Dexmedetomidine, an imidazole compound, is the pharmacologically active dextro-isomer of medetomidine that displays specific and selective $\alpha_2$ 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 $\alpha_2$ adrenoceptor agonist with a $\alpha_2:\alpha_1$ ratio of 1620:1.[3] $\alpha_2$-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.

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
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 dexmedetomodine injection.

His blood glucose measured soon after injection of dexmedetomodine 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 dexmedetomodine, 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 dexmedetomodine, in which higher doses ranging from 10 to 60 times the recommended infusion dose were administered by infusion. 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 dexmedetomodine, 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.

Bradyoaoida due to dexmedetomodine administration may occur with the recommended dose and definitively with overdosage. Bradycardia due to dexmedetomodine has been ascribed to central sympatholysis and peripheral ganglionic effect. Stimulation of the pre-synaptic \(\alpha_2\) adrenoceptors leads to a decreased catecholamine release. Hypotension was unusual because in previous cases of dexmedetomodine overdose there was hypertension at high plasma concentrations. Hypertension in response to the loading dose of dexmedetomodine occurs in less than 20% of patients. Some patients may develop hypotension in response to dexmedetomodine. An initial fall in cardiac output was seen following the loading infusion of dexmedetomodine, which may explain the hypotension observed.

Eye signs are common with the other \(\alpha_2\) adrenoceptor agonist-clonidine. Dexmedetomodine too was found by earlier workers to produce dose related pupillary constriction in awake volunteers. The child presented with miosis with normal light reflex. An eye sign, hitherto unreported with dexmedetomodine overdose or toxicity. The possible reasons for miosis observed in awake patients due to dexmedetomodine 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. In none of the previous reports of dexmedetomodine 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 dexmedetomodine 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. Furthermore, it causes significant increases in heart rate and so corrects the bradycardia associated with dexmedetomodine.

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

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 | 100 |
| 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 | 22 | 24 | 22 |

*Baseline value-30 min prior to incident, @Within 2 min of detected, *Adrenaline infusion started
Hypoglycaemia has been reported in a child with dexmedetomidine overdose who received 60 times the recommended infusion dose.\textsuperscript{[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.\textsuperscript{[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.\textsuperscript{[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 $\alpha_2$ adrenoceptor antagonist. It rapidly reverses sedation/analgesia induced by dexmedetomidine. However, there are no reports of it being used in dexmedetomidine overdose or toxicity.\textsuperscript{[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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**REFERENCES**

1. Gertler R, Brown HC, Mitchell DH, Silvius EN. Dexmedetomidine: A novel sedative-analgesic agent. Proc (Bayl Univ Med Cent) 2001;14:13-21.
2. Jorden VS, Pousman RM, Sanford MM, Thorborg PA, Hutchens MP. Dexmedetomidine overdose in the perioperative setting. Ann Pharmacother 2004;38:803-7.
3. Max BA, Mason KP. Extended infusion of dexmedetomidine to an infant at sixty times the intended rate. Int J Pediatr 2010;2010:1-6.
4. McGallum JB, Boban N, Hogan Q, Schmeling WT, Kampine JP, Bosnjak ZJ. The mechanism of alpha2-adrenergic inhibition of sympathetic ganglionic transmission. Anesth Analg 1998;87:503-10.
5. Venn M, Newman J, Grounds M. A phase II study to evaluate the efficacy of dexmedetomidine for sedation in the medical intensive care unit. Intensive Care Med 2003;29:201-7.
6. Bloor BC, Ward DS, Belleville JP, Maze M. Effects of intravenous dexmedetomidine in humans. II. Hemodynamic changes. Anesthesiology 1992;77:1134-42.
7. Larson MD, Talke PO. Effect of dexmedetomidine, an alpha2-adrenoceptor agonist, on human pupillary reflexes during general anaesthesia. Br J Clin Pharmacol 2001;51:27-33.
8. Phillips MA, Szabadi E, Bradshaw CM. Comparison of the effects of clonidine and yohimbine on pupillary diameter at different illumination levels. Br J Clin Pharmacol 2000;50:65-8.
9. Gillies M, Bellomo R, Doolan L, Buxton B. Bench-to-bedside review: Inotropic drug therapy after adult cardiac surgery: A systematic literature review. Crit Care 2005;9:266-79.
10. Bernard PA, Makin CE, Werner HA. Hypoglycemia associated with dexmedetomidine overdose in a child? J Clin Anesth 2009;21:50-3.
11. Brealey D, Singer M. Hyperglycemia in critical illness: A review. J Diabetes Sci Technol 2009;3:1250-60.
12. Pertovaara A, Haapalinna A, Sirvuo J, Virtanen R. Pharmacological properties, central nervous system effects, and potential therapeutic applications of atipamezole, a selective alpha2-adrenoceptor antagonist. CNS Drug Rev 2005;11:273-88.

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