine at the receptor site<sup>8</sup>; and collateral reinnervation, a process by which an additional number of acetylcholine receptors are recruited.<sup>9</sup>

Concurrent drug therapy can alter the efficacy of nondepolarizing muscle relaxants. Anticonvulsant therapy shortens the duration of pancuronium by more than 50% in neurosurgical patients,<sup>10</sup> and phenytoin therapy was found to increase pancuronium requirement by 80%.<sup>§</sup> A similar resistance was found for metocurine and vecuronium.<sup>11</sup> Azathioprine (Imuran<sup>®</sup>) had also been found to antagonize neuromuscular blockade produced by nondepolarizing muscle relaxants.<sup>12</sup> Azar *et al.* reported resistance to pancuronium in an asthmatic patient treated with aminophylline and steroids.<sup>13</sup> They speculated that the mechanism of aminophylline-induced resistance to muscle relaxants is based on the ability of aminophylline to inhibit the enzyme phosphodiesterase at the prejunctional membrane of the neuromuscular junction and thus increase c-AMP levels. The high c-AMP levels promote acetylcholine release, which in turn antagonizes the blocking effect of nondepolarizing muscle relaxants. Corticosteroids have been shown to facilitate neuromuscular transmission. Hydrocortisone has been reported to reverse pancuronium-induced paralysis in a patient following hypophysectomy.<sup>14</sup> Although the mechanism is not completely clear, corticosteroids antagonize the blocking effect of hemicholinium-3 at the neuromuscular junction, possibly by facilitating choline transport at the prejunctional membrane.<sup>15</sup>

In the patient we have presented, it is difficult to ascribe any one mechanism to explain this unusual resistance to the effects of succinylcholine and vecuronium. At best we can only speculate on a combination of factors that may explain in part some of the resistance encountered. Increased volume of distribution secondary to salt and water retention may explain some of the initial resistance observed. An increase in the number of acetylcholine re-

ceptors from testosterone augmented increase in skeletal muscle mass is another possibility. Finally, the anabolic steroid testosterone may simulate adrenocorticotrophic hormone and corticosteroids in enhancing neuromuscular transmission and possibly explain the resistance to nondepolarizing muscle relaxants encountered in this situation.

Steroids have been indiscriminately used by athletes all over the world to improve performance levels. Anabolic steroids have been incriminated in many of these instances. Whether steroids exert a positive effect at the neuromuscular junction in terms of enhancing neuromuscular transmission remains unestablished.

In summary, we encountered an unusual resistance to both depolarizing and nondepolarizing muscle relaxants in a transsexual receiving testosterone who underwent a total abdominal hysterectomy and bilateral salpingo-oophorectomy as part of sexual reassignment.

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## Respiratory Effects of Pain in a Child after Thoracotomy

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Postoperative pain management in children has not been extensively studied, and several reports have indicated that pain management is often inadequate.<sup>1,2</sup> Two arguments may be advanced in support of the need for improved pain relief in children. One is that relief of suffering is the responsibility of all physicians and humanitarian duty to patient calls for better pain relief. The second is that inadequately treated pain can lead to postoperative complications. Although it is often said that postoperative pain leads to splinting of the chest, which can lead to atelectasis and/or pneumonia, documentation of this statement in children is lacking. However, some may express the opinion that pain stimulates the patient to move and that opiates will lead to an increased risk of postoperative respiratory complications. I recently cared for a patient in whom there was clear documentation of an adverse respiratory effect of pain and the resultant splinting and improvement when adequate pain therapy was instituted.

### REPORT OF A CASE

The patient was 14 mo old when she presented for resection of a cystic adenomatoid malformation of the right upper and right middle lobes of her lung. She had been previously healthy, and at 7 mo of age a chest radiograph revealed cystic lesions in her lung. Surgery was electively planned.

She was premedicated with rectal sodium thiamylal, and venous and arterial catheters were inserted. A caudal catheter was inserted 4 cm into the caudal canal but was not immediately injected. Anesthesia was

induced with halothane, muscle relaxation was achieved with pancuronium, and the patient's trachea was intubated. Mechanical ventilation was begun, and the patient was positioned in the right lateral decubitus position. A right posterolateral thoracotomy was performed through the 5th intercostal space, and the right upper lobe was resected. Two chest tubes were left in place.

Approximately 1.25 h prior to the end of surgery, 0.75 mg of preservative-free (PF) morphine was injected *via* the caudal catheter (75  $\mu$ g/kg, patient weight = 10 kg). At the end of the procedure atropine and edrophonium were administered to reverse the residual neuromuscular blockade, and the patient's trachea was extubated while she was still deeply anesthetized, and she was taken to the recovery room. One hour later the patient was still sleepy, but airway reflexes were intact, and there was no evidence of pain. The patient was transferred to the intensive care unit.

Five hours and 30 min after the caudal administration of morphine, the patient was noted to be crying and splinting her chest and was unable to be consoled by her parents. She was using accessory muscles of respiration during exhalation. Arterial blood gas tensions while breathing 1 l/min oxygen were as follows:  $pH = 7.21$ ;  $P_{CO_2} = 64$  mmHg;  $P_{O_2} = 94$  mmHg. Because the position of the caudal catheter had not been confirmed and because the duration of pain relief was somewhat shorter than that expected after caudal morphine,<sup>3</sup> a total of 10 ml of 0.25% bupivacaine was injected *via* the caudal catheter. After 20 min splinting stopped and the patient appeared comfortable and also appeared to have a larger tidal volume. A pinprick sensory level at T6 was demonstrated. Arterial  $pH$  was 7.31,  $P_{CO_2}$  was 47 mmHg, and  $P_{O_2}$  was 149 mmHg. One milligram of PF morphine was administered *via* the caudal catheter with subsequent pain relief lasting for 8 h. When pain returned, the arterial  $pH$  was 7.28,  $P_{CO_2}$  was 52 mmHg, and  $P_{O_2}$  was 158 mmHg. PF morphine was again injected *via* the catheter, and after pain relief had been reestablished,  $pH$  was 7.33,  $P_{CO_2}$  was 44 mmHg, and  $P_{O_2}$  was 146 mmHg. Morphine was then administered *via* the caudal catheter every 8-12 h until it was removed on the third postoperative day. Satisfactory analgesia was maintained with acetaminophen with codeine, and the patient was discharged home on the fourth postoperative day.

### DISCUSSION

This case presentation documents clear adverse respiratory effects of pain, with resolution after pain control was reestablished. When the patient was seen in the ICU, she was in pain, with subjective respiratory effects of

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