

CASE REPORT

Death due to anaphylactic shock secondary to intravenous self-injection of Toradol[®]: A case report and review of the literature

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A fatality due to the intravenous self-injection of Ketorolac (Toradol[®]) is reported. Ketorolac is a nonsteroidal anti-inflammatory drug (NSAID) with marked analgesic activity. There is limited information of fatalities attributed to ketorolac toxicity. Here we report the case of a 53-year-old woman with a medical history of depression that was found deceased at home with no evidence of trauma or injuries. Near the body, a syringe and three empty vials (30 mg) of Toradol[®] were found. A fresh needle mark on the right arm was noticed. Toxicological analyses were performed using a gas chromatography-mass spectrometry (GC/MS) technique. The estimated ketorolac concentration in the blood was 8 µg/ml; urine and gastric content were negative for this compound. Based on the autopsy, histologic findings and toxicological results of anaphylactic shock associated with ketorolac self-administration was assumed to be the underlying pathophysiological mechanism of death and the manner, suicide.

Keywords Ketorolac; Acute intoxication; Anaphylactic shock; Anaphylaxis; GC/MS-MS; Forensic autopsy; Postmortem investigation

Introduction

Ketorolac, a prototypical nonsteroidal anti-inflammatory drug (NSAID), is used for the short-term management of acute pain. The drug is not indicated for use in minor or chronic painful conditions (1). Ketorolac provides similar analgesic efficacy to that of standard dosages of morphine and pethidine (meperidine), as well as less frequently used opioids and other NSAIDs (2,3). Haematic concentration reported after therapeutic dosage of ketorolac are in the range 0.22–3.5 µg/ml (4) and 0.87–4.5 µg/ml (5). Blood values of 4–4.5 µg/ml 30–60 min after the administration of 60 mg of intra-muscular (i.m.) ketorolac are also reported (6).

Ketorolac shares the toxic profile of other NSAIDs; adverse reactions to ketorolac are usually mild, dose-related, and reportedly occur in about 39% of patients. The most common adverse effects associated with short-term i.m. or oral therapy, are observed on the nervous and gastro-intestinal (GI) systems (1).

There is scarce information available on deaths caused by ketorolac treatments. Logan et al. described a death occurring shortly after the administration of an intramuscular injection of ketorolac. Death was attributed to an adverse reaction to the drug, resulting in anaphylaxis and cardiac arrest (7). In addition, through December 4, 1992, the manufacturer (AHFS Drug Information 2004) has accumulated information on 73 spontaneously reported deaths in patients receiving ketorolac (1).

The present article reports a fatality involving the intravenous (i.v.) self-injection of doses of ketorolac yielding plasma levels of 8 µg/ml. Blood specimens were analyzed by gas-chromatography coupled to mass-spectrometry.

Case history and autopsy findings

A 53-year-old woman with a medical history of depression was found deceased in the bedroom of her home with no evidence of trauma or injuries. Near the body, a syringe and three empty vials (30 mg) of Toradol[®] were found. A fresh needle mark on her right arm was immediately noticed.

The cadaver was refrigerated at 3°C until autopsy which was performed 48 hours after the discovery of the body.

The cadaver was 162 cm tall and weighed 48 kg. Postmortem rigidity was observed in such joints as the jaw, neck, elbow,

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and knee. Postmortem hypostasis, dark red in color, was also noted on the dorsal surface of the body. The time since death was estimated at a minimum of 2–3 days. No trauma or signs of violence were observed. The face was slightly congestive and cutaneous erythema of anterior region of the neck was noticed. Internally, every organ was moderately congestive. There was no skull fracture, nor any epidural, subdural, or subarchnoid hemorrhage. The brain was slightly atrophic and edematous (brain weight 1120 g). Laryngeal and pharyngeal moderate oedema was found. The heart weighed 300 g: the right and left coronary artery ostia originated unremarkably from the aorta, with diameters of 3 mm each. The left main coronary artery, circumflex artery, and right coronary arteries appeared normal. No evidence of significant atherosclerosis or thrombosis was present. The right and left lungs each weighed 800 g and were both edematous and congested with

pleural petechiae. The stomach contained scarce white material partly fluid. The liver and the spleen appeared congested. The rest of the organs were unremarkable. Heart blood, femoral blood, urine, and stomach content specimens were collected for toxicological analysis. Histological sections confirmed the presence of mild laryngeal oedema. The lungs were congested and mildly oedematous. There was no evidence of old or recent myocardial infarction and no evidence of myocarditis. The bronchi demonstrated mucosal oedema, inflammation with eosinophilia, and epithelial sloughing.

Toxicological analyses

Toxicological analyses were performed on heart blood, urine, and gastric content collected during the autopsy and stored

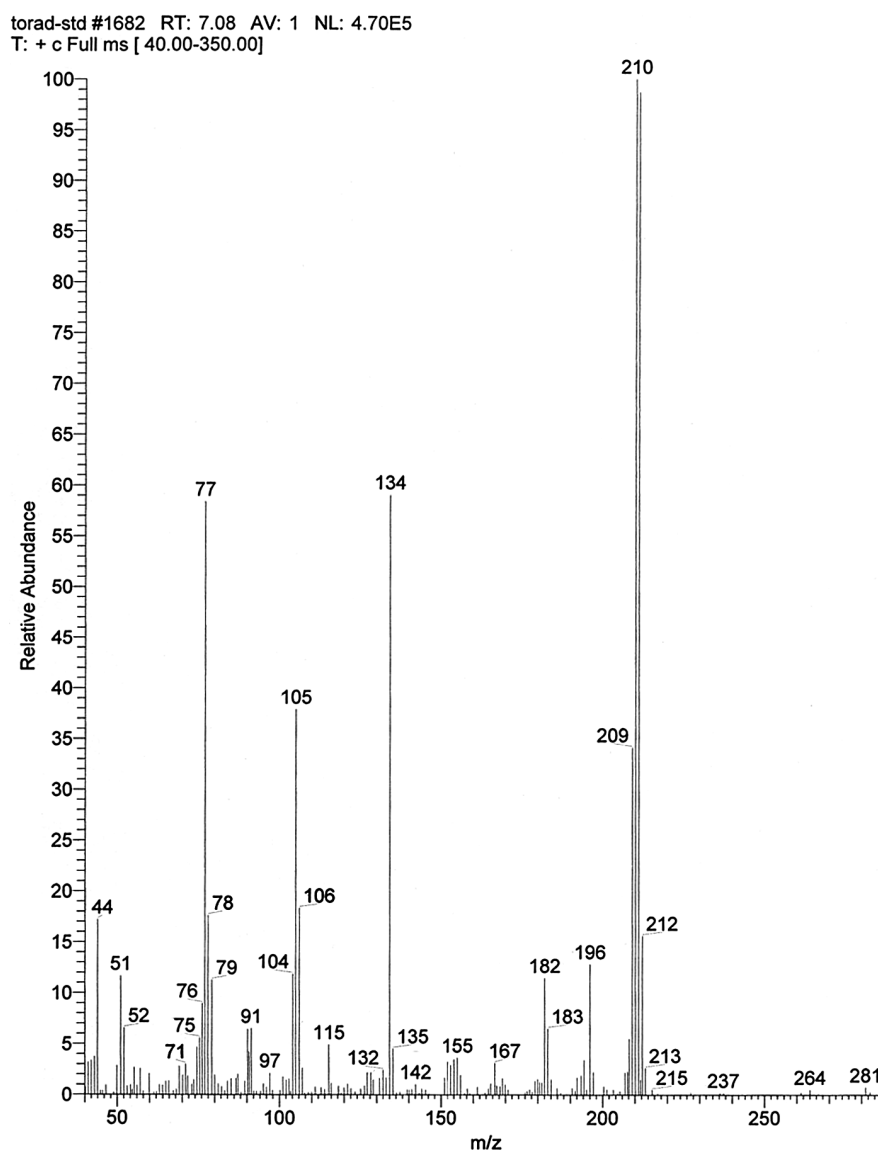


Fig. 1. Chromatographic pattern of a blood sample extract submitted for GC/MS analysis.

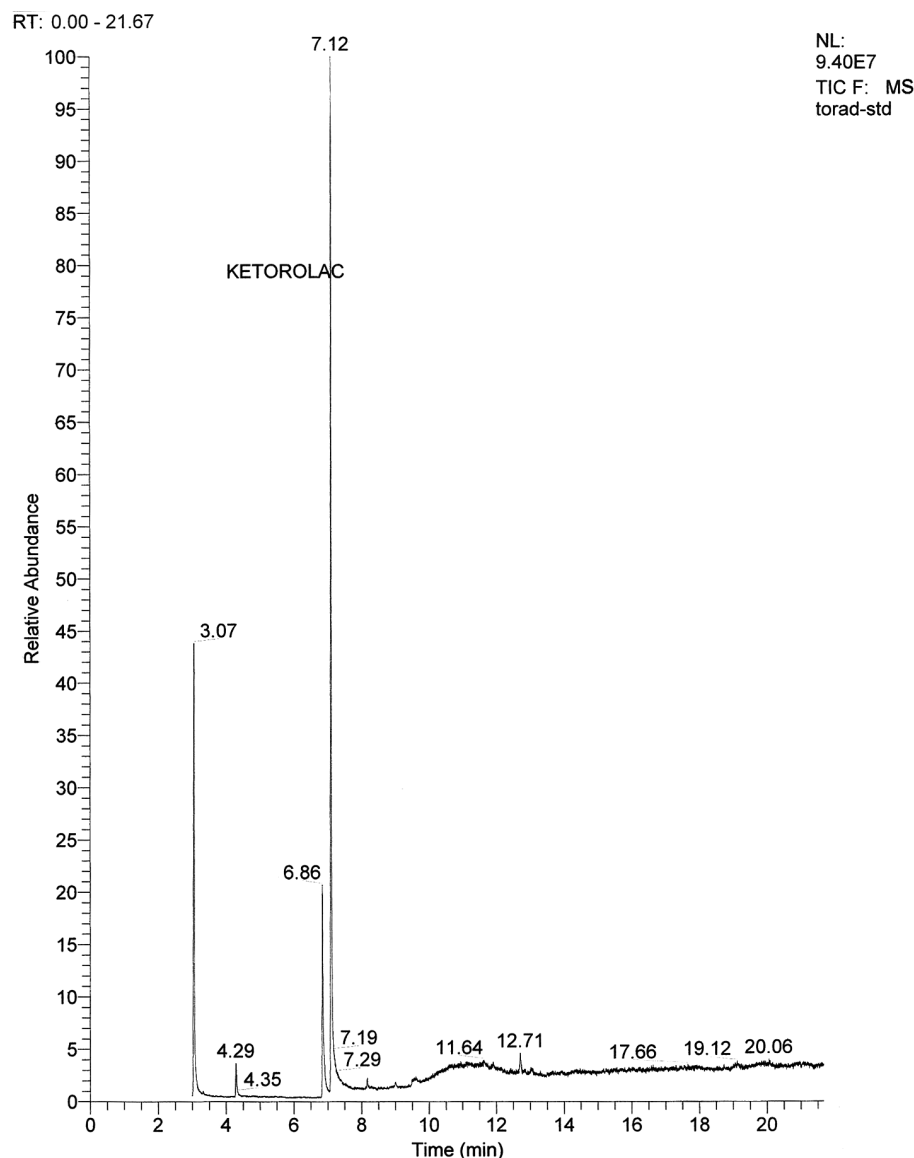


Fig. 2. Mass fragmentation of ketorolac (analytical conditions are reported in the text).

frozen until the analysis. Toxicological screening for alcohol, benzodiazepines, cannabinoids, opiates, methadone, tricyclic antidepressant, and amphetamines was negative. In particular for ketorolac, 2 ml of each biological sample was processed by liquid-liquid extraction (chloroform-isopropanol 9:1) at pH 8. After centrifugation, the organic phases were collected and evaporated to dryness under nitrogen stream. Thereafter, the residues were derivatized adding 30 μ l of BSTFA and kept at 80°C for 30 minutes. After the derivatization step, samples were submitted to GC/MS analysis. Quantitative analyses were performed on a Hewlett Packard 5890 gas chromatograph fitted with a split-splitless injector (270°C) equipped with a HP1 capillary column (12 m x 0.2 mm i.d.) 0.3 μ m film thickness methylsilicone. An external standard of ketorolac was used. Both standard and samples were run through a linear program from 120°C to 280°C at 10°C/min

increments with a 5 min. isothermal. Helium was employed as the carrier gas at a column head pressure of 10 psi. The capillary column was connected to a mass analyzer (HP 5971A) operated by electron impact (70 eV) in selective-ion-monitoring. Ions monitored for ketorolac were 210 m/z and 211 m/z.

Calibration curves were obtained from a blank biological sample (blood and urine) spiked with a ketorolac concentration in the range 2.5–5–10 μ g/ml, and treated as previously described for the samples.

Results and discussion

Autopsy revealed no evidence of significant trauma, injuries, and no natural disease relevant to the death was found. The

total amount of drug administered was unknown, but three empty vials (30 mg) of Toradol® were found near the body; the presence of a syringe and a fresh needle mark on the right arm of the victim were indicative of intravenous injection. Toxicological findings on blood revealed the presence of ketorolac with no other drug associated. Quantitative results obtained with external standard calibrator are shown in Figure 1. The estimated ketorolac concentration in the blood was 8 µg/ml; urine and gastric content were negative for this compound.

For the approved indications, a single i.v. or i.m. dose of 30 or 60 mg, respectively, is recommended in adult patients. The manufacturer also recommends that multiple-dose parenteral therapy with ketorolac is initiated and continued with i.m. or i.v. dosages of 30 mg every 6 hours in adults. The maximum daily dose should not exceed 120 mg. For multiple-dose parenteral therapy in geriatric patients and adults weighing less than 50 Kg, the manufacturer recommends a dose of 15 mg every 6 hours; the maximum daily dose in these patients should not exceed 60 mg (1).

The profile of target organ toxicity of ketorolac is similar to those of other NSAIDs; most clinically important adverse events affect the GI and/or renal function. In a case-control study on 1,505 patients receiving ketorolac, Garcia Rodriguez et al. estimated a 5-fold increase in the risk of gastrolesive events compared to all other NSAIDs (8); such level of excess risk was not confirmed by Strom et al. (9), who only noted an increased risk in elder subjects or in patients receiving high dosages for more than 5 days. Acute renal failure may occur after treatment with ketorolac, but it is usually reversible upon drug discontinuation (2,10).

Apart from GI and other organ toxicity, which should be classified as dose-related type A reactions (11), ketorolac has also been implicated in hypersensitivity type B reactions (2). Chen and Bennet reported ketorolac-induced bronchospasm in an aspirin-intolerant patient (12). Goetz et al. reported a case of anaphylactoid reaction to parenteral ketorolac in a patient with no prior history of allergies or risk factors associated with NSAID-induced hypersensitivity reactions (13).

Limited information is available on the acute toxicity of ketorolac. The acute lethal dose of ketorolac in humans is not known. The LD₅₀ of the drug given by the oral route is 200 mg/Kg in mice (1). In rats, mice, and monkeys, single oral ketorolac doses exceeding 100 mg/Kg produced diarrhea, pallor, labored breathing, rales, vomiting, and decreased activity (1).

Daily parenteral ketorolac dosages of 360 mg (three times the maximum daily recommended dose) for 5 days resulted in abdominal pain and peptic ulcers, which healed after drug withdrawal. Metabolic acidosis following intentional overdose of ketorolac (amount of drug not specified) have also been reported (1).

Despite a high incidence of serious adverse events associated to ketorolac administration, we were able to find only one report in the literature of a fatality caused by ketorolac (7). Our case shares some similarities to that described by Logan, although in the latter, the drug was found to be administered by the i.m. route.

In our case, the autopsy, histologic findings and the results of toxicological analyses reported are consistent with a fatal anaphylaxis associated to ketorolac self-injection. In fact, the estimated dosage (i.e., three times the usual dose for single administration) does not exceed by a larger extent the therapeutic dosage, and has been reported to be associated to mild, transient toxic events. We also consider that no tissue or organ damage reminiscent of dose-related ketorolac toxicity (i.e., GI bleeding, renal lesion, etc.) has been observed at autopsy.

Postmortem findings in our case, even in the absence of anaphylaxis-related substances in the serum, fulfill the diagnosis of an anaphylactic death. In fact, we found a non-specific pulmonary congestion, oedema, upper airway oedema, presence of petechial haemorrhages (suggesting an asphyxial component to the death), and a brain swelling suggestive of cerebral hypoxia.

In the literature there are only single case reports (14–17) describing postmortem findings after anaphylactic deaths; the only systematic study (18) concludes that no specific findings are present at necroscopy in most cases of fatal anaphylaxis; this is particularly true in the case of rapid onset of shock, such as in the case presented here.

Cases of anaphylactic reactions to parenteral ketorolac in patients with no prior history of allergies or risk factors associated with NSAID-induced hypersensitivity have been described before. Scala et al. (19) hypothesized that a type I hypersensitivity to ketorolac was the mechanism involved in this type of anaphylactic reaction.

The present report confirms previous observations and raises a concern on the fact that hypersensitivity to this compound – administered in the range of therapeutic doses – may have fatal effects. Our report adds further important information on the risk-benefit profile of ketorolac, and notes the need of a careful anamnesis for drug hypersensitivity in patients to be treated with this drug, especially in light of the increased use of injectable ketorolac in the ambulatory setting, as well as of the availability of oral formulation.

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