CASE REPORT

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Fatality Due to Gamma-Hydroxybutyric Acid (GHB) and Heroin Intoxication

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ABSTRACT: The first case of fatal intoxication due to ingestion of gamma-hydroxybutyric acid (GHB) and intravenous use of heroin is reported. A 42-year-old man, known to have been a heroin addict and to have taken other psychoactive substances, who had been in treatment with GHB for several months, was found dead. Anatomo-histopathologic examination showed generalized visceral congestion, edema and pulmonary anthracosis, chronic bronchitis and chronic active hepatitis. Toxicological findings included fluid and tissue distributions of GHB, morphine and 6-monoacetylmorphine. GHB and morphine concentrations were respectively 11.5 and 0.77 μg/mL (blood), 84.3 and 0.3 μg/mL (vitreous humor), 258.3 and 1.35 μg/mL (urine), 57.0 and 14.3 μg/mL (bile), 40.0 and 0.43 μg/g (brain), 43.0 and 0.60 μg/g (liver), 47.0 and 0.68 μg/g (kidney). Blood and urine levels of 6-monoacetylmorphine were 28.5 and 12.1 ng/mL respectively. The presumed mechanism of action and pharmacokinetics of GHB are briefly reviewed, with reference to its therapeutic use and to reports of non-fatal GHB intoxication.

KEYWORDS: toxicology, drugs, heroin, gamma-hydroxybutyric acid (GHB)

Gamma-hydroxybutyric acid (GHB) is an endogenous constituent of mammalian brain, where it is synthesized from gamma-aminobutyric acid (GABA) [*1,2*]. Evidence has been accumulated showing that GHB is not just a metabolite of GABA, but that it plays a role as a central neurotransmitter or neuromodulator [*3*].

GHB was formerly used as an intravenous anaesthetic agent [*4*] and in the treatment of narcolepsy [*5*]. It has recently been reintroduced into therapeutics for treating alcohol dependence [*6,7*], and has been also proposed in the treatment of various diseases such as cerebral and cardiac ischemia, osteochondrosis, narcolepsy and opiate withdrawal syndrome [*8–12*].

Recent works by American authors and agencies [*13–17*] have reported multiple cases of acute non-fatal poisoning attributed to ingestion of GHB, illicitly marketed in the USA. This paper describes the first report of fatal GHB and heroin intoxication.

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Case History

A 42-year-old man had been known to be addicted to heroin and to other psychoactive substances for the past 20 years. After various treatments over the years with methadone, buprenorphine or naltrexone, in April 1993 he began treatment with GHB (Alcover, Laboratorio C.T., Sanremo, Italy) at doses of 50 mg/kg divided into three daily oral administrations. On May 31, 1993 he was found dead on a river bank.

Autopsy Findings

An autopsy, requested by the judicial authorities, was performed two days after death. The body was that of a well-developed white male. External examination showed abrasions to the head and hands, and many marks of old and one mark of recent and vital acupuncture, all on the inner side of the right forearm. Internal examination revealed marked polyvisceral congestion, edema and pulmonary anthracosis. Histological examination confirmed acute visceral congestion and pulmonary edema, and also revealed bronchitis and active chronic hepatitis. All other organ systems were unremarkable.

Laboratory Findings

Toxicological analyses, indicated by the circumstantial and anatomopathological data, first aimed at screening for volatile and non-volatile acid, neutral and basic psychoactive substances. In particular, analyses were carried out as follows:

1. Comprehensive enzyme immunoassay (EIA) and gas chromatographic (GC) screening of blood (6.5 mL) and urine (12 mL), according to already published procedures and analytical conditions [*18*].
2. HPLC screening using an automated multi-column liquid chromatograph (REMEDi-Drug Profiling System; Bio-Rad, Hercules, CA).

To a 0.5 mL urine sample, 0.1 mL of an Internal Standard (N-ethyl-nordiazepam and chlorpheniramine) combination was added and a qualitative analysis was carried out following the manufacturer's instruction (Software Rev. 4.03).

3. Gas chromatographic/mass spectrometric (GC/MS) screening for acid, neutral and basic substances in blood.

1 mL of blood was hemolized with 20 mL of a 0.9% NaCl

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aqueous solution. The resulting mixture was centrifuged and filtered through glass wool. The filtrate was then passed through a SEP-PAK C18 column (Waters Associates, Milford, MA) previously conditioned with 5 mL of methanol and 5 mL of a 0.9% NaCl aqueous solution. The column was then washed with a 0.9% NaCl aqueous solution (5 mL twice) and pentane (5 mL twice) and elution was carried out with first 0.5 mL and then 1 mL of a 1:1 methanol/chloroform mixture. The eluate was evaporated to dryness under a nitrogen stream and the residue reconstituted with 1 mL of ethyl acetate. A 2 μL aliquot was injected into the chromatograph. GC/MS analysis was performed on a Hewlett Packard 5790 A gas chromatograph coupled to a Hewlett Packard 5970 A mass selective detector (MSD). Separation was carried out on a Hewlett Packard Ultra 2 bonded phase capillary column (12 m × 0.20 mm, 0.33 μm film thickness) connected to the MSD through a direct capillary interface. The injector port was a capillary split injector with a split silanized glass insert. Carrier gas (He) flow was 1 mL/min at 100°C and a split ratio of 20:1 was used. Injector and interface temperatures were 250 and 270°C respectively. The oven was initially held at 100°C for 0.5 min, then programmed at 9°C/min to a final temperature of 275°C. The MSD was used in the electron impact (70 eV) full scan mode and the electron multiplier was set 220 V above the autotune voltage.

4. GC/MS confirmation and quantitation of morphine and 6-monoacetylmorphine (6-MAM) in biological fluids and tissues.

1 mL of blood, urine and bile, 0.3 mL of vitrous humor and 1 g of brain, liver and kidney homogenates were enzymatically hydrolyzed by addition of 3000–5000 units of *Patella vulgata* glucuronidase (Sigma, St. Louis, MO) and 0.3 mL of 1 M pH 5 sodium acetate buffer. The mixture was incubated overnight at 55°C. Hydrolyzed samples were adjusted to pH 7 with NaOH/H_3PO_4. After centrifugation and addition of internal standards (morphine-D_3 and 6-MAM-D_3, Radian Corporation, Austin, TX) the supernatants were passed through a Bond-Elut Certify column (Analytichem International, Harbor City, CA) and extracted according to the manufacturer's recommended procedure. Eluates were evaporated to dryness under a nitrogen stream, derivatization was carried out by adding 0.1 mL of BSTFA + 1% TMCS, and 2 μL aliquots were injected into the chromatograph. GC/MS analyses were performed as above in the selected ion monitoring (SIM) mode. Ions monitored were: m/z 287, 324, 429 (TMS-morphine); m/z 290, 327, 432 (TMS-morphine-D_3); m/z 340, 399 (TMS-6-MAM); and m/z 343, 402 (TMS-6-MAM-D_3). Ions at m/z 429, 432, 399, 402 were used for quantitation.

5. Quali-quantitative determination of GHB in biological fluids and tissues.

This assay was carried out following an already published GC/MS method for GHB determination in plasma and urine [*19*], with some minor modifications.

In particular, vitreous humor and bile (0.5 mL each) were extracted using the same procedure as for urine.

Brain, liver and kidney homogenates (obtained with 1 g of tissue and 4 mL of water) were centrifuged and 2 mL aliquots of the supernatants, and 1 mL blood samples hemolized with 1 mL of water, were extracted using the procedure originally developed for plasma. All analytical results are reported in Table 1.

TABLE 1—*Concentrations of GHB, morphine, and 6-MAM in postmortem biological samples.*

Sample	GHB	Morphine	6-MAM
	μg/mL/g		ng/mL/g
Whole blood	11.50	0.77	28.50
Vitreous humor	84.30	0.30	ND
Urine	258.30	1.35	12.10
Bile	57.00	14.30	ND
Brain	40.00	0.43	ND
Liver	43.00	0.60	ND
Kidney	47.00	0.68	ND

NOTE: ND = Not detected (conc. ≤10 ng/mL or ≤20 ng/g).

Discussion

Overall evaluation of the circumstantial, anatomical, histopathological and toxicological data indicated that death was caused by acute cardiocirculatory and respiratory failure, due to intoxication by GHB and heroin.

Circumstantial data included evaluation of the death scene of a 42-year-old man, who had been in treatment with GHB for several months and who was known to be a heroin addict and to take other psychoactive substances.

Anatomical and histopathological findings showed generalized visceral congestion, edema and pulmonary anthracosis, chronic bronchitis, and chronic active hepatitis.

Toxicological findings (GHB, morphine and 6-monoacetylmorphine in biological fluids and tissues) indicated that there had been an additive depressive effect on the respiratory and vasomotor centers of the brain stem [*13*]. Moreover, damage due to hepatitis probably slowed GHB and heroin metabolism, with consequent enhanced toxic effects.

As regards the mechanism of action of GHB in the treatment of withdrawal from and craving for alcohol [*6,7,20,21*] and heroin [*12*], although several hypothesis exist, none has been validated so far.

Experimental evidence indicates that GHB interferes with the activity of serotonin [*22*], acetylcholine [*23*], GABA [*24*], and dopamine (DA) [*25*]. The interference of GHB with DAergic transmission may be more relevant for its suppressant effect on ethanol and opiate withdrawal syndromes. Indeed, recent studies have shown that both ethanol and morphine withdrawal syndromes are associated with profound inhibition of DA output in the nucleus accumbens and ventral caudate nucleus, as measured by brain microdialysis [*26–28*].

Contrary to observations following anesthetic doses of GHB [*29*], it has recently been found that nonanesthetic doses of the compound activate the brain rate of DAergic neurons [*30*], and Cheramy et al. [*31*] have reported that GHB increases DA release from the caudate nucleus of cats. Because the increase in DA output is considered to play an important role in the rewarding effects of morphine and alcohol [*32*], it is reasonable to hypothesize that the fall in DA output is involved in the negative symptoms of withdrawal; vice versa, a stimulation in DA output may be involved in the suppressant effect of GHB on withdrawal symptoms.

Alternatively, it should also be considered that GHB is a normal brain constituent, which seems to function as a neurotransmitter or neuromodulator [*33*]. Therefore, possible changes in its endogenous content and activity in the pathogenesis of withdrawal from opiates and alcohol are worth specific investigation. Whatever the mechanism of action of GHB, its efficacy in suppressing both opiate and alcohol withdrawal syndromes is of practical impor-

tance, because a combination of opiate and alcohol abuse is not uncommon.

Pharmacological studies and clinical observations on numerous alcohol addicts demonstrate that, at therapeutic doses, GHB produces subjective symptoms of dizziness or a sense of dullness only after the first dose, and that these symptoms disappear within 30–60 min and do not reappear after later doses [6,7].

Cases of adverse reactions reported to date deal with non-fatal acute poisoning in the USA [13–17], mainly among body builders who take illicitly marked GHB for its supposed growth hormone release action. However, GHB concentrations in biological fluids were not assayed in these cases.

The most commonly reported symptoms include sudden drowsiness, dizziness, and a "high." Other effects are headache, nausea, vomiting, myoclonic jerking, and short-term coma [16]. If product use is discontinued, full recovery with no long-term side effects is the usual result. No clear dose-response effect has been observed, and this may be attributable to differences in susceptibility, wide variations in doses taken by the same person, or the contemporary intake of other substances.

The first case of a fatality, reported here, falls into the category of the latter situation, that is, intake of another psychoactive substance, heroin. Pharmacokinetic studies carried out on animals, healthy volunteers and alcohol-dependent patients (with compensated liver disease) [34,35] have shown that:

- GHB is rapidly absorbed and excreted (peak plasma times, t_{max} = 20 − 45 min; terminal half-lives, $t_{1/2z}$ = 27 ± 5 SD min) after doses of 25 mg/kg
- significant increases in t_{max} with little change in peak plasma concentration (C_{max}), decreases in oral clearance (CLo) and increases in mean residence time (MRT) and $t_{1/2z}$ have all been found with increasing dosages
- both oral absorption and elimination of GHB is capacity-limited
- GHB does not bind to any significant extent to plasma proteins over the therapeutic concentration range
- urinary recovery of unchanged GHB is negligible (<1% of the dose)
- gamma-butyrolactone, the lactonic form of GHB, cannot be detected in either plasma or urine, indicating that lactonization does not occur in vivo
- multiple-dose regimens of GHB result neither in accumulation nor in time-dependent modification of its pharmacokinetics.

All circumstantial data and GHB levels in biological fluids and tissues found in the present case (see Table 1), interpreted in the light of pharmacokinetics, indicate that the subject had been taking GHB for some time and that the last dose may have been taken within 2 hours of death.

As regards the presence of opiates in biological fluids and tissues (Table 1), the following probabilities may be stated: the presence of 6-MAM indicates heroin intake; the low levels of morphine in urine, bile and tissues, and morphine and 6-MAM in blood indicate heroin intake 2 to 3 hours before death, after an interval without any intake of at least 10 hours.

In conclusion, it may be deduced from the fatal case described here and the many cases of non-fatal intoxication reported until now, that the therapeutic potential of GHB is associated with the risk of adverse reactions that cannot be neglected but that may be eliminated only when the exact neurobiological role and mechanism of action of GHB have been clarified.

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