An Exaggerated Hypertensive Response to Glycopyrrolate Therapy for Bradycardia Associated with High-Dose Dexmedetomidine

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At our institution, high-dose IV dexmedetomidine is used to provide sedation for pediatric patients undergoing nonpainful radiological imaging studies. Some of these patients exhibit marked bradycardia (more than 20% deviation from the lowest age-adjusted normal values) while maintaining an arterial blood pressure within an acceptable normal range. We report on three cases wherein treatment of dexmedetomidine-induced bradycardia with IV glycopyrrolate (5.0 μg/kg) not only resulting in resolution of bradycardia but also resulting in an exaggerated increase of arterial blood pressure.
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Infants, children, and some developmentally compromised adolescents frequently require sedation to ensure motionless conditions. Dexmedetomidine is a highly selective α-2 adrenoceptor agonist with sedative and analgesic effects. A protocol using high-dose dexmedetomidine (Precedex; Hospira, Lake Forest, IL) as the sole sedative drug for computerized tomography and magnetic resonance imaging (MRI) studies has evolved at our institution.[1–3] For MRI sedation, dexmedetomidine is administered at 3 μg/kg as a 10-min initial loading bolus with a subsequent infusion of 2.0 $\mu g \cdot kg^{-1} \cdot h^{-1}$. The bolus can be repeated up to three times to achieve adequate sedation, coincident with a minimum Ramsay Sedation Score of 4.[4]

This sedation protocol provides adequate sedation in 97.6% of patients. Although this sedation regimen is associated with a 16% incidence of bradycardia, the concomitant mean arterial blood pressures (MAP) are usually within 20% of age-adjusted normal range and accompanied by oxygen saturations (Spo_2) of 95% or higher.[3,5] Although this bradycardia has not been associated with adverse sequela or hemodynamic instability, we decided to treat bradycardia with IV glycopyrrolate 5.0 μg/kg for cases of marked bradycardia. We define marked bradycardia as a heart rate (HR) <20% of lowest age-adjusted awake norms.[5] Three children were outside of the established norms for HR after the decision to treat bradycardia. All were treated with glycopyrrolate. In all children, the glycopyrrolate elicited an immediate HR response with resolution of the bradycardia. However, each child coincidentally responded to the glycopyrrolate with immediate, exaggerated hypertension.

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CASE DESCRIPTION

Case 1

A 12-yr-old, 40 kg boy with a history of tuberous sclerosis and significant developmental delay presented for a brain MRI. He had a history of cardiac rhabdomyoma without evidence of intracardiac extension. Evidence of mild PR interval prolongation on a 12-lead electrocardiogram had previously prompted consideration of Lyme disease. IgM and IgG positive serology had resulted in a 3-wk course of doxycycline. A recent cardiology consult confirmed that he currently had no electrocardiogram abnormalities and no evidence of functional heart disease. He was receiving 30 mg TID of propranolol to reduce his hyperactive behavior.

On the day of his MRI, he presented in a nonagitated, calm state with a HR of 90 bpm, respiratory rate (RR) of 26 breaths/min and noninvasive arterial blood pressure (NIBP) measurement of 110/94 with MAP of 94 mm Hg. Room air Spo_2 was 99%. After placement of an IV catheter, dexmedetomidine was administered at 3 μg/kg over a 10-min period using an Iradimed 3850 mRidium MR IV pump (Iradimed Corp., Winter Park, FL). Vital signs (NIBP, Spo_2, RR, HR) were monitored continuously and documented every 5 min (Table 1). The child was successfully sedated (Ramsay Sedation Score 4) after completion of the dexmedetomidine bolus, at which time the infusion pump began to deliver a 2 $\mu g \cdot kg^{-1} \cdot h^{-1}$ continuous infusion. Within 1 min of completing the bolus, his NIBP was 100/62 (MAP 77 mm Hg), HR was sinus rhythm at 38 bpm, RR was 19 breaths/min, and room air $Spo_2$was 99%. Within 1 min, 400 μg of IV glycopyrrolate was administered. There was an immediate HR response to 55, 71, and 107 bpm at 1, 2, and 5 min, respectively. Within 5 min of receiving glycopyrrolate, the NIBP and MAP increased to 160/94 and 122 mm Hg, respectively. His NIBP remained elevated with MAPs between 101 and 109 mm Hg for 80 min, after which it

Table 1. Vital Signs for Three Patients

	Baseline	Postdexmedetomidine (at bradycardia)	Postglycopyrrolate (5 min)	Recovery room (at discharge)
HR (beats/min)				
Case 1	90	38	107	70
Case 2	88	37	158	99
Case 3	64	41	100	79
RR (breaths/min)				
Case 1	26	19	18	16
Case 2	18	10	24	23
Case 3	20	24	28	18
NIBP (mm Hg)				
Case 1	110/90	100/62	160/94	101/54
Case 2	89/57	128/80	175/118	106/76
Case 3	118/64	116/64	190/112	120/68
MAP (mm Hg)				
Case 1	94	77	122	66
Case 2	64	96	137	83
Case 3	83	82	148	82
Spo_2 (%)				
Case 1	99	99	96	98
Case 2	100	100	99	100
Case 3	100	100	99	100

HR = heart rate; RR = respiratory rate; NIBP = noninvasive arterial blood pressure; MAP = mean arterial blood pressure; Spo_2 = oxygen saturations.

returned to presedation baseline values. His HR response to glycopyrrolate persisted for 45 min, with a rate between 104 and 126 bpm, after which time the HR returned to the presedation baseline. The dexmedetomidine infusion continued for 70 min until the imaging study was successfully completed. The patient met Aldrete discharge criteria[6] after 45 min of recovery room time. His vital signs remained at presedation values during the entire recovery period. The patient was discharged home after a 2-h observation period without further sequelae noted at discharge or at the time of a 24-h follow-up phone call to his parents.

Case 2

A 3-yr-old, 20 kg boy with a craniosynostosis involving the right unilateral lamdoidal suture was scheduled for a brain MRI. Recent computed tomography scan showed synostosis without evidence of significant underlying brain anomalies or any signs of increased intracranial pressure. Prior MRI scans had excluded the presence of a Chiari malformation. He was taking no medications and his physical examination was unremarkable.

He presented in a calm state with HR of 88 bpm, RR of 18 breaths/min, a NIBP measurement of 89/57 (MAP 64 mm Hg), and a room air Spo_2 of 100% (Table 1). A bolus of dexmedetomidine 3 μg/kg was administered IV over 10 min followed by a continuous infusion of 2 $\mu g \cdot kg^{-1} \cdot h^{-1}$. Five minutes after initiating the infusion, his HR slowed to 37 bpm. His NIBP was 128/80 (MAP 96 mm Hg) and room air Spo_2 was 99%. The HR responded within 1 min to 200 μg of IV glycopyrrolate, increasing to 89 bpm. Concurrent with the HR response, the NIBP increased to 161/113 (MAP 135) and remained elevated with MAP between 117 and 148 mm Hg, during the 16-min dexmedetomidine infusion. After the MRI, the dexmedetomidine infusion was discontinued and the patient was transported to the recovery room. His NIBPs in recovery room were documented every 5 min and remained elevated for 30 min with MAP between 93 and 124 mm Hg. The patient met discharge criteria after 1 h and was discharged home with a HR 99 bpm and NIBP 106/76 (MAP 83 mm Hg). There were no further sequelae reported by his parents at the time of the 24 h follow-up phone call.

Case 3

A 13-yr-old, 50 kg boy with Type 1 neurofibromatosis and Klinefelter syndrome presented for a brain MRI. His physical examination and history were remarkable for short stature, delay in secondary sexual characteristics, and significant developmental delay. He was taking lithium, chlorpromazine, 8-D-arginine vasopressin, and aripiprazole to control his behavior and enuresis. He was also taking ranitidine. He had never received any treatment for the neurofibromatosis, and he had not been started on hormonal therapy for his Klinefelter syndrome.

He presented in a calm state with HR of 64 bpm, RR of 20 breaths/min, a NIBP measurement of 118/64 (MAP of 83 mm Hg), and a room air Spo_2 of 100% (Table 1). A bolus of dexmedetomidine 3 μg/kg was administered IV over 10 min. Nine minutes after initiating the bolus, the HR was sinus bradycardia at 41 bpm with a concurrent NIBP of 116/64 (MAP 82 mm Hg), and a Spo_2 of 100%. IV glycopyrrolate 400 μg was administered and his HR responded within 2 min, increasing to 71 bpm. Five minutes after glycopyrrolate administration, the HR was 100 bpm with a NIBP of 190/112 (MAP 148 mm Hg). The dexmedetomidine infusion was subsequently started at 2 $\mu g \cdot kg^{-1} \cdot h^{-1}$ and the NIBP, documented at 1-min intervals, remained elevated for 50 min (MAP between 115 and 134 mm Hg). After successful completion of the MRI, the dexmedetomidine infusion was discontinued and the patient was transported to the recovery room. After a 45-min recovery period, the patient met discharge criteria and was discharged home with a HR of 79 bpm and a NIBP of 120/68 (MAP 82 mm Hg). There were no adverse sequelae noted at discharge or at the time of 24-h follow-up phone call to his parents.

DISCUSSION

High-dose dexmedetomidine can induce bradycardia in children. In adults, increasing concentrations of dexmedetomidine decrease the HR, cardiac output, and stroke volume.[7] These changes may be associated with a progressive increase in arterial blood pressure because of a progressive increase in systemic vascular resistance.[7] At the dose of dexmedetomidine used in our protocol, bradycardia is uncommon but can be marked.[3] In our experience, arterial blood pressure during these episodes is usually within the normal

age-adjusted range.[3] The bradycardia associated with dexmedetomidine in children appears to be related to depression of sinus and atrioventricular nodal function.[8] Whether the bradycardia is the consequence of a decrease in sympathetic outflow from the central nervous system or reflex effects related to increases in systemic vascular resistance remains speculative.[8]

Treatment of dexmedetomidine-induced bradycardia has not been systematically studied. In healthy adults, administration of glycopyrrolate (15 μg/kg followed by an infusion of 7 $\mu g \cdot kg^{-1} \cdot h^{-1}$) in combination with dexmedetomidine (0.225 μg/kg followed by an infusion of 0.5 $\mu g \cdot kg^{-1} \cdot h^{-1}$) produced increases in HR and MAP, a decrease in stroke volume, and no change in cardiac output and systemic vascular resistance when compared with the baseline state.[9,10] The increases in arterial blood pressure seen in our patients after glycopyrrolate administration were presumably secondary to a HR-induced increase in cardiac output in the setting of elevated systemic vascular resistance from the sustained effect of dexmedetomidine on the α-2 receptors in the peripheral vascular smooth muscle.[7,11,12] It is interesting to theorize whether the presence of propranolol or vasopressin and chlorpromazine predisposed two of the patients, respectively, to either bradycardia with dexmedetomidine or hypertension after glycopyrrolate. The dosage of propranolol received by the child was minimal and, based on the presedation HR, had not induced a bradycardic effect. If this patient receiving propranolol had presented with evidence of β blockage (bradycardia), the administration of dexmedetomidine would have been deferred per our institutional protocol.

None of the children received antihypertensive therapy during their hypertensive response to glycopyrrolate. Subsequent to this report, our protocol for dexmedetomidine has been amended to limit glycopyrrolate therapy only for those situations of bradycardia coincident with hypotension, which is unresponsive to IV fluid boluses. No child has required glycopyrrolate for this indication. In the event of marked hypertension, which we define as a MAP of more than 20% highest age-adjusted awake normal values, the dexmedetomidine infusion is discontinued.[5] Should the child require adjuvant sedation to complete the imaging study, small doses of pentobarbital are administered. Based on our experience, we would recommend that administration of glycopyrrolate to treat bradycardia in normotensive children receiving dexmedetomidine be avoided. In the event that glycopyrrolate is administered to children receiving high-dose dexmedetomidine, extreme hypertension should be anticipated.

REFERENCES

1. Mason KP, Zgleszewski SE, Dearden JL, Dumont RS, Pirich MA, Stark CD, D'Angelo P, Macpherson S, Fontaine PJ, Connor L, Zurakowski D. Dexmedetomidine for pediatric sedation for computed tomography imaging studies. Anesth Analg 2006; 103:57–62, table of contents
2. Mason KP, Zgleszewski SE, Prescilla R, Fontaine PJ, Zurakowski D. Hemodynamic effects of dexmedetomidine sedation for ct imaging studies. Paediatr Anaesth 2008;18:393–402
3. Mason KP, Zurakowski D, Zgleszewski SE, Robson C, Carrier M, Hickey P, DiNardo JA. High dose dexmedetomidine as the sole sedative for pediatric MRI. Paediatr Anaesth 2008;18:403–11
4. Ramsay MA, Savege TM, Simpson BR, Goodwin R. Controlled sedation with alphaxalone-alphadolone. BMJ 1974;2:656–9
5. Nelson MD Jr. Guidelines for the monitoring and care of children during and after sedation for imaging studies. AJR Am J Roentgenol 1993;160:581–2
6. Aldrete JA, Kroulik D. A postanesthetic recovery score. Anesth Analg 1970;49:924–34
7. Ebert TJ, Hall JE, Barney JA, Uhrich TD, Colinco MD. The effects of increasing plasma concentrations of dexmedetomidine in humans. Anesthesiology 2000;93:382–94
8. Hammer GB, Drover DR, Cao H, Jackson E, Williams GD, Ramamoorthy C, Van Hare GF, Niksch A, Dubin AM. The effects of dexmedetomidine on cardiac electrophysiology in children. Anesth Analg 2008;106:79–83, table of contents
9. Wilkins BW, Hesse C, Sviggum HP, Nicholson WT, Moyer TP, Joyner MJ, Eisenach JH. Alternative to ganglionic blockade with anticholinergic and alpha-2 receptor agents. Clin Auton Res 2007;17:77–84
10. Wilkins BW, Hesse C, Charkoudian N, Nicholson WT, Sviggum HP, Moyer TP, Joyner MJ, Eisenach JH. Autonomic cardiovascular control during a novel pharmacologic alternative to ganglionic blockade. Clin Pharmacol Ther 2008;83:692–701
11. Murrell JC, Hellebrekers LJ. Medetomidine and dexmedetomidine: a review of cardiovascular effects and antinociceptive properties in the dog. Vet Anaesth Analg 2005;32:117–27
12. Bloor BC, Frankland M, Alper G, Raybould D, Weitz J, Shurtliff M. Hemodynamic and sedative effects of dexmedetomidine in dog. J Pharmacol Exp Ther 1992;263:690–7