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Editorial

Dexmedetomidine: Are There Going to be Issues with Prolonged Administration?

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Dexmedetomidine (Precedex, Hospira Worldwide Inc, Lake Forest, IL) is a centrally acting, α_2-adrenergic agonist which exerts its physiologic effects by activation of specific receptors throughout the central nervous system thereby producing its sedation, anxiolysis and analgesia. Although both dexmedetomidine and clonidine are imidazole compounds, clonidine exhibits an α_2:α_1 specificity ratio of 200:1 while that of dexmedetomidine is 1600:1. The shorter half-life of dexmedetomidine (2-3 hours versus 12-24 hours for clonidine) allows titration by a continuous infusion. Additionally, dexmedetomidine is available in a preparation for intravenous administration compared to clonidine, where the epidural formulation is generally used for the intravenous route.

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Dexmedetomidine initially received approval from the Food & Drug Administration (FDA) for the provision of sedation for up to 24 hours in adults during mechanical ventilation. More recently, FDA approval was granted for monitored anesthesia care or procedural sedation occurring within the operating room. Although not yet approved by the FDA for use in the pediatric population, given its beneficial physiologic effects and favorable adverse effect profile, there is an ever growing experience with its use in infants and children for various clinical indications including sedation during mechanical ventilation, procedural sedation, the treatment of withdrawal, and prevention of emergence agitation following anesthetic care.[1] The enthusiasm for this novel agent stems from several factors including the lack of an ideal agent for sedation during mechanical ventilation, adverse effects associated with the currently available agents, and recognition over the past 10 years of the potential deleterious physiologic effects of untreated pain in the acute care setting.[2]

When dexmedetomidine was first approved by the FDA for sedation of adults during mechanical ventilation, the trials were meant to evaluate its use for only 24 hours, thereby leaving us with limited data from these studies to guide its use for more prolonged periods of time. As we have learned from our experience with other agents used for sedation in the PICU setting, tolerance and physical dependency develop regardless of the agent used and when the agent or agents are abruptly discontinued, withdrawal behaviors can be seen.[3] Therefore, we are left with the question of whether such phenomena occur with the prolonged administration of dexmedetomidine.

In the pediatric population, although there are case series reporting long term infusions of dexmedetomidine, many of these are retrospective in nature, thereby limiting the ability to closely identify behaviors which may be indicative of withdrawal. Additionally, in these studies, the primary focus is generally the efficacy of sedation and, therefore, there is limited information on how the infusion was discontinued (abruptly or tapered) or if any problems occurred following the infusion. From what we know of the long term administration of other α_2-adrenergic

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agonists such as clonidine with documentation of withdrawal following the abrupt discontinuation of its administration by the oral, epidural, and transdermal route[4-6] and our extensive experience with other sedative and analgesic agents, unless there is something incredibly unique about the dexmedetomidine-receptor interaction, such issues should also occur with dexmedetomidine.

To date, there are limited reported data regarding dexmedetomidine infusions extending beyond 4-5 days.[7-10] Shehabi et al. retrospectively reviewed their experience with dexmedetomidine infusions in a cohort of critically ill adult patients with a median infusion duration of 71.5 hours (range, 35 to 168 hours).[7] There was no evidence of hemodynamic rebound or other withdrawal manifestations despite the abrupt discontinuation of the infusion. Hammer et al. reported no problems after a 4-day dexmedetomidine infusion for sedation following tracheal reconstruction in a 9-year-old patient.[8] Walker et al. retrospectively reviewed their experience with prolonged dexmedetomidine infusions varying from 2 to 50 days (median 11 days) in 65 pediatric patients (mean age 5 years) with thermal injuries.[9] When there was no longer a need for sedation, the infusions were tapered and discontinued over a 12 to 24 hour period. The authors reported no evidence of tachyphylaxis, withdrawal or rebound hemodynamic effects.

However, as early as 2006, anecdotal evidence suggested that as with other agents, tolerance to and withdrawal from dexmedetomidine may occur. Enomoto et al. administered dexmedetomidine for 2 months to an infant with respiratory failure following hepatic transplantation.[11] During the prolonged infusion, tolerance developed with the need to increase the infusion from 0.4 mcg/kg/hr to a maximum of 1.4 mcg/kg/hr to achieve the desired level of sedation. When the infusion was weaned over 48 hours to exclude drug-induced hepatic dysfunction, the child became anxious, developed hypertension, and his respiratory status deteriorated within 6 hours of stopping the infusion. These problems resolved upon restarting the dexmedetomidine infusion.

Two additional reports outline what appear to be withdrawal phenomena following the administration of dexmedetomidine for sedation in critically ill children.[12,13] In a report from Weber et al., a 2-year-old child developed hypertension, tachycardia, and emesis following the abrupt discontinuation of dexmedetomidine after 6 days of administration.[12] Adding to the evidence that these behaviors were indicative of withdrawal, the symptoms were effectively controlled by restarting the infusion and then incrementally decreasing it by 0.1 mcg/kg/hr every 8 hours. Darnell et al. used dexmedetomidine for sedation during mechanical ventilation to avoid respiratory depression with escalating doses of midazolam and fentanyl in an 8-week-old infant with respiratory failure due to pertussis.[13] The dexmedetomidine regimen included a loading dose of 1 mcg/kg followed by an infusion of 0.5 mcg/kg/hr. Once the dexmedetomidine infusion was started, the midazolam and fentanyl were discontinued after 187 hours of administration. Over the next 3 days, there was a suggestion of tolerance as the dexmedetomidine infusion was increased to 2 mcg/kg/hr in order to achieve the desired level of sedation. Dexmedetomidine was administered for a total of 3.5 days. Within 2 hours of discontinuing the infusion, the child developed agitation, tachycardia, dilated pupils, diarrhea, increased muscle tone, and sneezing. These symptoms persisted despite the administration of midazolam and morphine. Additionally, the patient went on to have a series of brief tonic-clonic seizures. Radiologic and laboratory investigations revealed no etiology for the seizures. The dexmedetomidine infusion was restarted and effectively controlled the symptoms except for increased muscle tone and diarrhea. After 14 hours, the dexmedetomidine infusion was again discontinued. At that time, the patient had another brief tonic-clonic seizure, but there were no other signs of withdrawal other than loose stools so the decision was made not to restart the dexmedetomidine. Although it is evident that withdrawal from opioids and benzodiazepines may have been the primary or at least a contributing factor in this last case, the potential role of dexmedetomidine cannot be excluded.

In this issue of the *Journal of Pediatric Pharmacology and Therapeutics*, there are additional reports suggesting withdrawal phenomena following the administration of dexmedetomidine to critically ill infants and children.[14,15] Miller et al. describe withdrawal following a 263-hour infusion of dexmedetomidine (total dose of 193.7 mcg/kg) to provide sedation following surgery for congenital heart disease in a 2-year-old child.[14] Although the child had received infusions of both fentanyl and midazolam along with the dexmedetomi-

dine, methadone and diazepam were started to prevent withdrawal from these two agents. Following the abrupt discontinuation of the dexmedetomidine, the patient developed episodes of blank staring, agitation, and decreased verbal communication. No hemodynamic changes were noted although there was pupillary asymmetry. No therapy was provided and the problems resolved over the ensuing 48 hours. Even more evidence for the potential for withdrawal from dexmedetomidine is provided by Honey et al. in their evaluation of adverse effects related to dexmedetomidine infusions used for sedation in the Pediatric ICU setting.[15] Over a 12-month period, data were collected on 36 children who received continuous infusions of dexmedetomidine. Although the median duration of the infusion was 20 hours, the range varied from 3 to 263 hours. Neurologic issues were noted in 4 patients following dexmedetomidine infusions. One patient who received dexmedetomidine for 11 days developed decreased verbal communication, facial drooping, and unilateral papillary dilatation when the infusion was discontinued without tapering. Transient neurologic events including increased agitation, abnormal chewing movements, non-reactive pupils, slow rhythmic jerking movements, and abnormal head turning were noted in 3 other patients who had received dexmedetomidine for 6 to 49 hours. The infusion was tapered in 2 of these patients. Of additional note, these authors suggest that adverse events related to dexmedetomidine were more likely when the cumulative dose was ≥ 8.5 mcg/kg.

Unfortunately, a heightened awareness of not only the humanitarian, but also the physiologic need for appropriate control of pain and anxiety in the Pediatric ICU patient has resulted in the difficult consequences of physical dependency, tolerance, and withdrawal.[3] The issues of tolerance, physical dependency and withdrawal are nothing new in the Pediatric ICU population as the first reports appeared in the literature in 1990.[16,17] Although both of these initial reports of withdrawal occurred following the administration of opioids, subsequent reports have identified such problems with all classes of agents used for sedation in the Pediatric ICU population including benzodiazepines, barbiturates, propofol, ketamine, and inhalational anesthetic agents.[18-24] Given the previous reports outlined above and the additional cases reported in the two articles from this edition of the *Journal of Pediatric Pharmacology and Therapeutics*, it appears that we must add dexmedetomidine to this list.

Factors determining tolerance and dependency are occupancy of the receptor by an agonist and the specificity or degree of binding of the agonist at the receptor. Tolerance develops more rapidly with the continuous versus the intermittent administration of sedative and analgesic agents. Because of their increased affinity for the opioid receptor, synthetic opioids may result in tolerance more rapidly than non-synthetic opioids, such as morphine. One of the advantageous physiologic properties of dexmedetomidine is its increased avidity for the α_2 versus the α_1 receptor (1600:1 for dexmedetomidine versus 200:1 for clonidine). Does this clinical advantage also lead to an increased rapidity of the development of tolerance as has been described when comparing the synthetic opioids with morphine?

The potential that patients may manifest withdrawal phenomena following dexmedetomidine should not limit its use or the administration of other agents that provide the appropriate level of sedation and analgesia in the Pediatric ICU setting. Rather we must develop ways to effectively identify what are the risk factors for physical dependency and withdrawal in addition to developing effective strategies for patients who have developed tolerance so that they do not develop withdrawal. The majority of data to date suggest that the risk of physical dependency and subsequent withdrawal are related to both the duration of the infusion as well as the total dose of drug administered. In infants and children receiving fentanyl infusions, which were weaned over a 48-hour period, a total fentanyl dose ≥ 1.5 mg/kg or an infusion duration ≥ 5 days was associated with a 50% incidence of withdrawal whereas a total fentanyl dose ≥ 2.5 mg/kg or an infusion duration ≥ 9 days was associated with a 100% incidence of withdrawal.[25] Similar findings correlating the total dose of medication administered and the risk of withdrawal have been reported with the inhalational anesthetic agents, midazolam, and pentobarbital. When using the inhalational anesthetic agent, isoflurane, for sedation during mechanical ventilation, Arnold et al. noted that withdrawal occurred only in patients who had received ≥ 70 MAC-hours of isoflurane.[26] The MAC or minimum alveolar concentration is a measure of the potency of an inhalational anesthetic agent.

It is defined as the alveolar concentration of the agent required to prevent 50% of patients from moving in response to a surgical incision. The MAC of isoflurane is 0.76%. One MAC-hour of isoflurane would be equivalent to the administration of 0.76% (1 MAC) of isoflurane for one hour or the administration of 0.5 MAC (0.38%) for 2 hours. Fonsmark et al. also noted the relationship between probability of withdrawal with total dose administered for both midazolam (total midazolam dose ≥ 60 mg/kg) or pentobarbital (total dose ≥ 25 mg/kg).[20]

The development of strategies to provide effective treatment of physical dependency and related problems requires the accurate identification and recognition of withdrawal symptoms. Ongoing or associated conditions that can manifest similar clinical signs and symptoms as withdrawal must be investigated and ruled out before concluding that the patient's symptoms are the result of withdrawal. In the Pediatric ICU patient, these associated conditions may include central nervous system insults or infections, ICU psychosis, delirium, metabolic abnormalities, hypoxia, hypercarbia, and cerebral hypoperfusion from alterations in cardiac output or cerebral vascular disease. In general, the signs and symptoms of withdrawal from sedative and analgesic agents include signs and symptoms related to the CNS, the gastrointestinal tract, and the sympathetic nervous system. CNS manifestations are generally those of increased irritability including decreased sleep, tremulousness, hyperactive deep tendon reflexes, clonus, inability to concentrate, frequent yawning, sneezing, delirium, and hypertonicity. In neonates and infants, additional signs of central nervous system stimulation include a high-pitched cry and an exaggerated Moro reflex. Seizures have been reported with withdrawal from opioids, benzodiazepines, barbiturates, propofol, and inhalational anesthetic agents while visual and auditory hallucinations have been described with opioid, benzodiazepine, barbiturate, inhalational anesthetic, and now dexmedetomidine withdrawal. Gastrointestinal manifestations include emesis, diarrhea, and feeding intolerance, which may be especially prominent in neonates and infants. When such problems occur in the absence of other signs and symptoms of withdrawal, they may be attributed to other problems and not withdrawal. Activation of the sympathetic nervous system with tachycardia, hypertension, dilated pupils, and tachypnea are prominent findings with withdrawal from any of the above-mentioned sedative/analgesic agents. Additional signs and symptoms of sympathetic hyperactivity include nasal stuffiness, sweating, and fever. From the limited literature regarding dexmedetomidine, it appears that the primary manifestations involve the central nervous system. Many of the manifestations are those of hyperactivity including agitation, hypertonicity, tonic-clonic movements, and what may be even overt seizure activity. These manifestations are not surprising as dexmedetomidine alters levels of the inhibitory neurotransmitter, γ-amino butyric acid, within the CNS. Additional findings have included decreased visual and verbal attentiveness. What is somewhat surprising is the lack of hemodynamic manifestations with dexmedetomidine. Although hypertension and tachycardia were reported by Weber et al.,[12] no hemodynamic changes were noted in the reports of Honey et al.[14] and Miller et al.[15]

Where should we go from here? Without a doubt, dexmedetomidine is a valuable agent for providing sedation and anxiolysis in the Pediatric ICU setting. As with other sedative and analgesic agents, it is apparent that physical dependency and withdrawal do occur following the prolonged administration of dexmedetomidine. Given that, until we have additional information, it may be prudent to avoid its abrupt discontinuation following infusions of more than 4-5 days. We certainly need to work out the appropriate means of tapering its administration. For now, options to allow for its discontinuation include a slow taper via the intravenous route, changing to subcutaneous administration,[27] or switching to clonidine (oral or transdermal).

Most importantly, prospective studies of both short term and long term dexmedetomidine infusions in infants and children are needed. In clinical practice, regardless of the agents used for sedation, ongoing observation for the signs and symptoms of withdrawal are needed as these medications are tapered and then withdrawn. Just as we use pain and sedation scoring systems during the administration of these agents, it seems prudent to use scoring systems to identify withdrawal as these agents are discontinued.[28-30] Additionally, we must continue to identify techniques that may limit some of these adverse ef-

fects such as daily interruption of the sedative/analgesic infusion or the use of rotating sedation regimens.

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REFERENCES

1. Tobias JD. Dexmedetomidine: Applications in pediatric critical care and pediatric anesthesiology. Pediatr Crit Care Med 2008;8:115-131.
2. Anand KSJ, Hickey PR. Halothane-morphine compared with high dose sufentanil for anesthesia and postoperative analgesia in neonatal cardiac surgery. N Engl J Med 1992;326:1-9.
3. Tobias JD. Tolerance, withdrawal, and physical dependency after long-term sedation and analgesia of children in the pediatric intensive care units. Crit Care Med 2000;28:2122-2132.
4. Schmidt GR, Schuna AA. Rebound hypertension after discontinuation of transdermal clonidine. Clin Pharm 1988;7:772-774.
5. Fitzgibbon DR, Rapp SE, Butler SH, et al. Rebound hypertension and acute withdrawal associated with discontinuation of an infusion of epidural clonidine. Anesthesiology 1996;84:729-731.
6. Karachalios GN, Charalabopoulos A, Papalimneous V, et al. Withdrawal syndrome following cessation of antihypertensive drug therapy. Int J Clin Pract 2005;59:562-570.
7. Shehabi Y, Ruettimann U, Adamson H, et al. Dexmedetomidine infusion for more than 24 hours in critically ill patients: sedative and cardiovascular effects. Intensive Care Med 2004;30:2188-2196.
8. Hammer GB, Philip BM, Schroeder AR, et al. Prolonged infusion of dexmedetomidine for sedation following tracheal resection. Paediatr Anaesth 2005;15:616-620.
9. Walker J, MacCallum M, Fisher C, et al. Sedation using dexmedetomidine in pediatric burn patients. J Burn Care Res 2006;27:206-210.
10. Hosokawa K, Shime N, Kato Y, et al. Dexmedetomidine sedation in children after cardiac surgery. Pediatr Crit Care Med 2010;11:39-43.
11. Enomoto Y, Kudo T, Saito T, et al. Prolonged use of dexmedetomidine in an infant with respiratory failure following living donor liver transplantation. Paediatr Anaesth 2006;16:1285-128
12. Weber MD, Thammasitboon S, Rosen DA. Acute discontinuation syndrome from dexmedetomidine after protracted use in a pediatric patient. Paediatr Anaesth 2008;18:87-88.
13. Darnell C, Steiner J, Szmuk P, Sheeran P. Withdrawal from multiple sedative agent therapy in an infant: Is dexmedetomidine the cause or the cure? Pediatr Crit Care Med 2010;11:e1-e3.
14. Miller JM, Allen C, Johnson PM. Neurologic withdrawal symptoms following abrupt discontinuation of dexmedetomidine infusion in a child. J Pediatr Pharmacol Ther 2010;15:38-42
15. Honey BL, Harrison DL, Gormley AK, Johnson PN. Evaluation of adverse events noted in children receiving continuous infusions of dexmedetomidine in the intensive care unit. J Pediatr Pharmacol Ther 2010;15:30-37.
16. Arnold JH, Truog RD, Orav EJ, et al. Tolerance and dependence in neonates sedated with fentanyl during extracorporeal membrane oxygenation. Anesthesiology 1990;73:1136-1140.
17. Tobias JD, Schleien CL, Haun SE. Methadone as treatment for iatrogenic opioid dependency in pediatric intensive care unit patients. Crit Care Med 1990;18:1292-1293.
18. Sury MRJ, Billingham I, Russell GN, et al. Acute benzodiazepine withdrawal syndrome after midazolam infusions in children. Crit Care Med 1989;17:301-302.
19. van Engelen BGM, Gimbrere JS, Booy LH. Benzodiazepine withdrawal reaction in two children following discontinuation of sedation with midazolam. Ann Pharmacother 1993;27:579-581.
20. Fonsmark L, Rasmussen YH, Carl P. Occurrence of withdrawal in critically ill sedated children. Crit Care Med 1999;27:196-199.

21. Tobias JD, Deshpande JK, Gregory DF. Outpatient therapy of iatrogenic drug dependency following prolonged sedation in the pediatric intensive care unit. Intensive Care Med 1994;20:504-507.
22. Byer DE, Gould AB Jr. Development of tolerance to ketamine in an infant undergoing repeated anesthesia. Anesthesiology 1981;54:255-256.
23. Au J, Walker S, Scott DHT. Withdrawal syndrome after propofol infusion. Anaesthesia 1991;46:238-239.
24. Arnold JH, Truog RD, Molengraft JA. Tolerance to isoflurane during prolonged administration. Anesthesiology 1993;78:985-988.
25. Katz R, Kelly W, Hsi A. Prospective study on the occurrence of withdrawal in critically ill children who receive fentanyl by continuous infusion. Crit Care Med 1994;22:763-767.
26. Arnold JH, Truog RD, Rice SA. Prolonged administration of isoflurane to pediatric patients during mechanical ventilation. Anesth Analg 1993;76:520-526.
27. Tobias JD. Subcutaneous dexmedetomidine infusions to treat or prevent drug withdrawal in infants and children. J Opioid Manag 2008;4:187-191.
28. Cunliffe M, McArthur L, Dooley F. Managing sedation withdrawal in children who undergo prolonged PICU admission after discharge to the ward. Paediatr Anaesth 2004;14:293-298.
29. Franck LS, Naughton I, Winter I. Opioid and benzodiazepine withdrawal symptoms in paediatric intensive care patients. Crit Care Nurs 2004;20:344-351.
30. Ista E, van Dijk M, Gamel C, et al. Withdrawal symptoms in critically ill children after long-term administration of sedatives and/or analgesics: A first evaluation. Crit Care Med 2008;36:2427-2432.