Safety of Mirtazapine in Overdose

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Introduction: We report 6 confirmed cases of substantial overdose with mirtazapine, a new antidepressant compound, that occurred up to January 1997 in the United States during postmarketing surveillance or in the clinical trials.

Results: In 6 patients, the mirtazapine doses ranged from 10 to 30 times the maximum recommended dose, and there were no serious adverse effects of overdose. Two patients at special risk, a 90-year-old man and a 3-year-old child, took higher-than-usual doses without serious sequelae. The 4 patients who combined other central nervous system (CNS) depressants with mirtazapine appeared to experience more CNS depression. One patient who ingested 60 mg of alprazolam had clinically significant respiratory depression in the emergency room but recovered fully within 24 hours.

Conclusion: After an overdose of substantial multiples of mirtazapine that exceed the maximum recommended daily dosage, the new antidepressant mirtazapine appears to be safe in a limited number of cases.

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Mirtazapine is a new centrally acting noradrenergic and specific serotonin antidepressant, with a 30-fold selectivity for α_2-adrenoceptors over α_1-adrenoceptors.[1] The blockade of presynaptic α_2-adrenergic autoreceptors and heteroreceptors results in the release of both norepinephrine and serotonin (5-HT).[2] Further, mirtazapine is a potent antagonist of 5-HT_2 and 5-HT_3 receptors and has no significant affinity for 5-HT_1 receptors; therefore, the released serotonin exerts its effect specifically upon 5-HT_1 receptors.[2] In clinical trials, mirtazapine showed good overall tolerability without serotonergic side effects, and it has a significantly lower incidence of anticholinergic and cardiovascular side effects than amitriptyline.[3]

Acute toxicity studies in mice and rats demonstrate that mirtazapine possesses relatively little acute toxicity (data on file, Organon, Inc., West Orange, N.J.). Oral LD_{50} values in male and female mice ranged from 600 mg/kg to 720 mg/kg, respectively, and oral LD_{50} values in the rat ranged from 320 mg/kg to 490 mg/kg. After the intraperitoneal administration of mirtazapine, death occurred about 1 hour after dosing, and the clinical symptoms observed included reduced locomotion, motor incoordination, twitches, convulsive seizures, labored respiration, hypersalivation, lacrimation, and mydriasis. The incidence and severity of clinical symptoms occurred at all dose levels and were generally dose related. Subchronic oral toxicity studies in beagles dosed at 20 mg/kg and 80 mg/kg resulted in vomiting, reduced motor activity, and bodily tremors, but no mortality occurred during the 13-week study (data on file, Organon, Inc., West Orange, N.J.).

Suicide attempts in patients on antidepressant medications represent a problem that should be given careful consideration when choosing what to prescribe. Tricyclic antidepressants (TCAs) are known to have a low therapeutic index, and newer antidepressants such as serotonin selective reuptake inhibitors (SSRIs) are often preferred because of their relative safety when compared with TCAs. In addition, appropriate cautions must be kept in mind when combining antidepressants or after patients have recently discontinued monoamine oxidase inhibitor therapy, because the serotonin syndrome can have serious consequences.[4,5]

The safety of mirtazapine in combination with other antidepressants in overdose has not been determined. There is 1 reported case of overdose and death in which mirtazapine was taken in combination with amitriptyline and chlorprothixene.[6] Plasma levels of mirtazapine were consistent with a dose of 30 to 45 mg, whereas plasma levels of amitriptyline and chlorprothixene were found to be at toxic levels. In addition, a recent published foreign report[7] described an overdose by an 81-year-old woman who ingested 900 mg of mirtazapine and 210 mg of midazolam. The patient became semicomatose, without other neurologic signs or symptoms, but showed no significant changes in vital signs or respiratory complications. The patient showed transitory somnolence after she awoke 1 hour following admission to the intensive care unit, but no other adverse experiences were reported. The following additional cases from mirtazapine clinical trials, and general use since its introduction in the United States, illustrate the lack of serious sequelae after mirtazapine overdose.

Table 1. Patient Demographics

Case	Age (y)	Sex	Dose of Mirtazapine[a]	Other Medications Used in Overdose	Past Medical History
1	27	M	975 mg (22×)	Clonazepam 30 mg	Generalized anxiety disorder, substance abuse
2	90	M	75 mg	None	Mild dementia/agitation
3	25	F	900 mg (20×)	None	Multiple antidepressants
4	3	F	60 mg	None	Not significant
5	32	F	900 mg (20×)	Toxicologic screen positive for tricyclic antidepressants	Suicide attempts, personality disorder, multiple antidepressants
6	49	F	450 mg (10×)	1 pint vodka	Alcohol abuse, suicide attempts, hypertension
7	65	F	1350 mg (30×)	Alprazolam 60 mg	Suicide attempts, anxiety disorder, eating disorder (anorexia)
8	57	F	750 mg (17×)	Alprazolam 25 mg, clonazepam 50 mg	Suicide attempts

[a]Number in parentheses indicates the multiples by which the dose taken was above the maximum recommended daily dose of 45 mg.

CASE REPORTS

The following is a review of 6 cases of substantial overdose with mirtazapine, which was ingested in doses ranging from 10 to 30 times the highest recommended dose of 45 mg/day. Two additional case reports of patients at special risk, a 90-year-old man and a 3-year-old child, were included because of their ages. Overdose in patient 1 occurred during the clinical trials, and overdose in the remaining cases occurred from August 1996 to January 1997 after the introduction of mirtazapine in the United States. Limited postmarketing surveillance information is available for these patients, and only the clinically relevant data that could be obtained on follow-up is presented in the tables.

Table 1 reviews the age, sex, dose of mirtazapine taken in overdose, any other medications ingested in excess of a standard dose, and past medical history for each patient. Patient 2, a 90-year-old man, received 75 mg of mirtazapine on 2 separate occasions and was taken to the emergency room, where he was described as confused, lethargic, and as having a dry mouth. He was treated and discharged back to the nursing home. Patient 4, a 3-year-old child, represents an accidental overdose of 60 mg of mirtazapine. The child was admitted to the emergency room for several hours and was found to be alert, responsive, and interactive. The patient had a rapid heart rate and recovered without adverse sequelae. The remaining patients all had a diagnosis of major depression, and patients 5 through 8 had a history of previous attempts at suicide. All patients recovered without adverse sequelae, and 4 of the patients (patients 1, 6, 7, and 8) also ingested other central nervous system depressants.

Table 2 provides all pertinent information that could be obtained during postmarketing surveillance. The majority of patients who were admitted to the emergency room did not have any significant electrocardiogram (ECG) changes. Patients 1, 3, and 4 had a rapid heart rate, and patient 6 experienced changes in her ECG. For patient 1, the ECG was normal about 16 hours after overdosing with mirtazapine. No additional information could be obtained for patients 2, 6, and 8. No ECG information is available for patient 3. Patient 5 had a 12-lead ECG, and no conduction abnormalities were noted; blood pressure was normal at admission. However, the patient was kept in the hospital for 24 hours because the elimination half-life of mirtazapine is 20 to 40 hours.

Four patients (patients 1, 2, 6, and 7) experienced central nervous system (CNS) depressant effects, which were possibly attributable to either advanced age or the concomitant ingestion of other CNS depressants. All patients except the patient in case 7 became more alert and responsive after treatment with either supportive measures or activated charcoal. No additional information could be acquired on the follow-up of patient 7 without patient consent, which was not obtained.

DISCUSSION

Safety in overdose is an important criterion in distinguishing between "safe" and "less safe" antidepressants. In their review of the safety of antidepressants, Swinkels and de Jonghe[8] state that an antidepressant is defined as "safe" when exposure to 14 times the therapeutic dose does not result in a threat to life in a healthy adult of average body weight. This knowledge is of importance to those with outpatient practices where depressed patients are more commonly seen. These patients commonly receive at least a 2-week supply of medication, which is often enough for a life-threatening overdose. Antidepressants are considered "safe" when a 2-week supply is not life-threatening in overdose.[8]

Overall, mirtazapine overdoses ranged from 10 to 30 times the prescribed dose. All patients recovered, and there were no serious adverse effects of overdose with mirtazapine. No seizures were reported, and no clinically significant changes in either vital signs or the ECG were reported. The patients who ingested mirtazapine with other CNS depressants experienced greater central nervous system depression than other patients, and significant respiratory depression occurred in 1 case involving a concomitant overdose with a benzodiazapine.

The lack of serious symptoms with mirtazapine overdose sharply contrasts with symptoms seen in overdose

Table 2. Emergency Room Sequelae*

Case	Signs and Symptoms Upon Admission to ER	Treatment in ER	Signs and Symptoms and/or Laboratory Work After ER Treatment	Discharge Summary
1	Disoriented and drowsy; impaired memory of recent events; ECG = rapid heart beat; laboratory results = wnl	Observation only	Drowsiness disappeared after 16 h, repeat ECG = wnl	Transferred to psychiatric ward for 3 d Discharged to home 2½-week follow-up: vital signs, laboratory results, ECG = wnl
2	Confused, lethargic, dry mouth; HR = 88; BP = 90/60	Intravenous fluids	No ECG changes	Discharged to nursing home
3	Conscious, coherent, responding to stimuli, agitated, and restless; HR = 130; RR = 52	Gastric lavage: 10 h after ingestion of mirtazapine	ECG/laboratory results not available	Admitted to ICU 1½ d Transferred to psychiatric ward for 6 d Discharged to home
4	Alert, responsive, interactive, but more subdued than normal; HR = 100; BP = 70/46; RR = 20	15 mL ipecac with water: patient vomited	Neurologic examination = wnl; ECG = HR of 139; HR = 120; BP = 74/56; RR = 20	In ER for several h and then discharged to home
5	Alert and oriented; ambulatory; positive gag reflex intact; 12-lead ECG = no conduction abnormalities; HR = 92; BP = 143/84; RR = 18	Activated charcoal	Toxicology screen positive for tricyclic antidepressants; no seizures, blurred vision, or dizziness. Laboratory electrolytes and SMA results = wnl; HR = 74; BP = 100/53; RR = N/A	Admitted to hospital for 24 h and then discharged
6	Lethargic, disoriented, and not responding to questions; weak gag reflex; ECG = T waves inverted in aVL, V_1, and V_2, no tachycardia; HR = 80; BP = 139/92; RR = 16	Gastric lavage with activated charcoal	More alert and responsive; blood work: (1) alcohol level = 0.32; (2) CBC, electrolytes, BUN, cr, and BS results = wnl; (3) toxicology screen = negative for amphetamines, benzodiazepines, barbiturates, PCP, and tricyclic antidepressants	Complaints of dizziness and somnolence; vital signs the day after overdose: ECG = T waves inverted in aVL, V_1, and V_2; BP = 160/86
7	Unresponsive to verbal stimuli; no gag reflex; respiratory depression; hemodynamically stable; pupils reactive to light; thyroid not palpable; pharynx clear	Intubated after succinylcholine and midazolam given Gastric lavage with 50 mg of charcoal with sorbitol	Laboratory results: (1) urine drug screen = positive for benzodiazepines, negative for barbiturates, tricyclic antidepressants, and opiates; (2) blood ethyl alcohol < 0.01%; (3) acetaminophen = 1.2 µg/mL; (4) salicylates < 0.5 µg/mL. ECG = wnl; HR = 84; BP = 158/74; RR = 0 (spontaneous) and 12 (ventilator-assisted)	Admitted to hospital Extubated after 2 d
8	Conscious, responsive	Information not available	Information not available	Admitted to hospital for 2 d and discharged

*Abbreviations: BP = blood pressure; BS = blood sugar; BUN = blood urea nitrogen; CBC = complete blood count; cr = creatinine; ECG = electrocardiogram; ER = emergency room; HR = heart rate; ICU = intensive care unit; Labs = results from standard laboratory chemistries; PE = physical examination; RR = respiration rate; wnl = within normal limits.

with tricyclic antidepressants, in which a lethal dose can be as low as 8 to 10 times greater than a typical therapeutic dose.[9] Electrocardiographic abnormalities have been observed in 70% to 90% of patients who present with acute TCA poisoning, and fatal overdoses are most often the consequence of heart block and/or arrhythmias.[10,11] In a limited number of cases, mirtazapine appeared to be safe in overdose after the ingestion of substantial multiples of the maximum recommended daily dosage.

Drug names: alprazolam (Xanax), amitriptyline (Elavil and others), chlorprothixene (Taractan), clonazepam (Klonopin), midazolam (Versed), mirtazapine (Remeron), succinylcholine (Anectine and others).

REFERENCES

1. de Boer T. The pharmacologic profile of mirtazapine. J Clin Psychiatry 1996;57(suppl 4):19–25
2. de Boer T, Ruigt GSF, Berendsen HHG. The α_2-selective adrenoceptor antagonist ORG 3770 (mirtazapine, Remeron®) enhances noradrenergic and serotonin transmission. Hum Psychopharmacol 1995;10(suppl): 107s–118s
3. Montgomery SA. Safety of mirtazapine: a review. Int Clin Psychopharmacol 1995;10(suppl 4):37–45
4. Power BM, Pinder M, Hackett LP, et al. Fatal serotonin syndrome following a combined overdose of moclobemide, clomipramine and fluoxetine. Anaesth Intensive Care 1995;23:499–502
5. Hoes MJ, Zeijpveld JH. Mirtazapine as treatment for serotonin syndrome [letter]. Pharmacopsychiatry 1996;29:81
6. Remeron [package insert]. West Orange, NJ: Organon Inc; 1996
7. Hoes MJ, Zeijpveld JH. First report of mirtazapine overdose. Int Clin Psychopharmacol 1996;11:147
8. Swinkels JA, de Jonghe F. Safety of antidepressants. Int Clin Psychopharmacol 1995;9(suppl 4):19–25
9. Frommer DA, Kulig KW, Marx JA, et al. Tricyclic antidepressant overdose: a review. JAMA 1987;257:521–526
10. Kopera H. Antidepressants in cardiac patients. In: Wheatley D, ed. Stress and the Heart. New York, NY: Raven Press; 1981:191–205
11. Glassman AH, Roose SP, Giardina E-GV, et al. Cardiovascular effects of tricyclic antidepressants. In: Meltzer HY, ed. Psychopharmacology: The Third Generation of Progress. New York, NY: Raven Press; 1987: 1437–1441