Fatal Serotonin Toxicity Caused by Moclobemide and Fluoxetine Overdose

Ming-Ling Wu[1,2], MD, MPH; Jou-Fang Deng[1], MD

Both moclobemide and fluoxetine are used in the treatment of depression, and have been shown to produce fewer side effects than conventional tricyclic antidepressants. A combination of moclobemide and fluoxetine has been used in refractory depression, however there is potential for severe serotonin toxicity. We describe a lethal case of serotonin toxicity in a 36 year-old woman after she ingested multiple drugs, including moclobemide 4500 mg, fluoxetine 200 mg, propranolol 300 mg and several benzodiazepines. The clinical features included coma, mydriasis, hyperthermia, tremor, hyperreflexia, rhabdomyolysis, renal failure and respiratory insufficiency. Eventually, the patient died of disseminated intravascular coagulation and circulatory collapse at 22.5 h postingestion. Toxicological analysis of the patient's blood confirmed high levels of moclobemide 150 μg/mL (therapeutic 1-3 μg/mL), fluoxetine 3750 ng/mL (therapeutic 47-469 ng/mL) and several benzodiazepines. In conclusion, a combination of moclobemide and fluoxetine should be avoided in depressed patients with high suicidal tendencies. Moreover, early recognition and aggressive intervention are the mainstays in the management of potentially life-threatening serotonin toxicity. *(Chang Gung Med J 2011;34:644-9)*

Key words: fluoxetine, moclobemide, serotonin toxicity

Serotonin toxicity is a predictable adverse drug reaction caused by excess intrasynaptic serotonin primarily resulting in activation of serotonin $_{2A}$ receptors in the central and peripheral nervous systems.[1,2] It is typically associated with combinations of drugs that augment serotonin synthesis, enhance its release, block its metabolism, inhibit its reuptake, or act as direct receptor agonists.[2] Serotonergic excess can also occur after overdose of a serotonergic drug.

Symptoms of serotonin toxicity are characterized by a clinical triad of (1) neuromuscular hyperactivity: tremor, clonus, myoclonus, hyperreflexia and in the advanced stage, pyramidal rigidity; (2) autonomic hyperactivity: diaphoresis, fever, mydriasis, tachycardia, moderately elevated blood pressure and tachypnea; and (3) altered mental status: excitement and agitation, with confusion in the advanced stages only.[3]

Moclobemide is a reversible selective inhibitor of monamine oxidase type A, with a short elimination half-life of 1-2 hours. It has a lower propensity for producing drug interactions than the first generation of irreversible, nonselective inhibitors of monamine oxidase.[4] Fluoxetine is a selective serotonin reuptake inhibitor (SSRI). Its half-life is 2-7 days, whereas that of its active metabolite "norfluoxetine" is 7-15 days.[5] Both moclobemide and fluoxetine are used in the treatment of depression, and have been shown to produce fewer side effects than conven-

From the [1]Division of Clinical Toxicology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan; [2]Department of Environmental and Occupational Medicine, Faculty of Medicine, School of Medicine, National Yang-Ming University, Taipei, Taiwan.

Received: Mar. 6, 2009; Accepted: Apr. 23, 2010

Correspondence to: Dr. Ming-Ling Wu, Division of Clinical Toxicology, Department of Medicine, Taipei Veterans General Hospital. 201 Sec. 2, Shih-Pai Rd., Taipei city 112, Taiwan, R.O.C. Tel: 886-2-28757525; Fax: 886-2-28739193;
E-mail: mlwu@vghtpe.gov.tw

tional tricyclic antidepressants. However fatal serotonin toxicity may develop after combined use of these two drugs.[6] We describe a case of full-blown serotonin toxicity with rhabdomyolysis, renal failure and disseminated intravascular coagulation (DIC) in addition to neurologic complications following intentional ingestion of a 10-day therapeutic dose of moclobemide and fluoxetine.

CASE REPORT

A 36-year-old woman was brought to the emergency room after she deliberately ingested multiple drugs. She was sent to a hospital nearby 5.5 h after ingestion. Her laboratory studies and electrocardiogram (ECG) were normal at that time and she underwent therapy with gastric lavage and activated charcoal. The serum tricyclic antidepressant level was 6.29 ng/ml (therapeutic level 100-300 ng/mL). Arterial blood gas analysis was pH 7.374, pCO_2 43.4 mmHg, pO_2 96.4 mmHg, and HCO_3 25.5 mmol/L. She was referred to our hospital about 9 h after ingestion of the drugs.

On arrival, the patient fell into a coma and her Glasgow coma scale was E2V1M1. Her blood pressure was 104/66 mmHg, pulse rate 89 beats per minute, respiratory rate 24 per minute and body temperature 40.6°C. Mydriasis, diaphoresis and generalized muscle twitching were also noted. Two 10 mg boluses of diazepam were given intravenously for control of seizure-like activity. Laboratory studies showed leukocytosis with a white blood cell count of 13,000/mL (84% neutrophils). Blood urea nitrogen, creatinine, creatinine phosphokinase and electrolytes were within normal limits. There were mild elevations of liver aminotransferses. Arterial blood gas analysis under oxygen at two liters per min was pH 7.4, pCO_2 41.8 mmHg, pO_2 41.2 mmHg, and HCO_3 27.4 mmol/L. The serial laboratory tests are summarized in the Table. Chest radiography disclosed no active lung lesions.

At 11.6 h postingestion, bradycardia, oxygen desaturation and a drop in blood pressure necessitated treatment with fluid resuscitation, atropine, vasopressors, intubation and mechanical ventilation. She was stabilized and admitted to the intensive care unit (ICU).

The patient had a history of major depression for several years and had attempted suicide once by taking an overdose of prescribed drugs. She was followed up in an outpatient psychiatric unit for one year and took regular medication including fluoxetine 20 mg per day; moclobemide 150 mg, propranol 10 mg, and alprazolam 0.5 mg, all three times a day; and estazolam 2 mg, bromazepam 6 mg, lorazepam 1 mg and midazolam 7.5 mg at bedtime. She took about a 10-day amount of prescribed medication and the estimated ingested doses were moclobemide 4,500 mg, fluoxetine 200 mg, propranolol 300 mg, estazolam 20 mg, bromazepam 60 mg, alprazolam 15 mg, lorazepam 10 mg and midazolam 75 mg.

Under mechanical ventilation in the ICU, her body temperature was 41.3°, pulse 140 beats/min, and blood pressure 70/30 mmHg, and her respiratory rate was mechanical ventilation dependent. There was no response to deep stimuli and the Glasgow coma scale was E1VTM1. Her pupils were 6 mm and isocoric without light reflex. The skin showed

Table Selected Hematological and Biochemical Findings in A Patient with Moclobemide and Fluoxetine Overdose

Laboratory findings (reference range)	5.5 h	9 h	18 h
White cell count (4,500-11,000/mL)	9,200	13,000	21,000
Hemoglobin (12-16 g/dL)	13.9	13.1	12.7
Platelets (150-400 x 1000/mL)	288	255	58
Sodium (135-147 mmol/L)	139	144	147
Potassium (3.4-4.7 mmol/L)	4.7	4.7	4.1
Glucose (65-115 mg/dL)	111	142	343
Blood urea nitrogen (7-20 mg/dL)	5	9	20
Creatinine (0.5-1.2 mg/dL)	1.1	1.0	2.4
Alanine aminotransferase (0-40 U/L)	35	43	
Aspartate aminotransferase (5-45 U/L)	38	46	
Creatinine phosphokinase (0-140 U/L)		60	3,718
Amylase (0-180 U/L)		45	122
γ-glutamyl transferase (4-51 U/L)		63	
pH (7.35-7.45)	7.374	7.425	7.592
pCO_2 (35-45 mmHg)	43.4	41.8	24.3
pO_2 (80-100 mmHg)	96	41.2*	195.4†
HCO_3 (22-26 mmol/L)	25.5	27.4	23.4

*: under oxygen two liters per minute; †: under FiO_2 100%.

severe sweating. She had unusual body movements including shivering and tremors. The four limbs were mildly rigid, the deep tendon reflexes were increased and the Babinski sign was positive. The ECG disclosed sinus tachycardia, a widening QRS and prolongation of the QT interval. At 18 h postingestion, the follow-up laboratory data showed her condition had deteriorated with leukocytosis (white blood cell count 21,000/mL) with a left shift, thrombocytopenia (platelets 58,000/mL) and elevated levels of creatinine (2.4 mg/dL), creatine phosphokinase (3,718 U/L), and glucose 343 mg/dL. Oral bleeding, ecchymosis, progressive hypotension and ventricular arrhythmias developed. Despite intensive treatment, she eventually died of DIC and circulatory collapse at 22.5 h postingestion. The determination of drug levels by a method using high performance liquid chromatography revealed high serum levels of moclobemide 150 μg/mL (therapeutic 1-3 μg/mL), fluoxetine 3750 ng/mL (therapeutic 47-469 ng/mL) and several benzodiazepines (estazolam 553 ng/mL, bromazepam 412 ng/mL, alprazolam 284 ng/mL, lorazepam 55 ng/mL, diazepam 175 ng/mL, and nordiazepam 163 ng/mL).

DISCUSSION

The typical clinical features of serotonin excess in humans are neuromuscular hyperactivity, autonomic derangement, and altered mental status.[1] Initially, our patient presented with coma and sustained tremor. Then she developed hyperthermia, and hypertonicity, which is a potentially life-threatening sign. Finally, rhabdomyolysis, renal failure, respiratory insufficiency, intractable hypotension and DIC ensued. The findings were consistent with a diagnosis of severe serotonin toxicity.

Based on current knowledge, serotonin toxicity develops due to actions at serotonin type 2 receptors in humans.[1] Central serotonin excess causes muscle hyperactivity which predisposes patients to hyperthermia, metabolic acidosis, rhabdomyolysis, impaired respiration, renal failure and DIC. The pathogenesis of DIC is not clear yet. It may arise as a consequence of hyperthermia and platelet activation.[2,7] Platelets contain serotonin in dense granules and have serotonin type 2 receptors, and may also contribute to development of coagulopathy and DIC with the release of platelet-derived serotonin.

Our patient had major depression. She was treated with moclobemide, fluoxetine, propranolol, and several benzodiazepines at a psychiatric clinic. Toxicological analysis of the patient's blood revealed high levels of moclobemide, fluoxetine and several benzodiazepines. In one report, patients ingesting up to 2,000 mg moclobemide alone showed only mild gastrointestinal symptoms or were asymptomatic.[8] Those ingesting 3000 to 4000 mg showed slight increases in blood pressure and depressed consciousness, while those ingesting 7000 to 8000 mg had fatigue, agitation, tachycardia, increased blood pressure, and mydriasis. In patients who ingested fluoxetine alone in Mill's study, the mean dosage was 341 mg in asymptomatic patients and 544 mg in symptomatic ones.[9] Our patient ingested 4,500 mg of moclobemide and 200 mg of fluoxetine and died of DIC and circulatory collapse within 24 hours postingestion.

Moclobemide is rapidly absorbed, reaching a peak plasma level within 0.5 to 2 hours after a single therapeutic dose. Blood concentrations following therapeutic administration of a single dose of 50-800 mg moclobemide are in the range of 0.36-7.76 μg/mL.[10] Post-mortem blood levels associated with assumed therapeutic use have been observed in the range of 0.2-2.1 μg/mL, while concentrations in lethal cases involving combined ingestion of moclobemide and other drugs were 1.9-58 μg/mL.[11,12] Blood concentrations in 3 reports of lethal overdoses of moclobemide alone were 15.5, 137, and 498 μg/mL.[10,13,14] Our patient had a blood moclobemide level of 150 μg/mL, which was a potentially lethal level.

Studies have reported that refractory depression might profit from a combination of moclobemide with other antidepressants, such as clomipramine or an SSRI, though the combination is associated with some risk of serotonin toxicity. However clinical concern was raised by an open study by Hawley et al. In that study, moclobemide (600 mg/day) was combined with either paroxetine or fluoxetine in patients with treatment-resistant depression. In 50 patients studied, there was a high rate of severe adverse events including one definite serotonin toxicity.[15] The Hawley group decided to stop their research because of high levels of moderately severe serotonergic side effects, especially with moclobemide plus venlafaxine. Isbister studied 106 moclobe-

mide overdoses from the Hunter Area Toxicology Service (HATS) database. Of these patients, 33 who ingested moclobemide alone and 52 who ingested moclobemide with a nonserotonergic drug did not have serotonin toxicity. One of the patients with a moclobemide-alone overdose (3%) developed serotonin toxicity. However, 52% of the 21 patients who ingested moclobemide combined with a serotonergic drug exhibited serotonin toxicity, even though the other serotonergic drug had often been ingested only in therapeutic quantities, not as an overdose. In 6 of these 21 cases (29%), severe serotonin toxicity developed with a body temperature > 38.5°C and muscle rigidity requiring intubation and paralysis.[16]

Moclobemide rarely precipitates serotonin toxicity in overdoses by itself, and it seldom produces significant serotonergic side effects in clinical use. The HATS database also disclosed an overdose of a SSRI alone produced only moderate serotonin toxicity in 14-16% of cases, but no serious sequele or fatalities.[17] The risk with moclobemide and serotonin reuptake inhibitors combined is almost certainly much lower than with older irreversible monoamine oxidase inhibitors and serotonin reuptake inhibitors combined. However, the combination of moclobemide and a serotonin reuptake inhibitor still has a predictable risk of serotonin toxicity.[4]

Management of serotonin toxicity begins with removal of the offending agents. Supportive care is the treatment of choice for most cases. Benzodiazepines are essential for management of serotonin toxicity, and can help control agitation and muscular hyperactivity. Moderate cases should have all thermal and cardiorespiratory abnormalities corrected and may benefit from the administration of serotonin antagonists. Patients with high blood pressure or tachycardia should be treated with short-acting agents such as esmolol or nitroprusside. Severe cases complicated by hyperthermia need to be treated aggressively, and should receive the above therapies as well as aggressive cooling, neuromuscular paralysis, endotracheal intubation and assisted ventilation.[1] Our case received only supportive care because the manifestations of severe serotonin effects had been overlooked, and because of the lethal combination doses of moclobemide and fluoxetine and the rapid progression of the illness. Physician's awareness of severe serotonin toxicity is important in treating these patients.

Serotonin toxicity is not an unusual event in psychopharmacological combination therapy. The pharmacokinetic and pharmacodynamic interactions between moclobemide and fluoxetine may result in some severe complications. Our patient received combination therapy with moclobemide and fluoxetine in therapeutic doses which did not cause a drug interaction. However, she developed lethal serotonin toxicity after intentional ingestion of only a 10-day amount. Although combinations of moclobemide and fluoxetine have been used in clinical practice, the possible risk of intentional overdose can not be overlooked. Therefore, these ill-advised combinations should be avoided in depressed patients with high suicidal tendencies.

REFERENCES

1. Boyer EW, Shannon M. The serotonin syndrome. N Eng J Med 2005;352:1112-20.
2. Dvir Y, Smallwood P. Serotonin syndrome: a complex but easy avoidable condition. Gen Hosp Psychiatry 2008;30: 284-7.
3. Dunkley EJ, Isbister GK, Sibbritt D, Dawson AH, Whyte IM. The Hunter Serotonin Toxicity Criteria: simple and accurate diagnostic decision rules for serotonin activity. QJM 2003;96:635-42.
4. Bonnet U. Moclobemide: therapeutic use and clinical studies. CNS Drug Rev 2003;9:97-140.
5. Fulton B, McTavish D. Fluoxetine: an overview of its pharmacodynamic and pharmacokinetic properties and review of its therapeutic efficacy in obsessive-compulsive disorder. CNS Drugs 1995;3:305-22.
6. Gillman PK. Serotonin toxicity, serotonin syndrome. Available form http://www.psychotropical.com/index.shtml Accessed March, 2009.
7. Mohammad-Zadeh LF, Moses L, Gwaltney-Brant SM. Serotonin: a review. J Vet Pharmacol Ther 2008;31:187-99.
8. Myrenfors PG, Eriksson T, Sandsted CS, Sjoberg G. Moclobemide overdose. J Intern Med 1993;233:113-5.
9. Mills KC. Serotonin syndrome: a clinical update. Crit Care Clin 1997;13:763-83.
10. Girous C, Horisberger B, Eap C, Augsburger M, Menetrey A, Baumann P, Mangin P. Death following acute poisoning by moclobemide. Forensic Sci Int 2004;140:101-7.
11. Druid H, Holmgren P. A compilation of fatal and control concentrations of drugs in postmortem femoral blood. J Forensic Sci 1997;42:79-87.
12. Musshoff F, Varchmin-Schultheiss K, Madea B. Suicide

with moclobemide and perazine. Int J Legal Med 1998;111:196-8.
13. Camaris C, Little D. A fatality due to moclobemide. J Forensic Sci 1997;42:954-5.
14. Gaillard Y, Pépin G. Moclobemide fatalities: report of two cases and analytical determination by GC–MS and HPLC-PDA after solid-phase extraction. Forensic Sci Int 1997;87:239-48.
15. Hawley CJ, Quick SJ, Ratnam S, Pattinson HA, McPhee S. Safety and tolerability of combined treatment with moclobemide and SSRIs: a systematic study of 50 patients. Int Clin Psychopharmacol 1996;11:187-91.
16. Isbister GK, Hackett LP, Dawson AH, Whyte IM, Smith AJ. Moclobemide poisoning: Toxicokinetics and occurrence of serotonin toxicity. Br J Clin Pharmacol 2003;56:441-50.
17. Isbister GK, Bowe SJ, Dawson AH, Whyte IM. Relative toxicity of selective serotonin reuptake inhibitors (SSRIs) in overdose. J Toxicol Clin Toxicol 2004;42:277-85.

Moclobemide 和 Fluoxetine 過量引起致死性神經激胺毒性

吳明玲[1,2] 鄧昭芳[2]

Moclobemide 和 Fluoxetine 都屬於抗憂鬱藥物，和傳統的三環抗鬱劑相比具有較少的副作用。我們報告一名服用 moclobemide 和 fluoxetine 自殺而引起神經激胺毒性的案例。病人在攝入多種藥物包括 4500 毫克 moclobemide、200 毫克 fluoxetine、300 毫克 propranolol 和數個苯二氮平類藥物，表現昏迷、瞳孔擴大、高體溫、全身震顫、反射增強、橫紋肌溶解症、腎衰竭和呼吸衰竭；22.5 小時後死於擴散性血管內凝血和循環衰竭。分析病人的血液證實高濃度的 moclobemide 150 μg/mL、fluoxetine: 3750 ng/mL 和苯二氮平類藥物。由於併用 moclobemide 和 fluoxetine 可能產生致死性神經激胺毒性，臨床醫師應認識此類中毒並及早採取積極性治療。(長庚醫誌 2011;34:644-9)

關鍵詞：選擇性神經激胺再吸收抑制劑，單胺氧化酶抑制劑，神經激胺毒性

[1]台北榮民總醫院 內科部 臨床毒物科；[2]國立陽明大學 醫學系與環境與職業衛生研究所
受文日期：民國98年3月6日；接受刊載：民國99年4月23日
通訊作者：吳明玲醫師，台北榮民總醫院 內科部 臨床毒物科。台北市112北投區石牌路二段201號。Tel: (02)28757525; Fax: (02)28739193; E-mail: mlwu@vghtpe.gov.tw