CASE REPORT

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A Fatality Involving Moclobemide, Sertraline, and Pimozide

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ABSTRACT: A case is described involving a suspected fatal interaction between moclobemide and sertraline, in combination with the use of pimozide.

KEYWORDS: forensic science, forensic toxicology, moclobemide, sertraline, pimozide, fatality, drug interaction

Moclobemide, a selective and reversible monoamine oxidase inhibitor (MAO-I) type A, has been demonstrated to be a clinically useful antidepressant. It is generally considered a relatively safe drug with few side-effects. On overdose, the main effects are drowsiness, nausea, hyporeflexia and disorientation (1). Although there have been no fatalities attributed to moclobemide as the sole drug of abuse, both non-fatal and fatal interactions with coingestion of imipramine, clomipramine or citalopram have been described (2–4). As these compounds, particularly clomipramine and citalopram, are strong serotonin reuptake inhibitors, it would appear that moclobemide, like the original non-selective irreversible MAOIs, can produce a central serotonin syndrome—a potentially lethal toxic hyperserotoninergic state (5).

Sertraline is another relatively new antidepressant structurally unrelated to the tricyclic, bicyclic, tetracyclic or MAOI compounds. Found to be clinically effective, its mechanism of action has been linked to its specific and potent inhibition of serotonin reuptake in the central nervous system. Sertraline has no reported effect on adrenergic, cholinergic, GABA or dopaminergic receptors, and consequently should not exhibit many of the side-effects observed with other antidepressants (6). In three cases involving known overdoses of sertraline, with amounts ranging from 750 to 2500 mg of the drug, all patients recovered completely with no specific therapy or pathological sequale. One fatality has also been described in which a toxic combination of sertraline and diphenhydramine was given as the cause of death (7). However, the circumstances of this report are scant and no postmortem pathological findings are described. Also, the concentrations of both sertraline and diphenhydramine were not remarkably elevated above therapeutic concentrations. We present here a suspected fatal interaction between moclobemide and sertraline in combination with the use of pimozide. To our knowledge, this is the first report of a fatal serotonin syndrome attributed to these drugs.

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Case Report

A 22-year-old male being treated for clinical depression admitted to taking a large quantity of pills. He was still conscious when an ambulance arrived, but appeared to be hallucinating and very drowsy. He was given charcoal but died six hours after admission to hospital.

Empty containers of pimozide, haloperidol and a near full container of benztropine mesylate were found in his room. Later discussions with his treating doctor, revealed that he was also prescribed moclobemide and sertraline.

An autopsy was performed within or approximately 24 h following death. This included complete macroscopic and microscopic examination. Macroscopically, there were severely congested and edematous lungs with surface bruising, peri-thoracic aortic hemorrhages, epicardial bruising and a carbon-like material within the stomach. Histologically, the lungs showed focal areas of intra-alveolar hemorrhage and a focus of subpleural hemorrhage. There was a moderate hepatic steatosis.

Postmortem specimens including blood, urine, liver, bile, and vitreous humor were collected and sent to the laboratory. A hospital blood sample collected 2 h after admission was also provided for toxicological analyses. These analyses detected and confirmed the presence of moclobemide, sertraline, and pimozide (Table 1). Haloperidol and benztropine were not detected. The cause of death was given as drug toxicity.

TABLE 1—*Drug concentrations of moclobemide, sertraline, and pimozide.*

Tissue	Moclobemide (mg/L or mg/kg)	Setraline (mg/L or mg/kg)	Pimozide (mg/L)
Antemortem blood	30	0.08	0.06
Postmortem Femoral blood	21	0.9	0.13
Liver	28	3.2	—
Bile	144	—	—
Vitreous humour	11	0.5	—

Methods

Toxicological analyses were conducted on blood and urine using a combination enzyme-multiplied immunoassay (EMIT) for drugs of abuse, gradient high performance liquid chromatography (HPLC) with photodiode array for detection of acid/neural substances (8), capillary gas chromatography (GLC) followed by mass-spectrometric confirmation for basic/neutral substances (9), and alcohol analysis.

Chemicals and Reagents

Moclobemide and R011-9900 (used as internal standard) were obtained as free bases from Roche Australia Ltd; Sertraline HCl was obtained from the Division of Analytical Laboratories of the New South Wales, Health Department, Australia; Pimozide was obtained from the Australian Government Laboratories, Pymble, Australia.

Stock solutions were prepared fresh in methanol (1 mg/mL), and dilutions made in deionized water. All chemicals used were of analytical reagent quality (AJAX, Australia). The solvents hexane, acetonitrile, methanol were HPLC grade (Mallinckrodt, Australia). Phosphate buffered saline (PBS) was prepared as follows: 1.7 g KH_2PO_4 and 4.5 g of NaCl were dissolved in 500 mL deionized water, and pH was adjusted to 7.4 with dilute orthophosphoric acid.

Instrumentation

The HPLC equipment consisted of a model 6AD constant flow pump, model SIL-6B autoinjector, system controller (SCL-6B), model SPD-6AV ultraviolet detector or a SPD-10A ultraviolet dual wavelength detector and a model CR-4A integrator/plotter (Shimadzu, Oceania).

Moclobemide Analysis

Moclobemide was measured using a modification of a previously described method for antidepressants (10). Briefly, a 1 mL blood/vitreous/bile or 0.5 mL liver homogenate, was added to silanized glass extraction tubes. Following the addition of 2 μg of internal standard (R011-9900), 1 mL of deionized water and 1 mL of 0.2 M Na_2CO_3 were successively added. Six mL hexane/butanol (95:5; v/v) was added and the tubes extracted for 30 min. Following centrifugation, the solvent layer was transferred to clean silanized glass tubes containing 100 μL 0.2% H_3PO_4 for blood/bile/vitreous and 400 μL 0.2% H_3PO_4 for liver homogenates, and again extracted for 30 min. Finally, after centrifugation, 30 μL of the aqueous layer was injected into the HPLC.

Separation of moclobemide was achieved using a Spheri-5RP-18 (100 × 4.6 mm) column (Applied Biosystems, Australia). The mobile phase of acetonitrile: 0.1 M $NaH_2PO_4 \cdot 2H_2O$: diethylamine (1% per volume of buffer) (15: 85; v/v), pH 5.8, was pumped at a flow rate of 0.9 mL/min. The detector was operated at 220 and 254 nm. The run time was 30 min.

Blood and vitreous standards (using PBS as the medium) were linear from 1.0 to 100 mg/L, bile standards were linear up to 300 mg/L and liver homogenates were linear up to 750 mg/kg.

Sertraline Analysis

Sertraline was extracted from 1 mL blood/vitreous or 0.5 mL liver homogenate with the following method. Using polypropylene plastic extraction tubes, 0.5 μg of pentazocine (internal standard) was added to blood or vitreous or 5.0 μg to liver homogenates, followed by 0.5 mL of 2% sodium tetraborate (pH 9.5). Eight mL of butyl alcohol/hexane (5/95, v/v) was added and the tubes extracted for 30 min. After centrifugation, the solvent was transferred to clean tubes containing 200 μL 0.2% H_3PO_4 (blood, vitreous) or 400 μL for liver homogenates, and extracted for a further 30 min. The aqueous layer was collected after centrifugation and 30 μL injected onto the HPLC.

Separation was achieved with a NovaPak-Phenyl (3.9 × 150 nm, 5 μm) column (Waters, Australia). The mobile phase of acetonitrile: 10 mM KH_2PO_4 (55: 45, v/v), pH 3.0, was pumped at a flow rate of 1.5 mL/min. The detector was operated at 214 nm, with a run time of 15 min.

Blood and PBS standards for vitreous analyses were linear ranging from 0.1 to 5.0 mg/L, and liver standards were linear from 2.5 to 50 mg/kg.

Pimozide Analysis

Pimozide was extracted from blood with the conditions as described for sertraline, using a calibration curve ranging from 0.01 to 0.5 mg/L. Chromatographic conditions were as described for sertraline.

Liver Homogenates

A liver homogenate was prepared by homogenizing 10 g of freshly minced liver in 10 mL of water. The pH was adjusted to 10 using 1 M NaOH. Ten mg subtilisin (Sigma, St. Louis, MO) was then added. The homogenate was incubated for 60 min at 55°C. The pH was finally adjusted to 7.0 ± 0.5 with dilute mineral acid. Homogenates were stored at −20°C until analysis.

Discussion

Moclobemide is absorbed rapidly and almost completely from the gastrointestinal tract and peak plasma concentrations are normally observed 1–2 h after a dose. The elimination half-life of moclobemide is generally 1–2 h. (1). Therapeutic blood concentrations of moclobemide probably range from 0.1 to about 8 mg/L (11). In five cases of suspected moclobemide overdose (all in combination with other medications), concentrations in postmortem femoral blood have ranged from 49–330 mg/L, liver from 80–460 mg/kg, bile from 505–1210 mg/L and vitreous from 21–210 mg/L (11).

Sertraline, on the other hand, is slowly absorbed with peak plasma concentrations occurring 6–8 h after ingestion. The elimination half-life is about 24–32 h (12). Following therapeutic administration, steady state plasma sertraline concentrations are in the 0.1 to 0.2 mg/L range (13).

Following oral administration, pimozide undergoes significant first-pass metabolism. Peak plasma concentrations have been observed after 4–12 h, but there are considerable interindividual variations in the concentrations achieved. Peak concentrations have ranged from 0.05–0.2 mg/L (14). Pimozide has a long elimination half-life, generally considered to be approximately 55 h (15).

In this case report, both the antemortem and postmortem concentrations of moclobemide are clearly higher than those normally expected following therapeutic use indicating excessive use, but lower than fatalities in which moclobemide has been involved.

Although the antemortem sertraline concentration is within the known therapeutic range, postmortem levels are significantly elevated in both femoral blood and vitreous humor. The sertraline liver concentration, however, is at the low end of the range for

such concentrations (3.9–20 mg/kg) reported for five individuals who died of unrelated causes while receiving sertraline therapeutically (12).

While the concentrations of pimozide are within the range of peak levels previously reported (14), the significance is difficult to interpret due to the reported high interindividual variations in plasma concentrations and the lack of postmortem data for this drug.

The discrepancy between antemortem blood and postmortem femoral blood concentrations of sertraline and pimozide may be a result of two phenomena. Firstly, as both sertraline and pimozide are slowly absorbed, compared to moclobemide, drug absorption may have continued (probably from the gastrointestinal tract) after the time of the hospital blood sampling, whereas moclobemide was probably completely absorbed prior to this hospital blood sampling. Alternatively, postmortem redistribution may have occurred. Postmortem release of drugs from tissue into blood has been shown to significantly elevate drug levels in blood, particularly with tricyclic antidepressants and antipsychotics (16). However, two reports of postmortem sertraline cases have found similar peripheral and central blood sertraline concentrations, suggesting no marked site dependence (7,12).

Considering the data presented in previous moclobemide and sertraline overdoses, it is possible to conclude that, in this case, neither moclobemide, sertraline nor pimozide alone at the concentrations found were clearly excessive and therefore would not be fatal individually in an otherwise healthy young male. However, the pathologist concluded that coingestion caused a lethal result. The Coroner also concluded death as a result of drug overdose.

This case suggests that the three drugs, in combination, may have produced a serotonin syndrome similar to that previously described with the interaction between moclobemide and the older tricyclic antidepressants, such as imipramine and clomipramine. The newer more specific serotonin reuptake inhibitors, sertraline, citalopram, fluoxetine, fluvoxamine and paroxetine may therefore carry a more serious risk of serotonin syndrome when given concomitantly with the MAOI moclobemide.

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