J Anesth (2012) 26:250–253
DOI 10.1007/s00540-011-1269-2

CLINICAL REPORT

Anesthetic management of a pediatric patient with neuroleptic malignant syndrome

Tarun Bhalla · Douglas Maxey · Amod Sawardekar · Joseph D. Tobias

Received: 27 July 2011 / Accepted: 13 October 2011 / Published online: 19 November 2011

Abstract Neuroleptic malignant syndrome (NMS) is a rare disorder which is clinically similar to malignant hyperthermia (MH). It is characterized by hyperthermia, autonomic instability, muscle rigidity, coma, rhabdomyolysis, and acidosis. Without immediate and appropriate therapy, mortality may result. NMS is associated with administration of antipsychotic medications, anti-emetic medications, and changes in the dosage of anti-parkinsonian drugs. As several similarities exist between NMS and MH, differentiating between them can be a challenge for the clinician. We report anesthetic care during magnetic resonance imaging of the brain of a 14-year-old female with bipolar and schizoaffective disorders and the recent onset of NMS.

Keywords Neuroleptic malignant syndrome · Pediatric anesthesia · Anti-psychotic medications

Introduction

Neuroleptic malignant syndrome (NMS) is an uncommon and life-threatening complication of treatment with some medications. It was first described by Delay and Deniker in the 1960s [1]. Administration of typical antipsychotic medications (haloperidol, fluphenazine, chlorpromazine), atypical antipsychotics (olanzapine, risperdone, clozapine), antiemetics (metoclopramide, haloperidol), and even an abrupt decrease in the dosage of or withdrawal from anti-parkinsonian drugs (bromocriptine, levodopa/carbidopa) can precipitate NMS. In fact, NMS has been reported postoperatively after a single dose of droperidol or metoclopramide [2–4].

The incidence of NMS is estimated at 0.07–2.2% of patients with the aforementioned triggering events [5–7]. Although NMS can present at any age, there is a male to female predominance of 2:1. However, this is likely to be because of the increased use of antipsychotic medication in males [3]. There may be a genetic component to NMS but this is controversial [1, 3]. A differential diagnosis of MH, serotonin syndrome, malignant catatonia, and other drug-induced disorders must be considered.

Various scenarios may arise whereby the anesthesia provider provides care for a patient with NMS. As noted, NMS may occur after administration of a single dose of a phenothiazine or anti-emetic agent such as metoclopramide in the treatment of, or to prevent, postoperative nausea and vomiting. Additionally, anesthesia may be required in patients with an acute episode of NMS or a history of the disorder. We review the anesthetic care during magnetic resonance imaging of the brain of a 14-year-old female with bipolar and schizoaffective disorders and the recent onset of NMS. The potential perioperative implications of NMS are reviewed.

Case report

Review of this patient's hospital record and presentation of the material in this format was approved by the Institutional Review Board of Nationwide Children's Hospital (Columbus, Ohio, USA). The patient was a 53 kg,

T. Bhalla (✉) · D. Maxey · A. Sawardekar · J. D. Tobias
Department of Anesthesiology and Pain Medicine,
Nationwide Children's Hospital and the Ohio State University,
700 Children's Drive, Columbus, OH 43205, USA
e-mail: Tarun.Bhalla@Nationwidechildrens.org

J. D. Tobias
Department of Pediatrics, Nationwide Children's Hospital
and the Ohio State University, Columbus, OH, USA

14-year-old girl who presented as an urgent case requiring a general anesthesia during magnetic resonance imaging (MRI) of the brain. She had a history of bipolar and schizoaffective disorders and 6 days earlier had presented to the emergency room (ER) at an outside hospital with mental status changes, muscle rigidity, and hypertension. Before this, there was a history of increasing aggression for 2 weeks and she had been started on Zydis®, an oral disintegrating tablet formulation of olanzapine, an atypical antipsychotic medication. Before that, she had been on other antipsychotic medications, including oxcarbazepine, trazadone, and quetiapine fumarate, without complication. A presumptive diagnosis of NMS had been made and supportive therapy instituted. During her preanesthetic examination, her vital signs included blood pressure 140/69 mmHg, heart rate 115 beats per minute, temperature 38.2°C, respiratory rate 20 breaths per minute, and oxygen saturation 99%. Additional positive findings on physical examination included catatonia, severe muscle rigidity, mutism, and obtundation. Significant laboratory findings included elevated creatine phosphokinase (6,868 mg/dL). After informed consent was obtained, the patient was transported to the induction room with an intravenous catheter in place. The anesthesia machine had been flushed with a high flow of oxygen for 2 h, the soda lime canister was replaced, and the vaporizers were removed. After obtaining the appropriate consents, the patient was brought to the induction room and standard American Society of Anesthesiologists' monitors were placed. An intravenous cannula was in place and preoxygenation was achieved by administration of 100% oxygen. Propofol (100 mg) was administered intravenously. Although bag-valve-mask ventilation was established, the patient was still severely rigid and therefore rocuronium (30 mg) was administered. Tracheal intubation was accomplished without difficulty. Maintenance anesthesia consisted of fentanyl (total dose 100 μg) and a propofol infusion (100–200 μg/kg/min). The MRI was completed without incident and the patient was transported to the Post Anesthesia Care Unit where her trachea was extubated. She was discharged back to the Pediatric ICU care unit. She made a full recovery from her episode of NMS and was discharged home.

Discussion

Neuroleptic malignant syndrome (NMS) is a serious adverse effect of neuroleptic medications, commonly atypical anti-psychotic medications. Although rare, this syndrome can be fatal. Mortality from NMS, which occurs in 10-38% of cases, results from cardiac causes including dysrhythmias or myocardial infarction, respiratory failure from chest wall rigidity, pulmonary embolism, or aspiration pneumonia, renal failure from rhabdomyolysis, bleeding from thrombocytopenia or disseminated intravascular coagulation, seizures, or sepsis [5–7]. Although the exact pathophysiologic mechanism remains unknown, two predominant theories that have been proposed, one involving alteration of central neurotransmitters and the other involving the periphery and the skeletal musculature [8]. Because dopamine is of central importance in thermoregulation, alteration of dopamine or its receptors have been implicated in the pathogenesis of NMS. The central theory involves the sudden blockade of dopamine (D_2) receptors in the basal ganglia and hypothalamus. Additional evidence for this theory is that agents with dopamine agonistic effects, for example bromocriptine or amantadine, may be effective in the treatment of NMS [9, 10]. The second theory to explain NMS focuses on the periphery and skeletal muscle. This mechanism shares similar features to another disorder that can result in muscle rigidity, hyperthermia, and rhabdomyolysis, MH. The link between NMS and MH was suggested given the clinical similarities between the two disorders, including clinical features (hyperthermia, rigidity, and rhabdomyolysis with an elevated creatine phosphokinase concentration), mortality of 10–30%, successful treatment of both disorders with dantrolene, and, in some patients, abnormal results of in-vitro halothane–caffeine contraction in patients with NMS [11].

Obviously, of major concern to the anesthesia provider is the potential association of NMS with MH. Although we used a non-triggering anesthetic regimen and prepared the anesthesia machine as we routinely do for patients with MH, the link between NMS and MH has been questioned. Caroff et al. reported that 5 of 7 patients with NMS were MH-susceptible, based on a 3% halothane response, and Araki et al. demonstrated abnormal contracture using caffeine stimulation in 6 patients with NMS [12, 13]. However, Adnet et al. found no MH-susceptibility in 13 of 14 patients with NMS and only equivocal results in one finding [14, 15]. Despite these findings, it is recommended that in the absence of a definitive test demonstrating lack of MH-susceptibility, a non-triggering anesthetic regimen should be used for patients with NMS.

Clinical manifestations of NMS develop over a 24 to 72 h period and are localized to 5 major areas:

1 autonomic instability;
2 hyperpyrexia;
3 altered mental status;
4 extrapyramidal symptoms; and
5 skeletal muscle with rigidity and rhabdomyolysis.

Signs and symptoms include fever, hypertension, tachycardia, muscle rigidity, mental status changes, metabolic acidosis, leukocytosis, and elevated creatinine

phosphokinase (CPK), aspartate aminotransferase (AST), and alanine aminotransferase (ALT). Myoglobinuria and hyperkalemia may also be evident. On the basis of the constellation of signs and symptoms outlined above, the Levenson criteria [16] for diagnosis of NMS have been developed. The Levenson criteria include major criteria (fever, rigidity, elevated creatinine phosphokinase) and minor criteria (tachycardia, abnormal blood pressure, tachypnea, altered mental status, diaphoresis, and elevated white blood cell count). Diagnosis rests on the presence of all 3 of the major criteria or 2 of the major criteria and 4 of the minor criteria.

Treatment includes the immediate discontinuation of the offending agent and initiation of supportive care based on the clinical signs and symptoms. The latter includes hydration, temperature management, neuromuscular blockade/sedation, and assisted ventilation. Although somewhat anecdotal, medications with dopamine agonistic properties, for example bromocriptine, amantadine, and carbidopa/levodopa, have been shown to be effective in controlling the signs and symptoms of NMS, supporting the D_2 receptor blockade hypothesis for the pathogenesis of NMS (see above). Dantrolene has also been used for treatment of NMS, because of the similarity of NMS to MH.

Using a literature review, Rosenberg et al. [17] evaluated treatment options for NMS in a cohort of 64 patients of which 11 received only supportive therapy. The others received a variety of therapy, including dantrolene ($n = 14$), bromocriptine ($n = 22$), benzodiazepine ($n = 1$), and combinations of these ($n = 9$). Efficacy of therapy was judged by the onset of the clinical response and time to complete recovery. Therapy with bromocriptine (5 mg enterally four times a day) was effective after 1 day, which was significantly more rapid than that achieved by supportive therapy alone. Complete resolution occurred most quickly with dantrolene (9 days; starting dose 2–3 mg/kg/day up to a maximum of 10 mg/kg/day) or bromocriptine (10 days) than with supportive therapy (15 days). The current literature seems to support combination therapy with bromocriptine, because of its central action, and dantrolene, because of its peripheral action [15].

Given the severity of the disorder and the need for diagnostic testing to rule out other conditions, patients with NMS may require anesthetic are as was the case with our patient who required anesthetic care during MR imaging. Because a common mechanism has been proposed for both NMS and MH, the possibility that a patient with a history of NMS may be vulnerable to developing MH should be considered. Because this issue has not been fully resolved, whenever feasible it is generally suggested that patients with NMS be considered as at-risk of the development of MH. Despite this, numerous case reports and case series have demonstrated the safe use of succinylcholine in patients with NMS. Hermesh et al. [18] reported there were no MH-like symptoms in patients with NMS or their relatives despite the repeated use of succinylcholine during electroconvulsive therapy (ECT). The cohort included 12 patients and a total of 147 administrations of succinylcholine (dose range 15–30 mg) in 12 patients.

Additional issues that should be considered perioperatively include consequences of skeletal muscle rigidity which may affect respiratory function. Although these manifestations may be limited to the extremities, generalized muscle rigidity may lead to increased tone with decreased chest wall compliance and respiratory insufficiency or failure. Attention to the hydration status is suggested, because intravascular volume depletion may be present from decreased intake from altered mental status, increased insensible losses due to hyperthermia, and diuretic therapy for myoglobinuria. Evaluation of preoperative electrolyte status and renal function is suggested, because rhabdomyolysis may result in metabolic acidosis, hyperkalemia, and myoglobinuria. Various factors may increase the risk of perioperative aspiration including altered mental status, delayed gastric emptying, incomplete nil per os (NPO) status during emergency procedures, and deficient barrier function. Postoperative monitoring should as be considered given the multi-system involvement of NMS and the need to monitor postoperative hemodynamic function, respiratory status, and body temperature.

In general, a variety of anesthetic agents can be used safely in patients with NMS. Given the similarities between NMS and MH, we chose to use a non-triggering anesthetic with propofol and a synthetic opioid. Numerous anecdotal reports from the literature have demonstrated the safe use of propofol in patients with NMS. Additional controversy surrounds the safety of non-depolarizing neuromuscular blocking agents (NMBAs). Despite two reports which anecdotally link their association with NMS, our case and others from the literature suggest the safety of these agents. Although the link between MH and NMS remains controversial, a clean technique and machine are suggested with ready access to and familiarity with the contents of the "malignant hyperthermia kit".

Conclusion

Neuroleptic malignant syndrome is a rare and life-threatening complication of treatment with certain types of medication. We report the anesthetic care during magnetic resonance imaging of the brain of a 14-year-old female with bipolar and schizoaffective disorders and the recent onset of NMS. Although clinically similar to MH, a variety of anesthetic agents have been used safely to anesthetize patients with NMS. The most important aspects of care

include the recognition and appropriate management of a patient with this syndrome.

References

1. Strawn JR, Keck PE Jr, Caroff SN. Neuroleptic malignant syndrome. Am J Psychiatry. 2007;164:870–6.
2. Edgar J. Droperidol-induced neuroleptic malignant syndrome. Hosp Med. 1999;60:448–9.
3. Shaw A, Matthews EE. Postoperative neuroleptic malignant syndrome. Anaesthesia. 1995;50:246–7.
4. So PC. Neuroleptic malignant syndrome induced by droperidol. Hong Kong Med J. 2001;7:101–3.
5. Gillman PK. Neuroleptic malignant syndrome: mechanisms, interactions, and causality. Mov Disord. 2010;25:1780–90.
6. Margetic B, Aukst-Margetic B. Neuroleptic malignant syndrome and its controversies. Pharmacoepidemiol Drug Saf. 2010;19:429–35.
7. Neuhut R, Lindenmayer JP, Silva R. Neuroleptic malignant syndrome in children and adolescents on atypical antipsychotic medication: a review. J Adolesc Psychopharmacol. 2009;19:415–22.
8. Adnet P, Lestavel P, Krivosic-Horber R. Neuroleptic malignant syndrome. Br J Anaesth. 2000;85:129–35.
9. Bond WS. Detection and management of the neuroleptic malignant syndrome. Clin Pharmacol. 1984;3:302–7.
10. McCarron MM, Boettger ML, Peck JI. A case of neuroleptic malignant syndrome successfully treated with amantadine. J Clin Psychiatry. 1982;43:381–2.
11. Tollefson G. A case of neuroleptic malignant syndrome: in vitro muscle comparison with malignant hyperthermia. J Clin Psychopharmacol. 1982;2:266–70.
12. Caroff SN. The neuroleptic malignant syndrome. J Clin Psychiatry. 1980;41:79–83.
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. Adnet PJ, Krivosic-Horber RM, Adamantidis MM, Haudecoeur G, Adnet-Bonte CA, Saulnier F, Dupuis BA. The association between the neuroleptic malignant syndrome and malignant hyperthermia. Acta Anaesthesiol Scand. 1989;33:676–80.
15. Krivosic-Horber R, Adnet P, Guevart E, Theunynck D, Lestavel P. Neuroleptic malignant syndrome and malignant hyperthermia. Br J Anaesth. 1987;59:1554–6.
16. Levenson JL. Neuroleptic malignant syndrome. Am J Psychiatry. 1985;142:1137–45.
17. Rosenberg MR, Green M. Neuroleptic malignant syndrome: review of response to therapy. Arch Intern Med. 1989;149:1927–31.
18. Hermesh H, Aizenberg D, Weizman A. A successful electroconvulsive treatment of neuroleptic malignant syndrome. Acta Psychiatr Scand. 1987;75:237–9.