CASE REPORT

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Fatal Moclobemide Overdose or Death Caused by Serotonin Syndrome?

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ABSTRACT: A 41-year-old man was found dead in a hotel room. He was previously diagnosed with depression. Multiple containers of medication and paraphenalia were found at the scene. Autopsy findings included fully developed rigor mortis and pulmonary edema with hemorrhage. Toxicologic analysis of different body fluids was performed and the following drugs were identified in the blood (mg/L): moclobemide (59.76), clomipramine (1.69), tramadol (10.89), diazepam (2.08), nordiazepam (0.82) and caffeine (9.64). A fatal serotonin syndrome was presumably developed as a result of moclobemide-clomipramine interaction as has been recently reported. Tramadol could have a synergistic effect on that syndrome. The forensic pathologists ruled that the cause of death was multiple drug intoxication resulting in serotonin syndrome and that the manner of death was suicide. However, an accidental death from drug abuse could be an alternative diagnosis.

KEYWORDS: toxicology, polyintoxication, serotonin syndrome, antidepressant, suicide, drug abuse

Moclobemide, a short-acting selective and reversible monoamine oxidase inhibitor (MAO-I) type A, has recently come into clinical use as an antidepressant. It is considered a relatively safe drug with few side-effects and pure moclobemide overdosage also seems to be benign [*1,2*]. The main effects of overdosage are severe drowsiness, nausea, hyporeflexia and disorientation [*3*]. Some CNS depression, fatigue, agitation, tachycardia and a rise in blood pressure have also been described in pure overdosage [*1*].

All these clinical manifestations are in contrast with those symptoms from classical irreversible MAO-I intoxication: convulsions, hyperthermia, muscle rigidity, pain and rhabdomyolysis. These symptoms also resemble the unusual neuroleptic malignant syndrome [*1*]. Nevertheless, irreversible and nonselective MAO inhibitors taken with serotoninergic agents can produce a central serotonin syndrome [*4*]. This is a potentially lethal toxic hyperserotoninergic state, most commonly resulting from an interaction between irreversible, nonselective MAO inhibitors and agents increasing central nervous serotoninergic activity, such as serotonin reuptake inhibitors. The more typical picture of serotonin syndrome is that of mental status changes (confusion, hypomania), loss of consciousness, agitation, tremor, hyperreflexia, muscular twitching, myoclonus, shivering, fever, sweating and diarrhea [*4*].

Digemanse [*5*] has suggested that moclobemide does not interact adversely with selective serotonin reuptake inhibitors. Moreover, the combination of reversible MAO inhibitors and serotoninergic agents has never been reported to cause serotonin syndrome. However, Spigset et al. [*6*] described a nonfatal but severe serotonin syndrome caused by a moclobemide-clomipramine interaction, and Neuvonen et al. [*2*] reported two fatal cases after coingestion of both agents and three more fatal cases after coingestion of moclobemide and citalopram (another selective serotonin reuptake inhibitor).

We present here a suspected and unwitnessed fatal serotonin syndrome developed in a polydrug intoxication. To our knowledge, this is the first medical examiner case described and the third fatal case of moclobemide-clomipramine interaction causing a serotonin syndrome.

Case Report

This case involved a 41-year-old male with a psychiatric history of depression and anxiety. He lived alone in a hotel room for the previous six months. He was last seen entering his room the day before at 9:30 p.m. by the clerk at the hotel reception desk. The day after, about 11:00 a.m., the clerk tried unsuccessfully to transfer a telephone call to him. Subsequently, the clerk went to his room, opened it and discovered him laying prone on the floor with his head on a cushion turned on the left side. He was fully clothed, but without shoes. A blue-greenish fluid was found spilled over the bedroom and bathroom floors. It appeared to be the same fluid contained in a glass on the bedroom table. A large variety of medications were found at the entrance of the room, in a small kitchen scullery and also in the bathroom. A dipper and two spoons were found in the kitchen, and contained material similar to that from the floor and the contents of the glass. The same material was also found in a 1.5 liter plastic bottle.

The deceased was not totally cold when touched at the scene

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but fully developed rigor mortis was noted. The arms were crossed in front of the chest. No fluid was found in the nostrils or mouth and there was no sign of violence evident on the clothing or the body. A 10 to 12 hour postmortem interval was initially estimated.

Autopsy Findings

At autopsy, performed five hours after discovery, the body was noted to be that of a muscular, well-developed white man. External examination failed to reveal any signs of violence. Severe rigidity and extensive lividity was noted. Examination of the lungs revealed bilateral small apical blebs and emphysema. Both lungs were congested and exhibited a hardness consistent with edematous turgescence. A reddish fluid was easily expressed with light pressure.

The heart was grossly normal, without evidence of ventricular hypertrophy. Ancilliary tests failed to disclose acute or chronic myocardial disease. Coronary arteries were patent. The normal amount of pericardial fluid was red-tinged.

The liver disclosed a moderately congested cut surface as did the spleen. The inflated stomach contained residue admixed with colored tablet fragments. A small yellow and round structure, later diagnosed as a single renal cyst, was noted in the right kidney. The rest of the organs were unremarkable.

Histopathological Examination

The only remarkable finding was severe high-protein aqueous fluid filling most of the alveoli with areas of red blood cell extravasation, showing pulmonary edema with hemorrhage. Generalized autolysis was diagnosed.

Drug Testing

Blood, urine, and pericardial fluid were submitted to the National Institute of Toxicology to be assayed for acidic, basic and neutral organic drugs using liquid-liquid extraction and further analysis by gas chromatography/nitrogen phosphorus detection. All presumptive positives were confirmed by gas chromatography/mass spectrometry. These routine screening procedures are described in detail elsewere [*7*].

The different kitchen tools found at the scene were separately washed with organic solvents under warm conditions, and the solutions obtained were further analyzed by the same chromatographic systems.

Results and Discussion

Table 1 presents the toxicologic data collected on the biological specimens. Blood was also tested for ethanol with a negative result. Data from the kitchen tools follows:

TABLE 1—*Drug concentrations in different body fluids.*

Drug (mg/L)	Blood	Urine	Pericardial fluid
Moclobemide	59.76	28.83	38.45
Clomipramine	1.69	2.45	3.16
Tramadol	10.89	1.15	3.34
Diazepam	2.08	1.01	3.13
Nordiazepam	0.82	0.68	N.D.
Caffeine	9.64	1.28	3.03

N.D.: Not detected.

• blue-greenish paste from glass and plastic bottle contained a mixture of caffeine, tramadol, moclobemide, clomipramine, diazepam and clorazepate.

• white-greenish powder from dipper and spoons contained tramadol, moclobemide and clorazepate.

• opened green capsules contained traces of tramadol, moclobemide, clomipramine, diazepam and clorazepate.

Since the history surrounding the victim suggested a fatal polydrug intoxication from suicide in a depressed patient, a comprehensive survey of the medical literature was performed in order to accurately interpret the toxicology results of this case.

An overall examination of the data shown in Table 1 suggested that the kinetic state could be the end of the absorptive period. Blood concentrations are higher than those from pericardial fluid, which are higher than those from urine, except those drugs with a large elimination half-life (such as diazepam) or a large volume of distribution (such as clomipramine). It is possible that death could have occurred two or four hours after ingestion of the beverage, which agrees with the postmortem interval estimated at the scene.

If we consider the blood concentrations of diazepam and nordiazepam together, they fall in the toxic range but do not reach the fatal threshold level. Even if the concentrations were elevated beyond the fatal threshold, another CNS depressant drug would be required to cause death [*8*].

The caffeine concentrations are far from the toxic level, so caffeine did not play an important role in this case. However, it was present in the glass and plastic bottle residues, indicating that coffee may have been mixed with the other ingredients.

Blood levels of tramadol are difficult to interpret since to our knowledge there are no fatal overdoses reported exclusively involving this drug. Tramadol is a new analgesic, a synthetic opiate agonist structurally related to morphine. Moreover, it has proven to be very safe without serious side effects when used to provide prolonged postoperative analgesia [*9*]. When compared with morphine, higher equipotent dose of tramadol resulted in transiently depressed rate of respiration, with absence of clinically relevant respiratory depression, while morphine caused apnea or considerable depression of ventilation [*10*]. The main side effects reported for tramadol are drowsiness, dizziness, fatigue, nausea, vomiting, constipation, dry mouth and sweating. Its effect on cardiovascular function and respiratory depression are minimal at therapeutic doses and it has low abuse potential [*11*]. In addition, tramadol may enhance the concentration of extraneuronal serotonin by interacting with serotonin transporter [*12*] resulting in inhibition of monoamine uptake mechanisms [*13*].

Blood concentration of moclobemide was about 20 to 60 times higher than therapeutic concentrations (1 to 3 mg/L) [*2*]. However, pure moclobemide overdose has a fairly benign course, even when very high doses are ingested [*1*] or patients attempt suicide by overdosing [*14*]. Therefore, moclobemide overdose should be ruled out.

The clomipramine blood concentration alone exceeds the fatal level to some extent (1 mg/L) [*8*], indicating that it played a significant role in the cause of death. However, the possibility of postmortem redistribution leading to higher blood concentrations cannot be excluded [*15*].

Eventually, we considered an alternative explanation in classifying the cause of death in this case. By evaluating the blood concentrations of moclobemide and clomipramine together it is reasonable to conclude that a fatal serotonin syndrome could have occurred.

This result has been recently reported after coingestion of both drugs in mixed overdoses [2,6]. This effect could be enhanced by tramadol or other opioids (such as meperidine, dextromethorphan) since they can increase the CNS serotonin content [4].

Some findings during scene investigation (such as severe rigor mortis, which could be the consequence of convulsions, muscle stiffness or hyperpyrexia) are consistent with the diagnosis of serotonin syndrome. In addition, the observed red-tinged pericardial fluid (carefully collected to avoid blood contamination) could fall in the context of those conditions causing rhabdomyolysis.

Therefore, by combining the history of this case and the toxicology findings, the forensic pathologist ruled that the cause of death was multiple drug intoxication leading very likely to fatal serotonin syndrome, and that the manner of death was suicide. However, if we bear in mind all the paraphernalia discovered during the scene investigation and the circumstances of the death, an accidental death from polydrug abuse should not be easily excluded. Interesting points to be considered include: all the implements were handled, several drugs were mixed in a dipper and agitated with spoons to get a paste, which was later placed into a plastic bottle with coffee and served in a glass, and clomipramine, moclobemide diazepam, and clorazepate were carefully introduced inside the green tramadol capsules for further ingestion. The Neuvonen cases [2] also used the drugs to get "high" and produce euphoria. Furthermore, in this case witnesses stated the day before the death of the victim, he was found cheerful but confused and disoriented.

This article is intended to assist medical examiners to recognize serotonin syndrome from scene investigation findings and toxicology reports, as well as to present a possible new method of drug abuse.

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