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CASE REPORT

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The distribution of laudanosine in tissues after death from atracurium injection

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Abstract A case is presented involving an acute fatality resulting from self-administration of atracurium, a muscle relaxant by a 45-year-old nurse. In the body, atracurium undergoes a spontaneous non-enzymatic degradation to laudanosine and an acrylate moiety. Laudanosine was quantified using gas chromatography coupled to mass spectrometry after extraction with chloroform-isopropanol-n-heptane (50 : 17 : 33 v/v) at pH 9.5 and separation on a HP5-MS capillary column. Laudanosine was subject to postmortem redistribution due to release from drug-rich tissues such as the lung and heart. The heart blood (917 ng/ml) to peripheral blood (390 ng/ml) ratio was 2.4. No other drugs, including ethanol were detected.

Key words Atracurium · Laudanosine · Fatality · Postmortem redistribution

Introduction

Atracurium (Tracrium) is a non-depolarizing skeletal muscle relaxant, used to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation. In France, atracurium is available as a 1% solution, in ampules of 2.5, 5 or 25 ml of the besylate salt, for intravenous administration. Controlled ventilation is always recommended, as stated in the instruction leaflet.

Following an intravenous dose, muscle relaxation begins in about 2 min and lasts for 15–35 min, depending on the dose [1, 2]. Atracurium undergoes spontaneous degradation via Hofman elimination, a non-enzymatic breakdown process occurring at physiological pH and temperature, to produce laudanosine (Fig. 1) and pentamethylene-1,5 diacrylate [3]. There is also some ester hydrolysis by non-specific plasma esterases. The drug is excreted in urine and bile, mostly as metabolites, and the elimination half-life is about 20 min.

Adverse effects of atracurium include itching, wheezing, bronchospasms, prolonged neuromuscular block, hypotension, respiratory failure and death [4].

A literature search for papers on "poisoning by atracurium" cited in the "Analytical Abstracts" and "Medline on CD-ROM" databases was unable to produce any citation. A recent case involving a suicide of a nurse, is presented to document the forensic aspects.

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Case report

A 45-year-old female, 1.67 m in height and weighing 48 kg, was found dead on the floor of the toilets of the surgery room in a clinic in Strasbourg. The deceased was known to be depressive. An empty syringe was found near the body, with a hand-written inscription "Tracrium". The woman was a nurse, recently employed by the clinic.

The autopsy was carried out at the Medico-Legal Institute of Strasbourg. No evidence of violence was noted by the medical examiner but a recent needle mark was found in a vein of the right wrist. No particular anatomical changes were present, except for a multivisceral congestion which is usual in all deaths involving CNS depressants, but cannot be considered specific for this etiology. The following postmortem samples were taken for toxicological analysis: cardiac blood, peripheral blood (femoral artery), urine, vitreous humour, gastric contents, liver, kidney, brain, lung, and myocardium.

Materials and methods

Laudanosine was assayed in the postmortem samples using gas chromatography coupled to mass spectrometry (GC/MS) after liquid-liquid extraction. Briefly, to 1.0 ml of biological fluid or tissue homogenate (one-part tissue in four-parts deionized water w/v) were added 1 ml of 1 M sodium phosphate buffer, pH 9.5, 5 ml of chloroform/isopropanol/n-heptane (50 : 17 : 33 v/v/v), and 200 ng of SKF 525 A (proadifen) as internal standard. After agitation, centrifugation and evaporation of the organic phase, the dried extract was resuspended in 30 µl of methanol and 1.5 µl of the sample was immediately injected into a GC/MS system consisting of a chromatograph (Hewlett-Packard 5890) and a mass selective detector (HP 5972) with a ion source temperature of 250 °C. The flow-rate of the carrier gas (He) was 1.0 ml/min. A HP-5 MS cap-

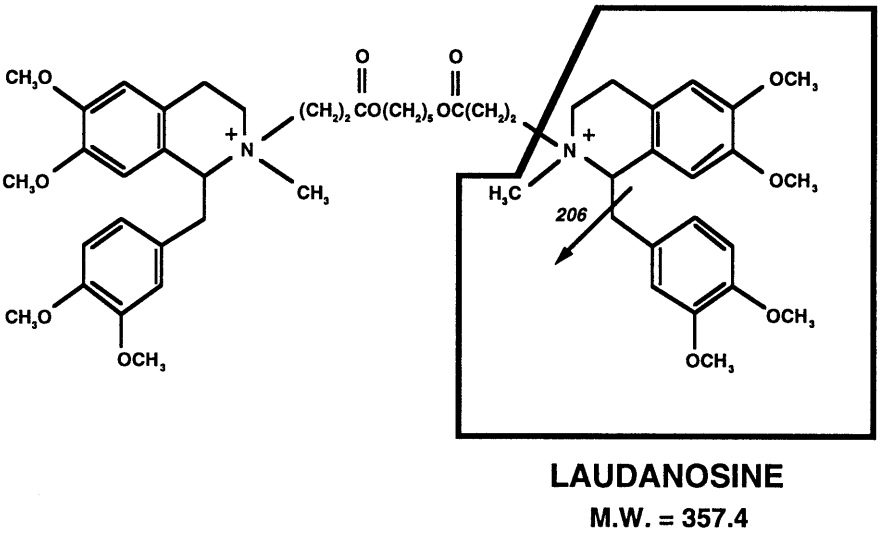

Fig. 1 Chemical structures of atracurium and laudanosine

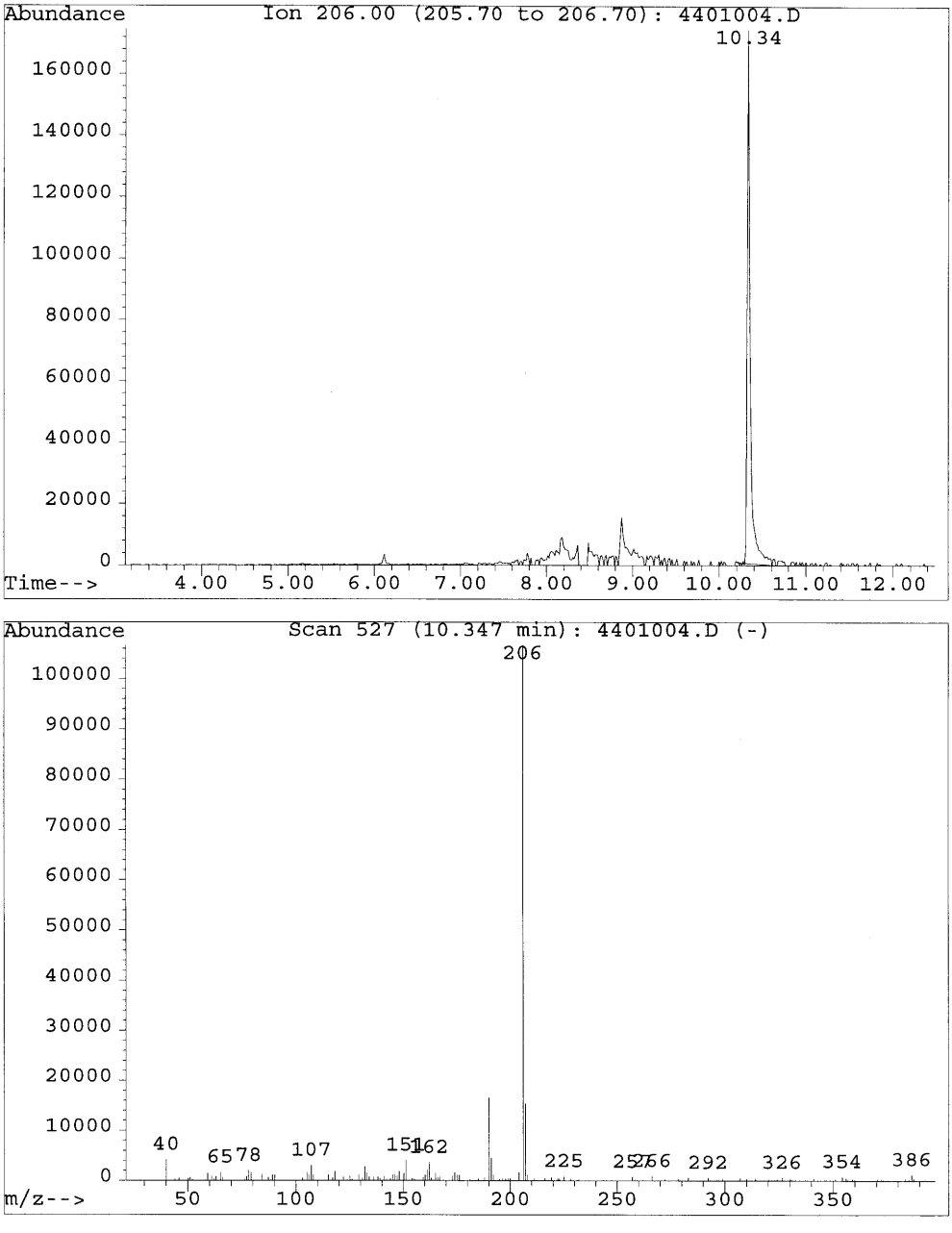

Fig. 2 *Above* Femoral blood extract in selected ion monitoring mode. The laudanosine concentration was 390 ng/ml. *Below* Electron impact mass spectrum of laudanosine

illary column, 30 × 0.25 mm i.d. was used. The column oven temperature was programmed from an initial step of 60°C for 1 min to 295 °C at 30 °C/min, then held at 295 °C for the final 5 min. Quantitation of laudanosine was carried out by SIM-mode at m/z 206, and by comparing the abundance to that of the internal standard (m/z 86).

In addition to laudanosine determination, a comprehensive toxicological screening was performed on postmortem blood and urine samples using fluorescence polarization immunoassay (FPIA) on the Abbott ADx analyzer, UV spectrophotometry (carbon monoxide), GC/MS and high-performance liquid chromatography coupled to diode-array detection (e.g. pharmaceuticals, drugs of abuse).

Results and discussion

As laudanosine was identified during the screening step, it was necessary to fully validate the analytical procedure. The response for laudanosine was linear in the range 10–1000 ng/ml (r = 0.998) and 20–5000 ng/g (r = 0.997) for spiked blood and liver homogenate, respectively. The extraction recovery, established for a blood concentration of 500 ng/ml was 69.6%, with a within-run precision (n = 8) less than 9%.

Under the chromatographic conditions used, there was no interference with the drug or the internal standard from any extractable endogenous material present in the biological specimens. Figure 2 shows the femoral blood extract in selected ion monitoring mode, along with the electron impact mass spectrum with characteristic ions at m/z 206, 190, 151 and 162. Retention times were 9.26 and 10.34 min for the internal standard and laudanosine, respectively.

Laudanosine was formally identified and quantified in all samples tested. Concentrations are summarized in Table 1. No other substances could be detected.

High levels of laudanosine were measured in the lungs, kidney and myocardium. Laudanosine was subject to postmortem redistribution, due to release from drug-rich tissues such as the lungs and heart. The heart blood (917 ng/ml) to peripheral blood (390 ng/ml) ratio was 2.4. This first observation should be confirmed with other similar cases. At the autopsy, the exact location of blood sampling has to be noted with respect to potential over-estimation of the amount of circulating drug.

Table 1 Postmortem concentrations of laudanosine detected in the case of suicide

Specimen	Laudanosine concentration
Femoral blood	390 ng/ml
Cardiac blood	917 ng/ml
Urine	597 ng/ml
Vitreous humour	18 ng/ml
Gastric contents	84 ng/ml
Lung	3124 ng/g
Kidney	2891 ng/g
Liver	470 ng/g
Myocardium	1907 ng/g
Brain	32 ng/g

The femoral blood concentration could not be compared with previous fatal reports as the literature lacks data concerning fatal poisoning by atracurium. However, this concentration is within the therapeutic ranges that are reported in anaesthesiology, with patients being mechanically ventilated but in the absence of ventilation, this concentration should be considered as potentially fatal. The striking differences of concentrations between tissues and urine, for example, should be considered as a sign of a short survival time after drug intake.

In view of the circumstances, the manner of death was listed as suicide.

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