# CASE REPORT

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# Massive Metoprolol Ingestion Associated with a Fatality—A Case Report

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**ABSTRACT:** An unusual fatality involving a 26-year-old male who intentionally ingested approximately 10 g of metoprolol is presented. Autopsy findings revealed foreign material in the gastric content with an acute thrombosis of the left anterior descending coronary artery. Microscopic studies showed evidence of an extremely early infarct. Metoprolol concentrations in the blood, liver, gastric content, and urine are reported by both capillary gas chromatography and ultraviolet spectrophotometric analysis. A review of the literature confirmed that little information has been published concerning intoxication with this drug.

**KEYWORDS:** toxicology, metoprolol, death, ingestion, acute thrombosis, analysis

Metoprolol tartrate (Lopressor®, Betaloc®, Seloken®) is an effective cardioselective beta-adrenergic blocking agent employed in the treatment of hypertension. Metoprolol tartrate is marketed in 50- and 100-mg tablet form, with average daily dosages ranging from 100 to 450 mg/day [*1,2*]. Peak plasma levels of metoprolol are reached 1 h after ingestion with a postabsorptive half-life of 4 to 5 h [*3-5*]. Metoprolol is rapidly absorbed from the gastrointestinal tract, and in cases of massive overdose, signs of toxicity appeared as early as 20 min after ingestion [*6,7*]. The predominant clinical features of metoprolol intoxication include bradycardia, hypotension, low cardiac output, cardiac failure, and cardiogenic shock [*6,8*]. The following case report contributes both toxicological and pathological information concerning a rare metoprolol intoxication resulting in a fatality. Also included is a summary of the information published on other metoprolol intoxications.

## Case History

A 26-year-old white male was seen to ingest the contents of a pill bottle later found to have contained approximately 100 100-mg metoprolol tartrate tablets. The exact amount of time that elapsed between ingestion and death is unknown as a result of conflicting witness state-

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ments, but ranges between 1/2 to 3 h. It was noted by one witness that the victim was lying on a sofa bed "gasping for breath" before emergency rescue was notified.

Emergency rescue personnel found the victim to be unconscious, with his pupils fixed and dilated. The body was pale, cold, and clammy with an absence of respiration, pulse, or blood pressure. An hour of advanced cardiopulmonary resuscitation was unsuccessful.

The deceased was depressed because his wife recently left him and he had previously attempted suicide by ingesting lorazepam and threatening to slash his wrists. He was recently prescribed metoprolol tartrate for high blood pressure.

## Analytical Procedures

### *Materials*

Metoprolol tartrate (standard) was obtained from the Ciba-Geigy Corporation, Suffern, New York.

Propranolol HCl (internal standard) was obtained from Ayerst Laboratories Inc., New York, New York.

Ethyl ether, *N*-butyl chloride, and methylene chloride were all analytical grade.

Sodium chloride, sulfuric acid, and sodium bicarbonate were all analytical grade.

### *Instrumentation*

Dual column gas chromatographic (GC) analysis was employed using a Hewlett-Packard 5880A. Samples were analyzed in the splitless mode at a 1:20 ratio. The J&W Scientific DB-5, 0.25-$\mu$m film thickness, 15- by 0.252-mm internal diameter (ID) and J&W Scientific DB-17, 0.15-$\mu$m film thickness, 15- by 0.252-mm (ID) fused silica columns were connected to dual nitrogen phosphorus detectors. The oven temperature was programmed beginning at 50°C, held for 1 min, increased by 25°C/min to 190°C, held for an additional minute, and finally increased by 10°C/min to 280°C. The injection port temperature was 250°C and the detectors were maintained at 300°C. Helium carrier gas flow was 1 mL/min, air flow was 60 mL/min, and hydrogen flow was 3.5 mL/min.

Ultraviolet spectrophotometric analysis was carried out using a Cary 118 dual beam spectrophotometer (UV). The absorbance range setting was 1.0 with a gain of 3.0. Silica cells with a 1-cm light path were used.

### *Gas Chromatographic Analysis*

A modification of an extraction procedure described by Wu Chen et al. [*9*] was used on all samples and standards. Stock standards of 500 $\mu$g/mL were prepared as a free base in distilled water for metoprolol and propranolol. Care was taken in the storage of both metoprolol and propranolol because of their sensitivity to light. A series of nine metoprolol standards ranging from 0.5 to 10 $\mu$g/mL were prepared for extraction along with multiple dilutions of blood, urine, gastric, and liver homogenate. To 15-ml conical centrifuge tubes was added 1 mL of sample or standard followed by 0.5 mL of propranolol internal standard (10 $\mu$g/mL). Next, 1.0 mL of freshly prepared saturated sodium bicarbonate solution was added to the tubes. The tubes were briefly vortexed and 7.0 mL of *N*-butyl chloride was added to each tube. The tubes were then gently agitated for 10 min and centrifuged. Finally, the organic layer was removed and filtered into a 15-mL conical centrifuge tube and evaporated in a 50°C sand bath under a stream of air. The resulting residue was reconstituted with 100 $\mu$L of 1:1 hexane/ethanol solvent, briefly vortexed, and 2 $\mu$L was injected into the 5880 GC.

An average recovery of 66% was obtained using this method. Six replicate metoprolol samples with a mean concentration of 1.01 mg/L had a coefficient of variation of 8%.

*UV Spectrophotometric Analysis*

Analysis of the various samples was conducted using a modification of an extraction procedure described by Sunshine et al. [*10*]. Added to 250-mL separatory funnels along with an equal volume of saturated sodium chloride solution were 5 g (mL) of blood, urine, gastric, metoprolol standard (50 μg/mL) and 25 g of liver. One millilitre (5 mL to liver) of 50% sodium hydroxide was added to all separatory funnels, followed by the addition of 150 mL of extraction solvent (4 : 1 ethyl ether/methylene chloride). The contents of the separatory funnels were shaken and allowed to stand for 1/2 h. The organic layer was filtered into a second 250-mL separatory funnel. Two consecutive extractions were performed on the organic layer using 5 mL of 0.5*N* sulfuric acid and 5 mL of 7.2*N* sulfuric acid with the same extraction technique described above. The acid layers were scanned between 360 and 210 nm using the corresponding acids as reference blanks. The UV maximum occurred at 218 nm and an extracted metoprolol standard (50 μg/mL) produced a reading of 1.17 optical density units. An 83.5% recovery was obtained.

## Results

The initial screening and quantitations were achieved by UV analysis followed by GC confirmation and final quantitations. The metoprolol concentrations in blood, liver, gastric, and urine are listed in Table 1. Quantitations of the various tissues using GC were obtained using linear regression analysis of the nine metoprolol standards. The GC results reflect the average obtained from several dilutions of each tissue sample. The urine sample concentration was not reported using the UV procedure because of a high background interfering with the metoprolol peak.

## Discussion

*Pathology*

The autopsy examination was remarkable for several reasons. First, this 26-year-old had severe atherosclerosis with 90% occlusion of the left anterior descending (LAD) coronary artery. Second, he had thrombosis of the LAD. Third, he had multiple foci in the heart of ischemic necrosis with a predominantly lymphocytic and monocytic reaction (Figs. 1 and 2). Finally, the stomach contained a small quantity of grayish foreign material.

The patchy cardiac necrosis appeared to predate the fatal ingestion by several days. It appeared to be "stress cardiomyopathy" and probably represented another aspect of his anxiety and depression which brought about his suicide [*11*].

TABLE 1—*Metoprolol tissue quantitations.*

| Tissue | UV Results, mg/L, mg/kg | GC Results, mg/L, mg/kg |
|---|---|---|
| Blood | 82.1 | 75.0 |
| Liver | 142.0 | 159.7 |
| Urine | *[a] | 1.0 |
| Gastric total recovery[b] | 92.7 mg | 79.9 mg |

[a]*interference with sample background.

[b]Milligrams recovered from total gastric content of 10.5 grams.

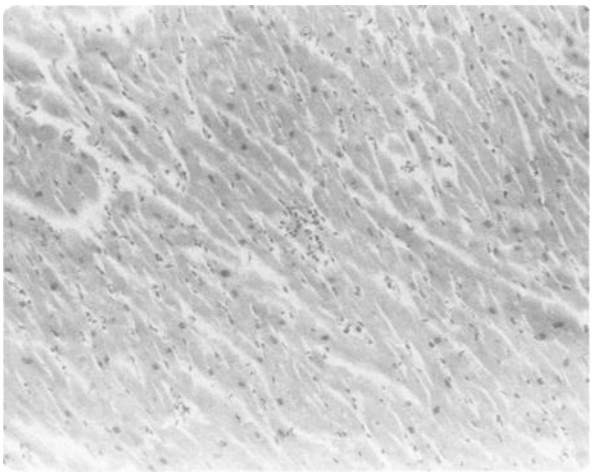

FIG. 1—*Focus of ischemic necrosis (hematoxylin-eosin ×100).*

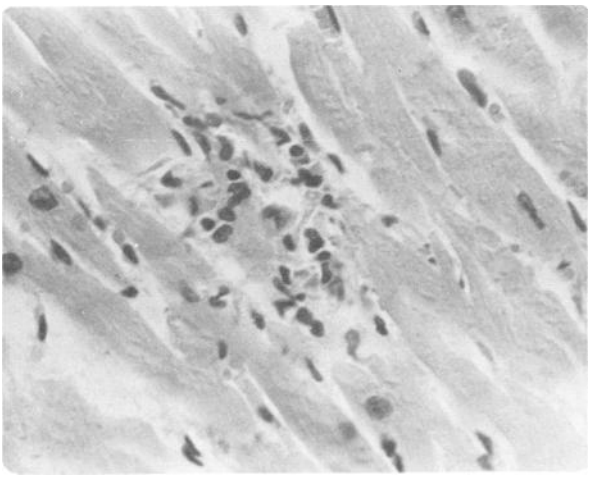

FIG. 2—*Enlargement of affected area in Fig. 1 (hematoxylin-eosin ×160).*

If the history of metoprolol ingestion had not been available, the autopsy findings of atherosclerosis and coronary thrombosis would have been sufficient to explain death. However, the thrombosis of the LAD had no evidence of organization and probably was caused in part by bradycardic hypotension produced by the massive ingestion of metoprolol. The main pattern seen in the heart is one of extremely early ischemic necrosis with only dilation of capillaries and congestion (Fig. 3).

*Toxicology*

Self-poisoning with beta blocking drugs is uncommon [*8*], and when properly administered, there is a wide margin of safety between therapeutic and toxic doses [*7*]. Table 2 is a

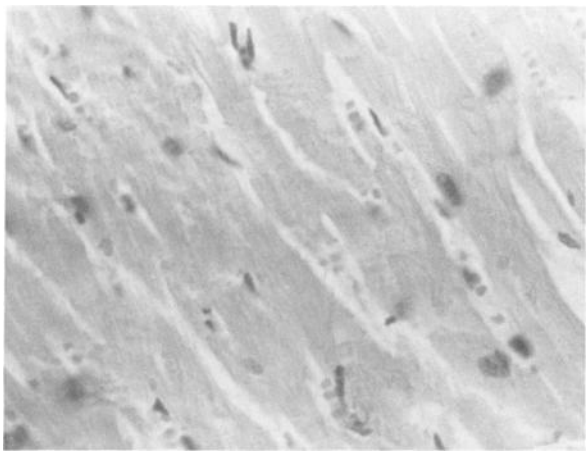

FIG. 3—*Typical pattern of dialated and congested capillaries (hematoxylin-eosin ×160).*

TABLE 2—*Metoprolol intoxication summary table.*

| Age | Sex | Estimated Ingested Dose, mg | Tissue Analyzed | Approximate Time Lapse Before Analysis, h | Metoprolol Level, mg/L | Other Drugs | Results | References |
|---|---|---|---|---|---|---|---|---|
| 19 | M | 10 000 | plasma | 2[a] | 12.2 | ... | recovery | *12* |
| | | | | 10[a] | 5.7 | ... | | |
| 17 | F | 10 000 | plasma | 11 | 13.1 | EtOH | recovery | *5* |
| | | | | 28 | 0.9 | diazepam | | |
| 39 | F | 7 500 | ... | ... | ... | EtOH | death | *13* |
| 38 | F | 7 500 | ... | ... | ... | EtOH | death | *13* |
| 26 | M | 10 000 | blood | postmortem | 78.5 | EtOH | death | *[b] |
| | | | liver | | 150.8 | 0.04% | | |

[a]Hours after admission.
[b]*Subject of case report.

summary of the metoprolol intoxications published in literature. Metoprolol has an average therapeutic plasma concentration of 0.116 mg/L [*1*]. It can be seen from Table 2 that individuals with blood concentrations exceeding 100 times the therapeutic dose have recovered.

## Conclusion

The subject of this case report underwent rapid and nearly complete absorption of metoprolol which was indicated by the small amount of metoprolol (79.9 mg) recovered from the gastric content. Although there are conflicting stories as to the exact time elements involved, the absorption probably took place within a 2- to 3-h period. Good correlation was seen between the GC and UV quantitative procedures. The blood value of 75.0 mg/L is 600 to 700 times higher than a therapeutic concentration of metoprolol and represents the highest value reported in the literature to date.

As a result of the pathological findings of atherosclerosis it would be inaccurate to state that metoprolol was the sole cause of death. However, the overwhelming toxicological evidence coupled with the pathological findings of an extremely early infarct strongly suggested that metoprolol intoxication was the primary factor involved in the death of this individual. Metoprolol's suspected mechanism of action resulted in severe bradycardiac hypotension which would facilitate clot formation. This clot formation and the ensuing infarct was possibly augmented by the presence of atherosclerosis.

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