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Case Report

Mirtazapine fatal poisoning

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ABSTRACT

Mirtazapine is a noradrenergic and specific serotoninergic antidepressant agent that stimulates norepinephrine and serotonin release while also blocking serotonin receptors (5-HT2 and 5-HT3).

Although the drug is used extensively, at present we do not know of any fatal cases due to mirtazapine alone. On the contrary, the published literature describes several fatal poisoning cases related to the intake of mirtazapine together with other drugs.

Here we describe a fatal case of mirtazapine self-poisoning, since the other drug detected (lorazepam), was within the therapeutic range. Analyses were performed by LC–MS/MS on body fluids and a hair sample and mirtazapine concentration measured in blood was very high: 9.3 mg/L. *N*-Desmethylmirtazapine was also quantitated. We then compared our results with those of previously published cases.

In conclusion, even though mirtazapine can be considered a relatively safe drug, taking a large amount alone or in combination with other drugs, could lead to death.

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1. Introduction

Mirtazapine is a noradrenergic and specific serotonergic antidepressant (NaSSA) which has been evaluated in the treatment of major depression. Mirtazapine has a unique mode of biochemical action: it affects both the serotonin and norepinephrine systems in the central nervous system, but it lacks the anticholinergic and cardiovascular effects of other antidepressants, such as tricyclic antidepressants. Mirtazapine, due to its characteristic pharmacological action (enhancement of central noradrenergic and serotonergic activity), is able to neutralize or reverse some side effects that are likely to occur when other classes of antidepressants are administered. It means that mirtazapine could improve tolerability to antidepressants already in use, increasing their therapeutic effects [1]. Nevertheless, its interactions with some drugs should not be underestimated: mirtazapine can increase the sedative effects of antipsychotics, benzodiazepines and antihistamines as well as the depressive effects of ethanol. Therefore, patients should be closely monitored, in order to avoid the serotoninergic system overstimulation [2].

Mirtazapine is generally taken orally, and is well absorbed by the gastrointestinal tract; the presence of food does not affect its absorption. Following the intake of a 30 mg single dose, bioavailability is approximately 50% [3] quite a low percentage due to losses from passage through the intestinal wall, and first-pass hepatic metabolism [4]. Steady state is achieved between 4–6 days [5].

The drug is metabolized in the liver, through different biotransformation pathways, catalysed by cytochrome P450. About 40% undergoes hydroxylation resulting in 8-OH-mirtazapine, followed by conjugation with glucuronic acid (8-OH-mirtazapine glucuronide) or to a lesser extent with sulphuric acid. Approximately 25% of mirtazapine is oxidized into mirtazapine-*N*-oxide; the same amount is demethylated into *N*-desmethylmirtazapine and subsequently conjugated with sulphuric acid. Finally, about 10% of the absorbed mirtazapine undergoes glucuronidation, resulting in mirtazapine-*N*-glucuronide [4,6]. *N*-Desmethylmirtazapine is an active metabolite produced through the hepatic first-pass: it enters the bloodstream and enhances mirtazapine's activity.

Mirtazapine's half-life ranges from 20 to 40 h regardless of dose, regimen and number of administrations [7], and rather depends on the patient's age and sex [8].

The published literature describes several fatal poisonings involving mirtazapine in combination with other drugs, but the authors have not been able to find one report related to

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mirtazapine alone. This paper describes a fatal overdose of mirtazapine with tissue concentrations quantified by a LC–MS/MS method; the results are discussed in relation to previously published findings.

2. Case report

A 59-year-old man, who had tried to commit suicide twice, called a friend at 19:10 telling him "I did it". Because of his personal history, the friend called the emergency number and the man was taken to hospital, where he arrived at 20:45. He was admitted to hospital exhibiting psychomotor agitation and mental confusion; blood pressure was 140/75 mmHg, cardiac frequency 80 bpm and SaO_2 95%. The man said that he had taken an entire bottle of Remeron® solution (containing 990 mg of mirtazapine) and some 2.5 mg lorazepam tablets. Activated charcoal was administered but gastric lavage was not carried out. No electrocardiographic changes were observed at that time. At 22:24 the man – extensively agitated – was transferred to the psychiatric ward where he spent the night alternating states of drowsiness and agitation. At 7:00 blood pressure was 110/60 mmHg and cardiac frequency 68 bpm. At 7:35 the patient suffered a cardiac arrest, adrenaline and atropine were administered, but he died at 8:35 (at least 13 h after the drug intake).

3. Materials and methods

3.1. Chemicals

All solvents were of HPLC grade or better and were obtained from Panreac (Milan, Italy). Water was purified by filtering deionized water on a Milli-Q Simplicity 185 filtration system from Millipore (Bedford, MA, USA). Pure formic acid for mass spectrometry was purchased from Sigma-Aldrich (St. Louis, MI, USA). *N*-Methyl-*N*-(trimethylsilyl)trifluoroacetamide (MSTFA) was purchased from Sigma-Aldrich (Milan, Italy). Bond Elut Certify cartridges were purchased from Agilent (Milan, Italy). Mirtazapine, *N*-desmethylmirtazapine and halazepam, standards were obtained from SIGMA (Milan, Italy).

3.2. Toxicological analyses

The following analyses were performed on blood sample: quantitative determination of ethanol, and systematic toxicological analysis (STA) to detect acidic, neutral and basic drugs including those that are commonly prescribed, non-prescribed and illicit drugs. STA was carried out using gas chromatography–mass spectrometry (GC–MS) technique preceded by a solid phase extraction with mixed-mode cartridges Bond Elut Certify using the method detailed in a previously published study by Polettini et al. [9]. Instrumental analysis was accomplished with an Agilent Model 6890 gas chromatograph equipped with a Model 5975 mass-selective detector, a Model 7673 automatic injector and an Agilent Ultra 2 (5% phenyl, methylsilicone) fused-silica capillary column. GC-MS data files were processed using an original procedure for the automated purification of mass spectra from the total ion chromatogram [10].

Quantitative analysis of lorazepam was performed by LC–MS/MS using the method detailed in a previously published study [11].

3.3. LC–MS/MS quantitative analysis of mirtazapine and N-desmethylmirtazapine

The method has been fully validated on blood sample [11], the most important matrix in order to determine the cause of death. Briefly, aliquots of 0.2 mL of blood were spiked with mirtazapine and *N*-desmethylmirtazapine standard in the range 0.05–1 mg/L, as shown below. The samples were diluted in 0.4 mL methanol and 0.1 mL of halazepam methanol solution (1 mg/L) as internal standard were added. Halazepam is routinely used as an internal standard in our laboratory because it is no longer prescribed and used in Italy.

The samples were shaken for 1 min and centrifuged at 13,000 rpm for 10 min. 0.2 mL supernatant were diluted in 0.2 mL acetonitrile and then agitated and centrifuged following the above mentioned procedure. Finally, 0.2 mL supernatant were diluted with 0.8 mL of formic acid 0.1%, and an aliquot of 10 μL injected in the LC–MS/MS system. Validation main criteria such as linearity, accuracy, precision, sensitivity and specificity, matrix effects and carry over were evaluated [12].

3.4. Instrumental parameters

Quantitative analyses were developed with an Agilent 1100-1200 Series LC system (Agilent Technologies, Palo Alto, CA, USA) interfaced to a 4000 Q-Trap MS system (AB Sciex, Foster City, CA, USA) by an electrospray (ESI) Turbo V™ Ion Source.

The LC injector needle was externally washed with methanol prior to any injection. A Hypersil Gold a.Q. (100 × 3 mm i.d., 2.1 μm particle size, Thermo Fisher, CA, USA), was kept at 25 °C during the analysis. The flow rate was kept constant at 0.2 mL/min and the mobile phases consisted of acid formic 0.1% (mobile phase A) and acetonitrile (mobile phase B). The gradient elution was set as follows: 95% A was kept for 2.5 min, then decreased to 5% within 5 min; 5% A was kept for 7 min; rinsing step at 95% A for 8 min. The column oven was kept at 25 °C. LC flow was directed into the ion source using the following settings: ion-spray voltage: 4500 V, source temperature: 450 °C, nebulization and heating gas (air): 30 and 35, respectively, curtain gas (nitrogen): 15. Multiple Reaction Monitoring (MRM) was performed using nitrogen as collision gas (with pressure set at medium level) and a dwell time of 100 ms. During the screening method a dwell time of 30 ms was used for each transition. For the single quantification of the substances the dwell time was set at 100 ms for each transition. Table 1 shows MRM parameters. The transitions in bold were used for quantification.

3.5. Real samples preparation

Amounts of 0.2 mL of femoral blood, urine and bile (kept frozen until the time of analysis) were submitted for quantitative analysis, using the procedure already described for the validation of the method.

A hair sample of about 3 cm length was collected. A hair strand was washed with 1 mL methylene chloride and 1 mL methanol. After drying, the sample was cut in 1–2 mm segments and weighed. 50 mg hair were added to 0.6 mL methanolic solution containing 2 ng halazepam as internal standard, and sonicated two

Table 1
MRM parameters.

Analyte	Q1 (m/z)	Q3 (m/z)	DP[a] (V)	CE[b] (eV)	CXP[c] (V)
Mirtazapine	**267.0**	**196.0**	100	35	8
	267.0	72.0	100	32	9
N-Desmethylmirtazapine	**252.0**	**195.2**	95	32	8
	252.0	209.1	95	32	9
Halazepam	**353.1**	**241.4**	90	54	11
	353.1	222.4	90	44	10

Transitions for quantitative determination are in bold.
[a] Declustering potential.
[b] Collision energy.
[c] Cell exit potential.

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