

## Severe acute lactic acidosis and hypoglycemia due to isolate tramadol poisoning

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apeutic dosages include nausea, dizziness, somnolence, drowsiness, enhanced sweating, vomiting and dry mouth.<sup>12,13</sup> Both in therapeutic and toxic doses, seizure and apnea have been reported as the most severe adverse reactions,<sup>9,10,14</sup> along with hypoglycemia, hyperamylasemia, liver and kidney dysfunctions.<sup>15,16</sup> As such, evaluation of laboratory findings including plasma electrolytes, blood gas analysis, kidney and liver function tests play a pivotal role for patient monitoring in the suspicion or confirmed diagnosis of tramadol poisoning and/or toxicity.

We describe here a case of severe lactic acidosis triggered by a tramadol intentional overdose.

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### Abstract

The article describes a case of severe acute lactic acidosis and hypoglycemia after intentional ingestion of tramadol overdose.

### Introduction

Tramadol is a widely used synthetic, centrally acting analgesic with both opioid and non-opioid actions.<sup>1,2</sup> The drug has low affinity for  $\mu$ - and  $\kappa$ -opioid receptors, and exerts inhibitory effects of the reuptake of both norepinephrine and serotonin (5-hydroxytryptamine).<sup>2</sup> It has also been demonstrated that tramadol stimulates the dopamine (D2) receptors and inhibits the gamma amino butyric acid (GABA) release in central nervous system.<sup>3,4</sup> This pharmacodynamic complexity translates into a wide range of clinical actions and even toxic effects, which are often not fully predictable. Briefly, tramadol is an increasingly used analgesic drug, available as both parenteral and enteral formulations, originally introduced in Germany in the late 1970s as a weak opioid with atypical clinical profile.<sup>5</sup> Common therapeutic doses of tramadol are comprised between 100 and 400 mg/day.<sup>2,6</sup>

Up to 90% percent of tramadol is excreted in the urine, ~30% of which as unmetabolized drug. About 10% is metabolized by N- and O-demethylation, followed by conjugation with glucuronic acid and sulfate. O-desmethyltramadol (ODT) is an active metabolite displaying 2 to 4 times the analgesic activity of the parent drug and longer half-life, so sharing also some toxic effects of the parent compound.<sup>7,8</sup>

Soon after the approval, tramadol abuse, misuse, and overdose have been increasingly observed worldwide due to its opioid properties.<sup>9-11</sup> The most frequent side effects at ther-

### Case Report

A 33-year-old man was brought to the Emergency Department (ED) of the Academic Hospital of Parma for stupor and respiratory depression. He was usually taking clonazepam, trazodone and biperidene, all administered at appropriate dosage by prison officers, since the time he has been jailed, 3 years before. At ED presentation the patient was unresponsive, midriatic, bradypneic, normotensive (110/60 mmHg). No convulsions have been witnessed and/or recorded. Immediately after ED admission, abundant vomiting of gastric juice started. The patient was hence immediately treated with intravenous (i.v.) glucose 33% 20 mL, naloxone 0.8 mg and flumazenil 1 mg, obtaining only a partial response. An additional dose of naloxone 0.8 mg i.v. was then administered, obtaining a relative full recovery of consciousness. A gastric lavage and an administration (through naso-gastric tube) of activated charcoal 50 g were then established, followed by administration of magnesium sulphate 30 g. Two hours later the patient become again unresponsive, thus leading to the additional administration of naloxone 0.8 mg, which was followed by prompt clinical response. The essential blood tests were characterized by: neutrophilic leukocytosis (WBC  $21.1 \times 10^9/L$ ; neutrophils  $16.8 \times 10^9/L$ ); hypoglycemia (serum glucose 39 mg/dL); acute renal failure (serum creatinine 2.7 mg/dL; eGFR assessed with to the CKD-EPI equation, 32 mL/min); slight increase of lipase (64 U/L; upper limit of the reference range, 58 U/L); moderate increase of troponin I (1.2 ng/mL, upper limit of the reference range, 0.05 ng/mL); moderate and transient increase of alanine-aminotransferase (ALT; 471 U/L; upper limit of the reference range, 40 U/L); slight positivity for quantitative benzodiazepines and/or their metabolites assay in urine; ethanol was absent in the blood sample. We did not search for salicylates, metformin, and iron (all potential triggers of lactic

acidosis), since the patient did not have access to these drugs (he was jailed, as previously reported). The value of creatine kinase (CK), a well-established biomarker of rhabdomyolysis (*i.e.*, a frequent complication of opioid and tramadol overdose),<sup>17,18</sup> was normal. The electrocardiogram (ECG) remained always normal. An echocardiogram, prescribed to investigate the nature of the troponin increase, failed to show contractility defects. A severe and worsening lactic acidosis, initially associated with respiratory acidosis, was however observed (Table 1), and slowly improved during the first 24 hours of hospital staying.

Approximately 2 hours after ED admission, a prison officer brought to the emergency physician six empty bottles of tramadol (drops) detected in the jail cell of the patient, corresponding to a total dosage of ~6000 mg. No other substances were found in the prison. The officer also informed us that the patient ate some food (an usual dinner) about 7 hours before the clinical manifestations. He also confirmed, with provisional documentation, that the patient did not suffer from other diseases. A frozen vial of the patient's blood was then sent to a specialized laboratory for assessment of tramadol and O-demethyl-tramadol (the main metabolite), which yielded blood concentrations of 26.1 mg/dL of tramadol (largely exceeding the serum therapeutic range of 0.28-0.61 mg/dL) and 5.3 mg/dL of O-demethyl-tramadol, respectively.<sup>19</sup> Interestingly, it was lately found that the patient had obtained the tramadol bottles by another jailed man, who was using the drug for chronic post-traumatic pain.

During the hospital staying the patient underwent a magnetic resonance imaging (MRI) of the brain, heart and abdomen, which did not show any pathological findings.

## Discussion

Hypoglycemia has been extensively described as a possible, albeit rare, adverse effect of tramadol, even at therapeutic dosages, surprisingly especially in patients without a history of diabetes mellitus, and not taking anti-diabetic drugs.<sup>20</sup> Our case is, however, the very first case report of severe acute lactic acidosis triggered by tramadol, although in presence of concomitant transient and promptly corrected hypoglycemia.

Theoretically, some metabolic interactions between tramadol and the other drugs taken by the patient (in particular clonazepam that is extensively metabolized in the liver) are conceivable, but unfortunately it was impossible for us to demonstrate this possibility.

It is also conceivable that some form of interaction between tramadol and trazodone (chronically taken by the patient at therapeutic dosages) could be occurred, but we obviously did not have the resources to demonstrate it.

A single case of tramadol toxicity leading to refractory shock and asystole has been previously described.<sup>21</sup> The patient, however, took a massive overdose of tramadol, alongside with hydroxyzine, gabapentin, and clonazepam. He had a long-lasting seizure, hypotension, hypothermia, and a prolonged QTc at the ECG, thus showing several clinical characteristics that clearly distinguished he from the case here described.

## Conclusions

In conclusion, tramadol poisoning should always be considered in the differential diagnosis of metabolic (most of all lactic) acidosis, especially when obvious or alternative diagnoses are unlikely.

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**Table 1. Blood gases and acid-base balance values during the first day of hospital staying.**

	Time (h.min)					
	9.49	11.01	12.13	12.51	17.27	22.05
pH	7.007	6.979	7.054	7.19	7.37	7.42
pCO <sub>2</sub> (mmHg)	60.1	67.7	48.1	45.2	44.9	44.8
pO <sub>2</sub> (mmHg)	79.1	78.3	75.5	86.1	91.4	94.3
HCO <sub>3</sub> (mmol/L)	14.3	13.7	12.8	17.4	19.2	23.7
BE (mmol/L)	-18.2	-18.3	-17.9	-8.1	-4.9	-1.1
Na (mmol/L)	145	142	143	144	142	143
K (mmol/L)	3.8	4.5	4.8	4.7	4.6	4.6
Anion gap (mmol/L)	19.9	16.3	17.0	12.5	11.7	11.2
Lactate (mmol/L)	10.6	11.3	10.4	7.3	3.8	2.1
Glucose (mg/dL)	64	88	99	101	98	97

BE, base excess.

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