

## Hypoglycemia in a Child with Tramadol Poisoning

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### ABSTRACT

Tramadol is a central acting analgesic of the opioid group used for moderate to severe pain. Tramadol overdose can be accidental or intentional and is more common in adolescent and adult males. We report the case of a 4-year-old boy presenting with hypoglycemia following tramadol poisoning with loss of consciousness and convulsion; he was managed conservatively and made remarkable improvement without any sequelae.

**Key words:** Analgesic, hypoglycemia, overdose, tramadol

ملخص البحث :

يستخدم عقار (Tramadol) دواءً مسكناً لعلاج الآلام الشديدة. وتعتبر الجرعة المفرطة من هذا العقار أما مقصودة أو بطريق الخطأ، وتكثر لدى المراهقين والبالغين. يعرض الباحثون حالة لطفل في الرابعة من العمر يعاني من هبوط في سكر الدم بعد تناوله جرعة مفرطة من هذا الدواء مما أدى إلى فقدان وعي الطفل وإصابته بتشنجات. وقد تم علاجه بدون مضاعفات.

### INTRODUCTION

Tramadol is a synthetic centrally acting analgesic, which has two stereoisomers with dual mechanism of action-opioid and monoaminergic. Its major metabolite O-desmethyl tramadol (M1) has a weak affinity on the  $\mu$ -opioid receptors (MORs) as an agonist. The monoaminergic activity of tramadol acts synergistically on serotonergic and noradrenergic mechanisms of pain transmission. More specifically, tramadol enhances spinal pain inhibitory pathways by inhibiting neuronal re-uptake of serotonin (5-hydroxytryptamine [5-HT]) and noradrenaline, stimulating 5-HT release.<sup>[1]</sup> Tramadol poisoning is rare in children because it is not commonly used for children. Common presentations include respiratory and central nervous system (CNS) depression.<sup>[2]</sup> However, we highlight the case of a 4-year-old boy,

who in addition to the above-mentioned presented with hypoglycemia.

### CASE REPORT

A 4-year-old boy was referred to our pediatric emergency unit with the complaint of unintentionally ingesting 6 tablets of (200 mg tablets) tramadol an hour before presentation. He was given lemon drink at home before presenting to the emergency unit. He vomited several times and convulsed twice on the way to the referring hospital and lapsed into unconsciousness.

On examination, he was unconscious with Glasgow coma scale score of 3/15, and pupils were 1 mm in size bilaterally, respiratory rate of 19/min with oxygen saturation of 85% (in room air); the pulse rate was 110 b/min, blood pressure-90/60 mmHg. He was hypoglycemic with random blood sugar (RBS) of 2.0 millimoles/liter. Electrocardiogram showed normal sinus rhythm, and other laboratory investigations, which included full blood count, electrolytes, urea and creatinine and liver function tests were normal.

Hypoglycemia and hypoxia were corrected with dextrose infusion (RBS-5.5 mm/L) and intranasal oxygen (SPO<sub>2</sub> 96%) respectively. He regained consciousness 7 h after admission with no new seizures recorded. He

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was discharged home after 24 h to return for follow-up 72 h later. No neurologic deficit was documented on the follow-up visit.

## DISCUSSION

Tramadol hydrochloride is a central acting analgesic used for the control of moderate to severe pain in adults and adolescents, but not routinely recommended for children because its safety and efficacy in patients under 16 years of age have not been established. However, pediatric therapeutic dose of 1-2 mg/kg/dose and a maximum dose of 8 mg/kg/dose or 400 mg/day are occasionally prescribed.<sup>[3,4]</sup>

Few cases of overdoses with tramadol have been reported. Ingested doses with some fatalities have ranged from 3 to 5 g with the lowest dose reported as between 500 and 1000 mg in a woman who weighed 40 kg.<sup>[5]</sup> The International Association of Forensic Toxicologists reported blood levels in adults ranging from 0.1 to 0.8 mg/L, 1-2 mg/L and greater than 2 mg/L represent therapeutic, toxic and lethal doses respectively.<sup>[6]</sup> However, we were unable to measure the serum concentration in the index case due to nonavailability of such services.

Apart from its analgesic effect, tramadol hydrochloride may produce a constellation of symptoms such as dizziness, somnolence, nausea, constipation, sweating and pruritus similar to those of other opioids, but in contrast to morphine, tramadol rarely causes histamine release. At therapeutic doses, tramadol hydrochloride has no effect on heart rate, left-ventricular function or cardiac index. Constipation and respiratory depression are less common but may occur in overdose as was reported in the index case. Tramadol may increase the risk of seizures especially in those with a history of epilepsy, but is rarely associated with idiopathic seizures except at very high doses<sup>[1]</sup> as was witnessed in this case. Previous reports have shown that tramadol-induced seizure is dose dependent. However, there is no direct correlation of blood concentration to occurrence or severity of seizure.<sup>[7]</sup> Tramadol overdose can also present with features of serotonin syndrome, which is potentially life-threatening especially when used concomitantly with serotonergic drugs and with drugs which impair the metabolism of tramadol. However, there was no such association in the case under discussion. Hypoglycemia is an uncommon presentation of tramadol toxicity; though there have been a few reported cases in adults:<sup>[8]</sup> the case of hypoglycemia in a suicidal 54-year-old

woman, with a past history of partial hepatectomy following hepatic metastasis of gastrointestinal stromal tumour, who ingested 3,000 mg of tramadol.<sup>[9]</sup> The French pharmacovigilance (Adverse Drug Reports) database also reported 2 cases of hypoglycemia following tramadol poisoning, one in an 88-year old nondiabetic woman and the other in an 8-year-old diabetic girl.<sup>[10]</sup> However, unlike our patient, these patients had other co-morbidities which affected the control of glucose metabolism with the risk of hypoglycemia. Studies in rats have shown that activation of MOR, which is the principal target of tramadol found mainly in CNS and liver hepatocytes results in an increased glucose utilization and/or reduction of hepatic gluconeogenesis probably through a noninsulin-mediated mechanism causing hypoglycemia.<sup>[11]</sup> Furthermore, serotonin increases insulin concentration in mice; induce  $\beta$  endorphin release and stimulate muscle glucose utilization through the activation of MORs by a mechanism which is neither dose nor insulin-dependent. However, a few cases of hypoglycemia associated with selective serotonin re-uptake inhibitor treatment have been reported.<sup>[12]</sup> However, what is not clear is the role this played in this case since other clinical features of serotonin syndrome were absent.

Treatment of the index case was mainly supportive. We avoided giving naloxone, fearful that it might aggravate the seizure. However, he was closely monitored, and he improved remarkably without any neurologic complications.

## CONCLUSION

Hypoglycemia may occur in patients with tramadol overdose and though it is not very common, physicians should be on the lookout for it in any patient with acute tramadol poisoning.

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