

**MALIGNANT HYPERTHERMIA, ANESTHESIA, AND DEXMEDETOMIDINE:
A SAFE ALTERNATIVE IN THREE CHALLENGING PATIENTS**

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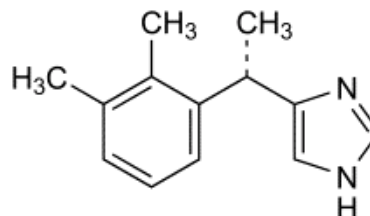
ABSTRACT: In this paper, we present our experiences with dexmedetomidine involving a series of three challenging patients undergoing anesthesia. Two patients had a strong family history of malignant hyperthermia (MH) and one patient had a masseter spasm during previous anesthetic. We used dexmedetomidine, an α -2 agonist as an adjunct during total intravenous anesthesia (TIVA), awake fiberoptic intubation and monitored anesthesia care (MAC) with excellent results. Dexmedetomidine provided adequate sedation, amnesia and analgesia without respiratory depressant effects. It proved safe and effective in patients with MH precautions, helping to avoid exposure to MH-triggering agents and preventing an airway emergency. These cases are also a useful teaching topic for residents to educate them about MH, and about planning a safe anesthetic with the various agents at their disposal.

INTRODUCTION

Malignant hyperthermia (MH) is a life-threatening hypermetabolic condition resulting from a genetic sensitivity of skeletal muscles to volatile anesthetics and depolarizing neuromuscular blocking drugs that occurs during or after anesthesia. Although the exact incidence of MH is unknown, some sources cite the incidence around 1 in 50,000 anesthetics in adults and 1 in 15,000 in children [1]. However, certain regions of the world contain clusters of populations with higher than average incidence of MH [2,3]. There are some established MH triggering agents such as inhalational anesthetics (such as halothane, desflurane, sevoflurane, isoflurane) and depolarizing muscle relaxants such as succinylcholine [4]. IV induction agents such as propofol as well as thiopental and ketamine are thought to be safe. It is well-established that testing for MH cannot completely rule out a future MH occurrence, and that a patient with previous uneventful anesthetic administration may develop MH during a consequent anesthetic administration [5].

Often, we encounter patients who have a family history of MH but have never been tested themselves, or patients who exhibited possible MH symptoms during a previous anesthetic. As we plan the anesthetic for such patients, we may decide to exercise MH precautions and use a “clean anesthetic” technique by avoiding known triggering agents. There are, of course, many different anesthetic techniques one could employ, such as local anesthesia, regional anesthesia, conscious sedation or general anesthesia while avoiding the use of MH triggering agents. Below we present our experiences with three difficult patients in whom we chose to exercise MH precautions. We used an old, but newly rediscovered drug, dexmedetomidine, as a safe adjunct for our anesthetics in those patients.

Dexmedetomidine-Old Drug, New Uses. Dexmedetomidine is an imidazole compound which displays specific and selective α -2 adrenoceptor agonism (selectivity for α -2 receptors is 1620:1 versus 220:1 for clonidine). The difference in stereospecificity (α -2 versus α -1) between dexmedetomidine and clonidine is clinically significant. With dexmedetomidine, the linear dose response curves allow for a wider dosing regimen. Considered safe in MH-susceptible patients, it has been shown to have sedative, amnestic, and analgesic properties, and to maintain cardio-respiratory stability [6]. It has a rapid onset of action and distribution, undergoes hepatic metabolism and urinary excretion, and has a terminal half-life of approximately 2 hours. Although dexmedetomidine was approved by the Food & Drug Administration (FDA) in 1999 for use in humans as short-term medication for analgesia and sedation in the intensive care unit, we have significant experience using it as an adjunct infusion to our balanced general anesthetic techniques, as well as for conscious sedation and for awake fiberoptic intubations [7,8].



Dexmedetomidine is generally well-tolerated, and the most common treatment-related adverse

events reported include hypotension, nausea, bradycardia, and dry mouth [9]. Because of its anxiolytic, sedative, analgesic, sympatholytic and amnesic properties, dexmedetomidine has significant clinical utility. It appears to be particularly safe with respect to respiratory function. *Ebert et. al.* showed that the respiratory system remains relatively uncompromised during dexmedetomidine infusions, even at high doses [10]. Continuous infusion maintains unique sedation (patients appear to be asleep, but are readily roused), analgesic sparing effect, and minimal depression of respiratory drive. Experiments have shown anxiolytic effects in humans using intramuscular doses of 2.4mcg/kg and potentiation of the anxiolytic effect of midazolam in rats [11]. Finally, it provided some immediate (not retrograde) memory impairment [6].

Ebert et. al. also demonstrated that dexmedetomidine at low dose infusions (0.2-0.8 mcg/kg/min) lowered the mean arterial pressure by 13% [10]. One plausible explanation is that plasma levels of norepinephrine were decreased by 60-85% thus blunting the sympathetic response during the perioperative period. In addition, intramuscular or intravenous administration of dexmedetomidine induced bradycardia and caused a decrease in cardiac output in a dose-dependent manner. The drug seemed to produce its cardiac depressant effects via activation of the brain α -2 adrenoceptors, resulting in inhibition of the vasomotor center and the consequent decrease in the central sympathetic drive reaching the heart and the blood vessels via the spinal cord. Furthermore, the ability of dexmedetomidine to induce diuresis and to enhance sodium excretion may contribute to its hypotensive action [9]. The hemodynamic effects of dexmedetomidine related to its α -2 agonist properties are of potential clinical benefit. By decreasing heart rate, dexmedetomidine contributes to increase in coronary blood supply to the left ventricle through prolongation of diastole. The reduction in heart rate would be associated with decreased myocardial oxygen consumption [12]. In addition, by decreasing blood pressure, dexmedetomidine may reduce procedure-related blood loss.

The ability of dexmedetomidine to suppress transmission of experimentally induced pain has been shown in various models of pain. Dexmedetomidine was found to activate α -2 receptors located

on the spinal terminals of the primary sensory neurons, leading to hyperpolarization of the terminals and suppression of release of the pain neurotransmitters. It stimulates α -2 adrenergic receptors in the spinal cord to enhance analgesia, and causes sympatholysis via central and peripheral mechanisms [13]. *Hall et. al.* found that visual analogue scale (VAS) pain scores during cold pressor testing (CPT) were decreased 30% with 0.2-0.6 mcg/kg/hr infusions [6]. Similarly, *Ebert et. al.* demonstrated significantly lower VAS scores during CPT with increasing doses of dexmedetomidine [10], and *Arain et. al.* found that patients who received dexmedetomidine during surgery had decreased morphine requirements postoperatively [14].

Adding Dexmedetomidine to the “Clean” Anesthetic Technique – Our Experiences. Below are brief summaries of three recent cases involving difficult patients with MH precautions. We safely managed their anesthetics, using dexmedetomidine as an adjunct drug in all three cases.

CASE 1: Morbid obesity, difficult airway, family history of MH.

A 67 year-old male with prostate cancer presented for brachytherapy. He had a cousin who died as a result of malignant hyperthermia and eight out of ten close family members tested positive for the trait. The patient did not undergo any testing. His medical history was significant for morbid obesity with a height of 70 inches and a weight of 140 kg and significant history of obstructive sleep apnea. On examination, the airway was Mallampati class IV and neck extension was limited. Regional anesthesia was performed with a spinal placed at the L3-4 interspace. He had difficulty remaining still during brachytherapy (important for mapping accuracy). Instead of using respiratory depressants such as propofol and fentanyl (which he did not tolerate well), we maintained sedation with a dexmedetomidine infusion at 0.5-0.6 mcg/kg/hr. During the procedure, the patient maintained stable heart rate and blood pressure, good oxygen saturation on a 3 liter face mask, and normal respirations with no evidence of airway obstruction. The entire procedure proceeded uneventfully and was well-tolerated by the patient.

Δ Case 1 Comments: This case presented several challenges. The patient was morbidly obese with a potentially difficult airway, had severe obstructive sleep apnea, and had a strong family history of MH. Morbidly obese patients can often present with airway difficulties. The key here was to provide a safe anesthetic while avoiding any airway emergencies that would potentially expose the patient to

MH-triggering agents. We were able to maintain adequate spontaneous ventilation and keep the patient still. A regional anesthetic (spinal) proved very useful in this case. The use of dexmedetomidine helped to avoid respiratory depression associated with propofol and fentanyl.

CASE 2: Mental retardation, difficult airway, awake fiberoptic intubation, history of masseter spasm.

A 17 year-old, 50 kg uncooperative male patient with the history of cerebral palsy presented for teeth extraction under general anesthesia. His previous anesthetic history was significant for masseter rigidity and body temperature elevation and MH was suspected (patient was never tested, but previous case was aborted). The patient had limited mouth opening and neck extension, Class IV airway, excessive drooling at the mouth, and became very anxious and uncooperative. He also had a history of PONV. In addition to intramuscular ketamine and midazolam, the patient was administered a total of 50 mcg of dexmedetomidine to facilitate an awake fiberoptic intubation. We used a total intravenous anesthesia (TIVA) technique, and supplemented propofol and fentanyl with a dexmedetomidine infusion (0.5-0.7mcg/kg/min) for the duration of the case.

Δ Case 2 Comments: This was an uncooperative, difficult patient with multiple medical problems, excessive mouth secretions, and a difficult airway. According to the ASA Difficult Airway Algorithm, awake airway management is a safe and effective mainstay. In this case, it was important to maintain spontaneous ventilation without the use of inhalational agents. Dexmedetomidine proved a useful supplement, minimizing the use of other medications. Drug infusions can be made with propofol, midazolam, ketamine, dexmedetomidine, antihistamines, and short-acting opioids. A thorough knowledge of pharmacology and drug interactions is essential. The benefit of combining a small dose of various drugs is synergistic effect and decreased likelihood of side effects. Our technique of combining dexmedetomidine with other conventional agents facilitated a challenging awake fiberoptic intubation and prevented an unnecessary exposure to MH-triggering agents such as succinylcholine and inhalational anesthetics.

CASE 3: General anesthesia, egg and soybean oil allergy, family history of MH.

A 43 year old, 75 kg female patient underwent diagnostic laparoscopy for an ovarian mass. The patient had a sister who apparently died from MH, although the patient had never been tested. She was otherwise healthy except for mild asthma and most notably an allergy to soybean oil and eggs. This was the patient's first anesthetic. The decision was made to proceed with total intravenous anesthesia (TIVA) with an endotracheal intubation, and to avoid propofol. Intraoperatively, the patient received intermittent fentanyl boluses (total of 400mcg), midazolam (5mg), and vecuronium, and her anesthetic was supplemented with a dexmedetomidine infusion at the rate of 0.5-0.7 mcg/kg/min. The patient tolerated the procedure well, remained hemodynamically stable, and had no evidence of intraoperative awareness.

Δ Case 3 Comments: This patient presented several challenges. There was a significant family history of MH, and anesthetic planning was complicated by the fact that the patient was allergic to soybean oil and eggs and had no prior history of exposure to propofol. We therefore decided not to use propofol and also to exercise MH precautions. The use of dexmedetomidine as a supplement allowed us to maintain a safe anesthetic while decreasing the amounts of opioids and benzodiazepines used. This patient was highly satisfied with her anesthetic, had no intraoperative recall, and we were able to avoid the use of any MH-triggering agents and propofol.

Below is the table summarizing all three cases.

<i>Patient Age</i>	<i>MH history</i>	<i>Procedure</i>	<i>Anesthetic</i>	<i>Dexmedetomidine</i>
17	? Prior Anesthetic	Awake Fiberoptic Intubation followed by Teeth Extraction	IV Sedation TIVA	yes yes
67	Family	Brachytherapy	Spinal/MAC	yes
43	Family	Laparoscopy	TIVA	yes

DISCUSSION

Although there are patients with a definitive history of MH, we may occasionally encounter a patient with a vague family history MH, or with questionable MH-like symptoms associated with a previous anesthetic. With often limited clinical information, the anesthesiologist must exercise his or her judgment regarding MH precautions in such patients. Our experiences with the three difficult patients above show the importance of good planning – the result was a safe anesthetic with high patient and surgeon satisfaction. We found dexmedetomidine a very useful drug in such cases - an alternative technique during a “clean” anesthetic, especially in patients with co-existing comorbidities and difficult airways. Dexmedetomidine has an excellent safety profile, and it provides good amnesia, analgesia and sedation, maintains respiratory function, and decreases the need for other medications such as opioids, benzodiazepines, ketamine and propofol [13,15]. In our experience, dexmedetomidine did not induce any MH symptoms.

The high cost associated with dexmedetomidine has prevented its inclusion in the formularies of many hospitals, and has been a concern in implementation of its use amongst anesthesiologists. Dexmedetomidine is roughly eight times as expensive as propofol. However, the actual costs associated with utilizing dexmedetomidine for MAC have not been studied. This cost is likely partially offset by decreased requirements of other anesthetic agents and their associated side effects including respiratory depression, PONV, and delayed time-to-discharge. In the operating room, dexmedetomidine has been shown to decrease the requirements of volatile anesthetics and opioids. Thus the cost of utilizing dexmedetomidine is partially offset by decreased amounts of other medications [16].

Use of dexmedetomidine appears to be particularly safe with respect to respiratory function. *Ebert et. al.* showed that the respiratory system remains relatively uncompromised during dexmedetomidine infusions, even at high doses. PaO₂ remained stable with increasing plasma

concentrations of dexmedetomidine (0.5-8.0 ng/ml), and there were mild increases in PaCO₂ [10]. As a side note, at high plasma concentrations the measured arterial PaCO₂ only increased to 46-47 mm Hg. Patients receiving dexmedetomidine did not exhibit any clinically perceptible respiratory depression, and no significant difference in respiratory frequency, oxygen saturation or blood gases were observed after extubation in dexmedetomidine group versus placebo. Several other experimental observations make dexmedetomidine a particularly attractive drug. It has been shown to enhance the anesthetic effect of various gaseous general anesthetics such as halothane and isoflurane. The drug reduced the minimal alveolar concentration (MAC) of the agent by 30-90%. This has been clearly shown in dogs [9].

Because dexmedetomidine possesses anxiolytic, sedative, analgesic and sympatholytic properties [17], it has significant clinical utility, including in patients with MH precautions and co-existing co-morbidities. Further dexmedetomidine studies would include cost effectiveness, neurobehavioral outcome, and time studies (PACU time and time-to-discharge). If the results of these studies are favorable, then dexmedetomidine might play a more crucial role in high-risk patients.

ON RESIDENT EDUCATION

There is no question that resident teaching should include increasing knowledge of recognition and treatment of MH symptoms, as well as enabling residents to make a safe anesthetic plan for MH-susceptible patients. In fact, ACGME cites six main competencies in anesthesiology, emphasizing the importance of providing educational experiences for residents so that they can demonstrate

“... Medical knowledge about established and evolving biomedical, clinical, and cognate sciences, as well as the application of this knowledge to patient care,” and also be exposed to *“... Practice-based learning and improvement that involves the investigation*

and evaluation of care for their patients, the appraisal and assimilation of scientific evidence, and improvements in patient care [18].”

Our experiences with the above patients demonstrate thinking “outside-the-box.” Of course, there are many drug combinations that are used in MAC, regional and general anesthesia. We have found that dexmedetomidine, with its sedative, amnestic, analgesic, and non-respiratory depressant properties is a useful adjunct in difficult patients. The key is to individualize the pharmacologic plan for each patient, titrate to effect, and understand the pharmacology and side effects of each medication choice. Whether MH precautions are being exercised or not, residents need to remember that vigilance, attention to detail, and patient safety always come first.

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