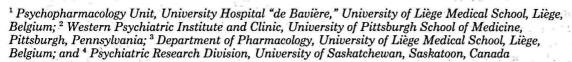
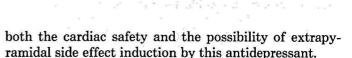
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Extrapyramidal Signs Following Zimelidine Overdose

MARC ANSSEAU, MD,¹ CHARLES F. REYNOLDS III, MD,² DAVID J. KUPFER, MD,² ADRIENNE DOUMONT, MD,¹ VINCENT GEENEN, MD,¹ ALBERT E. DRESSE, MD, PHD,³ AND AUGUSTO V. JUORIO, PhD⁴





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

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. 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

Address requests for reprints to: Dr. M. Ansseau, Psychopharmacology Unit, University Hospital "de Bavière," B-4020 Liège, Belgium.

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 | 115/80 | 115/80 | 2 7 2 2 | 120/80 | |
| (mm Hg) | 28 8 | , a . | 14.11 | 255 E | |
| EKG:frequency | 4 2 | | | | |
| 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 | 0 | +++ | +++ : | ++ | + |
| Zimelidine plasma | | 747 | 1985 | | 433 |
| level (ng/ml) | d 4. | n 9 | K 8 | a | |
| 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. 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). 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).

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 alcohol¹¹: 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 dopaminereceptor blockade activity4,5 (even if its affinity for postsynaptic antagonistic dopamine receptors in rat striatal tissue in vitro is very low2). 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 inhibition13 and of rat and mouse striatal homovanillic acid. 4,5,14 Moreover. zimelidine reduces mouse striatal p-tyramine and increases mouse striatal m-tyramine. 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 Boulton⁵ 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. 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, 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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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."