

Case Report

Acute Intoxication by Bisoprolol and Drowning: Toxicological Analysis in Complex Suicides

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Abstract: In complex suicides, more than one suicide method is applied at the same time or one after the other. The most common complex suicide includes the ingestion of drugs combined with drowning. A case of acute intoxication by Bisoprolol and drowning is reported. The dead body of a 40-year-old woman was discovered on a river side, soon after her husband found a suicide note at home. In the woman’s vehicle four empty boxes of Bisoprolol, a widely used beta blocker, were also found. Main autopsy findings were consistent with drowning and represented by plume of froth at the mouth and nostrils with frothy fluid also in the airways, water into the stomach, and a remarkable pulmonary edema as a result of fluid aspiration. Toxicological analyses were performed on peripheral blood, urine and gastric content samples using liquid and gas chromatography, coupled with mass spectrometry. Toxicological results were negative for ethanol and other common drugs of abuse. High levels of bisoprolol were found in blood (7.54 mg/L), far exceeding the therapeutic range, in the urine (1.14 mg/L), and gastric content (13.12 mg/L). Bisoprolol intoxication was assessed as a relevant contributing condition to the immediate cause of death represented by drowning. Although Bisoprolol would certainly have a heart-depressing effect, it is not possible to determine if the victim fell unconscious or if she simply collapsed into the water with a secondary drowning.



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1. Introduction

The use of more than one potentially lethal method together or sequentially in order to commit suicide is defined as “complex suicide”. Complex suicides are rare, accounting for 1.5 to 5% of all suicides [1]. The combination of different suicidal methods can be applied to raise the chances of success in order to make sure that death will occur even if the first method fails [2]. The most common complex suicide includes the ingestion of drugs combined with drowning or suffocation by a plastic bag. The ingestion of drugs is also used to make suicides less painful [1]. Planned and unplanned complex suicides are reported in the literature: two or more methods are usually applied simultaneously in planned suicides, whereas in unplanned suicides, the mode of performance is changed after the first method chosen fails [2].

An interesting planned complex suicide has been observed in our routine forensic practice. The body of a 40-year-old woman was found on a river side and the main autopsy findings (plume of froth at the mouth and nostrils with frothy fluid also present in the airways, water into the stomach, and a remarkable pulmonary edema as result of fluid aspiration) were consistent with drowning as the immediate cause of death. However, toxicological analysis showed the presence of lethal concentration of Bisoprolol in the blood, urine, and gastric content.

Bisoprolol fumarate is one of the most commonly used beta blockers, which is a highly selective beta-1 receptor antagonist [3,4].

Beta blockers, such as Bisoprolol, lower blood pressure and heart rate, and are widely used for the treatment of hypertension, tachycardia, cardiac angina, and heart failure in adults [5]. In particular, Bisoprolol is widely used for the prevention of cardiovascular events following a heart attack in patients with risk factors [4,6], arrhythmias [7], and as a second-line agent for hypertension [8]. Bisoprolol generally is well tolerated. However, common side effects include dizziness [9], headache, feeling tired, diarrhea, and swelling in the legs [10]. More severe side effects include worsening asthma, blocking the ability to recognize low blood sugar, and worsening heart failure [10–13].

Although beta blockers are usually safe and well-tolerated drugs, cases of acute intoxication, even fatal ones, are reported in the literature [14–22]. In the present case, the heart-depressing effect of Bisoprolol was assessed as contributory condition to the immediate cause of death (asphyxia due to drowning).

Complete toxicological analysis performed on biological fluids was negative for the most common drugs of abuse and alcohol. However, high levels of Bisoprolol were found in blood whose concentration far exceeded the therapeutic range. The main autopsy findings and toxicological results are illustrated in detail.

2. Case Report

A 40-year-old woman was found dead on a river side on the same day she was reported missing by her husband after he found a suicide note at home. In the woman's vehicle four empty boxes of Bisoprolol were also found. Each empty box was of 28 pills and each pill was of 1.25 mg Bisoprolol. Therefore, 140 mg of Bisoprolol were hypothetically ingested in total by the victim, who was on treatment with the beta blocker in order to control hypertension related to her dysthyroidism.

A forensic autopsy with toxicological analysis was requested.

2.1. Sampling

During the autopsy, biological samples were collected for a complete toxicological analysis. Blood, urine, bile, gastric content, liver, and brain were sampled in tubes containing sodium fluoride.

2.2. Toxicological Analysis

The toxicological analysis was performed on biological fluids, urine and blood, using gas chromatography coupled with mass spectrometry (GC-MS) for different classes of drugs of abuse and pharmaceuticals, following the procedures previously reported [23,24]. In order to fill the gap with respect to thermolabile and nonvolatile analytes, analyses were also performed using liquid chromatography–tandem mass spectrometry (LC-MS/MS) for different classes of drugs of abuse, pharmaceuticals, and their metabolites.

Blood was tested for alcohol, and for other volatile substances, by headspace gas chromatography with flame ionization detection (GC-HS/FID).

The detection of Bisoprolol in the peripheral blood, urine, and gastric content was performed on LC-MS/MS instrumentation after samples preparation procedure, as described by Gang-yi Liu et al., 2009 [25].

Aliquots of 1 mL of peripheral blood were extracted with the addition of 2 mL of Acetonitrile (1:2) containing Pinazepam [50 ng/mL] as an internal standard (IS). The mixture was vortexed thoroughly for 10 min and centrifuged at 6000 rpm for 5 min. Aliquots of the gastric content and urine were progressively diluted with 0.5% formic acid in water solution (*v/v*) (eluent A). A filtered aliquot of the clear extract for each sample was transferred into vials for the LC-MS/MS autosampler. The injection volume was 10 µL.

Liquid chromatographic separation was achieved on Agilent 1200 equipped with a Zorbax DB-C₁₈ column (4.6 × 50 mm, particle size 1.8 µm) at a temperature of 55 °C by using a gradient program of two different mobile phases (eluent A and B) at a flow rate of 0.9 mL/min. Eluent A consisted of 0.5% formic acid in water (*v/v*), and eluent B of 0.5% formic acid in acetonitrile (*v/v*). The initial gradient was started with 95% eluent A and

held for 0.2 min and then decreased to 5% mobile phase A at 5 min, and held until 7 min, during which the analytes were eluted. Subsequently, the eluent B content was reverted to 5% re-equilibrating the original conditions and giving a total run time of 10 min. The retention time for Bisoprolol was 3.6 min.

Mass spectrometric data were acquired by a triple quadrupole mass spectrometer (API 3200, AB Sciex, Carlsbad, CA, USA) using multiple reaction monitoring (MRM). The following Turbo Ion Spray source conditions, in electrospray ionization (ESI) positive mode, were applied: temperature, 400 °C; curtain gas, 30 (arbitrary units); GS1 and GS2, 50; CAD gas pressure, low; ion spray voltage, 5500 V. Monitored ions were the precursor ion of m/z 326.3 to 116.3 product ion for Bisoprolol, and m/z 309.2 to 241.1 for IS Pinazepam.

Stock solution of Bisoprolol was made in methanol (1000 µg/mL). Working standard solutions of Bisoprolol were diluted with methanol and stored at 4 °C when not in use. A five-point calibration curve, in the range 10–1000 ng/mL, was prepared by spiking drug-free samples with Bisoprolol working standard solutions (at 10, 25, 50, 100, 1000 ng/mL) adopting the most appropriate dilution factor before the protein precipitation. Bisoprolol limit of detection (LOD) was 2 ng/mL, and the lower limit of quantification (LLOQ) was 10 ng/mL. In order to test the recovery and accuracy of the applied method, three known concentrations of the standard Bisoprolol (10–50–100 ng/mL) were spiked to drug-free whole blood and assayed in three replicates. After the protein precipitation, a mean recovery and accuracy of 85% and 90%, respectively, were calculated by LC–MS/MS analysis.

2.3. Results

At autopsy, macroscopic signs consistent with drowning were represented by a plume of froth at the mouth and nostrils with frothy fluid also present in the airways. At autopsy, the lungs were remarkably overinflated and heavy due to water filling (610 g for the right lung and 550 g approximately for the left lung). Some water was also found in the stomach. The gastric content was a small fluid volume of approximately 100 cc, brownish in color with no intact pills of medication clearly visible. The histopathological features of the lung tissue showed gross pulmonary edema due to the accumulation of external fluid in the lung with the dilatation and rupture of the alveoli, along with a thinning of the walls and compression of the capillaries due to water filling.

The toxicological analysis of biological fluids was negative for the most common drugs of abuse and alcohol. Qualitative and quantitative analyses using LC–MS/MS were positive for Bisoprolol (beta blocker) in all biological samples (blood, urine, and gastric content): blood 7.54 mg/L; urine 1.14 mg/L; gastric content: 13.12 mg/L.

Toxicological results for Bisoprolol are shown in Table 1 and in Figure 1. High levels of Bisoprolol have been found in blood whose concentration far exceeded the therapeutic range. (Table 1).

Table 1. Results of quantitative analysis positive for bisoprolol in blood sample, compared to the therapeutic range.

Sample	Toxicologic Results	Therapeutic Range
Blood	7.54 mg/L	0.01–0.06 mg/L

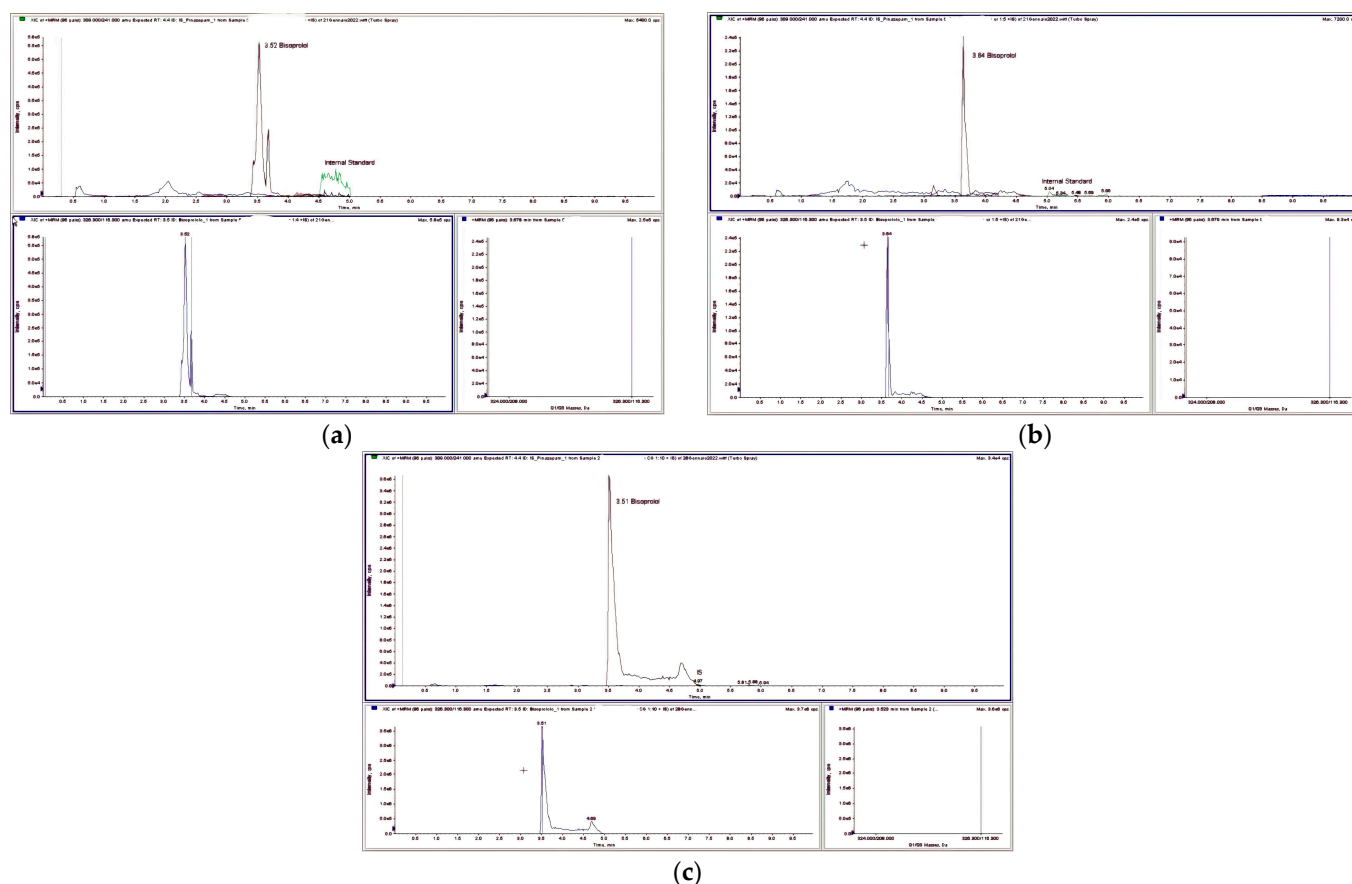


Figure 1. Figure 1 shows the LC-MS/MS chromatograms for Bisoprolol and internal standard in postmortem biological matrices (a) blood, (b) urine, and (c) gastric content.

3. Discussion

Complex suicides can be often a challenge for pathologists due to the combination of different suicidal methods, each one potentially lethal. In these cases, the determination of the cause of death is not always easy, nor is the assessment of the manner of death differentiating between suicidal methods, homicide, or even accident [26]. Therefore, the general characteristics of complex suicide victims should be well understood. Careful examination of the crime scene, detailed statements from the relatives and witnesses of the victims, evaluation of the victims' medical history, and a complete autopsy with toxicological analysis might be necessary [1,27].

In this case, according to the circumstantial data and the history case, the 40-year-old woman planned a complex suicide by applying two different methods in sequence. The first method was certainly represented by the ingestion of Bisoprolol in a large amount as indicated by the four empty boxes found in her vehicle and the high concentration of this medication found by the complete toxicological analysis on gastric content, blood, and urine. The second method was represented by drowning.

Drowning is still a well-known diagnosis of exclusion since there are no pathognomonic autopsy findings to indicate drowning as a cause of death [28]. For example, the presence of foam over the mouth and nostrils or in the airways is a nonspecific sign of drowning and may be seen in other types of deaths, including drug overdoses and pulmonary edema due to congestive heart failure. However, apart from the frothy fluids in the air passages, other signs of drowning were found, such as water into the stomach, overinflation of heavy lungs, and pulmonary edema due to water filling. These findings were considered enough evidence of the aspiration of a large amount of water, since only a combination of macroscopic and microscopic pathological signs can support a final di-

agnosis of drowning [29]. According to these findings, the victim was still alive during submersion. However, it is well known that drowning can be associated with the abuse of illicit and licit drugs as in our case [1].

The heart-depressing effect of Bisoprolol contributed for sure to drowning although it is not possible to determine if she fell unconscious or if she simply collapsed into the water with a secondary drowning. There is no evidence that one of the two potentially lethal methods superseded the other in causing the death, but it is plausible that the suicidal lethal ingestion of Bisoprolol and drowning were combined to cause the death.

Toxicological analyses performed by GC/HS showed very high levels of Bisoprolol in peripheral blood (7.54 mg/L), urine (1.14 mg/L), and gastric content (13.12 mg/L), whereas ethanol or any other drugs or substances of abuse were not found. Based on toxicological results, the victim was certainly impaired prior to and during submersion in the river by the dizziness due to Bisoprolol effect. Therefore, the heart-depressing effect of Bisoprolol, due to its high concentration in blood and other body fluids, far exceeding the therapeutic range, was considered a relevant contributory condition to the asphyxia by drowning, assessed as the immediate cause of death. The oxygenated blood supply was prevented by both the entry of water into airways and lungs and the beta-blocker-related low heart contraction. The manner of death was a suicide based on a manuscript note found at home by her husband.

According to the results of the toxicological analysis, the levels of Bisoprolol in the body fluids far exceeded the therapeutic range. The serum therapeutic concentration range of Bisoprolol is 0.01 to 0.06 mg/L, with peak plasma concentrations reached 2 to 4 h after oral administration. The daily tolerated dose of Bisoprolol Fumarate is up to 20 mg, whereas the victim ingested up to 140 mg of Bisoprolol based on the 28 pills of 1.25 mg each, missing in the empty four boxes. Bisoprolol is almost completely absorbed after oral administration and undergoes only minimal first-pass metabolism. It is moderately liposoluble and rapidly and widely distributed in the body. Approximately 50% of a dose is metabolized in the liver to pharmacologically inactive polar metabolites that are then excreted by the kidneys; the remaining 50% is excreted unchanged by the kidneys. Less than 2% of a dose is excreted in feces [30]. The high concentration of Bisoprolol in gastric content (13.12 mg/L) confirmed the intentional oral ingestion of pills. The Bisoprolol blood concentration (7.54 mg/L) exceeded the urine concentration (1.14 mg/L) by almost seven times, confirming the ingestion of the drug a few times before death. Blood concentration exceeded the serum therapeutic concentration (0.01–0.06 mg/L) by almost seven hundred times, confirming the potential toxic effects of the drug. In the present case it is not possible to determine when the peak concentration was reached and when the toxic effect took place. However, based on the very high levels of Bisoprolol in the body fluids, early manifestations of beta-blocker toxicity, such as a heart-depressing action, are certainly plausible and they occurred before drowning.

Generally, beta blockers show a wide toxic–therapeutic margin, but there is a great variability among individuals, and no definite correlations have been established between plasma levels and clinical effects [20]. It has been reported that an overdose of Bisoprolol can lead to fatigue, hypotension [11], hypoglycemia, bronchospasms, and bradycardia [10,12]. However, cases with relatively few toxic effects have been described in the literature too [20].

As widely used drugs, beta-blocker poisoning is a common overdose mechanism that can lead to significant morbidity and mortality. In 2015, according to the American Poison Controls Centers (AAPCC) database, 10,577 single-exposure cases of beta blockers were reported, mostly represented (82% of cases in total) by unintentional or accidental intoxications [31]. In 2018, beta-adrenoreceptor antagonists were ranked by the AAPCC seventh out of the top 25 substances associated with death, with 122 cases in 2018, making up 3.9% of substances involved in fatalities [15,32].

In 2015, in Italy, 379 beta-blocker intoxications occurred, of which 99 were caused by Bisoprolol: 28 cases of Bisoprolol intoxication involved children younger than six

years old, 6 cases involved children aged between 6 and 19 years old, 65 cases involved adults older than 19 years old, 61 cases were accidental intoxication, 31 cases were intentional intoxications, and 1 adverse reaction was attributed to individual susceptibility. In 80 cases, no long-term side effects were reported, and in 19 cases moderate to major outcomes occurred [33].

Manifestations of beta-blocker toxicity are generally an extension of the drugs' therapeutic effects; however, intoxicated patients may present along a spectrum from asymptomatic to cardiovascular collapse, depending on the properties of the ingested drug, the dose, and the patient's history [34]. There are three main signs of beta-blocker poisoning: decreased blood pressure, bradycardia, and conduction disturbances, variously associated in clinical forms from asymptomatic to intermediate, to severe forms [35]. Patients may rapidly become comatose, with undetectable blood pressure and pulse, along with circulatory arrest or seizures occurring up to 12 h after the ingestion [36–38].

Beta blockers, such as Bisoprolol, decrease the adrenergic tone/stimulation of the heart muscle and pacemaker cells, leading to a lower contractility of the heart muscle and lowered heart rate in pacemakers. Bisoprolol has a negative inotropic and chronotropic effect, decreasing the heart contractions and heart rate and, consequently, reducing oxygen consumption of myocardial cells [39]. As plasma concentrations of beta blockers increase, hypotension accompanies the fall in cardiac output and myocardial perfusion is compromised, with death ensuing from inotropic failure, rather than the development of malignant arrhythmias [40]. Thus, bradycardia associated with hypotension may be the first clue to diagnose beta-blocker overdose, followed by hypoglycemia and altered mental status [31]. Respiratory depression can also develop as a result of severe circulatory impairment or from a central drug effect, while seizure activity can be seen in beta-blocker poisoning secondary to hypotension, hypoxia, hypoglycemia, or they can be connected to beta blockers which have central-nervous-system-depressant activity [41].

Therefore, based on the potentially lethal concentrations of Bisoprolol detected in the victim's peripheral blood, the hypotension and bradycardia induced by the beta-blocker intoxication were assessed as a relevant contributing factor to drowning that was the immediate cause of death.

4. Conclusions

Complex suicides include at least two deadly methods among which drug abuse is commonly applied. In our case, based on the toxicological results of body fluids, far exceeding the serum therapeutic concentration, acute intoxication by Bisoprolol occurred just before drowning. Bisoprolol intoxication was assessed as a contributory condition to the immediate cause of death represented by drowning. Although Bisoprolol would certainly have a heart-depressing effect, it is not possible to determine if the victim fell unconscious or if she simply collapsed into the water with a secondary drowning. The suicidal lethal ingestion of Bisoprolol and drowning were combined to cause the death. There is no evidence that one of the two potentially lethal methods superseded the other in causing the death. The manner of death was assessed as suicide based on the recovery of a suicide note at home and the four empty boxes of Bisoprolol in the woman's vehicle.

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