Fatal intoxication due to tramadol alone
Case report and review of the literature

Koen De Decker*, Jan Cordonnierb, Werner Jacobsc, Vera Coucked, Paul Schepensd, Philippe G. Jorensa

*a Department of Critical Care Medicine, University Hospital of Antwerp, Edegem, Belgium
b Chemiphar Toxicology Laboratory, Bruges, Belgium
c Department of Forensic Pathology, Antwerp University Hospital, Edegem, Belgium
d Toxicological Centre, Antwerp University, Wilrijk, Belgium

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Abstract
Poisoning may also lead to both coma and multiple organ failure, also in youngsters without a known major medical history. As not all toxic agents are routinely screened when a poisoning is suspected, it is useful to consider less frequently encountered poisons in certain cases. We describe the occurrence of asystole and multiple organ failure which occurred in a young man after a suspected tramadol overdose. The tramadol concentration on admission in the ICU was indeed 8 mg/ml (mg/l), far above the therapeutic range. Subsequently, the patient developed severe acute liver failure, finally leading to death. Post-mortem toxicology did not reveal any other poison responsible for this unfavourable course as only very high serum and tissue tramadol and desmethyltramadol concentrations were found. Only a few fatal poisonings attributable to tramadol alone, as observed in our case, have been reported. An overview of these cases is presented.

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1. Introduction

The opioid analgesic tramadol was initially introduced in Germany in 1977. Because of its limited abuse potential it has been prescribed extensively, both for patients in the postoperative period and also in pain clinics for more chronic pain syndromes [1]. Tramadol has a dual mechanism of action: a weak agonistic effect on the μ-opioid receptor as well as an inhibition of neurotransmitter reuptake (mainly serotonin and norepinephrine). Its analgesic potency is similar to codeine and meperidine [1,2].

Frequently reported side effects include nausea, vomiting, drowsiness, vertigo, constipation, headache and somnolence. In case of poisoning however, more rare and severe complications may occur including seizures [1]. Symptoms generally resolve within 24 h and even accidental ingestions in children are well tolerated.

We report on the case of a young patient with known tramadol use, who was found unconscious and presented with asystole. After a successful resuscitation, signs of multiple organ failure and especially massive hepatic failure occurred, finally leading to death. Blood and urine analysis revealed a tramadol intoxication, which was confirmed at the medicolegal autopsy. We review the literature on fatal intoxications only attributable to a tramadol overdose, which turned out to be a rare entity.

2. Case report

A 28-year old Caucasian man, with a medical history of Munchausen’s syndrome and stress incontinency, was admitted in the evening hours at the urology ward for a series of diagnostic examinations. He consulted a psychologist on a regular basis and was treated with tramadol for several months because of rather vague abdominal complaints. He was not taking any other drugs or herbal medicines. According to the
other patients on the ward, he had ingested a benzodiazepine before going to sleep and snored all night. In the morning, one of his fellow patients witnessed apnea and alerted the nurses and the medical team. On arrival, asystole was observed and advanced life support was started. An arterial blood gas taken during CPR showed extreme acidosis and hypoglycaemia (5 mg/dl, normal value 75–110 mg/dl), for which hypertonic glucose and sodium bicarbonate were administered. Cardiac output was restored within 10 min and the patient was admitted to the intensive care ward. On arrival the Glasgow Coma Scale score was 3/15, no pupillary reactions neither reflexes could be found. An ECG showed sinus tachycardia and a transthoracic echocardiography showed no abnormalities. A chest X-ray revealed a consolidation of the left lower lobe necessitating a bronchoscopy.

Blood-, urine- and gastric lavage samples were taken for clinical toxicological screening. An arterial blood gas reconfirmed an extreme metabolic acidosis and the lab results suggested acute hepatic as well as acute renal failure. Routine clinical toxicological screening of both serum and urine revealed neither the presence of potentially toxic drugs nor high or toxic levels of other drugs. An extensive GC–MS (gas chromatography–mass spectrometry) analysis of the serum on admission at the ICU showed only the presence of tramadol. In view of a proposed availability of arsenic by the family, arsenic poisoning was considered. This was excluded by the absence of toxic arsenic serum and urinary levels. A pulmonary artery catheter was inserted to guide fluid and inotropic therapy. The patient was ventilated in a pressure-controlled mode.

Because of progressive hepatic failure, with ammonia levels as high as 175 IU/l, a liver biopsy was performed the next day, showing both steatosis and centrolobular necrosis.

Therapy was mainly supportive including the initiation of antibiotics, pulmonary artery catheter guided fluid management, inotropics and vasopressor therapy, enemas with lactulose because of high ammonia levels as well as correction of coagulation abnormalities. Nevertheless, we were unable to prevent acute renal failure, progressing to multiple organ failure of which the patient died two days later.

3. Methods and materials

Systematic toxicological analysis was performed on the post-mortem samples to investigate for illegal and prescribed drugs, alcohol, volatile substances and other poisons. Screening for the presence of drugs of abuse in urine and serum was carried out using fluorescence polarization immunoassay (FPIA) on an Abbott ADx analyzer. Radioimmunoassay (RIA) was used to screen for LSD in urine and benzodiazepines in blood. Presumptive colour tests (according to the manufacturer’s specifications) were used to detect salicylates, paracetamol, phenothiazines and imipramines. UV spectrophotometry was used for quantification of carbon monoxide and cyanide in blood. Thin layer chromatography–mass spectrometry and HPLC-DAD were used to screen for the presence of acidic (blood), neutral (blood) and basic drugs (urine and stomach content). Screening for the presence of basic drugs in urine and stomach content was performed by GC–MS and in blood by HPLC-DAD.

4. Results

An autopsy revealed pulmonary edema, diffuse hemorrhagic mucosa of the gastrointestinal tract and a shock liver. Microscopy findings were all characteristic of multiple organ failure: alveolar hemorrhages in the lung, pericentral ischemia of the liver and acute tubular necrosis of the kidneys. Toxicological analysis of serum and gastric lavage specimens, obtained on admission at the ICU revealed a tramadol concentration of 8 and 400 mg/l, respectively. Post-mortem analysis by GC–MS (liver and kidney) and HPLC-DAD (blood) analysis [3,4] detected both tramadol and metabolite N-desmethyltramadol in the blood, liver and kidney; tramadol concentrations were 5.2 mg/l, 6.5 µg/g tissue 4.5 µg/g tissue respectively; N-desmethyltramadol was not quantitated.

5. Discussion

The central acting analgesic tramadol has been used increasingly the last two decades because of its low abuse potential and because less respiratory depression is observed in comparison with the classical opioid analgesics, such as morphine. It provides relief from moderate to severe pain at oral doses of 50–100 mg QID. Thirty per cent of the drug is excreted through the kidneys in an unchanged manner, while the remaining is metabolised by N- and O-demethylation, followed by conjugation with glucuronic acid and sulphate [5]. The peak serum level is reached after 2–3 h. The active metabolite, O-mono-desmethyltramadol, has a longer half-life and is apparently two to six times more potent than the parent drug [5,6]. This metabolite is also believed to cause some of the toxic side effects of the drug [6].

Tramadol levels can be determined by both gas chromatography–mass spectrometry and HPLC-DAD [2–4,6]. Therapeutic blood levels in adults are believed to range from 100 to 300 ng/ml [5,7,8]. In lethal cases, additional tissue sampling may add proof of tramadol intoxication.

Initially the manufacturer claimed a low incidence of typical opioid side effects. Indeed, in view of the (+)-enantiomer’s low affinity for the µ-opioid receptor, tramadol was also originally thought to have a low potential for abuse, tolerance and dependence [6,9]. Nevertheless, recent reports describe the potential for abuse and the occurrence of seizures and anaphylactoid reactions. Currently tramadol is not recommended for patients with past or present histories of addiction to or dependency on opioids, in patients with allergies to tramadol or other opioids, and in patients taking concomitant drugs that may reduce the seizure threshold (such as tricyclic antidepressants and selective serotonin reuptake inhibitors). Another possible side effect, that has received little attention, is hypoglycaemia. This was particularly demonstrated in rats: the activation of opioid µ-receptors by tramadol, increased the utilization of glucose and/or decreases the hepatic gluconeogenesis causing low plasma glucose levels in diabetic rats [10]. After repeated oral administration in humans [11], the main sings of intoxication
include central nervous symptoms, from vomiting to convulsions or eventually anoxic brain damage [12].

Fatal reports after tramadol poisoning and overdose have been seldomly reported. Moreover, the number of patients in whom death could be attributed to tramadol poisoning alone is limited to 8, including this case, as summarized in Table 1 [3,8,13–15]. In only one other case than ours, the clinical course before death was known [15]. As blood concentrations in tramadol-associated deaths overlap with subjects arrested for tramadol-associated impaired driving [3], in moderate excess the drug might not be a principle cause of death in suicidal or accidental cases.

Indeed, virtually all reported fatal tramadol poisonings have been reported in conjunction with the detection of other drugs, such as propanolol, trazodone, alcohol and especially central nervous system depressants, particularly benzodiazepines, barbiturates and drugs with serotonin effects [2,4,6,16–18]. Clarkson et al. reviewed a very large series of 66 deaths in which tramadol was detected in the decedent’s blood, in order to assess the role tramadol was determined to have played [3].

Tramadol was consistently found together with other analgesics, muscle relaxants or CNS depressant drugs, apart from the cases summarized in Table 1.

Our patient died as a consequence of multiple organ failure, including hepatic insufficiency as revealed by hepatic failure during the ICU observation and massive hepatic necrosis at autopsy [19]. Liver failure following accidental tramadol poisoning has been reported once [5]. Management in our patient was mainly supportive and no literature is available on the usefulness of molecular absorbent recirculating systems or eventually anoxic brain damage [12].

In conclusion, after its introduction in the 70s, tramadol gained great interest because of its low abuse potential, but in rare cases overingestion may lead to fatal complications. Therefore, early diagnosis is very important. As no data on urgent liver transplantation are available, the management of this intoxication associated liver failure is limited to supportive interventions.

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References


