Case Report

Dexmedetomidine overdosage: An unusual presentation

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ABSTRACT

We present a case of dexmedetomidine toxicity in a 3-year-old child. The case report describes the features and outlines the treatment strategy adopted. The child presented with bradypnoea, bradycardia, hypotension, deep hypnosis and miosis. He was successfully managed with oxygen, saline boluses and adrenaline infusion. He became haemodynamically stable with adrenaline infusion. He started responding to painful stimuli in 3 h and became oriented in 7 h. Dexmedetomidine, a selective α_2 adrenoceptor agonist, is claimed to have a wide safety margin. This case report highlights the fact that dexmedetomidine administered in a toxic dose may be life-threatening may present with miosis and adrenaline infusion may be a useful supportive treatment.

Key words: Dexmedetomidine, miosis, overdose

INTRODUCTION

Dexmedetomidine, an imidazole compound, is the pharmacologically active dextro-isomer of medetomidine that displays specific and selective α_2 adrenoceptor agonism. Activation of the receptors in the brain and spinal cord inhibits neuronal firing, causing hypotension, bradycardia, sedation and analgesia.[1] It is utilised to sedate patients in intensive care units, sedation during the regional anaesthesia and as an adjunct to general anaesthesia. It is recommended to be administered as a two-stage infusion, consisting of a loading dose of 1 mcg/kg over 10 min followed by a maintenance infusion of 0.2-0.7 mcg/kg/h.[2] Dexmedetomidine is a highly selective α_2 adrenoceptor agonist with a α_2:α_1 ratio of 1620:1.[3] α_2-adrenoceptor agonists have been described as having a "remarkably wide safety margin."[2]

We present a case of a child, who developed profound haemodynamic instability with miosis as a result of accidental intra-venous injection of bolus of dexmedetomidine in a toxic dose and management of the same. Informed consent of the child's father was obtained for reporting this case.

CASE REPORT

A 3-year-old male child, weighing 11 kg and 87 cm in height diagnosed with pyogenic meningitis, was being treated at our facility with intra-venous ceftriaxone and dexamethasone. He was responding well to the treatment. As a result of a clerical error, he was accidentally administered 100 mcg of dexmedetomidine as an intra-venous bolus. Within minutes, he became unconscious, heart rate: 65/min, respiratory rate (RR): 8-10/min, blood pressure: 70/40 mm of Hg, oxygen saturation (SpO_2) was 85% and constricted pupils with normal eye reflex [Table 1]. Auscultation of the chest was unremarkable.

With oxygen supplementation by Venturi mask (FiO_2 of 0.5), in the next 10 min [Table 1] his SpO_2 improved to 98% and his RR increased to 14-16/min. As the incident occurred early in the morning, the child was in a fasting state and so deemed at a low risk for aspiration. Considering this and his improved respiratory parameters, endotracheal intubation was deferred. When the patient did not respond to two intra-venous 100 ml bolus of normal saline (10 ml/kg), he was then started on intra-venous infusion of adrenaline 0.04 mcg/kg/min, which was gradually

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Table 1: Haemodynamic data at various time intervals after the incident

Time from incident	Baseline*	Immediately@	10 min	20# min	30 min	1 h	2 h	3 h	4 h	6 h	8 h
Heart rate (per minute)	110	65	67	67	84	80	114	112	112	110	90
Blood pressure (mm of Hg)	100/60	70/40	75/42	75/42	98/60	106/70	108/62	106/60	105/62	110/60	100/60
Oxygen saturation (%)	99	85	98	99	100	100	100	100	100	100	100
Respiratory rate	24	10	16	22	22	22	22	22	24	22	22

*Baseline value-30 min prior to incident, @Within 2 min of detected, #Adrenaline infusion started

increased to 0.08 mcg/kg/min. His blood pressure gradually improved in the next 1 h to 106/70 mm of Hg and heart rate to 80/min. The dose of adrenaline could be gradually tapered and was finally stopped after 7 h of the dexmedetomidine injection.

His blood glucose measured soon after injection of dexmedetomidine was 96 mg/dl and it continued to remain within normal limits.

Size of the pupils observed in ambient light was found to be 0.5-1 mm approximately. The direct light reflex and consensual light reflex were normal bilaterally. The pupillary size had normalised to 2-2.5 mm by 2 h.

Patient, unconscious since the bolus injection of dexmedetomidine, started responding to painful stimuli after 3 h. After 4 h, the child started responding to calling by name and after 7 h he became conscious and oriented.

DISCUSSION

There have been reports of over dosage of dexmedetomidine, in which higher doses ranging from 10 to 60 times the recommended infusion dose were administered by infusion.[2] In two of these cases, there were mild haemodynamic perturbations in the form of hypotension/hypertension. They showed biphasic haemodynamic response-hypotension at low plasma concentrations and hypertension at high plasma concentrations. The fall in arterial pressure, heart rate and cardiac output was modest and significant hypertensive response was also absent. Deep hypnosis resolved within 1 h of drug discontinuation. Only one case of administration of twice the loading dose (2 mcg/kg) of dexmedetomidine, over 2 min, (i.e., over one-fifth the minimum time recommended) has been reported. Again no severe adverse effects were noted. In the case reported here, a dose approximately, nine times the recommended loading dose was administered as a bolus to a child.

Bradycardia due to dexmedetomidine administration may occur with the recommended dose and definitely with overdosage. Bradycardia due to dexmedetomidine has been ascribed to central sympatholysis and peripheral ganglionic effect.[4] Stimulation of the pre-synaptic α_2 adrenoceptors leads to a decreased catecholamine release.[1] Hypotension was unusual because in previous cases of dexmedetomidine overdose there was hypertension at high plasma concentrations. Hypertension in response to the loading dose of dexmedetomidine occurs in less than 20% of patients.[2] Some patients may develop hypotension in response to dexmedetomidine.[5] An initial fall in cardiac output was seen following the loading infusion of dexmedetomidine, which may explain the hypotension observed.[6]

Eye signs are common with the other α_2 adrenoceptor agonist-clonidine. Dexmedetomidine too was found by earlier workers to produce dose related pupillary constriction in awake volunteers.[7] The child presented with miosis with normal light reflex. An eye sign, hitherto unreported with dexmedetomidine overdose or toxicity. The possible reasons for miosis observed in awake patients due to dexmedetomidine is that it removes the inhibitory mechanisms exerted upon the pupilloconstrictor nucleus by the awake state and that it reduces peripheral sympathetic tone of the iris musculature.[8] In none of the previous reports of dexmedetomidine overdose or toxicity there is any mention of any eye-sign. Whether it is related to the speed of injection or to the dose, needs to be probed further. Unlike in previous reports, in the case described here, the bolus dose of dexmedetomidine was administered intravenously, approximately 60 times faster than the recommended time (15 min).

Adrenaline infusion was used for management of the overdose. Adrenaline in a dose of 0.03 mcg/kg/min produces significant increases in cardiac index and heart rate of 24.1% and 14.1% respectively.[9] Furthermore, it causes significant increases in heart rate and so corrects the bradycardia associated with dexmedetomidine.

The baroreceptor reflex is well-preserved in patients who receive dexmedetomidine and the reflex heart rate response to a pressor stimulus is augmented.[1] These effects have been successfully treated with atropine,

ephedrine and volume infusion.[1]

Hypoglycaemia has been reported in a child with dexmedetomidine overdose who received 60 times the recommended infusion dose.[10] The cause of hypoglycaemia was ascribed to decrease in circulating norepinephrine. Furthermore, an overdose of dexmedetomidine might inhibit β-adrenergic stimulation leading to hypoglycaemia.[10] In the case described here, blood glucose levels remained normal. This may be ascribed to the adrenaline infusion. Adrenaline, like other catecholamines is known to raise blood glucose concentration through up-regulation of glycogenolysis and gluconeogenesis.[11] Hence, the treatment strategy employed in the case, i.e., adrenaline infusion may have had the added advantage of correcting or preventing hypoglycaemia.

Atipamezole is a non-selective α_2 adrenoceptor antagonist. It rapidly reverses sedation/analgesia induced by dexmedetomidine. However, there are no reports of it being used in dexmedetomidine overdose or toxicity.[12] Moreover, at higher doses, it produces subjective symptoms, such as motor restlessness and hypertension.

Severity of side-effects of dexmedetomidine seems more related to the speed of injection and less to the actual dose administered by infusion. Furthermore, dexmedetomidine may be associated with miosis; cause for the same may be probed further.

CONCLUSION

Dexmedetomidine overdose by bolus injection can result in life-threatening bradycardia and hypotension and may also be associated with miosis. The side-effects, including hypoglycaemia, may be effectively managed by adrenaline infusion. There is a paucity of information regarding treatment options for dexmedetomidine overdose or toxicity.

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