Clinical Reports

Neuroleptic malignant syndrome and mivacurium: a safe alternative to succinylcholine?

Dermot Kelly MRCPI FFARCSI, Sorin J. Brull MD

Neuroleptic malignant syndrome (NMS) and malignant hyperthermia (MH) may have a common pathogenic mechanism; therefore, it has been suggested that known triggering agents for MH (such as succinylcholine) should be avoided in patients with NMS. Electroconvulsive therapy (ECT) continues to play a major therapeutic role in contemporary psychiatry, and succinylcholine has been the muscle relaxant of choice in attenuating violent muscle contractions induced by ECT. Mivacurium is a non-depolarizing muscle relaxant with a relatively rapid onset and a short duration of action, and to date it has been proved safe in MH-susceptible patients. In this case report, following succinylcholine use during ECT, a patient with NMS developed an increase in temperature and serum creatine kinase (CK) level, possibly due to an MH reaction. Since the patient's mental status necessitated further ECT, mivacurium was administered during subsequent treatments and resulted in effective attenuation of muscle contractions without elevation of patient temperature or CK levels. In addition, there was no marked prolongation of the anaesthetic. Mivacurium is a suitable agent for patients with NMS undergoing ECT, as it has not been associated with precipitation of an MH response.

Le syndrome malin des neuroleptiques (SMN) et l'hyperthermie maligne (HM) semblent avoir une mécanisme pathogène commun; c'est pourquoi on a suggéré d'éviter dans le SMN les agents qui déclenchent l'HM (ex., la succinylcholine). L'électroconvulsivothérapie (ECT) continue de jouer un rôle majeur en pyschiatrie et la succinylcholine est présentement le myorelaxant de choix pour atténuer les violentes contractions musculaires induites par l'ECT. Le mivacurium est un myorelaxant non dépolarisant dont le début d'action est relativement rapide et la durée d'action courte, et jusqu'à maintenant, on a jugé qu'il ne présentait aucun danger pour les patients susceptibles à l'HM. Dans le cas présent, à la suite de l'administration de succinylcholine pour un ECT, un patient porteur du SMN a présenté une élévation de température et de la concentration de la créatine kinase sérique (CK), peut-être par réaction d'HM. Comme son état nécessitait des traitements additionels d'ECT, le mivacurium a été administré au cours des traitements ultérieurs et a atténué les contractions musculaires sans élévation de température ou des concentrations de CK. Il n'a pas eu non plus de prolongation appréciable de l'anesthésie. Le mivacurium est un agent approprié pour le SMN et il n'est pas associé au déclenchement de l'HM.

Key words
COMPLICATIONS: malignant hyperthermia;
NEUROMUSCULAR RELAXANTS: mivacurium, succinylcholine.

From the Department of Anesthesiology, Yale University School of Medicine, 333 Cedar Street, T-3, New Haven, CT 06510.

Address correspondence to: Dr. Sorin J. Brull, Department of Anesthesiology, Yale University School of Medicine, 333 Cedar Street, T-3, New Haven, CT 06510.

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Neuroleptic malignant syndrome (NMS) is an uncommon, but life-threatening complication associated with the administration of neuroleptic agents. The syndrome is characterized by hyperthermia, muscle rigidity, altered consciousness and autonomic instability (manifested as extremes of heart rate, blood pressure lability, diaphoresis and incontinence). Treatment consists of prompt diagnosis, discontinuation of neuroleptic medications and supportive measures – cooling of the patient, support of the respiratory, renal and cardiovascular systems, physiotherapy and nursing care. Airway protection and mechanical ventilation may be required.

The pathophysiology of the NMS has not been fully

elucidated. The similarities that exist between it and malignant hyperthermia (MH) suggest common pathogenetic mechanisms for both disorders.[1,2] In addition, a substantial proportion of NMS patients may show MH susceptibility using *in vitro* muscle contracture tests.[3] Therefore, several authors have suggested that known triggering agents for MH should be avoided when anaesthetizing a patient with NMS.[3-5] Bromocriptine, amantadine, anticolinergic agents, dantrolene, and electroconvulsive therapy (ECT) have been used in the treatment of NMS.

The principal role of ECT in contemporary psychiatry is in the treatment of refractory depression. It is estimated that over 100,000 ECT treatments are administered in the United States each year.[6] The therapeutic mechanism of ECT lies in the generalized seizure it induces; however, it also causes violent muscle contractions which can result in bone fractures and personal injury. Succinylcholine is the muscle relaxant most frequently used to attenuate this muscular response. However, a short-acting, nondepolarizing relaxant may be preferable in patients with NMS because succinylcholine may precipitate an MH crisis or hyperkalaemia. This case report describes the use of the short-acting nondepolarizing muscle relaxant mivacurium in a patient with NMS undergoing ECT for treatment of depression.

Case report

A 29-yr-old woman with a 12-yr history of bipolar disorder with psychotic features was admitted through the emergency room with increasing hallucinations, disorientation and agitation of four weeks' duration. Her medications on admission included lithium carbonate, divalproex sodium, and clozapine. Her past medical history was significant for three previous hospitalizations due to acute psychosis, which responded to various antipsychotic medications. She had never undergone general anaesthesia, and had no personal or family history of malignant hyperthermia or other anaesthetic-related problems.

On physical examination, the patient weighed 49 kg, had an arterial blood pressure (BP) of 110/60 mmHg, sinus tachycardia at 100 beats · min^{-1}, and was afebrile at 98° F. She was anxious, yet cooperative, with increased psychomotor activity. Thought content revealed delusions of persecution and auditory hallucinations. Cognitive testing revealed the patient to be orientated, but with decreased attention span. The rest of the mental and physical examinations were essentially normal. Serum concentration of electrolytes, liver function tests, thyroid function tests, serum glucose and complete blood count were all within normal limits. Her chest radiograph and electrocardiogram (ECG) were unremarkable.

The patient was admitted to the psychiatric ward for treatment. The dose of clozapine was increased by 25 mg each day to 300 mg daily. Despite this, and the addition of chlorpromazine 50 mg as needed, her agitation escalated. Haloperidol 3 mg (*im*) every two hours (to a maximum of 9 mg in 24 hr) was commenced, and a total of 7 mg of this neuroleptic agent was administered over the next 36 hr. Due to the marked agitation and absence of response to her antipsychotic regimen, her clozapine, lithium, and haloperidol were discontinued. The divalproex sodium was continued, and lorazepam 1 mg *im* was prescribed for extreme agitation as required.

On her 16th day of hospitalization, the patient's mental status deteriorated and she experienced increasing confusion, disorientation and hallucinations. She developed a fever of 38.1° C with increased muscle tone and clinical evidence of dehydration. Neuroleptic malignant syndrome was suspected, and all psychotropic medications were discontinued. The patient's fluid and electrolyte balance were maintained, and a septic screen was performed (urine and blood cultures were negative). Over the next three days, the serum concentrations of creatine kinase (CK) increased to 1,710 units · L^{-1}. A diagnosis of NMS was made based on the patient's fever, rigidity, altered mental state, and elevated CK. The onset of these signs and symptoms was temporally related to the use of neuroleptics and there was no organic pathology to explain her condition. Because of the persistent psychosis and lack of suitable pyschotropic medication, emergency ECT was scheduled. The patient was fasted overnight and transferred to the anaesthetic recovery room, where an initial course of ECT was administered. Intravenous access was established first, and the monitoring employed consisted of continuous ECG, oscillometric BP cuff, precordial stethoscope, pulse oximetry, end-tidal carbon dioxide monitor and a rectal temperature probe. This routine was followed for all 12 courses of ECT.

For the first ECT treatment, anaesthesia was induced with 175 mg thiopentone *iv*, followed by succinylcholine 30 mg, to attenuate the muscular contractions associated with seizure activity. The patient's lungs were ventilated with 100% oxygen by facemask. A 1.25-second electrical pulse (70 Hz, 0.8 V) was delivered via bipolar electrodes placed bilaterally over the frontal regions, producing a 112-sec seizure which was recorded on the electroencephalogram (EEG); there were no muscular manifestations of seizure activity. The anaesthetic course and recovery period were uneventful. However, that evening the patient's temperature increased from 38.1 to 39° C, and the serum CK levels increased from 1,500 to 3,000 units · L^{-1}. Arterial blood gas analysis while breathing room air showed a mild metabolic acidosis with a pH

of 7.34, $PaCO_2$ of 31 mmHg, PaO_2 of 98 mmHg and a serum bicarbonate concentration 16.1 $mEq \cdot L^{-1}$. The differential diagnosis included worsening of her NMS, MH secondary to succinylcholine, or a succinylcholine- or seizure-induced elevation of CK with a coexisting septic process. There was no evidence of hyperkalaemia or myoglobinuria.

Her poor psychiatric status necessitated continuation of ECT, and 48 hr later a second treatment was scheduled. The same precautions and monitoring procedures were undertaken as during the initial treatment with the addition of a nerve stimulator. On this occasion, after induction of anaesthesia with 175 mg of thiopentone *iv*, mivacurium 7 mg was administered. Again, 100% oxygen was delivered by facemask and ventilation was assisted. The electrical stimulus delivered to induce seizure activity was identical to that used in the first treatment and was administered two minutes after the mivacurium. A 103-sec seizure was detected on the EEG, but no motor activity was visible. The haemodynamic response to the treatment was similar to that witnessed two days earlier – arterial BP increased from 115/65 to 145/85 mmHg, while the heart rate increased from 90 to 118 $beats \cdot min^{-1}$. Both haemodynamic variables returned to baseline within six minutes. Spontaneous ventilation returned within 12 min of mivacurium administration. No reversal agents were deemed necessary, as after 14 min the mechanographic train-of-four (TOF) ratio exceeded 0.8, and a 50-Hz tetanus for five seconds induced a sustained contraction of the adductor pollicis muscle. Thirty minutes after induction, the patient was alert and awake. There was no elevation of body temperature, serum potassium or CK during the peri-anaesthetic period.

During the subsequent four weeks, the patient underwent ten further ECT treatments. Induction of general anaesthesia with thiopentone and mivacurium, in dosages of 0.12–0.16 $mg \cdot kg^{-1}$, with mask ventilation was the technique employed in all cases. Reversal agents (edrophonium 0.3 $mg \cdot kg^{-1}$ and atropine 0.01 $mg \cdot kg^{-1}$) were administered during five of the ten anaesthetics when subjective assessment of the response to TOF and tetanic stimulation revealed residual block (i.e., TOF < 0.7, or fade in response to tetanic stimulation at 50 Hz for five seconds) at the end of the procedure. Each treatment was without complication. The pyrexia settled after the fourth ECT treatment and the elevated serum CK level gradually returned to normal.

The patient was discharged five days after her last ECT treatment with normal vital signs and improved mental status. Performance of a contracture test to determine her MH susceptibility was not undertaken because of patient refusal.

Discussion

Neuroleptic agents have an established role in the treatment of a variety of psychotic conditions. They exert their therapeutic effects by blocking dopaminergic systems in the central nervous system (CNS). Many side effects of neuroleptic medications have been described, of which NMS is the most serious. The incidence of NMS may be as high as 1.4% among those receiving neuroleptic agents,[7] with an estimated mortality rate of 15%.[1] The majority of the deaths are attributable to cardiac arrhythmias, myocardial infarction, aspiration pneumonia, pulmonary embolism, respiratory failure, sepsis and renal failure secondary to rhabdomyolysis.[8]

The aetiology of the NMS remains unknown. It shares many clinical and laboratory similarities with MH – fever, muscle rigidity, hypermetabolism, diaphoresis, rhabdomyloysis, elevated serum CK levels, and possible therapeutic response to dantrolene. This suggests that the two disorders may be related. However, apparent differences exist between the two conditions; MH episodes are triggered by inhalational anaesthetics and depolarizing muscle relaxants, whereas NMS, by definition, is precipitated by neuroleptic drugs. In addition, the muscle rigidity in NMS, in contrast to MH, may be neurogenic in origin, as relaxation has been achieved in NMS patients using neuromuscular blocking drugs or benzodiazepines.[1,8] Recent studies suggest that NMS may result from primary abnormalities in the CNS, most likely secondary to neuroleptic antagonism of dopamine receptors, resulting in dopaminergic hypoactivity.[9,10] Dopamine receptor blockade impairs thermoregulation and results in decreased heat dissipation. Neuroleptic agents also act on the basal ganglia, causing muscle rigidity and heat generation.[10] On the other hand, MH is a genetically inherited disorder associated with abnormal excitation-contraction coupling and elevated intracellular calcium levels in skeletal muscle.

When tested *in vitro*, muscle of MH patients exhibits a greater contracture response to halothane and caffeine than normal. This response appears to be sensitive and specific for MH.[4,11] Similarly, muscle biopsy specimens from several patients with NMS have demonstrated an increased contractile response to halothane, and these patients have been termed MH-susceptible.[3,12,13] However, conflicting observations on the susceptibility of NMS patients to MH were made by other investigators.[14,15] Caroff *et al.* suggest that NMS may represent a heterogenous group of patients, both in terms of aetiology and response to drugs.[3] This heterogeneity, coupled with lack of standardization between studies, may explain the different findings of MH susceptibility in NMS patients.

In NMS patients, succinylcholine can induce hyperkalaemia,[16] and may increase the risk of triggering an

MH crisis. Nevertheless, succinylcholine has traditionally been used as part of the anaesthetic management for NMS sufferers undergoing ECT because of the short nature of the procedure and the lack of a suitable nondepolarizing relaxant.

Mivacurium is a new, benzylisoquinolinium nondepolarizing relaxant with a relatively rapid onset and short duration of action.[17] Mivacurium has so far proved safe in MH patients and there are no reports in the literature of its triggering an MH crisis.[18] In addition, because of its nondepolarizing (competitive) mechanism of action, mivacurium eliminates the risk of hyperkalaemia, which has been reported with succinylcholine in NMS.[16] The short duration of action would not necessitate a marked prolongation of the anaesthetic for ECT. The ED_{95} (the dose required to produce 95% suppression of the adductor pollicis muscle twitch response to ulnar nerve stimulation) of mivacurium is 0.07–0.08mg · kg^{-1} in adults receiving opioid/N_2O/O_2 anaesthesia.[20] When this dose is administered, the time to spontaneous return of the single twitch to >95% of control is 18.6 min ± 2.8.[17] At equipotent doses, its elimination half-life of 2–3 min[19] compares favourably with that of atracurium (22 min) and vecuronium (71 min), the two most popular intermediate-acting nondepolarizing agents. The time to recovery of adequate neuromuscular function can be shortened further by using lower doses of mivacurium and/or administering anticholinesterase agents.

The optimal dose for succinylcholine during ECT is suggested as 0.5 mg · kg^{-1} (approximately 2 × ED_{95} dose), well below the usual intubating dose of 1.0–1.5 mg · kg^{-1}.[20] Thus, a dose of mivacurium of approximately 0.15 mg · kg^{-1} (2 × ED_{95} dose) should likewise attenuate the ECT-induced muscular contractions adequately in most cases, while not causing clinically significant histamine release or hypotension – the side effects most frequently associated with its use.[21] Furthermore, when coupled with antagonism by anticholinesterase agents, this dose would allow rapid (six to eight minutes) recovery of neuromuscular function.

Given the controversy that surrounds MH susceptibility in NMS patients, this case highlights the usefulness of mivacurium in this patient group. Mivacurium effectively attenuates the seizure response without unduly prolonging anaesthetic time for the procedure. In addition, it eliminates the risk of an MH crisis or a precipitous rise in serum potassium concentration in NMS patients, thus minimizing the potential morbidity and mortality. It remains to be seen whether, given its pharmacological profile, mivacurium will replace succinylcholine for routine ECT procedures. Regardless, mivacurium appears to be a safer alternative to succinylcholine in patients with NMS or MH susceptibility.

References

1 *Levenson, JL.* Neuroleptic malignant syndrome. Am J Psychiatry 1985; 142: 1137–45.

2 *Geiduschek J, Cohen SA, Khan A, Cullen BF.* Repeated anesthesia for a patient with neuroleptic malignant syndrome. Anesthesiology 1988; 68: 134–7.

3 *Caroff SN, Rosenberg H, Fletcher JE, Heiman-Patterson TD, Mann SC.* Malignant hyperthermia susceptibility in neuroleptic malignant syndrome. Anesthesiology 1987; 67: 20–5.

4 *Liskow BI.* Relationship between neuroleptic malignant syndrome and malignant hyperthermia (Letter). Am J Psychiatry 1985; 142: 390.

5 *Weinberg S, Twersky RS.* Neuroleptic malignant syndrome. Anesth Analg 1983; 62: 848–50.

6 *Holden C.* A guarded endorsement for shock therapy. Science 1985; 228: 1510–1.

7 *Pope HG Jr, Keck PE Jr, McElroy SL.* Frequency and presentation of neuroleptic malignant syndrome in a large psychiatric hospital. Am J Psychiatry 1986; 143: 1227–33.

8 *Sangal R, Dimitrijevic R.* Neuroleptic malignant syndrome – successful treatment with pancuronium. JAMA 1985; 254: 2795–6.

9. *Hashimoto F, Sherman CB, Jeffery WH.* Neuroleptic malignant syndrome and dopaminergic blockade. Arch Intern Med 1984; 144: 629–30.

10 *Henderson VW, Wooten GF.* Neuroleptic malignant syndrome: a pathogenetic role for dopamine receptor blockade? Neurology 1981; 31: 132–7.

11 *Rosenberg H, Reed S.* In vitro contracture tests for susceptibility to malignant hyperthermia. Anesth Analg 1983; 62: 415–20.

12 *Denborough MA, Collins SP, Hopkinson KC.* Rhabdomyolysis and malignant hyperpyrexia. BMJ 1984; 288: 1878.

13 *Araki M, Takagi A, Higuchi I, Sugita H.* Neuroleptic malignant syndrome: caffeine contracture of single muscle fibers and muscle pathology. Neurology 1988; 38: 297–301.

14 *Tollefson G.* A case of neuroleptic malignant syndrome: *in vitro* muscle comparison with malignant hyperthermia. J Clin Psychopharmacol 1982; 2: 266–70.

15 *Scarlett JD, Zimmerman R, Berkovic SF.* Neuroleptic malignant syndrome. Aust N Z J Med 1983; 13: 70–3.

16 *George AL Jr., Wood CA Jr.* Succinylcholine-induced hyperkalemia complicating the neuroleptic malignant syndrome (Letter). Ann Intern Med 1987; 106: 172.

17 *Savarese JJ, Ali HH, Basta SJ, et al.* The clinical neuromuscular pharmacology of mivacurium chloride (BW B1090U). A short-acting nondepolarizing ester neuromuscular blocking drug. Anesthesiology 1988; 68: 723–32.

18 *Sufit RL, Kreul JF, Bellay YM, Helmer P, Brunson DB, Will J.* Doxacurium and mivacurium do not trigger malig-

nant hyperthermia in susceptible swine. Anesth Analg 1990; 71: 285–7.

19 *Ali HH, Savarese JJ, Embree PB, et al.* Clinical pharmacology of mivacurium chloride (BW B1090U) infusion: comparison with vecuronium and atracurium. Br J Anaesth 1988; 61: 541–6.

20 *Messick JM Jr, MacKenzie RA, Nugent M.* Anesthesia at remote locations. *In*: Miller RD (Ed.). Anesthesia, 3rd ed. New York: Churchill Livingstone, 1990: 2061–88.

21 *Savarese JJ, Ali HH, Basta SJ, et al.* The cardiovascular effects of mivacurium chloride (BW B1090U) in patients receiving nitrous oxide-opiate-barbiturate anesthesia. Anesthesiology 1989; 70: 386–94.