

CASE REPORT

*M. Holzbecher,¹ M.Sc.; R. A. Perry,² M.D.;
and H. A. Ellenberger,³ Ph.D.*

Report of a Metoprolol-Associated Death

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ABSTRACT: The case history and toxicological findings relative to a death associated with metoprolol overdose are described. Metoprolol concentrations in blood, vitreous humor, and bile were 5.6, 4.2, and 28 mg/dL, respectively; the maximum liver concentration was 260 µg/g. Concentrations in the liver obtained by direct extraction, Ketodase (β-glucuronidase) digestion, and hydrochloric acid digestion are compared.

KEYWORDS: toxicology, metoprolol, death

Many patients suffering from hypertension are treated with such antihypertensive agents as β-adrenoceptor blocking drugs [1]. Metoprolol tartrate (Lopressor®) is a β-adrenoceptor antagonist released for clinical use in the United States in 1978 [2]. Therapeutic concentrations of metoprolol in plasma are quoted in the literature to range from 5.9 to 26.7 µg/dL [3]. Two cases of metoprolol overdose have been reported for which plasma levels were determined to be 1.2 mg/100 g [4] and 1.3 mg/100 g [5]. In both cases the patients survived; this report describes the first known fatality from an overdose of metoprolol.

Case History

A 17-year-old female with no history of psychiatric illness had an argument with a girl friend, apparently over changes in allegiance between them and their friends. Near midnight her brother heard her in distress upstairs. She was pale, shaking, and incoherent. When asked if she had taken anything, she pointed to her throat and indicated "yes." Several pill bottles were found on her bureau, including Fiorinal-C 1/4® and Lopressor (her father's prescription). She was able to walk to the car but was unconscious when she arrived at the hospital. She was transferred to another hospital, where she died 3 h later.

Toxicological findings before death included traces of barbiturate and 29 mg/dL

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¹Technologist, Department of Pathology, Victoria General Hospital, Halifax, Nova Scotia, Canada. Currently, R.C.M.P. Crime Detection Laboratory, Halifax, Nova Scotia, Canada.

²Chief medical examiner for Halifax County, Department of Attorney General, Halifax, Nova Scotia, Canada.

³Toxicologist, Department of Pathology, Victoria General Hospital, and assistant professor, Dalhousie University, Halifax, Nova Scotia, Canada.

salicylate. Autopsy findings were nonspecific. The stomach contained 25 mL of a brownish-green, slightly granular liquid.

Method

Reagents and Equipment

The following reagents were used: metoprolol (Ciba-Geigy Canada, Ltd.), benzene (Fisher Scientific Co., pesticide grade), sodium chloride (BDH, as received), trifluoroacetic anhydride (Aldrich Chemical Co., Inc. as received), 9-bromophenanthrene (Aldrich Chemical Co., Inc.), and Ketodase—beef liver β -glucuronidase buffered with acetate to pH 5, 5000 Fishman units per millilitre (General Diagnostics Division, Warner Lambert). Samples were analyzed with a Hewlett-Packard Model 5730A Gas Chromatograph equipped with ^{63}Ni electron capture detector and a 1.2-m (4-ft) long, 4-mm inside diameter glass column packed with 3% OV-17 on 80-100 mesh Chromosorb 750 (Chromatographic Specialities Ltd., Brockville, Ontario, Canada).

Analysis of Biological Fluids

Metoprolol was determined by a slightly modified method of Ervik [6]. One millilitre of blood, vitreous humor, or bile from the female was mixed with 0.5 g of sodium chloride and 0.5 mL 1M sodium hydroxide. This mixture was extracted with 5 mL of benzene. After the centrifuging, 2 mL of the organic layer were mixed with 0.1 mL of trifluoroacetic anhydride and allowed to stand at 35°C for 60 min. The mixture was evaporated to dryness under a stream of dry nitrogen. The residue was dissolved in benzene (0.5 mL in the case of blood and vitreous humor; 1.5 mL for bile) containing 1 mg/dL 9-bromophenanthrene, the internal standard. Aqueous standards of 1, 2, and 5 mg/dL were run concurrently. Samples and standards were injected into a gas chromatograph operated at 215°C with a nitrogen flow rate of 65 mL/min.

Analysis of Liver

Five grams of tissue were taken from the female's liver and were homogenized in 20 mL of distilled H_2O with a Brinkmann Polytron homogenizer. This mixture was diluted to a volume of 50 mL with distilled water. Aliquots (1 mL) of the homogenate were treated as follows:

- (1) mixed with 0.5 g of sodium chloride and 0.5 mL of 1M sodium hydroxide and extracted directly with 5 mL of benzene;
- (2) mixed with 1 mL of Ketodase and digested at 37°C for 24 h [7]. After the digestion, 0.5 g of sodium chloride and 0.5 mL of 1M sodium hydroxide were added, and the pH was adjusted to 11 or above by using several drops of 9N sodium hydroxide. The mixture was then extracted with 5 mL of benzene; or
- (3) mixed with 0.2 mL of concentrated hydrochloric acid and boiled for 30 min. After cooling, 0.5 g of sodium chloride and 0.5 mL of 1M sodium hydroxide were added and the pH was adjusted to 11 or above with 9N sodium hydroxide. The mixture was again extracted with 5 mL of benzene.

For standards, liver tissue was spiked with metoprolol at concentrations of 1 and 2 mg/100 g and carried through Procedure 1.

One millilitre of the benzene layer of each of the above extracts was mixed with 0.1 mL of trifluoroacetic anhydride and treated the same as for biological fluids. The residue was dissolved in 0.5 mL of benzene containing 9-bromophenanthrene.

Results and Discussion

Calculation of metoprolol concentrations was based upon the use of the aqueous standards because recoveries obtained with aqueous standards were equal to or 85% of those obtained from the spiked liver. Similar recoveries were reported by Ervik [6]. Blood, vitreous humor, and bile were found to contain 5.6, 4.2, and 27.6 mg/dL, respectively. The concentrations found in the liver were 23 mg/100 g by direct extraction and 26 mg/100 g by Ketodase digestion and subsequent extraction. Hydrolysis by hydrochloric acid did not give reliable results: several gas chromatographic peaks were observed in the region corresponding to the retention time of metoprolol, suggesting a breakdown of the drug. Although Ketodase digestion yielded higher results, the increase over direct extraction is not considered significant. The concentration of salicylate in postmortem blood was found to be 22 mg/dL by the Trinder procedure [8]. No other drugs were detected.

While it would appear that the person died from a metoprolol overdose, there is no conclusive evidence. What role the salicylate level could have played in causing death is also open to conjecture.

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Address requests for reprints or additional information to
Dr. R. A. Perry
Chief Medical Examiner
Department of Attorney General
5788 University Ave.
Halifax, N.S., Canada B3H 1V8