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CASE REPORT

F. Musshoff · K. Varchmin-Schultheiss · B. Madea

Suicide with moclobemide and perazine

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Abstract A 51-year-old woman who was diagnosed as suffering from depression was found dead in her flat. The autopsy revealed no morphological changes sufficient to explain death. Toxicological analysis was performed and the drugs moclobemide (49.9 mg/l), perazine (1.27 mg/l) and some metabolites were identified in the blood. A combined drug intoxication resulting in synergistic effects to cardiovascular disorders was proposed as the cause of death.

Key words Suicide · Moclobemide · Perazine

Introduction

Moclobemide [*p*-chloro-N-(2-morpholinoethyl) benzamide] is a short-acting, selective and reversible monoamine oxidase inhibitor type A (MAO-A) with a wide spectrum of antidepressant activity [5, 8]. In contrast to classical MAO-A inhibitors it is considered a relatively safe drug with few side effects and a pure moclobemide overdose seems to be benign [13, 14, 16, 17, 23, 29]. Fatal moclobemide overdoses have been documented concomitant with treatment with serotonergic agents producing a central serotonin syndrome [1, 3, 7, 15, 21, 22, 24, 26, 27]. This is a potentially lethal toxic hyperserotonergic state, most commonly resulting from an interaction between MAO inhibitors and agents increasing stimulation of 5-HT-receptors, such as serotonin reuptake inhibitors [28].

Perazine [10-[3′-(4″-methyl-1″-piperazinyl)-propyl]-phenothiazine] is used as a low-potency neuroleptic drug in inpatient and outpatient treatment [6]. Even when administered over many years, it has proven to be effective and to produce few side effects [25]. Extrapyramidal motor symptoms (EPMS) as well known adverse effects of neuroleptic drugs were observed only in a minor part of perazine patients [12].

F. Musshoff (✉) · K. Varchmin-Schultheiss · B. Madea
Institute of Legal Medicine, Stiftsplatz 12,
D-53111 Bonn, Germany

Case report

This case involved a 51-year-old woman with a 20-year history of psychiatric depression and anxiety, who repeatedly voiced suicidal intentions. She was last seen the day before at 8:00 p.m. and was found dead at 11:50 a.m. by her mother. She was discovered lying on her back on the bed with the head turned to the left side on a cushion. She was correctly clothed in pyjamas. A farewell letter was found together with empty packings of Aurorix and Taxilan. There were no signs of violence on the clothing or the body.

Autopsy findings and histopathological examination

External examination of the body of a 51-year-old obese woman failed to reveal any signs of external violence. At autopsy slight pulmonary edema and congestion of all inner organs were found. The stomach contained 20 ml of a dark brownish fluid. A slight steatosis of the liver was found. The autopsy revealed no further remarkable findings and no pre-existing diseases, in particular no cardiovascular alterations.

Drug testing

Various body fluids and organ tissues were assayed for ethanol and drugs of abuse (acidic, basic and neutral organic drugs) using routine methods including immunochemical procedures and liquid-liquid as well as solid-phase extraction procedures with further analysis by high performance liquid chromatography with diode array detection (HPLC/DAD) and gas chromatography/mass spectrometry (GC/MS).

Materials: moclobemide (Ro 11-1163) and the five metabolites (Ro 11-1903, Ro 12-5637, Ro 12-8095, Ro 16-3177, Ro 46-8787) were obtained from Hoffmann-La-Roche (Basle, Switzerland). p-Iodo-N-(2-morpholinoethyl) benzamide (Ro 11-9900) was used as internal standard. Perazine was purchased from Promonta (Hamburg, Germany). All other chemicals in HPLC or p.a. quality were obtained from Merck (Darmstadt, Germany).

HPLC: a Shimadzu LC-6A pump was used with a SPD-M10A detector. For analysis of moclobemide a Hypersil 120-5 ODS column (Macherey & Nagel, Dueren, Germany) was used. The mobile phase was a mixture of acetonitrile with 0.05 M potassium phosphate buffer (180 : 820 v/v; pH 2.8; flow 0.4 ml/min). Perazine was analysed using a Lichrosorb RP8 column (5 μm; 250 × 4.0 mm;

Merck) and a mobile phase of 30 % acetonitrile in potassium phosphate buffer (pH 2.3; flow 1 ml/min).

GC/MS: a HP 5890 gas chromatograph with a HP 5972 mass selective detector (MSD) and a HP 5 MS column (30 m × 0.25 mm internal diameter, 0.25 µm film thickness) was used. Temperature program: 80 °C (1 min), 10 °C/min at 300 °C for 5 min.

Extraction procedures: for extraction 1 ml or 1 g of biological sample (tissues after mechanical homogenization) was adjusted to pH 11 (for extraction of moclobemide) or pH 9 (for extraction of perazine) with 19 ml of potassium phosphate buffer. The mixtures were applied on Extrelut-20 extraction columns (Analytichem International, Frankfurt a.M., Germany) and extracted twice with 20 ml of dichloromethane. The eluates were evaporated to dryness at 60° C under a stream of nitrogen, the residues were reconstituted in methanol and aliquots were analysed by HPLC.

For GC/MS analysis of moclobemide a re-extraction procedure was used, whereby a blood sample of 1 ml was alkalinized with 0.5 ml of 5 M sodium hydroxide and extracted with 5 ml of dichloromethane. The organic layer was transferred to another tube containing 3 ml of 0.1 M hydrochloric acid. After shaking (5 min) and centrifugation the acid phase was removed, alkalinized with 0.5 ml of 5 M sodium hydroxide and extracted with 5 ml of dichloromethane. Following centrifugation the solvent was evaporated to dryness under a stream of nitrogen at 50 °C. The residue was dissolved in 100 µl of methanol and a 2-µl aliquot was subjected to GC/MS.

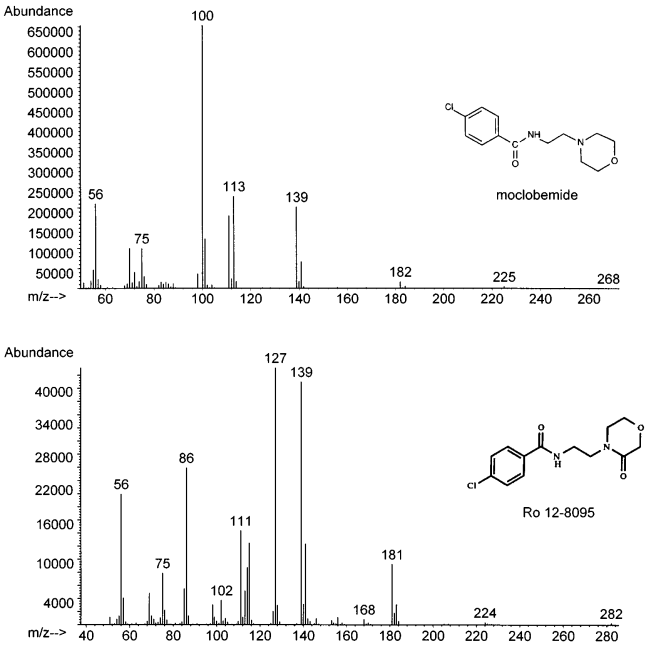

Fig. 1 Mass spectra of moclobemide and the oxo-metabolite recorded by analysis of the blood sample

Results

As shown in Table 1 moclobemide was found in the femoral blood in a concentration of 49.9 mg/l, in the brain moclobemide was calculated at 56.7 mg/kg and in liver and kidneys in concentrations of 79.7 mg/kg and 81.4 mg/kg respectively. Additionally the moclobemide metabolites p-chloro-N-[2-(3-oxomorpholino) ethyl]benzamide (oxo-metabolite; Ro 12-8095), p-chloro-N-[2-[(2-hydroxyethyl) amino] ethyl] benzamide (ring-opened metabolite; Ro 16-3177), and p-chloro-N-(2-morpholinoethyl) benzamide-N′-oxide ((N-oxide metabolite; Ro 12-5637) were found in concentrations of 7.75 mg/l, 1.80 mg/l and 0.85 mg/l, respectively. Using the extraction procedure and GC/MS method described, the parent compound moclobemide and the main metabolite (oxo-metabolite) were confirmed in the blood sample (Fig. 1).

Perazine was found in the blood sample in a concentration of 1.27 mg/l, in the brain, the liver and the kidneys concentrations were calculated at 0.39 mg/kg, 0.77 mg/kg, and 0.83 mg/kg respectively. Desmethylperazine was also detected. All other tests for ethanol and drugs of abuse were negative.

Table 1 Results of toxicological analysis

Compound	Blood [mg/l]	Liver [mg/kg]	Kidneys [mg/kg]	Brain [mg/kg]
Moclobemide (Ro 11-1163)	49.9	79.7	81.4	56.7
Oxo-metabolite (Ro 12-8095)	7.75	–	–	–
Ring-opened metabolite (Ro 16-3177)	1.80	–	–	–
N-oxide metabolite (Ro 12-5637)	0.85	–	–	–
Perazine	1.27	0.77	0.83	0.39
Desmethylperazine	+	++	+	–

Discussion

In the case described here the postmortem blood concentration of moclobemide was found to be 20–30 times the therapeutic level and perazine was found at 10 times the therapeutic level. Generally moclobemide has been suggested to be an effective antidepressant with relatively few adverse effects. Potentially dangerous cases involved a combined ingestion of moclobemide and other drugs, especially serotonine reuptake inhibitors. Neuvonen et. al. [24] reported five fatal cases after combined ingestion of moclobemide with clomipramine or citalopram. The authors concluded that moclobemide and serotonergic agents could likely cause a dangerous serotonin syndrome when ingested even in moderately low mixed overdoses. Other fatal cases with symptoms due to a serotonin syndrome have been reported including combinations of moclobemide with fluoxetine, sertraline with pimozide, imipramine or multiple drug intoxication [1, 3, 7, 15, 21, 22, 26, 27]. The combination of moclobemide and pethidine was also demonstrated to induce fatality [11]. In cases of overdoses with only moclobemide fatal intoxications are in the minority. Iwersen and Schmoldt [19] reported three suicide attempts with moclobemide (one case in combination with clomipramine) and plasma concentrations at 10–30 times the therapeutic level which were not associated with major toxic effects. Only in two cases was death determined to be solely due to a single moclobemide inges-

tion with postmortem blood concentrations of 137 mg/l and 15.5 mg/l respectively [4, 9].

Metabolism of moclobemide occurs mainly at the morpholino ring [10] by hydroxylation followed by dehydrogenation to the main metabolite p-chloro-N-[2-(3-oxomorpholino) ethyl] benzamide (Ro 12-8095), N-oxidation to p-chloro-N-(2-morpholinoethyl) benzamide-N′-oxide (Ro 12-5637) and ring opening with oxidative deethylation to p-chloro-N-[2-[(2-hydroxyethyl) amino] ethyl] benzamide (Ro 16-3177). As shown by other authors [10, 18, 20] the unchanged parent compound as well as the oxo-metabolite, the ring-opened metabolite and the N-oxide metabolite were detected in the blood of the case described here.

Perazine is considered to be a relatively safe neuroleptic drug and normally the neuroleptic malignant syndrome (NMS) as the most severe and potentially lethal EPMS complication is only described after long term treatment. Metabolites demonstrable in the plasma are demethylperazine and perazine sulfoxide, the latter being present in lower concentrations [2]. In the case described here the unchanged parent drug was found in the blood sample at 10-fold therapeutic level and the main metabolite desmethylperazine was also identified in the blood, liver and kidneys.

Generally it is not possible to discuss the effects of a combined drug ingestion without clinical observations. However, in this case by the exclusion of other causes of death, a combined drug intoxication with perazine and moclobemide was determined as the cause of death. In our opinion the overdose combination resulted in peripheral effects of alpha-adrenoceptor antagonist properties of perazine and serotonin receptor stimulation. These synergistic effects resulted in functional cardiovascular disorders which were responsible for the death.

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