CASE REPORT

Dexmedetomidine to Control Agitation and Delirium from Toxic Ingestions in Adolescents

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Dexmedetomidine is an α_2-adrenergic agonist that is approved by the Food and Drug Administration for the provision of short term (less than 24 hours) sedation of adults during mechanical ventilation. Given its beneficial physiologic effects including sedation and anxiolysis, various applications have been reported in the pediatric-aged patient. We report the use of dexmedetomidine to control the agitation and violent behavior which resulted from the ingestion of illicit drugs in 3 adolescents. The utility of dexmedetomidine in these scenarios is discussed and its potential beneficial effects on cardiovascular and respiratory function are reviewed.

KEYWORDS adolescents, dexmedetomidine, toxicity

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INTRODUCTION

The provision of intensive care may be complex in adolescents who ingest toxic substances either inadvertently or for recreational use. In most

see Editorial on page 4

cases, the care of these patients is supportive with the treatment of adverse physiologic effects related to the ingested medication. In the adolescent community, various agents are used for recreational purposes including street drugs such as 2,4-methlenedioxymethamphetamine (MDMA or ecstasy) and over-the-counter (OTC) medications which contain dextromethorphan. Care in the Intensive Care Unit (ICU) may be further complicated by the adverse effects of these agents, including delirium, agitation, and even violent behaviors. Control of these central nervous system effects is mandatory, not only to allow for routine ICU care, but also to prevent inadvertent harm to the patients or healthcare providers. We present 3 adolescents who manifested severe delirium and agitation following the use of illicit substances. The delirium and agitation were controlled by the administration of the α_2-adrenergic agonist, dexmedetomidine. The potential applications of dexmedetomidine in this scenario are discussed.

ABBREVIATIONS AV, atrioventricular; BP, blood pressure; BUN, blood urea nitrogen; CT, computed tomography; HR, heart rate; ICU, Intensive Care Unit; MAP, mean arterial pressure; MDMA, 2,4-methlenedioxymethamphetamine; OTC, over-the-counter; PICU, Pediatric Intensive Care Unit; SBP, systolic blood pressure

CASE REPORTS

Review of the patients' medical records and presentations of these cases were approved by the Institutional Review Board of the University of Missouri.

Case 1

A 16-year-old, 61 kg girl was brought to the

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emergency department for altered mental status, severe agitation, and violent behavior. She was found in her bedroom after ingesting 8-10 tablets of an OTC cold medication containing dextromethorphan (Coricidin HBP Cough & Cold Tablets, Schering-Plough, Kenilworth, NJ). On arrival in the Pediatric Intensive Care Unit (PICU), the initial physical examination revealed an adolescent with erratic and violent behavior who was swinging a closed fist at healthcare providers. She was restrained by 5 healthcare workers for placement of an intravenous cannula and to obtain initial laboratory evaluations. The initial laboratory evaluation including complete blood count, electrolytes, glucose, blood urea nitrogen (BUN), creatinine, liver function tests, ammonia, calcium, and pregnancy test were unremarkable. Vital signs revealed a temperature of 38.1°C, a heart rate (HR) of 160-180 beats/minute, a blood pressure (BP) of 140-178/84-98 mmHg, a respiratory rate of 14-16 breaths/minute, and an oxygen saturation of 97% on room air. Additional positive physical findings included dilated pupils (5-6 mm) that were reactive to light. The remainder of the neurological examination was non-focal. The patient continued to have intermittent periods of violent behavior and incomprehensible speech. No change in the behavior was noted despite the administration of two, 2 mg doses of lorazepam. Dexmedetomidine was administered as a loading dose of 1 mcg/kg over 10 minutes followed by an infusion of 1 mcg/kg/hr. After the administration of the loading dose of dexmedetomidine, the patient became quiet and had no further episodes of agitation that required physical restraint. Repeat vital signs obtained 15-20 minutes after the dexmedetomidine loading dose revealed a temperature of 36.8°C, HR 64-76 beats/minute, BP 106-122/64-78 mmHg, a respiratory rate of 10-12 breaths/minute, and an oxygen saturation of 95-97% on room air. Once the agitation had been controlled, a computed tomography (CT) scan of the head was obtained which was unremarkable. An additional bolus dose of dexmedetomidine (1 mcg/kg) was administered after moving the patient from the stretcher to the CT imaging table to ensure immobility during the CT scan. The dexmedetomidine infusion was continued at 1 mcg/kg/hr for 12 hours and then decreased to 0.5 mcg/kg/hr. Sixteen hours after admission, the patient was responsive to questions and the dexmedetomidine infusion was discontinued. The patient was transferred to the inpatient ward for subsequent care.

Case 2

A 14-year-old, 58 kg girl was brought to the emergency department for altered mental status and violent behavior. She had been at a friend's house and had ingested 6-8 tablets of an OTC cold medication containing dextromethorphan (Coricidin HBP). On arrival in the PICU, she was nonresponsive to direct questions and demonstrated violent behavior manifested as screaming and yelling as well as kicking at healthcare providers. She was restrained by several healthcare workers for placement of an intravenous cannula and to obtain initial laboratory evaluations. The initial laboratory evaluation including complete blood count, electrolytes, glucose, BUN, creatinine, liver function tests, ammonia, calcium, and pregnancy test were unremarkable. Vital signs revealed a temperature of 38.1°C, a HR of 154-176 beats/minute, a BP of 138-168/80-96 mmHg, a respiratory rate of 12-16 breaths/minute, and an oxygen saturation of 95-97% on room air. Additional positive physical findings included dilated pupils (5 mm) that were reactive to light. The remainder of the neurological examination was non-focal. The patient continued to have intermittent periods of violent behavior and incomprehensible speech. Dexmedetomidine was administered as a loading dose of 1 mcg/kg over 10 minutes followed by an infusion of 1 mcg/kg/hr. After the administration of the loading dose of dexmedetomidine, the patient became quiet, but continued to have a few episodes where she would awaken and become agitated, at times hitting the side-rails of her bed. An additional 1 mcg/kg of dexmedetomidine was administered approximately 15 minutes after the initial loading dose. This was followed by increasing the infusion to 1.5 mcg/kg/hr. There were no further episodes of agitation that required physical restraint. Repeat vital signs obtained approximately 15-20 minutes after the second dexmedetomidine loading dose revealed a temperature of 36.7°C, HR 66-82 beats/minute, BP 102-118/60-76 mmHg, a respiratory rate of 10-12 breaths/minute, and an oxygen saturation of 95-97% on room air. Once the agitation had been controlled, a CT scan of the head was unremarkable. No additional sedation was required for the CT scan. The dexmedetomidine infusion was continued at 1.5 mcg/kg/hr for 8 hours and

then decreased to 1 mcg/kg/hr. Twelve hours after admission, the patient was responsive to questions. The dexmedetomidine infusion was discontinued after 12 hours of administration and the patient was transferred to the inpatient ward for subsequent care.

Case 3

A 16-year-old, 78 kg boy was brought to the emergency department for altered mental status, severe agitation, and violent behavior. He had been out with his friends and started acting strangely. This progressed to incoherent speech and violent behavior. No other history was available at the time of arrival in the PICU. The initial physical examination revealed an adolescent with violent behavior who was swinging closed fists at healthcare providers. He was restrained by several healthcare workers for placement of an intravenous cannula and to obtain initial laboratory evaluations. The initial laboratory evaluation, including complete blood count, electrolytes, glucose, BUN, creatinine, liver function tests, ammonia, and calcium were unremarkable. The urine toxicology screen was positive for amphetamine and the blood result identified the compound as 2,4-methlenedioxymethamphetamine (MDMA or ectasy). Vital signs revealed a temperature of 41.2°C, a HR of 164-176 beats/minute, a BP of 166-178/88-102 mmHg, a respiratory rate of 14-16 breaths/minute, and an oxygen saturation of 97% on room air. Additional positive physical findings including dilated pupils (5-6 mm) that were reactive to light. The remainder of the neurological examination was non-focal. The patient continued to have intermittent periods of violent behavior and incomprehensible speech. Dexmedetomidine was administered as a loading dose of 1 mcg/kg over 10 minutes followed by an infusion of 1 mcg/kg/hr. After the administration of the loading dose of dexmedetomidine, the patient became quiet and had no further episodes of agitation which required physical restraint. Repeat vital signs that were obtained 10-15 minutes after the dexmedetomidine loading dose revealed a temperature of 38.1°C, HR 78-86 beats/minute, BP 112-138/76-84 mmHg, a respiratory rate of 10-12 breaths/minute, and an oxygen saturation of 95-97% on room air. The dexmedetomidine infusion was continued at 1 mcg/kg/hr for 8-10 hours and then decreased to 0.5 mcg/kg/hr. Twelve hours after admission, the patient was responsive to questions. The dexmedetomidine infusion was discontinued after approximately 12 hours and the patient was transferred to the inpatient ward for subsequent care.

DISCUSSION

Various OTC cold medications and cough suppressants have been used in large doses as a recreational drug because they contain the medication, dextromethorphan. In pharmacologic doses, dextromethorphan is used as an antitussive agent in these OTC cold medications.[1,2] In large doses, dextromethorphan has psychoactive effects and its use as a recreational drug is increasing. Websites have even appeared detailing which OTC medications contain dextromethorphan.[1,2] Dextromethorphan is the dextrorotatory isomer of the codeine analogue, levorphanol. It provides an anti-tussive effect through its interaction with the sigma opioid receptor, thereby avoiding other opioid related effects such as analgesia or respiratory depression when used at recommended doses. Dextromethorphan undergoes hepatic metabolism via CYP2D6 isoenzyme of the cytochrome P_{450} system to a phencyclidine-like agent, dextrorphan, which acts as an NMDA (N-methyl-D-aspartate) antagonist, thereby resulting in psychoactive effects including euphoria, dysphoria, hallucinations, and agitation. Sources of dextromethorphan for such abuse include both OTC cough suppressants and more recently Coricidin HBP Cough & Cold tablets.[3] When used for illicit purposes, the potential adverse effects of dextromethorphan in the OTC medication, Coricidin HBP Cough & Cold tables, may be further complicated as the newer formulation, released in 2002, contains the antihistamine, chlorphenamine (4 mg per tablet) in combination with dextromethorphan (30 mg per tablet). Chlorphenamine also has anticholinergic properties that can, by themselves, have serious adverse effects including CNS activation, delirium and seizures. Additionally, both agents are metabolized by CYP2D6 isoenzyme of cytochrome P_{450}, which may increase the plasma concentration of both drugs by competing for the same isoenzyme.

Ectasy or MDMA is an illicit street drug which is classified as a hallucinogenic amphetamine analog. Its original pharmacological use in the

early 1900's was as an appetite suppressant.[4] The molecular structure of MDMA resembles that of both the hallucinogenic agent, mescaline, and the stimulant, amphetamine. Unlike dextromethorphan, which is available in OTC medications, MDMA is produced illegally.[5] MDMA results in the increased release and decreased re-uptake of various neurotransmitters such as serotonin, dopamine and norepinephrine in the central nervous system.[6] The adverse effects of this agent include tachycardia, hypertension, mydriasis, agitation, delirium, and hyperthermia.[7]

With many toxic ingestions, therapy is supportive with control of the end-organ effects of the toxic agent. With both dextromethorphan or MDMA, control of the CNS effects of agitation and delirium are also frequently required. In such settings, a rapidly acting agent that can be titrated by intravenous administration may be beneficial. Dexmedetomidine (Precedex, Hospira Worldwide Inc, Lake Forest, IL) is the pharmacologically active dextro-isomer of medetomidine.[8] Its end-organ effects are mediated via post-synaptic α_2-adrenergic receptors and subsequent activation of a pertussis toxin-sensitive guanine nucleotide regulatory protein (G protein), which results in decreased activity of adenylyl cyclase. CNS stimulation of parasympathetic outflow and inhibition of sympathetic outflow from the *locus cereleus* in the brainstem play a prominent role in the sedation and anxiolysis produced by dexmedetomidine. Currently, its only FDA-approved indication is the provision of short term sedation (less than 24 hours) in adult patients in the ICU setting who are initially intubated and receiving mechanical ventilation.

Dexmedetomidine's physiologic effects of providing sedation, as well as blunting the sympathetic nervous system. proved to be effective in our patients in not only controlling their agitation and violent behavior, but also decreasing the pathologic increases in HR and BP. In our first patient, dexmedetomidine was effective, despite the fact that lorazepam had failed while it was used as a first-line agent in the other two patients. Although the current recommended dosing guidelines for adults includes an initial loading dose of 1 mcg/kg over 10 minutes followed by an infusion of 0.2-0.7 mcg/kg/hour, in our 3 patients and in the pediatric population in general, higher infusions rates have been required in various clinical scenarios.[8]

As with any agent used for sedation and anxiolysis, adverse effects on cardiovascular and respiratory function may be seen. However, the adverse effect profile of dexmedetomidine in the pediatric patient has been limited. This may be particularly beneficial when caring for patients with toxic ingestions since synergistic interactions between the agent ingested and the agent used for sedation may enhance the adverse effects on physiologic functions. Hypotension and bradycardia have been reported in adult patients, especially in the presence of co-morbid cardiac disease, when dexmedetomidine is administered with other medications that possess negative chronotropic effects or following large or rapid bolus doses. In healthy adult volunteers, there is a biphasic effect on BP with an initial increase in systolic blood pressure (sBP) and a reflex decrease in HR followed by a stabilization of sBP and HR at a value below the baseline.[9] Stimulation of peripheral postsynaptic α_{2B}-adrenergic receptors may result in vasoconstriction and an initial increase in SBP, while the eventual decrease in BP and HR result from central presynaptic α_{2A}-adrenergic receptor stimulated sympatholysis. The potential for adverse hemodynamic effects with dexmedetomidine in patients with co-morbid features is illustrated in an adult ICU population of 98 cardiac and general surgery patients who received dexmedetomidine for sedation during mechanical ventilation.[10] Hypotension (MAP ≤ 60 mmHg or a ≥ 30% decrease from baseline) occurred in 18 of 66 patients. Eleven of the episodes occurred during the bolus dose. Although no morbidity or mortality was noted, the infusion was temporarily (n=3) or permanently (n=3) discontinued. and treatment with atropine (n=2) or temporary cardiac pacing (n=4) was necessary. Bradycardia and sinus arrest have also been reported with dexmedetomidine.[11-13] In a study combining dexmedetomidine with propofol to induce anesthesia in adults, 2 of the first 4 patients had brief and self-limited periods of sinus arrest after laryngoscopy.[11] The protocol was subsequently amended with a decrease of the dexmedetomidine loading dose and no subsequent problems were noted. Anecdotal reports in the adult population have outlined the occurrence of bradycardia, cardiac arrest, and death temporally related to the administration of dexmedetomidine in patients with co-morbid cardiac diseases[14,15], while a prospective trial in the pediatric population demonstrated depressed

sinus and atrioventricular (AV) node function.[16] These concerns have led to the caveat that dexmedetomidine should not be administered to patients with known sinus node or AV node dysfunction, patients who cannot mount a stress-induced stimulation of the sympathetic nervous system, and those with limited sympathetic reserve.[17] Despite these concerns, we found the sympatholytic effect of dexmedetomidine helpful in controlling the tachycardia and hypertension manifested in our 3 patients secondary to the agitation from the ingestion of dextromethrophan or as a primary effect of the MDMA. Additional potentially protective effects of dexmedetomidine on myocardial performance, which may be particularly beneficial in the setting of toxic ingestions, include preservation of myocardial function following ischemia and prevention of catecholamine-induced arrhythmogenesis.[18,19]

When compared with other medications used for sedation, including benzodiazepines and opioids, dexmedetomidine has been shown to have limited effects on respiratory function with a limited potential for causing apnea or respiratory depression.[8,20,21] When compared with propofol for procedural-sedation in pediatric patients for magnetic resonance imaging, a decrease in the oxygen saturation to less than 93% occurred in 4 of 30 children sedated with propofol versus 0 of 30 sedated with dexmedetomidine.[22] Furthermore, dexmedetomidine has been used successfully to provide sedation and facilitate non-invasive ventilation in adults.[23]

In addition to providing sedation and controlling the cardiovascular changes in our patients, dexmedetomidine may be theoretically helpful in controlling hyperthermia, either related to the agitation or as a direct result of the ingested substance. The latter may be particularly important with MDMA ingestions as hyperthermia is one of the leading causes of death.[24] In mice, dexmedetomidine can result in profound hypothermia, an effect that is attenuated in animals that are genetically deficient in the α_2-adrenergic receptor.[25] Hypothermia results from the activation of α_2-adrenergic receptors in the hypothalamus and a reduction in metabolic heat production.[26] Dexmedetomidine decreases thermoregulatory vasoconstriction and shivering thresholds.[27] Additionallydexmedetomidine through its effects on α_2-adrenergic receptors in adipocytes, inhibits lipolysis and non-shivering thermogenesis.[28]

In summary, dexmedetomidine provided effective sedation and controlled the agitation and violent behaviors of 3 adolescents following the ingestion of MDMA or high doses of dextromethorphan. In addition to controlling the agitation, dexmedetomidine provided adequate sedation to allow for CT imaging. Its sympatholytic effects were a useful adjunct to the control of the tachycardia and hypertension while having limited effects on respiratory function. As with many pediatric applications, we noted that doses higher than those currently recommended in adults patients were required, including a loading dose of 1 mcg/kg and an infusion of 1-1.5 mcg/kg/hr.

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