CASE REPORT

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Fatal Intoxication by Remoxipride

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ABSTRACT: The case history and toxicologic findings of a 23-year-old woman who committed suicide with Remoxipride are described. Remoxipride® is a recently developed neuroleptic drug of the benzamide type. Remoxipride was detected in the liver, stomach content, blood, and urine. The concentration of Remoxipride in the blood was 230 mg/L. The recommended therapeutic level for Remoxipride should not exceed 7 to 8 mg/L. The victim had no blood alcohol, but an ethanol concentration of 0.048 g/100 L was detected in the urine. The mechanism of death from Remoxipride intoxication is not known. In clinical studies, sinus bradycardia and infrequent supraventricular and ventricular ectopic beats have been noted.

KEYWORDS: pathology and biology, toxicology, Remoxipride, suicide, medicolegal autopsy, intoxication

Remoxipride, S-3-bromo-*N*-[(1-ethyl-2-pyrrolidinyl)methyl]-2,6-dimethoxybenzamide hydrochloride monohydrate, is a substituted benzamide that is being marketed by Astra Pharmaceuticals, Sweden, as a potential neuroleptic drug. As yet, the drug was used in a clinical trial at the university mental hospital which also supervises the use. The toxicity of the drug has been considered low grade though adverse events such as tiredness, restlessness, headache, concentration disturbances, nausea, dizziness, salivary gland dysfunction, dyspepsia, muscle pain, and muscle weakness have been reported in clinical studies with volunteers [*1*]. A survey of the literature failed to reveal reports of fatalities from overdoses of Remoxipride.

Case History

A 23-year-old female was found dead in her home. She had, in her father's words, suffered from "a crisis of growing up," for which she had received psychiatric treatment. Once she had cut the electric cords of her refrigerator, an act which was regarded as an attempt of self-destruction. She had not shown other suicidal tendencies. At the scene were found an empty box of triazolam tablets and three bottles that had contained Remoxipride tablets.

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Autopsy Findings

The body was 171 cm long and weighed 70 kg. The face and fingernails were moderately bluish. The brain weighed 1565 g. Apart from the edema, the brain was grossly and microscopically unremarkable. There was blood-tinged froth in the airways. The lungs were rubbery with microscopic signs of edema and vascular congestion. The heart weighed 270 g. It was grossly and microscopically unremarkable. The stomach contained some 300 mL of light-yellow thick fluid with a large number of small whitish flakes. The contents of the

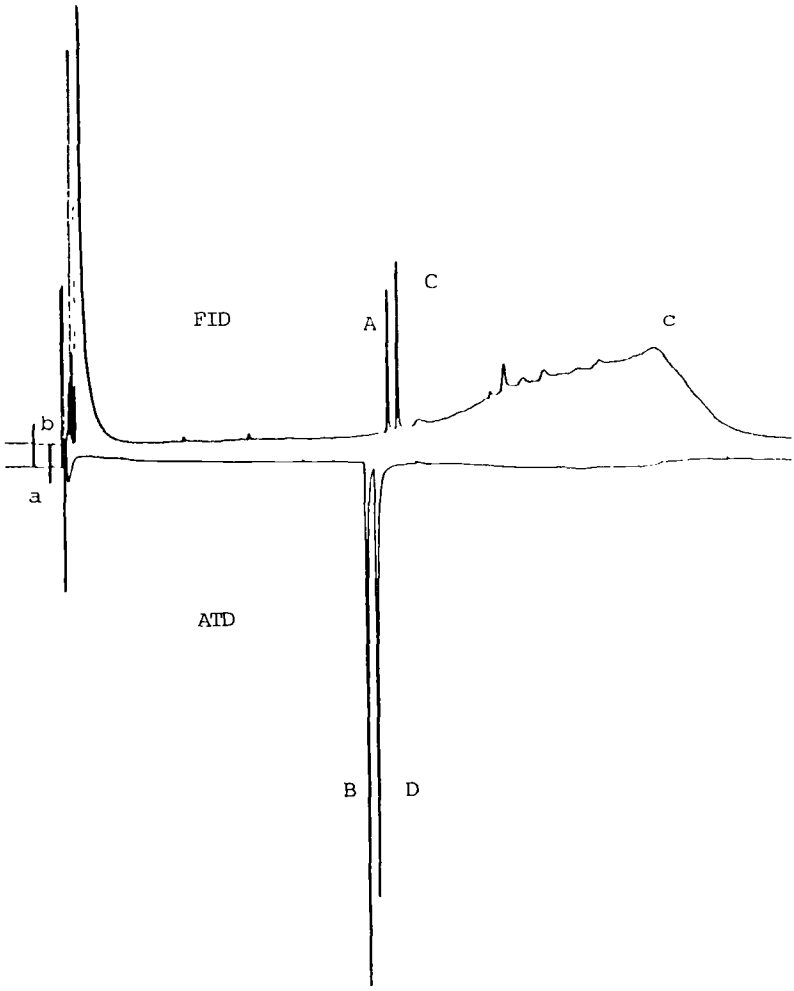

FIG. 1—*Detection of Remoxipride using a dual channel capillary gas chromatograph. Dibenzepine was used as an internal standard. The ATD channel analysis starts at* a *and the FID channel analysis at* b. *The dibenzepine peaks are at* A *and* B *and the remoxipride peaks at* C *and* D. *The analysis was finished at* c.

duodenum and the proximal half of the small intestine had a similar appearance. The liver weighed 1790 g. It showed focal subcapsular steatosis. The kidneys, spleen, pancreas, and adrenal glands were of normal appearance. There was no odd smell of the body and no findings that clearly suggested the mechanism of death.

Toxicologic Analysis

A 10-g liver sample was digested with subtilisin using a modification of Hammond and Moffat's method [*2*]; Soerensen's phosphate buffer (pH 7.4) was used instead of the original Tris buffer. Remoxipride was detected in the basic extract (pH 11 with ammonia, ether) of the digested liver by using thin-layer chromatography. The solvent system was a mixture of acetone, toluene, ethanol, and concentrated ammonia (150 mL + 150 mL + 20 mL + 2 mL), and the plates were Merck 5554. The rate frontier value of Remoxipride was 0.4 and it could be visualized with ultraviolet light and Dragendorf's reagent (yellow spot). For quantitative analysis, Remoxipride was extracted with heptane containing 1.5% isoamyl alcohol from basic blood and homogenized organ samples. Micromat HRGC 412, a dual channel capillary gas chromatograph equipped with two SE 54 columns and flame-ionization (FID) and alkali-thermo-ionization (ATD) detectors, was used. The temperature program started at 140°C and was increased 8°C/min up to 240°C. Dibenzepine was used as an internal standard and the relative retention time of remoxipride was 1.04 (Fig. 1); the recovery was 80%. Remoxipride was also identified using mass spectrometry (Hewlett Packard 5970). It has only one main peak at 98 *m/z* and a minor peak at 245 *m/z* (Fig. 2). Remoxipride was found as follows: blood 230 mg/L, urine 220 mg/L, liver 490 mg/kg, and stomach contents 5000 mg/kg.

No triazolam could be detected when tested with chromatographic methods. An ethanol concentration of 0.048 g/100 L was detected in the urine.

Discussion

Remoxipride is rapidly absorbed, and mean maximum plasma concentrations are obtained within 1.5 h after administration of an oral aqueous solution [*1*]. The elimination half-time of Remoxipride ranges from 3 to 14 h, mean value 4.9 h, after single oral doses, with slightly shorter half-lives after repeated oral doses. Remoxipride is excreted in urine in both the unchanged form and as a metabolite.

In clinical studies, sinus bradycardia with secondary electrocardiogram (ECG) aberrations and infrequent supraventricular and ventricular ectopic beats were noted in some volunteers. The findings may have a causal relationship with Remoxipride.

With neuropsychological testing, significant impairment in performance was noted, indi-

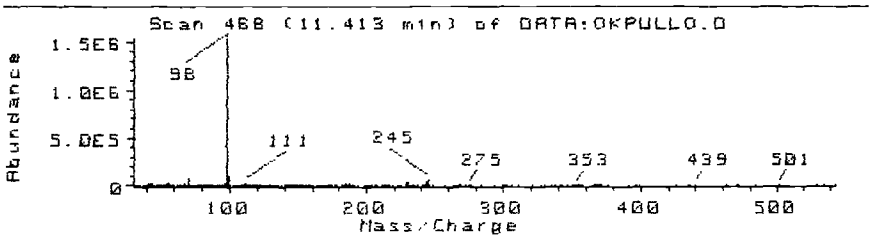

FIG. 2—*Remoxipride as detected at mass spectrometry. It has one main peak at 98* m/z *and a minor peak at 245* m/z.

cating sedative effects or changes of perception after 70- and 140-mg single oral doses. A decreased response, suggesting adaptation, occurred at steady state [*1*].

A drug-related increase in plasma prolactin concentration was observed, indicating antidopaminergic activity of Remoxipride [*1*].

At autopsy, there was no alcohol in the blood, but a concentration of ethanol in the urine of 0.048 g/100 L was revealed. The possible enhanced toxic effect of ingested alcohol with Remoxipride remains obscure.

Given the markedly elevated blood Remoxipride concentration and the absence of signs of disease and violence, the cause of death was attributed to Remoxipride poisoning.

References

[*1*] *Astra Pharmaceutical's Research Manual on Remoxipride,* Astra Läkemedel AB, Södertälje, Sweden, 1987.

[*2*] Hammond, M. D. and Moffat, A. C., "The Stability of Drugs to the Conditions Used in the Enzymic Hydrolysis of Tissues Using Subtilisin Carlsberg," *Journal of the Forensic Science Society,* Vol. 22, No. 3, July 1982, pp. 293–295.

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