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Case Report

Cardiac arrest related to dexmedetomidine administration after liver transplantation: a report of two cases

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Abstract: Dexmedetomidine is an alpha-2 adrenergic agonist used for sedation and anxiolysis. Its' sympatholytic action and effect on vagal tone cause hypotension and bradycardia. However, fatal bradycardia is uncommon, and very few cases of dexmedetomidine-related cardiac arrest have been reported. Previously reported cases of cardiac arrest associated with dexmedetomidine are that of patients in the intensive care unit or during surgery. Here, we report and compare two cases of severe bradycardia leading to cardiac arrest in the ward and intensive care unit after liver transplantation. In both cases, the patients had liver dysfunction, but cardiac arrest was fully monitored in the ICU; therefore, early detection and treatment were performed in the ICU rather than in the ward. For this reason, cautious administration of dexmedetomidine is necessary in patients with liver dysfunction, and the drug should be infused under careful monitoring.

Keywords: Dexmedetomidine, asystole, delirium, liver transplantation

Introduction

Dexmedetomidine is a strong alpha-2 adrenergic agonist. The hemodynamic effect of dexmedetomidine is characterized by an initial transient hypertension followed by hypotension and bradycardia owing to its sympatholytic action [1]. The most well-known adverse effects of dexmedetomidine are hypotension and bradycardia [2]. The incidence of dexmedetomidine-related bradycardia ranges from 9% to 42% [2, 3]. However, life-threatening bradycardia is uncommon and dexmedetomidine-related cardiac arrest is also rare [4]. Previously reported cases of cardiac arrest associated with dexmedetomidine was that of a patient in the intensive care unit or during surgery [4-6]. Very few cases of cardiac arrest with the use of dexmedetomidine after liver transplantation have been reported. Here, we present and compare two cases of severe bradycardia leading to cardiac arrest associated with dexmedetomidine infusion in the ward and intensive care unit after liver transplantation.

First case

A 51-year-old man with multiple hepatocellular carcinomas related to alcoholic liver cirrhosis and hepatitis B virus was scheduled for a living-donor liver transplant from his brother. He had a medical history of cerebral infarction diagnosed 6 years ago. He also had a history of appendectomy with ileocecectomy 13 years prior. He was an ex-smoker of 30 pack-years and had been drinking 114 g of alcohol for 5 days per month for 30 years.

He looked chronically ill, but his physical examination results were normal. His blood pressure was 125/63 mmHg, heart rate (HR) was 55 beats per minute (bpm), and body temperature was around 36.5°C. His mental state was alert and well oriented. His laboratory data before the operation showed slightly elevated liver enzyme levels (AST 40 U/L and ALT 45 U/L) and a slightly decreased platelet count of 10400/μL. He was positive for hepatitis B virus surface antigen and negative for hepatitis C

Table 1. Vital signs and drugs administered on the day of cardiac arrest

Postoperative day 10		Vital sign		
Time	Medication	Blood pressure (mmHg)	Heart rate (bpm)	SpO_2 (%)
00:50	Midazolam 5 mg	159/76	72	U
	Olanzapine 10 mg (IM)			
	Haloperidol 5 mg (IM)			
01:25	Olanzapine 10 mg (IM)	102/60	81	95
03:50	Olanzapine 10 mg (IM)	U	U	U
	Haloperidol 5 mg (IM)			
09:40	Meperidine 50 mg	U	U	U
11:00	Dexmedetomidine 0.2 mcg/kg/h	138/88	100	96
11:20	Olanzapine 10 mg (IM)	U	126	96
	Haloperidol 5 mg (IM)			
12:00	Dexmedetomidine 0.4 mcg/kg/h	118/48	68	90 (ambient air)
18:30	Dexmedetomidine 0.4 mcg/kg/h	103/54	50-60	100 (3 NP)
18:46	Cardiac arrest	U	U	U
	Dexmedetomidine was stopped			

bpm: beats per minute; SpO_2: oxygen saturation; IM: intramuscular; U: unchecked; NP: nasal prong.

virus antibody. His electrocardiography showed sinus bradycardia with an HR of 58 bpm without any special abnormal findings, and his echocardiography findings were normal. His chest X-ray showed normal findings.

The transplantation was performed without complications, and his vital signs were stable with dopamine and norepinephrine infusions. After the surgery, he was transferred to the surgical intensive care unit (SICU), and then kept under routine hemodynamic monitoring and sedated with remifentanil. His vital signs were stable. He was extubated on postoperative day (POD) 1, and remifentanil, dopamine, and norepinephrine infusions were discontinued. After waking from sedation, he complained of insomnia. On POD 6, the patient was transferred to the general ward. He continued to experience insomnia and showed agitation and aggressive behavior. He was treated with haloperidol and lorazepam daily.

On POD 10, in an attempt to control his irritability and aggression, he was transferred to the casualty ward. Noninvasive blood pressure, oxygen saturation, and electrocardiography were monitored. Midazolam was injected once; olanzapine and haloperidol were injected three and two times, respectively. Furthermore, meperidine was injected once. Finally, dexmedetomidine infusion was started at 11:00 h at a rate of 0.2 mcg/kg/h without a loading dose. Additional boluses of olanzapine and haloperidol were administered; 1 h later, the dose of dexmedetomidine was increased to 0.4 mcg/kg/h. His blood pressure was 118/48 mmHg and HR was 68 bpm, but oxygen saturation in the ambient air dropped to 90%. Therefore, a nasal prong (NP) was applied and oxygen was delivered at 3 L/min. Seven and a half hours after the dexmedetomidine infusion, the blood pressure was 103/54 mmHg, HR was between 50 and 60 bpm, and oxygen saturation was 100% with an NP of 3 L/min. Abruptly, his HR decreased, and electrocardiography showed asystole. His peripheral and carotid pulses were not checked, and spontaneous breathing was not detected. The cardiopulmonary resuscitation (CPR) team was called and chest compression was started. Atropine and epinephrine were administered, and dexmedetomidine was stopped. The total dexmedetomidine infusion time was 466 min and the total infusion dose was 203 mcg. The administered drugs and vital signs on POD 10 before cardiac arrest are summarized in **Table 1**. After 22 min of CPR, his spontaneous circulation recovered. Oxygen saturation dropped to 85% on administration of 10 L/min oxygen via facial mask, and the patient was intubated. His blood pressure was 84/48 mmHg and HR was 101 bpm. Therefore, after central line insertion, dopamine was started at 10 mcg/kg/min, and the patient was transferred to the SICU. He

was sedated with remifentanil 0.1 mcg/kg/min and midazolam 5 mg. After 40 min, his blood pressure dropped to 42/28 mmHg and HR to 40 bpm; thus, a second round of CPR was started. Remifentanil was stopped, and norepinephrine, amiodarone, and epinephrine were administered. Bedside echocardiography findings indicated stress-induced cardiomyopathy. CKMB and troponin I were elevated to 125 and 10.926 ng/mL (normal range: 0-5 and 0-0.78 ng/mL), respectively. Owing to refractory hypotension (50/42 mmHg), extracorporeal membrane oxygenation (ECMO) was initiated. On POD 13, ECMO was stopped, and the patient was extubated. CKMB/troponin I was 56 ng/mL/32 ng/mL. Follow-up echocardiography indicated ischemic cardiomyopathy with slightly decreased left ventricular systolic function (ejection fraction, 40%-45%). On POD 46, his psychological problem, that is, insomnia, was resolved. On POD 60, the patient was discharged without any further cardiac problems.

Second case

A 31-year-old woman was hospitalized for liver transplantation owing to drug-induced acute hepatic failure with encephalopathy. She had uncontrolled hyperthyroidism. Her free thyroxine (FT4) and thyroid-stimulating hormone (TSH) levels were 10.60 ng/dL (reference, 0.89-1.8 ng/dL) and 0.01 uIU/mL (reference, 0.35-5.5 uIU/mL), respectively.

She had an acute ill-looking appearance and grade 3 hepatic encephalopathy. Her blood pressure was 120/50 mmHg, HR was 70 bpm, and body temperature was around 36.6°C. Her laboratory data before the operation showed elevated liver enzyme levels (AST 112 U/L and ALT 83 U/L) and a decreased platelet count of 50000/μL. She was positive for hepatitis B virus surface antigen and negative for hepatitis C virus antibody. Her electrocardiography showed a normal sinus rhythm, and her chest X-ray showed no active lung lesions. Her echocardiography showed normal LV and RV systolic function, no regional wall motion abnormality, 62% LVEF, and mild pulmonary hypertension.

Her deceased donor liver transplantation was done without complications, and her vital signs were stable with dopamine infusion (3 mcg/kg/min). After the surgery, she was transferred to the intensive care unit; she was kept in the ICU without extubation because her vital signs were unstable without dopamine infusion.

On POD 6, to control her irritability and to sedate her, a dexmedetomidine infusion was started at 1:30 h at a rate of 0.5 mcg/kg/h without a loading dose. After 30 min, the dose of dexmedetomidine was increased to 0.6 mcg/kg/h. On the same day, her blood pressure dropped (74/46 mmHg). A continuous infusion of norepinephrine (0.05 mcg/kg/min) was applied for the treatment of hypotension.

On POD 8, extubation was performed in the SICU. Immediately after extubation, her HR slowly decreased. Moreover, her blood pressure decreased. Immediately, her electrocardiography showed asystole and her mean BP was 61 mmHg. She was immediately woken up by shaking, and the dexmedetomidine infusion was stopped. The total dexmedetomidine infusion time was 2 days 6 h, and the total infusion dose was approximately 2314 mcg. Immediately, her HR and BP recovered (HR, 60 bpm; BP, 123/49 mmHg). Shortly after, the electrocardiography showed asystole again. Atropine 0.5 mg was immediately injected, and her HR recovered. The administered drugs and 12 s-interval vital signs during the cardiac event are summarized in **Table 2**. Aspiration pneumonia occurred 3 weeks after surgery, and she required mechanical ventilation for 1 month. On POD 26, she complained of left arm weakness. Thus, a brain CT scan was taken, and the findings showed Rt. MCA infarction. She received antiplatelet and anticoagulation therapies for ischemic stroke. On POD 95, the patient's condition improved, and she was discharged.

Discussion

As an alpha-2 adrenergic agonist, dexmedetomidine and its hemodynamic effects have been reported. Bloor [1] demonstrated a decrease in HR at 2 min after the administration of dexmedetomidine at four incremental doses (0.2, 0.5, 1.0, and 2.0 mcg/kg). In another study, an increase in the plasma concentration of dexmedetomidine, using a computer-controlled infusion pump, resulted in a maximal decrease of 29% in the HR. Additionally, a decrease in the HR was recorded when the

Table 2. Vital signs and events on the day of cardiac arrest

Postoperative day 8		Vital sign		
Time	Event	Blood pressure (mmHg)	Heart rate (bpm)	SpO_2 (%)
07:36:36		144/59	63	100
07:36:48		139/52	61	100
07:37:00	Extubation	135/48	49	U
07:37:12		131/43	39	90
07:37:24	Shaking	61 (mean)	0	U
07:37:36	Dexmedetomidine was stopped	118/46	0	U
07:37:48		123/49	60	U
07:38:00		129/62	71	U
07:38:12	Atropine 0.5 mg IV	40 (mean)	0	U
07:38:24		142/71	0	U
07:38:36		132/66	99	U
07:38:48		143/63	102	100
07:39:00		144/56	108	100
07:39:12		144/53	62	100

bpm: beats per minute; SpO_2: oxygen saturation; IV: intravascular; U: unchecked.

plasma dexmedetomidine concentration was 1.2 ng/mL, and it lasted up to 210 min after the discontinuation of the infusion [7].

Bradycardia due to dexmedetomidine infusion is an expected effect. The incidence of dexmedetomidine-related bradycardia is reported to be approximately 9%-42% [2, 3]. In our first case, dexmedetomidine was used to control agitation and delirium on POD 10 in the ward. There was no loading dose, and the infusion dose was 0.2-0.4 mcg/kg/h. Dexmedetomidine was initially approved in the US with a maximal dose of 0.7 mcg/kg/min [3, 8-10]. Additionally, in a study in patients undergoing surgery requiring mechanical ventilation, effective sedation was achieved with dexmedetomidine at an initial rate of 0.2-0.4 mcg/kg/h without a loading dose [11]. Because dexmedetomidine is metabolized in the liver through glucuronide conjugation and biotransformation in the cytochrome P450 enzyme system, it is known that hepatic clearance may be decreased by as much as 50% of the normal value in severe liver diseases [12]. Considering that the patient was in a post-liver transplantation state and his liver enzyme levels were elevated on the day of cardiac arrest (AST 59 U/L and ALT 133 U/L), we might presume that even lower doses might evoke adverse effects in patients with liver dysfunction.

The administration of meperidine may be a possible provocation factor that worsened bradycardia. In a study in dogs, meperidine injection in combination with dexmedetomidine resulted in more incidence of bradycardia than dexmedetomidine alone. One of the reasons for this was the increased level of sedation induced by the drug combination produced profound sedation. A decrease in awareness caused the dogs to be less stimulated to the surroundings and show a lower HR than the control groups [13].

Other co-injected drugs might also be considered as factors for cardiac arrest. Midazolam reduces systemic vascular resistance and causes hypotension. It is mainly metabolized by the liver. Although we considered that the hepatic function of this patient was decreased, the gap between midazolam administration and cardiac arrest appears too long for midazolam to be considered the main cause of cardiac arrest. Haloperidol is a typical antipsychotic drug that blocks the dopamine D2 receptor and olanzapine is an atypical antipsychotic drug. The most common cardiovascular adverse effects of atypical antipsychotics such as olanzapine are tachycardia, orthostatic hypotension, and QT interval prolongation in electrocardiography [14]. QT prolongation and Torsade de Pointes are well known cardiovascular adverse effects of haloperidol [15]. It appears that these medications are more related to tachycardia rather than bradycardic episodes, and thus, they do not show a significant relationship with this attack. However, as there

are no clinical trials that combine all these drugs together; therefore, we cannot assert that these co-injected drugs had no influence on this case.

Finally, his baseline HR was 58 bpm showing sinus bradycardia. The low resting HR implies a higher vagal tone than that of individuals with higher HR (around 80 bpm). Poorly conditioned patients with a higher HR and lower vagal tone should be less susceptible to bradycardia mediated by increased gain in the baroreceptor system [1].

In the second case, the patient was in a post-liver transplantation state and with liver dysfunction, as in the first case. Although dexmedetomidine doses were in the normal range, cardiac arrest occurred. The reason for introducing the second case is to demonstrate the importance of monitoring the use of dexmedetomidine in patients with liver dysfunction.

A comparison between the first and second cases revealed varying levels of progress under similar situations. As the patient in the first case was in the general ward, continuous vigilant monitoring could not be performed. The vital signs were only checked every 4 h. It was difficult to monitor the changes in the vital signs. However, the patient in the second case was fully monitored; she was under constant monitoring in the ICU. Thus, in her case, quick detection and treatment could be achieved. Only the awakening and atropine injections allowed the patient to recover. Furthermore, there were no co-injected drugs.

In summary, we report two cases of cardiac arrest related to dexmedetomidine infusion. We suggest that continuous infusion without thorough and vigilant monitoring should be avoided. Especially in patients with liver dysfunction or low baseline HR, severe bradycardia might arise even with a low infusion rate.

Disclosure of conflict of interest

None.

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References

[1] Bloor BC, Ward DS, Belleville JP and Maze M. Effects of intravenous dexmedetomidine in humans. II. Hemodynamic changes. Anesthesiology 1992; 77: 1134-1142.

[2] Mateos Gaitan R, Vicent L, Rodriguez-Queralto O, Lopez-de-Sa E, Elorriaga A, Pastor G, Baneras J, Lorenzo B, Garcia-Rubira JC, Corbi M, Ariza A and Martinez-Selles M. Dexmedetomidine in medical cardiac intensive care units. Data from a multicenter prospective registry. Int J Cardiol 2020; 310: 162-166.

[3] Bharati S, Pal A, Biswas C and Biswas R. Incidence of cardiac arrest increases with the indiscriminate use of dexmedetomidine: a case series and review of published case reports. Acta Anaesthesiol Taiwan 2011; 49: 165-167.

[4] Amano E, Tateda T and Inoue S. Asystole during administration of dexmedetomidine with spinal anesthesia: a case report. Journal of St Marianna University 2018; 9: 81-85.

[5] Takata K, Adachi YU, Suzuki K, Obata Y, Sato S and Nishiwaki K. Dexmedetomidine-induced atrioventricular block followed by cardiac arrest during atrial pacing: a case report and review of the literature. J Anesth 2014; 28: 116-120.

[6] Aikaterini A, Ioannis D, Dimitrios G, Konstantinos S, Vasilios G and George P. Bradycardia leading to asystole following dexmedetomidine infusion during cataract surgery: dexmedetomidine-induced asystole for cataract surgery. Case Rep Anesthesiol 2018; 2018: 2896032.

[7] Ebert TJ, Hall JE, Barney JA, Uhrich TD and Colinco MD. The effects of increasing plasma concentrations of dexmedetomidine in humans. Anesthesiology 2000; 93: 382-394.

[8] Ingersoll-Weng E, Manecke GR Jr and Thistlethwaite PA. Dexmedetomidine and cardiac arrest. Anesthesiology 2004; 100: 738-739.

[9] Shah AN, Koneru J, Nicoara A, Goldfeder LB, Thomas K and Ehlert FA. Dexmedetomidine related cardiac arrest in a patient with permanent pacemaker; a cautionary tale. Pacing Clin Electrophysiol 2007; 30: 1158-1160.

[10] Sichrovsky TC, Mittal S and Steinberg JS. Dexmedetomidine sedation leading to refractory cardiogenic shock. Anesth Analg 2008; 106: 1784-1786.

[11] Ickeringill M, Shehabi Y, Adamson H and Ruettimann U. Dexmedetomidine infusion without loading dose in surgical patients requiring mechanical ventilation: haemodynamic effects and efficacy. Anaesth Intensive Care 2004; 32: 741-745.

[12] Panzer O, Moitra V and Sladen RN. Pharmacology of sedative-analgesic agents: dexmedetomidine, remifentanil, ketamine, volatile anesthetics, and the role of peripheral Mu antagonists. Anesthesiol Clin 2011; 29: 587-605.

[13] Grint NJ, Burford J and Dugdale AH. Does pethidine affect the cardiovascular and sedative effects of dexmedetomidine in dogs? J Small Anim Pract 2009; 50: 62-66.

[14] Minns AB and Clark RF. Toxicology and overdose of atypical antipsychotics. J Emerg Med 2012; 43: 906-913.

[15] Wenzel-Seifert K, Wittmann M and Haen E. QTc prolongation by psychotropic drugs and the risk of torsade de pointes. Dtsch Arztebl Int 2011; 108: 687-693.