haloperidol. Gen Hosp Psychiatry 1979;1:240–6.
7. Shulman R. Haloperidol therapy for agitated cardiac patients. Int Drug Ther Newletter 1984;19(2):8.
8. Ayd FJ Jr. Haloperidol: 20 years clinical experience. J Clin Psychiatry 1978;39:807–14.
9. Settle EC Jr, Ayd FJ Jr. Haloperidol: a quarter century of experience. J Clin Psychiatry 1983;44:440–8.
10. Adams F. Neuropsychiatric evaluation and treatment of delirium in the critically ill cancer patient. Cancer Bull 1984;36:156–60.
11. Sos J, Cassem NH. Managing postoperative agitation. Drug Therapy 1980;10:103–6.
12. Cassem NH. Critical care psychiatry. In: Shoemaker WC, Thompson WL, Holbrook PR, eds. Textbook of critical care. Philadelphia: WB Saunders, 1984;981–9.
13. Ayd FJ Jr. Intravenous haloperidol-lorazepam therapy for delirium. Int Drug Ther Newsletter 1984;19(9):33–5.
14. Dencker SJ. High-dose treatment with neuroleptics in the acute phase of mental disease. Proc Roy Soc Med 1976;69(suppl 1):32–4.

Extrapyramidal Signs Following Zimelidine Overdose

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A 35-year-old woman with depression attempted suicide by taking an overdose of zimelidine (5 g), which was confirmed by zimelidine and norzimelidine plasma levels. Physical examination and repeat EKGs performed 2, 6, 9, and 12 hours later showed no alteration in her level of consciousness and only a slight increase in QT duration. However, the patient exhibited a distinct extrapyramidal syndrome, a finding consistent with animal data suggesting that zimelidine may possess some dopamine-receptor blockade properties. (J Clin Psychopharmacol 1985;5:347–349)

OVERDOSAGE of tricyclic antidepressants may result in serious complications, such as cardiotoxicity, respiratory depression, and convulsions, and remains a problem in the management of depressed patients.[1] New antidepressants not chemically related to tricyclics have been recently developed and appear to possess less toxic potential.

Zimelidine has been the first antidepressant marketed with specific serotonin reuptake inhibition properties.[2] Its cardiac toxicity appears to be low.[3] However, recent animal data have shown that zimelidine affects striatal dopamine turnover and tyramine concentrations in a fashion similar to that observed for neuroleptics and suggest that it may induce similar side effects.[4,5] The following case report of zimelidine overdose supports both the cardiac safety and the possibility of extrapyramidal side effect induction by this antidepressant.

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Case Report

A 35-year-old woman had been hospitalized 4 times since age 17 for recurrent major depressive disorder with melancholia. During her last hospitalization at the University Hospital of Liège, Belgium, her physical examination, EKG, chest x-ray, and routine laboratory tests were normal, and she was treated with zimelidine, 200 mg/day, with clinical improvement after 2 weeks of treatment, allowing a hospital discharge 2 weeks later. The patient was followed on an outpatient basis without change in pharmacologic therapy. Four months after hospitalization, the patient attempted suicide by ingesting 5 g of zimelidine (25 tablets at 200 mg) at 9 a.m. No other medication or alcoholic beverage was taken. She was admitted to the emergency room of the University Hospital of Liège 2 hours later (11 a.m.) and discharged the same day at 10 p.m. Complete physical examinations (including EKG) were performed at 11 a.m., 3 p.m., 6 p.m., and 9 p.m.; moreover, blood samples were collected at 11 a.m., 3 p.m., and 9 p.m. for measurement of zimelidine and norzimelidine (the major metabolite of zimelidine) by gas chromatography.[6] The blood toxicologic screening for alcohol and psychotropic drugs was negative. No treatment was administered. During this hospitalization, the patient's level of consciousness remained totally unaltered. The evolution of selected cardiac and neurologic parameters (compared to physical examination and EKG performed during the previous hospitalization 4 months earlier, after a 2-week drug-free period), with zimelidine and norzimelidine plasma levels, is shown in Table 1. The EKG did not reveal any significant modification compared to baseline drug-free record, except for a slight increase in QT duration. Compared to the baseline

TABLE 1. Changes over time in selected clinical and EKG parameters following zimelidine overdose at 9 a.m.

	Baseline	11 a.m.	3 p.m.	6 p.m.	9 p.m.
Blood pressure (mm Hg)	115/80	115/80	115/80	120/80	120/80
EKG:frequency per minute	100	96	88	80	90
AV (sec)	0.13	0.14	0.15	0.16	0.13
QT (sec)	0.36	0.40	0.40	0.41	0.39
Tremor[a]	0	+++	+++	++	+
Rigidity[a]	0	+++	+++	++	+
Zimelidine plasma level (ng/ml)		747	1985		433
Norzimelidine plasma level (ng/ml)		1213	1995		1238

[a] +, slight; ++, moderate; +++, marked.

neurologic examination, however, examinations 2 and 6 hours following zimelidine overdose (performed by two neurologists) were characterized by marked parkinsonian tremor and rigidity (with a distinct cogwheeling), which had decreased 9 hours after the overdosage. A physical examination performed 1 week later did not show any residual neurologic sign.

Discussion

The peak plasma levels of zimelidine (1985 ng/ml) and norzimelidine (1995 ng/ml) measured in this patient are consistent with the overdose of 5 g and much higher than the plasma steady state levels of zimelidine and norzimelidine (100 and 500 ng/ml, respectively) reported in a group of patients with endogenous depression after 2 weeks of treatment with zimelidine, 150 mg/day.[7] The current levels of zimelidine and norzimelidine are also much higher than those reported 12 hours following a 1.75-g overdosage (600 and 380 ng/ml, respectively).[8] Finally, the evolution of plasma levels is in agreement with the longer half-life of norzimelidine compared to the parent compound (15.5 vs. 5.1 hours).[9]

This case report suggests low toxicity of zimelidine. Indeed, after an overdose representing 25 times the daily dose, we observed only minimal EKG modification, without respiratory depression or epileptic seizures. Moreover, the absence of diminished level of consciousness following this overdose is in agreement with zimelidine's reported lack of sedative effect.[10] These findings confirm a previous report of zimelidine overdose without sedation and with only insignificant EKG T-wave changes following an acute intake of 1.75 g.[8] Drowsiness and vomiting were the only symptoms noted following the ingestion of 2.8 g of zimelidine and an unknown amount of alcohol[11]; however, convulsions were reported in another patient with a family history of epilepsy who had taken about 1.7 g of zimelidine, despite the administration of emetic within the 30 minutes of the ingestion.[12]

To the authors' knowledge, this is the first report of extrapyramidal signs related to zimelidine. In this regard, zimelidine (in addition to its serotonergic uptake blockade properties) may exhibit neuroleptic-like dopamine-receptor blockade activity[4,5] (even if its affinity for postsynaptic antagonistic dopamine receptors in rat striatal tissue in vitro is very low[2]). Zimelidine produces an increase in dopamine turnover in animals, as shown by its ability to increase levels of both rat brain dopa after aromatic-L-aminoacid decarboxylase inhibition[13] and of rat and mouse striatal homovanillic acid.[4,5,14] Moreover, zimelidine reduces mouse striatal *p*-tyramine and increases mouse striatal *m*-tyramine.[5] These effects are all similar to those of chlorpromazine and other neuroleptic drugs.[15–18] Therefore, this case report provides support for the observation of Juorio and Boulton[5] that zimelidine may possess some of the side effects of neuroleptic drugs, especially if administered at the high dose levels.

The data from this case report would also be viewed from another perspective. Tremor and rigidity have been described as signs of the serotonin syndrome, which consists of a paradoxical excitatory reaction which follows the administration of a serotonin precursor (tryptophan of 5-hydroxytryptophan) in animals pretreated with drugs that further increases the availability of serotonin in the central nervous system, such as monoamine oxidase inhibitors (MAOI).[19] Moreover, the serotonin syndrome has also been reported in rodents receiving drugs which, like zimelidine, inhibit serotonin reuptake (e.g., clomipramine or fluoxetine) following pretreatment by an MAOI or in patients given clomipramine or tryptophan associated with an MAOI.[19] However, dopamine may contribute to the expression of the syndrome, as prior depletion of brain dopamine with α-methyl-*p*-tyrosine prevents the usual increase in activity following an MAOI plus tryptophan.[20]

In fact, various interactive neurotransmitter systems are involved in the physiology of the nigrostriatal tract: dopaminergic, cholinergic, serotonergic, adrenergic, and opioid.[21] Besides its serotonergic and possibly dopaminergic properties, zimelidine exhibits slight noradrenergic reuptake inhibitor properties and low agonistic affinity for α-adrenergic receptors as well as limited anticholinergic activity,[2] which may also contribute to the appearance of extrapyramidal signs.

It is unclear, however, whether these particularities of the drug are related to the incidence of other neurologic side effects (Guillain-Barré syndrome) that led to the withdrawal of the drug from the market.[22]

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References

1. Crome P. Antidepressant overdosage. Drugs 1982;23:431–61.
2. Heel RC, Morley PA, Brogden RN, Carmine AA, Speight TM, Avery GS. Zimelidine: a review of its pharmacological properties and therapeutic efficacy in depressive illness. Drugs 1982;24:169–206.
3. Pottage A, Groschinsky Grind M. Cardiovascular effects of zimelidine. Acta Psychiatry Scand 1983;68(suppl 308):125–30.
4. Juorio AV. The effect of zimelidine of brain dopamine (DA) turnover and tyramine (TA) concentration. Paper presented at the 5th Catecholamine Symposium, Abstract 249 in Prog Neuropsychopharmacol Biol Psychiatry (Suppl).
5. Juorio AV, Boulton AA. The effects of zimelidine and amitriptyline on the brain concentration of some indolic and phenolic monoamines in the mouse. Eur J Pharmacol 1984;97:191–6.
6. Hogberg K, Lindgren J-E, Hogberg T, Ulff B. Simultaneous GLC determination of zimelidine and norzimelidine. Synthesis of secondary amines as closely related internal standards. Acta Pharm Suec 1979;16:299–308.
7. Hansen LB, Thomsen IS, Vestegard P, Larsen NE, Hvidberg EF. Plasma levels of zimelidine and norzimelidine in endogenous depression. Psychopharmacology 1980;69:157–60.
8. Georgotas A, Mann J, Bush D, Gershon S. Safety data on zimelidine hydrochloride following an overdose. Acta Psychiatr Scand 1981;63(suppl 290):257–61.
9. Brown D, Scott DHT, Scott DB, Meyer M, Westerlund D, Lundstrom J. Pharmacokinetics of zimelidine: systemic availability of zimelidine and norzimelidine in human volunteers. Eur J Clin Pharmacol 1980;17:111–6.
10. Seppala T, Linnoila M. Effects of zimelidine and other antidepressants on skilled performance: a comprehensive review. Acta Psychiatr Scand 1983;68(suppl 308):135–40.
11. Loudon JB, Tiplady B, Ashcroft GW, Waddell JL. Zimelidine and amitriptyline in the treatment of depressive illness in general practice. Acta Psychiatr Scand 1981;63(suppl 290):454–63.
12. Simpson RJ, Lawton DJ, Watt MH, Tiplady B. Effect of zimelidine, a new antidepressant, on appetite and body weight. Br J Clin Pharmacol 1981;2:96–8.
13. Carlsson A, Lindqvist M. Effects of antidepressant agents on the synthesis of brain monoamines. J Neural Transm 1978;43:73–91
14. Waldmeier PC. Effects of antidepressant drugs on dopamine uptake and metabolism. J Pharm Pharmacol 1983;34:391–8.
15. Andén N-E, Roos B-E, Werdinius B. On the occurrence of homovanillic acid in brain and cerebrospinal fluid and its determination by a fluorometric method. Life Sci 1963;2:448–58.
16. O'Keeffe R, Sharman DF, Vogt M. Effect of drugs used on psychosis on cerebral dopamine metabolism. Br J Pharmacol 1970;38:287–304.
17. Juorio AV. Effects of chlorpromazine and other antipsychotic drugs on mouse striatal tyramines. Life Sci 1977;20:1663–8.
18. Juorio AV. Drug-induced changes in the formation, storage and metabolism of tyramine in the mouse. Br J Pharmacol 1979;66:377–84.
19. Gerson SC, Baldessarini RJ. Motor effects of serotonin in the central nervous system. Life Sci 1980;27:1435–51.
20. Green AR, Grahame-Smith DG. The role of brain dopamine in the hyperactivity syndrome produced by increased 5-hydroxytryptamine synthesis in rats. Neuropharmacology 1974;13:949–59.
21. Penney JB, Young AB. Speculations on the functional anatomy of basal ganglia disorders. Ann Rev Neurosci 1983;6:73–94.
22. Nilsson BS. Adverse reactions in connection with zimelidine treatment: a review. Acta Psychiatr Scand 1983;68(suppl 308):115–9.

Correction

In the August issue (vol. 5, no. 4), page 248, the title of the letter should read "Managing a Case of Bipolar Disorder, Diabetes, and Hypertension."