Office-based General Anesthesia for a Patient With a History of Neuroleptic Malignant Syndrome

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First described in 1956 subsequent to a reaction reported to the newly introduced antipsychotic drug chlorpromazine, neuroleptic malignant syndrome (NMS) is a rare, potentially life-threatening reaction to antipsychotic drugs characterized by high fever, muscle rigidity, altered mental status, and autonomic instability. All neuroleptics, including newer antipsychotics, have been linked to this condition. Due to similar symptoms, it is debatable if individuals with NMS can be susceptible to malignant hyperthermia (MH). This case report presents the anesthetic care of a 30-year-old male undergoing general anesthesia in the office-based dental environment. The rationale behind the selected total intravenous anesthesia technique without NMS or MH triggering agents is outlined as well as other agents that may still be questionable regarding their trigger effect for NMS.

Key Words: Neuroleptics; Neuroleptic malignant syndrome; Malignant hyperthermia; General anesthesia.

INTRODUCTION

Neuroleptic malignant syndrome (NMS) is a rare, potentially life-threatening reaction to antipsychotic drugs characterized by high fever, muscle rigidity, altered mental status, and autonomic instability. It was first described in 1956[1] reportedly following a reaction to the newly introduced antipsychotic drug chlorpromazine. Interestingly, all neuroleptics have been linked to this condition including newer antipsychotics. Due to similar symptoms, it is debatable if individuals with NMS are highly susceptible to malignant hyperthermia (MH).

The following case report discusses the anesthetic management of a patient with a history of NMS scheduled to undergo comprehensive dental rehabilitation in the office-based ambulatory dental environment. A concise review of NMS is also included, covering basic pathophysiologic theories, potential triggering agents, therapeutic interventions, and anesthetic considerations.

CASE PRESENTATION

A 30-year-old male (height 75 inches; weight 127 kg; body mass index [BMI] 35 kg/m^2) was scheduled by his pediatric dentist for comprehensive oral rehabilitation under intubated general anesthesia provided by a dentist anesthesiologist assisted by a critical care registered nurse. The patient's past medical history was significant for autism spectrum disorder level 2 (requiring substantial support per *Diagnostic and Statistical Manual of Mental Disorders* Fifth Edition) and well-controlled seizure disorder. His reported medications included oxcarbazepine (75 mg twice a day) and the atypical antipsychotic lurasidone (40 mg in AM and 80 mg in PM). Although the patient had no known drug allergies, a possible sensitivity to dairy and wheat was also reported.

The patient's medical history was reviewed with his parents preoperatively, and a comprehensive history and physical report was obtained from his primary care physician, which included NMS diagnosed 2 years earlier when the patient was hospitalized for behavioral management issues. He was administered haloperidol to help control explosive mood impulses and subsequently developed a high fever, muscle rigidity, and altered mental status. The patient was diagnosed with NMS and managed by discontinuing the haloperidol and providing supportive care that included antipyretics (specifics not provided), sedation with non-NMS-triggering agents, support to maintain autonomic stability, euvolemic fluid therapy, and monitoring of serum electrolytes and creatinine phosphokinase. It was unclear whether the patient required dantrolene or bromocriptine during the acute phase of that NMS episode. He was discharged from the hospital a few days later

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following the NMS diagnosis without any long-term complications or sequela.

Due to the mixed opinions in the existing literature regarding a potential association between NMS and MH, a nasotracheally intubated general anesthetic using a total intravenous anesthesia (TIVA) approach without any MH-triggering neuromuscular blocking agents was selected for this patient's care. Realistic expectations presented to the parent/guardian included either an intravenous (IV) induction if the patient was cooperative or intramuscular (IM) ketamine/midazolam followed by placement of an IV line once adequately sedated if uncooperative. Mask induction with volatile inhalation agents like sevoflurane was not offered as an option for this patient due to potential concerns for MH. Furthermore, moderate or deep sedation was not deemed to be an effective option due to the patient's high BMI and the complexity of the treatment plan as well as lack of cooperation by the patient.

On the day of the procedure, the patient presented to the pediatric dentist's office having appropriately fasted. He received his morning dose of oxcarbazepine but was scheduled to receive the lurasidone in the afternoon postsurgery. He was healthy upon evaluation without any acute respiratory distress or other concerning signs or symptoms. His preoperative vital signs were as follows: blood pressure, 127/62 mm Hg; heart rate, 88 beats/min; oxygen saturation 98% on room air; and skin temperature, 36.0°C.

Upon arrival to the procedure room and with parental involvement, standard American Society of Anesthesiologists monitors (noninvasive blood pressure, pulse oximetry, skin temperature probe, 5-lead electrocardiogram, and capnography) were placed. Bispectral index (BIS) monitor was added after induction. A peripheral 20-gauge IV catheter was placed without the need for presedation. The patient was induced with IV boluses of midazolam 2 mg, ketamine 30 mg, fentanyl 50 mcg with an additional 25 mcg 2 hours after induction. Oxymetazoline nasal spray in both nostrils and IV boluses of dexamethasone 12 mg and magnesium 2 gm were also administered at induction along with a single IV bolus of propofol 350 mg. After induction, the patient was mask ventilated with 100% oxygen with no difficulty. Video laryngoscopy was performed with a McGrath MAC (Covidien USA) using a size 4 blade, and upon visualizing the vocal cords, 2% lidocaine plain (40 mg total) was administered for laryngotracheal topical anesthesia. The patient was successfully intubated with a 7.5-mm Parker Flex-Tip (Parker Medical) performed nasal endotracheal tube. Spontaneous ventilations were maintained throughout the dental procedure with concurrent administration of oxygen and nitrous oxide 50/50% and proper scavenging of exhaled gases. Mechanical ventilation was not required at any time during the procedure.

The dental treatment plan consisted of a full mouth exam with intraoral radiographs, periodontal scaling and prophylaxis, multiple restorations, and extraction of an unrestorable mandibular right first molar (tooth #30). For the extraction, local anesthesia was utilized, consisting of buccal and lingual infiltration with 2% lidocaine (36 mg) with 1:100 000 epinephrine (0.018 mg). Local anesthesia was not used for the remaining dental treatment.

General anesthesia was maintained with a propofol continuous infusion utilizing a Baxter AS50 infusion pump (Baxter Health) at a rate ranging between 150 and 170 mcg/kg/min. BIS values were maintained in the upper 30s during intubation, the upper 40s to lower 50s throughout the procedure, and then titrated upwards to the lower 70s, which correlates to moderate sedation,[2] at the end of the procedure to facilitate a faster emergence, recovery, and discharge. In the final 30 minutes of the procedure, IV ketorolac 30 mg and IV ondansetron 4 mg were administered for postoperative analgesia and antiemetic purposes, respectively.

Total surgical time was 2 hours, and the patient was extubated awake <5 minutes after concluding the surgical procedure. A 34 French nasopharyngeal airway was placed to help ensure adequacy of ventilation during the initial phases of recovery. Total recovery time from extubation to discharge home was 45 minutes, and he was lucid, able to drink water, and able to walk with minor assistance at that time. The patient's postoperative recovery and discharge was uneventful, and in a follow-up telephone conversation with his parents, they reported he was happy, comfortable, and eating well with no complications.

DISCUSSION

NMS was first reported in 1956,[1] describing complications associated with the newly introduced antipsychotic drug chlorpromazine. Since then, there have been several articles published describing the clinical findings of NMS, its triggers, and effective management of acute NMS events. While avoidance of typical or first-generation antipsychotics like haloperidol and chlorpromazine has reduced the incidence of NMS significantly, atypical or second-generation antipsychotics like risperidone and clozapine[4,5] have still been linked to this syndrome. Abrupt cessation of dopaminergic medications like levodopa can also precipitate NMS. Incidence of NMS ranges from 0.2% to 3.2% of psychiatric inpatients. While NMS is rare, it can be life threatening if unrecognized and not managed properly.[3]

The pathogenesis of NMS is currently unknown. However, the 2 main postulated theories to explain NMS include central dopamine receptor blockade[6] or muscle defect.[7,8] Drugs that act to antagonize dopamine D2 receptors are usually found in most NMS cases, and a sudden decrease in central dopaminergic activity due to D2 blockade explains many of NMS's clinical features. Central dopamine receptor blockade within the hypothalamus is thought to contribute to thermoregulatory failure and autonomic dysfunction seen in NMS, while the muscle rigidity likely results from blockade of dopamine receptors in the nigrostriatal system. Interestingly, D2 receptor blockade fails to explain all the clinical features found with NMS. Serotonin stimulation in the hypothalamus leads to heat production, and dopamine inhibits this process resulting in hyperthermia.

Behan et al[8] described the muscle changes associated with 3 cases of NMS through ultrastructural microscopic examination. The muscles were grossly swollen and edematous in all cases, in 1 with such severe local involvement that the diagnosis of sarcoma was considered. On microscopy, there was conspicuous edema. In some fascicles <10% of fibers were affected whereas in others >50% were pale and enlarged. There was a spectrum of changes: tiny to large vacuoles replaced most of the sarcoplasm and were associated with necrosis. A striking feature in some fibers was the presence of contraction bands separating segments of edematous myofibrils. Severe edema of the endomysium was also detectable. There was a scanty mononuclear infiltrate but no evidence of regeneration. The authors indicated that such changes were valuable in differential diagnosis.

Patients with NMS typically develop signs and symptoms within hours or days following exposure to a triggering agent that characteristically include fever, muscle rigidity, dysautonomia, and mental status changes ranging from mild drowsiness, agitation, or confusion to severe delirium or coma.[3] Autonomic instability, the primary cause of mortality associated with NMS, can include labile blood pressure, tachypnea, tachycardia, skin pallor, sialorrhea, diaphoresis, and incontinence. Electrolyte imbalance, which can include hyperkalemia, hypernatremia, hypomagnesemia, and hypocalcemia, acute renal failure, arrhythmias, and rhabdomyolysis may ensue. In addition to the electrolyte imbalance, laboratory tests will likely show elevated creatine kinase.

Extrapyramidal findings in NMS can include Parkinson-like symptoms, dystonia, dyskinesia, and akathisia. While there is no diagnostic testing for NMS, the above listed symptoms in association with trigger agent therapy (ie, an antipsychotic) are highly indicative. If not treated swiftly by discontinuing the triggering agent and instituting supportive therapy (Table 1), this condition can be fatal. In extreme cases, the use of dantrolene sodium to inhibit the release of calcium from the sarcoplasmic reticulum and/or use of bromocriptine mesylate a dopaminergic agent is common.

Table 1. Types of Treatment

Treatment types
Supporting autonomic instability
Euvolemic fluid therapy
Management of electrolyte imbalance
Management of hyperpyrexia
Possible use of dantrolene sodium
Dopaminergic medications (such as bromocriptine mesylate or amantadine)

Most NMS cases resolve within 2 weeks with a reported mean recovery of 7 to 11 days. Cases with catatonic and motor signs persisting up to 6 months have been reported[4] in individuals with antipsychotic use and concomitant brain disease. Mortality is 5% to 20% depending on the extent of complications and comorbidities.

NMS and MH

The literature offers mixed opinions regarding the association between NMS and MH. It is the muscle defect theory that links the pathophysiology of both conditions together. Caroff et al[9] assessed MH susceptibility in NMS patients using in vitro contracture testing and found that the caffeine halothane contracture test (CHCT) results in 7 patients with a history of NMS were as severe as the 6 patients with a history of MH and much more severe than the 6 control patients. That study concluded there was clinical evidence supporting a pathophysiologic association between MH and NMS. However, that conclusion was contradicted by Krivosic-Horber et al[10] in a European study that utilized the same in vitro CHCT method on 6 NMS survivors. They reported 1 subject that demonstrated contracture to caffeine but not halothane and concluded no association between the pathophysiology of MH and NMS. Miyatake et al[11] evaluated the presence of 6 mutations in the skeletal muscle ryanodine receptor, which is typical for MH, using a single-strand conformation polymorphism analysis and found no association between the unrelated NMS patients and this mutation, concluding that there was no link between MH and NMS.

All things considered, the close association of clinical manifestations for both NMS and MH continues to

Table 2. Neuroleptic and Non-Neuroleptic Medications Associated With NMS

Neuroleptics		*Non-neuroleptics (with anti-dopaminergic activity)*
Typical antipsychotics	*Atypical antipsychotics*	1) Metoclopramide
Haloperidol	Clozapine	2) Tetrabenazine
Fluphenazine	Risperidone	3) Reserpine
Chlorpromazine	Olanzapine	4) Droperidol
Prochlorperazine	Quetiapine	5) Promethazine
Trifluoperazine	Ziprasidone	6) Amoxapine
Thioridazine	Aripiprazole	7) Diatrizoate
Thiothixene		*Dopaminergics (withdrawal)*
Loxapine		1) Levodopa
Perphenazine		2) Dopamine agonists
Bromperidol		3) Amantadine
Clopenthixol		4) Tolcapone
Promazine		*Others*
		1) Lithium
		2) Phenelzine
		3) Dosulepin
		4) Desipramine
		5) Trimipramine

create confusion among clinicians.[12] Despite the increasing evidence that the pathophysiology of MH and NMS is not interconnected, many clinicians opt to treat individuals with confirmed NMS as being MH susceptible, electing to avoid the use of volatile inhalation anesthetics and succinylcholine.[13] This was the fundamental determinant for choosing the TIVA plan utilized for this patient, avoiding any agents that would put the patient at risk for developing MH.

Common Anesthetic Agents

Dopamine-blocking prokinetic and antiemetic drugs like metoclopramide, promethazine, and droperidol, among others (Table 2) have been reported to trigger NMS in individuals with neuromuscular pathology. Antiemetics such as metoclopramide and prochlorperazine have been implicated in 39% of perioperative NMS episodes.[15] Antidopaminergic drugs like metoclopramide and promethazine should be avoided in patients with a history of NMS. The use of 5-HT_3 receptor antagonists like ondansetron, which are commonly used for antiemetic prophylaxis during ambulatory anesthesia, have very low affinity for dopamine receptors[15] and are not contraindicated in individuals with a confirmed history of NMS.

How About Dexmedetomidine?. There have been case reports in the literature[14] linking the use of dexmedetomidine for sedation in an intensive care unit setting with acute hyperpyrexia and autonomic instability Discontinuing the dexmedetomidine resulted in resolution of the hyperpyrexia within hours in all reported cases. This raises the question of whether dexmedetomidine is a weak trigger for NMS. At this time, there is no conclusive evidence either way, which leaves the clinician to decide whether to use dexmedetomidine as part of an anesthetic management plan given its beneficial clinical effects or to avoid its use due to the questionable association as a potential trigger for NMS. The decision was made to avoid the use of dexmedetomidine in this case.

CONCLUSION

NMS is a rare but potentially fatal condition that may manifest perioperatively. Patients with a history of NMS or those managed with antipsychotics or other triggering agents must be diligently monitored and emergently managed if NMS signs and symptoms arise. Although the pathophysiologic link between NMS and MH remains somewhat questionable, it has not been eliminated. Anesthesia providers, particularly those in nonhospital environments, should consider treating individuals with NMS as being potentially at risk for MH. Use of a TIVA protocol without any MH-triggering agents may be preferred. Avoiding any dopamine-blocking antiemetics like metoclopramide or promethazine is also strongly recommended. Some case reports have suggested that dexmedetomidine could be a NMS triggering agent. As there is currently a lack of conclusive evidence, avoiding its use may be prudent until a more definitive answer is determined.

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