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Delayed-Onset Malignant Hyperthermia in Association with Rocuronium Use

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Abstract:

Purpose Two cases of malignant hyperthermia suspected to be related to the use of a nondepolarizing neuromuscular blocker are reported.

Summary A pharmacogenetic disorder that may occur in as many as 1 in 3000 anesthesia procedures, malignant hyperthermia has been linked to the use of certain anesthetic gases and depolarizing neuromuscular blocking agents (e.g., succinylcholine). Although nondepolarizing neuromuscular blockers were cited as contributing to the development of malignant hyperthermia in a small number of published reports, the agents are generally considered safe for use in at-risk patients. Here investigators report two cases in which the nondepolarizing agent rocuronium is thought to have triggered malignant hyperthermia in patients with no known history of the disorder. In one case, a critically ill 27-year-old man undergoing an induced-hypothermia protocol developed a fever about 4 days after receiving rocuronium infusions, with temperatures rising over 11 days to a maximum of 105.2 °F. In the other case, a 63-year-old man being treated for serious complications of elective surgery developed extreme fever (maximum temperature of 107.1 °F) about 4 days after receiving two bolus doses and a continuous infusion of rocuronium. In both cases, the discontinuation of rocuronium therapy was followed by the rapid diminution of fever over 12–36 hours. After consultations with medical staff and consideration of other potential causal and contributory factors (e.g., neurologic injury, antimicrobial-induced fever), rocuronium was deemed the most likely trigger of the severe febrile response experienced by these two patients.

Conclusion A 27-year-old man and a 63-year-old man received rocuronium and subsequently developed delayed-onset malignant hyperthermia, which resolved after the rocuronium was discontinued.
Malignant hyperthermia, an inherited, autosomal-dominant disorder of skeletal muscle, is triggered by certain anesthetic gases and neuromuscular blocking agents.\textsuperscript{1–9} There are several theories regarding the pathophysiology of this adverse reaction, which has been most often reported in association with the use of depolarizing neuromuscular blockers such as succinylcholine.

Succinylcholine produces transient muscle paralysis by acting on postsynaptic receptors, leading to depolarization of the sarcolemmal membrane; according to one theory on the etiology of malignant hyperthermia, this depolarization opens the dihydropyridine voltage-gated calcium channels, causing the ryanodine-receptor channels to release calcium and resulting in muscle contraction and markedly elevated body temperatures.\textsuperscript{1,2} Another theorized etiologic mechanism for malignant hyperthermia focuses on the proliferation of acetylcholine receptors in genetically susceptible patients. When succinylcholine is administered, an unusually high signal input to the ryanodine-receptor channels causes even larger amounts of calcium release, further potentiating malignant hyperthermia.\textsuperscript{1}

The physical manifestations of malignant hyperthermia result from an uncontrolled release of intracellular calcium from skeletal muscle sarcoplasmic reticulum.\textsuperscript{1–3} This increase in intracellular calcium leads to sustained hypermetabolism, resulting in muscle contraction, increased consumption of oxygen, production of carbon dioxide, breakdown of adenosine triphosphate, and increased heat production.\textsuperscript{2–5} These metabolic changes manifest in the typical signs and symptoms of malignant hyperthermia, including a rapid rise in end tidal carbon dioxide, generalized and masseter-muscle rigidity, hyperthermia, tachycardia, tachypnea, rhabdomyolysis, respiratory and metabolic acidosis, myoglobinuria, increased creatinine kinase levels, and hyperkalemia.\textsuperscript{2–5}

Nondepolarizing neuromuscular blockers act by competing for cholinergic receptors at the motor end plate, a mechanism very different from that of succinylcholine. The occurrence of malignant hyperthermia with the administration of either benzylisoquinolinium or aminosteroidal nondepolarizing neuromuscular blockers is not well established.\textsuperscript{10–13} Therefore, the use of nondepolarizing neuromuscular blockers, particularly aminosteroidal neuromuscular blockers such as rocuronium, is generally considered safe in patients at risk for malignant hyperthermia.\textsuperscript{1–3,6,14} Here we describe two patients in whom rocuronium was the most likely trigger for the development of malignant hyperthermia.

Case reports

Patient 1

A 27-year-old Caucasian man (weight, 70 kg; height, 178 cm) with a history of alcohol, tobacco, and illicit drug use was taken to the hospital after being found unconscious for an unknown period of time. Emergency medical services found the patient asystolic. Advanced cardiac life support was initiated, including endotracheal intubation, cardiopulmonary resuscitation, i.v. epinephrine therapy, and i.v. atropine therapy. Spontaneous circulation returned with sinus tachycardia rhythm. On the patient’s arrival at the hospital, laboratory measures were notable for a urine drug screen positive for opioids and tetrahydrocannabinol and anion-gap metabolic acidosis. Arterial blood gas measurements revealed the following: pH, 7.04; partial pressure of carbon dioxide (pCO\textsubscript{2}), 77 mm
Hg; partial pressure of oxygen (pO₂), 26 mm Hg; and bicarbonate concentration, 20.9 mmol/L. The neurologic examination revealed 2-mm round pupils that were sluggishly reactive to light. The patient was admitted to the intensive care unit (ICU), where a 48-hour hypothermia procedure was initiated per institutional protocol using external cooling devices to achieve a target temperature of 91.4 °F with continuous bladder temperature monitoring. During the initial 48 hours, a propofol infusion (titrated to achieve a bispectral index score of 40–60) and a rocuronium infusion (initiated at 8 μg/kg/min and titrated to achieve a train-of-four score of 2) were used to manage shivering during the induction of the hypothermia protocol. The rocuronium infusion was discontinued on hospital day 2 on completion of the rewarming process, and no shivering was noted; however, the patient developed acute respiratory distress syndrome (ARDS) with ventilator asynchrony requiring the reinitiation of the rocuronium infusion on the same day and prone positioning (initiated on day 3 of hospitalization) for alveoli recruitment. On hospital day 6, an initial elevated axillary temperature of 101.4 °F occurred. An infectious diseases consultation was obtained, which resulted in the initiation of broad-spectrum antibiotics including piperacillin–tazobactam 4.5 g i.v. every 6 hours, vancomycin 1 g i.v. every 12 hours, and fluconazole 200 mg i.v. every 24 hours. The patient continued to demonstrate a rise in temperature, to a maximum of 105.2 °F, through hospital day 9 (Figure 1). The patient had a white blood cell (WBC) count of 10,500/mm³. On evaluation by physician specialists in infectious diseases, including an assessment of culture results and all sites of catheter placement, no source of infection was identified. Although piperacillin–tazobactam has been associated with drug–induced fever, the infectious diseases specialists determined this agent to be an unlikely cause of the patient’s fever, and therapy was continued. Other concurrent medications were critically reviewed for possible causation of the febrile response. These medications included fluconazole; vancomycin; propofol, lorazepam, and fentanyl i.v. continuous infusion; methylprednisolone 40 mg i.v. every 8 hours; insulin infusion (titrated to achieve a blood glucose concentration of 90–130 mg/dL); diltiazem hydrochloride 5 mg/hr i.v.; famotidine 20 mg i.v. every 12 hours; enoxaparin sodium 40 mg subcutaneously every 24 hours; acetaminophen 650 mg via a feeding tube every 4 hours as needed (i.e., for a temperature of >101.5 °F); and indomethacin 50 mg via a feeding tube every 12 hours as needed (i.e., for a temperature of >101 °F unresponsive to acetaminophen therapy). Physician specialists in infectious diseases, pulmonology, and neurology determined that these concurrent medications were highly unlikely to be causative agents, and no changes to medication therapy were ordered. Other complications at the time of the occurrence of malignant hyperthermia included hypertension (153/90 mm Hg), anoxic encephalopathy, elevated creatine phosphokinase (351 units/L), and resolving hypernatremia (150 mmol/L). Rocuronium was discontinued at 11 a.m. on hospital day 10 due to a suspicion of drug-induced malignant hyperthermia. One hour after the discontinuation of the neuromuscular blocker, the patient’s temperature began to decline, reaching a nadir of 99.4 °F by day 11 of the hospitalization (Figure 1). The patient’s fever did not return. Due to the close temporal relationship of the patient’s temperature decline and the discontinuation of rocuronium, he was believed by the physician specialists to have experienced malignant hyperthermia consequent to rocuronium use.
Figure 1 Sequential temperature measurements for patient 1 (panel A) and patient 2 (panel B), with the points of rocuronium initiation and discontinuation indicated in green and red.

**Patient 2**

A 63-year-old Caucasian man (weight, 90 kg; height, 173 cm) was admitted to the hospital for the surgical repair of a paraesophageal hernia, which included herniation of the stomach, colon, and
pancreas. He was taken to the operating room on day 1 of the hospitalization, and an open reduction of the paraesophageal hernia was performed and deemed successful. Postoperatively, the patient experienced respiratory failure and declining mental status while in the recovery room. He was subsequently reintubated and transferred to the ICU. After the transfer, the patient developed hemodynamic instability and was noted to have lactic acidosis. Arterial blood gas measurements revealed a pH of 7.23, a pCO₂ of 62 mm Hg, a pO₂ of 239 mm Hg, and a bicarbonate concentration of 26 mmol/L. Broad-spectrum antimicrobial therapy with meropenem 500 mg i.v. every 8 hours was initiated empirically for potential sepsis, a low-grade fever (100.2 °F), and the presence of a left shift of the WBC count (2800/mm³, with neutrophil bands of 58%). The patient also received volume resuscitation with 0.9% sodium chloride and norepinephrine (i.v. continuous infusion titrated to achieve a mean arterial pressure of >65 mm Hg) due to his hemodynamic instability. During the patient’s second hospital day a rocuronium infusion (initiated at 8 μg/kg/min and titrated to a train-of-four score of 2) was started for the management of ventilator asynchrony after other pharmacologic measures, including lorazepam 2 mg/hr by i.v. continuous infusion and fentanyl i.v. continuous infusion, were exhausted. On hospital day 4, the patient developed abdominal compartment syndrome and was returned to the operating room for decompression. During surgery, the patient received desflurane (2.1–3%) and two 50-mg bolus doses of rocuronium in addition to the continuous infusion of rocuronium. Intraoperatively, the patient experienced cardiac arrest with pulseless electrical activity requiring chest compressions and the use of epinephrine and atropine. The patient regained spontaneous circulation and was returned to the ICU, with the continuation of the rocuronium infusion. The patient was diagnosed with ARDS and septic shock on day 5 of the hospitalization. Anidulafungin 100 mg i.v. every 24 hours, vancomycin 1500 mg i.v. every 24 hours, ciprofloxacin 400 mg i.v. every 12 hours, and activated drotrecogin alfa 24 μg/kg/hr i.v. continuous infusion for 96 hours were initiated for the treatment of sepsis, in addition to prone positioning for alveoli recruitment. On hospital day 8, the patient returned to the operating room a third time for the replacement of the temporary abdominal closures and the placement of a negative-pressure wound therapy device. The rocuronium infusion was continued throughout the procedure and after the patient’s return to the ICU. Postoperatively, fever was immediately noted, with temperatures continuing to rise through hospital day 8 to a maximum of 107.1 °F (Figure 1). Considering the pattern of the recorded temperature values, the infectious diseases specialists did not believe the patient’s febrile response had an infectious etiology, believing instead that it likely resulted from neurologic injury or was medication related. Antimicrobial therapy was changed due to the continued suspicion of drug-related fever after all other potential sources of infection were evaluated and the patient’s catheter was removed. Meropenem, vancomycin, and ciprofloxacin were discontinued, and tigecycline 100 mg i.v. every 24 hours was initiated. Other concurrent medications were critically reviewed for possible causation of the febrile response; those medications included drotrecogin alfa (activated), fentanyl, lorazepam, total parenteral nutrition, nebulized albuterol, nebulized acetylcysteine 20%, pantoprazole 40 mg i.v. every 24 hours, amiodarone (a 150-mg i.v. bolus followed by a 750-mg i.v. infusion), norepinephrine (titrated to maintain a mean arterial pressure of >65 mm Hg), vasopressin 0.03 unit/min by i.v. continuous infusion, and a regular insulin infusion titrated to achieve a blood glucose concentration of 90–130 mg/dL. Atrial fibrillation was present at the time of the febrile response, with the serum potassium concentration (4.2 mmol/L) noted to be within
normal limits. Neurology specialists were consulted for the evaluation and management of what was believed to be a malignant hyperthermia event. At that time, the rocuronium was discontinued, and the patient was treated with dantrolene sodium (an initial dose of 200 mg followed by 100 mg i.v. every 6 hours) and bromocriptine (2.5 mg per gastrointestinal tube every 8 hours) for the presumptive treatment of malignant hyperthermia. Twelve hours after the discontinuation of rocuronium, the patient’s temperature began to decline; a nadir of 97.7 °F was achieved 18 hours after the discontinuation of rocuronium and 4 hours after the first doses of dantrolene and bromocriptine were administered (Figure 1). The fever did not return, and both dantrolene and bromocriptine were discontinued after 48 hours of treatment. As a result of the temporal relationship between the patient’s temperature decline and the discontinuation of rocuronium (and the initiation of dantrolene and bromocriptine), the patient was believed by physician specialists to have experienced malignant hyperthermia as a result of rocuronium use.

Discussion

Cases of malignant hyperthermia have increased in the United States in recent years, with an estimated occurrence of up to 1 in 3000 patients undergoing anesthesia procedures.6,19 Men appear to be more likely to suffer an episode of malignant hyperthermia; however, women are at higher risk for dying from the disorder. Associated mortality rates in adults range from 6.5% to 16.9%, while children have a much lower mortality rate (0.7%).19

Genetic predisposition to malignant hyperthermia was not considered in the two cases described here, as neither patient had a known personal or family history of the disorder. Many susceptible patients can receive multiple “trigger” agents without developing malignant hyperthermia.1 Therefore, previous exposure to nondepolarizing neuromuscular blockers does not preclude a suspicion of drug-induced malignant hyperthermia with subsequent exposures.

Malignant hyperthermia may occur at any point during and after anesthesia administration, although it is most common within 140 minutes after the administration of halogenated anesthetics and within 35 minutes of the administration of a depolarizing neuromuscular blocker.2,7 In the second case reported here, the patient was exposed to an anesthetic gas, but malignant hyperthermia developed more than four days after the exposure; based on the delayed onset, the anesthetic gas was not believed to be responsible for the development of malignant hyperthermia in this patient.

Although the majority of published reports indicate that the use of depolarizing neuromuscular blockers can trigger malignant hyperthermia in susceptible patients, a small number of case reports suggest the possibility that nondepolarizing neuromuscular blockers may be contributing agents.10–13 Polta et al.10 described the development of isolated masseter-muscle spasm—a common finding in patients experiencing malignant hyperthermia and a risk factor for the development of the disorder—after the administration of pancuronium in a 20-year-old man undergoing corrective surgery for congenital aortic stenosis2,10; he received pancuronium a second time during orotracheal intubation and experienced a recurrence of the rigidity of the jaw muscles. The patient recovered fully without treatment in both instances.
Two cases of isolated masseter-muscle rigidity with the use of a non-depolarizing neuromuscular blocker were reported by Albrecht and colleagues. In one of those cases, a 22-year-old woman experienced masseter-muscle rigidity after receiving atracurium. On discontinuation of anesthesia including thiopental, midazolam, fentanyl, isoflurane, and nitrous oxide, the patient recovered fully without treatment. In the other case reported by Albrecht et al., a 33-year-old woman experienced isolated masseter-muscle rigidity after receiving vecuronium followed by atracurium and mivacurium. That patient also fully recovered after the discontinuation of anesthesia including midazolam, fentanyl, thiopental, and desflurane and the reversal of the effects of the neuromuscular blocker with atropine and edrophonium.

Increased body temperature in combination with other signs of malignant hyperthermia in patients receiving nondepolarizing neuromuscular blockers has been documented in four case reports. Waterman et al. reported the case of a 25-year-old man with malignant hyperthermia manifesting as tachycardia and increased temperature five minutes after the administration of pancuronium. In that case, anesthesia including fentanyl, diazepam, and thiamylal sodium was abruptly discontinued at the time of the event, and the patient was treated with a cooling blanket, iced saline, droperidol, dexamethasone, and procainamide, resulting in a full recovery. During subsequent surgery in this patient, neuromuscular blockers were avoided, and malignant hyperthermia did not recur. Albrecht et al. reported on the case of an 11-year-old boy who received thiopental, atracurium, isoflurane, and nitrous oxide during an orthopedic surgical procedure. Three hours after receiving anesthesia, the patient experienced tachycardia, masseter-muscle rigidity, and an increase in temperature of <1 °C. The discontinuation of isoflurane and the administration of dantrolene resulted in the patient’s full recovery. In another case described in the same report, a 49-year-old woman with a family history of anesthesia-related death developed masseter-muscle rigidity with a temperature increase of 1 °C during anesthesia (fentanyl, diazepam, thiopental, and atracurium) despite treatment with dantrolene before surgery. The patient experienced a full recovery after ice was applied for cooling. Four years later, the same patient underwent anesthesia with propofol, fentanyl, nitrous oxide, and vecuronium; no masseter-muscle rigidity or other indications of malignant hyperthermia were noted. None of these reports demonstrated a definitive causal relationship between the use of neuromuscular blockers and the development of malignant hyperthermia, as many of the patients involved received concomitantly administered anesthetic gases, which are well-documented potential inducers of malignant hyperthermia in susceptible patients.

In the cases described in this article, the patients experienced the delayed onset of malignant hyperthermia after rocuronium administration. This presentation has only been suggested in one other reported case, that of a 28-year-old man who received fentanyl, midazolam, rocuronium, nitrous oxide, and desflurane in preparation for maxillofacial surgery after a motor vehicle accident. Seven hours after anesthesia induction, the patient was noted to have an elevated end tidal carbon dioxide concentration and an increased temperature. The patient was determined to have malignant hyperthermia, so surgery was not performed, desflurane was discontinued, the carbon dioxide canisters and anesthesia machinery were changed, a cooling blanket was applied, and dantrolene, cold i.v. fluids, and diuresis were administered. Surgery was attempted again, with dantrolene administration one day before the procedure and the use of propofol, midazolam, and
rocuronium for anesthesia. No adverse events were reported during the second procedure. The authors of the case report were unable to definitively determine whether rocuronium played a role because dantrolene was administered prior to the subsequent administration of rocuronium.

In the cases reported here, the application of the algorithm of Naranjo et al. indicated a possible adverse reaction to rocuronium, particularly given the temporal sequence of symptom onset with rocuronium initiation followed by a recognized pattern of recovery on discontinuation of the drug.

Unfortunately, due to the complex symptomatology of critically ill patient populations, it is difficult to demonstrate a definitive cause for this adverse drug reaction. In the two cases described in this report, it is possible that other variables unrelated to rocuronium use may have led to the development of malignant hyperthermia. For example, rhabdomyolysis is similar to malignant hyperthermia in its clinical and laboratory manifestations, which can include tachycardia, hypercarbia, pyrexia, rigidity, and elevated creatine kinase. Rhabdomyolysis may have played a role in the cases described here, as elevations of creatine phosphokinase occurred in both patients, although a diagnosis of rhabdomyolysis was not made in either patient. Both patients developed ARDS, received prone positioning, and received concomitant corticosteroids. Although few cases of rhabdomyolysis induced by prone positioning have been reported, it is unknown if prone positioning could have precipitated a malignant hyperthermia event or other skeletal muscle abnormality in our patients; further, prone positioning has not been documented to affect temperature homeostasis.

The development of myopathies when neuromuscular blockers are administered concurrently with corticosteroid therapy is well documented, with necrotizing myopathies reported in some cases. It is not known whether the malignant hyperthermia experienced in the two cases reported here may have been induced by other skeletal muscle abnormalities. Neuroleptic malignant syndrome and serotonin syndrome can also have a presentation similar to that of malignant hyperthermia, but those syndromes were not considered in our patients’ differential diagnosis because neither had received excessive doses of serotonergic agents or dopamine antagonists.

It is important to consider the temporal relationship of the two cases described here. The patients were hospitalized within the same month at the same institution, suggesting the possibility of an impure lot of rocuronium as the cause of their malignant hyperthermia; however, this was unable to be determined.

Other variables that may have contributed to the hyperthermia events described in this report include the use of antimicrobials and brain injury resulting from cardiac arrest. Antimicrobial-induced fever may develop at any point during the use of the drugs, although it is most commonly noted within six to eight days of the initiation of therapy, with recovery typically occurring soon after the discontinuation of therapy. Antimicrobial-induced fever was ruled out in our patients, as the febrile symptoms persisted despite changes in therapy in one of the patients and, in the other patient, resolved without antimicrobial manipulation. With regard to the potential role of brain insult in these two cases, it is possible that the observed hyperthermia was a symptom of neurally mediated impairment of thermoregulation as a result of the patients’ cardiac arrest; however, in
light of their abrupt recovery from hyperthermia after the discontinuation of rocuronium, that possibility was not considered likely by the health care providers involved in the cases.

Despite a number of potential confounding factors and the complexity of the two patients’ clinical courses, there was a striking correlation between the temperature decline and the discontinuation of rocuronium in both cases. Thus, these cases suggest that nondepolarizing neuromuscular blockers should be considered (along with other potential offending agents) if symptoms of malignant hyperthermia are suspected.

Due to the limited published evidence regarding this adverse reaction, best practices for the management of at-risk patients are unclear. The maximization of adjunctive anesthesia support (e.g., sedative and opioid therapy) in an effort to avoid neuromuscular blockade, or at least minimize the dosing requirements and duration of use, may be appropriate. In addition, the early discontinuation of neuromuscular blockade and the administration of dantrolene and bromocriptine in managing suspected cases of malignant hyperthermia may be considered.

Conclusion

A 27-year-old man and a 63-year-old man received rocuronium and subsequently developed delayed-onset malignant hyperthermia, which resolved after the rocuronium was discontinued.

Footnotes

Dr. Powers serves on the speakers bureaus of Sage Pharmaceuticals, Hollister-Stier Laboratories, and Kinetic Concepts. The other authors have declared no potential conflicts of interest.

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