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ORIGINAL ARTICLE

Forensic toxicology findings in deaths involving gamma-hydroxybutyrate

Fredrik C. Kugelberg · Anita Holmgren · Arne Eklund · Alan Wayne Jones

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Abstract Concentrations of the illicit drug gamma-hydroxybutyrate (GHB) were determined in femoral venous blood and urine obtained at autopsy in a series of GHB-related deaths (N=49). The analysis of GHB was done by gas chromatography after conversion to gamma-butyrolactone and quantitation of the latter with a flame ionization detector. The cutoff concentration of GHB in femoral blood or urine for reporting positive results was 30 mg/L. The deceased were mainly young men (86%) aged 26.5±7.2 years (mean± SD), and the women (14%) were about 5 years younger at 21.4±5.0 years. The mean, median, and highest concentrations of GHB in femoral blood (N=37) were 294, 190, and 2,200 mg/L, respectively. The mean urine-to-blood ratio of GHB was 8.8, and the median was 5.2 (N=28). In 12 cases, the concentrations of GHB in blood were negative (<30 mg/L) when the urine contained 350 mg/L on average (range 31–1,100 mg/L). Considerable poly-drug use was evident in these GHB-related deaths: ethanol (18 cases), amphetamine (12 cases), and various prescription medications (benzodizepines, opiates, and antidepressants) in other cases. Interpreting the concentrations of GHB in postmortem blood is complicated because of concomitant use of other psychoactive substances, variable degree of tolerance to centrally acting drugs, and the lack of reliable information about survival time after use of the drug.

Keywords Autopsy · Toxicology · GHB · Intoxication

Introduction

Gamma-hydroxybutyric acid (GHB) is an endogenous metabolite formed during biosynthesis and degradation of the major inhibitory neurotransmitter gamma-aminobutyric acid [1, 2]. Medicolegal interest in GHB stems from its use as an illicit recreational drug and powerful depressant of the central nervous system. The mechanism of action of GHB is similar to that of ethanol, barbiturates, and benzodiazepines [3]. In some countries, GHB is also available on prescription as sodium oxybate (Xyrem®), which is used to treat cataplexy in patients suffering from narcolepsy [4]. Another therapeutic application of GHB is in the field of addiction medicine to relieve withdrawal symptoms and also help to prevent relapse in recovering alcoholics [5, 6].

GHB was first classified as a scheduled substance in Sweden in 2000 (class II) in an effort to curb its use as a recreational drug [7]. However, abuse of GHB persists because some people resort to using the pro-drugs, gamma-butyrolactone (GBL) and 1,4-butanediol, both of which are rapidly metabolized into GHB [8, 9]. Furthermore, GHB has gained notoriety in the media as a so-called date-rape drug, although evidence for its widespread use in chemical submission is rather flimsy [10, 11]. The short elimination half-life of GHB (30–40 min from plasma) means that body fluids intended for toxicological analysis should be taken without delay [12, 13]. The hepatic enzymes responsible for metabolism of GHB become saturated after high doses, and concentration time profiles in blood are best described by nonlinear Michaelis–Menten kinetics rather than first-order kinetics [14].

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F. C. Kugelberg · A. Holmgren · A. Eklund · A. W. Jones (✉)
Department of Forensic Genetics and Forensic Toxicology,
National Board of Forensic Medicine,
Artillerigatan 12,
587 58 Linköping, Sweden
e-mail: wayne.jones@rmv.se

The first GHB-related deaths in Sweden occurred in 2000 [15], and abuse of this substance has led to many acute poisonings that require emergency hospital treatment [16]. Driving under the influence of GHB is also well documented in Sweden with roughly 50–60 cases per year sent by the police for toxicological analysis [17]. GHB is also a common finding in blood samples from people arrested for use of illicit drugs not necessarily in connection with driving [17].

Here, we present the forensic toxicology results from 49 autopsies in which GHB was identified in femoral venous blood and/or urine. The age and gender of the deceased were evaluated in relation to GHB concentrations in blood and urine, whether other licit or illicit drugs were present and the manner and cause of death according to the pathologists report. We also investigated whether the deceased was registered in our database for drug-related crimes, including impaired driving and petty-drug offences.

Materials and methods

Collection of samples

Forensic autopsies in Sweden (population 9 million) are performed at six regional pathology units located at the university teaching hospitals throughout the country. Sampling of blood and other body fluids is done according to guidelines promulgated by the National Board of Forensic Medicine (Stockholm, Sweden). For toxicology, the pathologists take femoral venous blood samples along with a specimen of urine and if possible also vitreous humor. These body fluids are preserved with sufficient potassium fluoride to give a final concentration of 1–2% *w/w*.

About 5,000 forensic autopsies have been performed annually between 1996 and 2007, although a general screening analysis of GHB is not in use. Blood and urine are analyzed for GHB if there is suspicion of drug-related deaths or after a direct request by the responsible pathologist or if the police reports suggest that GHB or one of its precursors were being abused. The analytical toxicology results as well as information about the circumstances, cause, and manner of death were compiled from the national forensic toxicology (TOXBASE) and pathology (RÄTTSBASE) databases [18].

Toxicological analysis

Toxicological investigations begin with a screening analysis by enzyme immunoassay methods on urine if available otherwise on blood after precipitation of proteins. Six major classes of drugs are tested for, namely opiates, cannabis, amphetamines, cocaine + metabolites, and benzodiazepines. All positive screening results are verified by use of more specific analytical methods. Opiates and cocaine are determined by gas chromatography-mass spectrometry (GC-MS) after solid-phase extraction [19]. Amphetamines are analyzed by liquid/liquid extraction followed by GC-MS analysis [20]. Capillary gas chromatography fitted with a nitrogen-phosphorus detector is the method used for analysis of a wide range of basic, neutral, and acidic prescription drugs [21]. Ethanol was determined in blood and urine by head-space GC according to a previously described method [22].

Determination of GHB

GHB was determined in blood or urine by gas chromatography with a flame ionization detector (FID) after conversion to GBL. After precipitation of blood proteins with acetone and centrifugation, the supernatant was acidified with sulfuric acid to produce the lactone GBL. The latter was back-extracted into dichlormethane, and after reducing the volume of solvent to 50–100 μL by carefully heating (maximum 50°C), an aliquot was injected into the GC-FID instrument. Care was taken not to evaporate the solvent to dryness, owing to volatility of GBL and thus loss of sample. An aliquot (2 μL) of the dichlormethane extract was injected into the GC, which was fitted with a DB-5 column (30 m×0.25 mm) and with a film thickness of 0.25 μm and with gamma-valerolactone as internal standard. The temperature program was ramped from 60°C to 115°C at a rate of 10°C/min and thereafter to 300°C at a rate of 30°C/min. The retention time of GHB under these conditions was 5.54 min and 4.98 min for the internal standard.

For quantitative analysis, ratios of the GC response from GBL and internal standard were measured and interpellation from a six-point calibration curve prepared with sodium oxybate (Sigma Chemicals, St. Louis, MO, USA) or with 4-hydroxybutyrate (Radian) by addition to aliquots of whole blood obtained from the hospital blood bank without citrate additives.

The extraction recovery for GHB exceeded 80%, and the GC-FID-GBL method was linear from concentrations of 8–1,000 mg/L. The limit of detection of GHB by this method was 2 mg/L, and the limit of quantification (LOQ) was 8 mg/L. However, because several studies have shown that GHB concentrations can increase after death, especially if the body is decomposed and when heart blood is sampled, we used a cutoff concentration of 30 mg/L for reporting positive results [23, 24]. Use of a 30-mg/L cutoff is also supported by our own unpublished studies involving storage of autopsy blood at various temperatures with or without fluoride added as a preservative. We are aware that some laboratories recommend a 50 mg/L cutoff concentra-

tion for GHB when cardiac blood is the blood specimen analyzed [25].

Results

Development in number of GHB cases

Figure 1 displays the annual number of forensic autopsies performed in Sweden between 1996 and 2007 with an average of about 5,000 per year. Also plotted on this graph is the number of cases in which GHB was analyzed (N=719), although the vast majority (93%) were negative (<30 mg/L). GHB was reported positive in only 49 cases at concentrations in blood or urine >30 mg/L.

Age and gender of GHB-related deaths

In this autopsy study, we identified 49 GHB-related deaths comprising 42 men (86%) aged 26.5±7.2 years (mean±SD) and seven women (14%) aged 21.4±5.0 years (p>0.05). In 12 cases, GHB was negative in blood (<30 mg/L) but positive in urine (data not shown in Table 1). The mean and median concentrations of GHB in blood were not significantly different between men and women (p=0.7 according to Mann–Whitney test).

Concentrations of GHB in blood from living and dead

Figure 2 compares the concentrations of GHB in autopsy femoral blood with concentrations in venous blood from apprehended drivers (N=163, mean 83 mg/L, median 70 mg/L) and nontraffic cases (N=288, mean 124 mg/L, median 110 mg/L). This graph shows considerable overlap in the concentrations in living and dead. However, in the autopsy material, there were 18 cases (49%) for which the GHB concentrations were above 200 mg/L, and this compares with six traffic cases (3.6%) and 39 nontraffic cases (13.5%) above this threshold. The highest GHB concentration was 2,200 mg/L in one autopsy case, although this is not plotted in Fig. 2 for clarity.

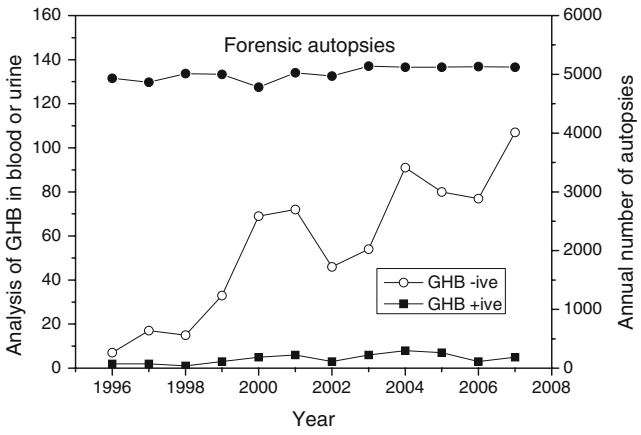

Fig. 1 Annual number of forensic autopsies performed in Sweden (1996–2007) in relation to the analysis of GHB and the numbers of GHB-positive and GHB-negative cases

Table 1 Age, gender and concentrations of GHB in femoral venous blood taken at autopsy in GHB-related deaths

Gender	Number (%)	Age (years)	Blood GHB (mg/L)
		Mean±SD	Mean (median) highest
Men	30 (81)[a]	26.6±7.4[b]	290 (190) 2,200[c]
Women	7 (19)	21.4±5.0	310 (220) 1,000
Both	37 (100)	25.6±7.2	294 (190) 2,200

[a] p<0.01; proportion of men exceeds women
[b] p>0.05, Student's t test; no significant age difference between men and women
[c] p=0.70, Mann–Whitney test; no statistically significant gender difference in concentration of GHB in blood

Toxicological findings in GHB-related deaths

Table 2 (Electronic Supplementary Material) reports the concentrations of GHB in blood and/or urine in 49 GHB-

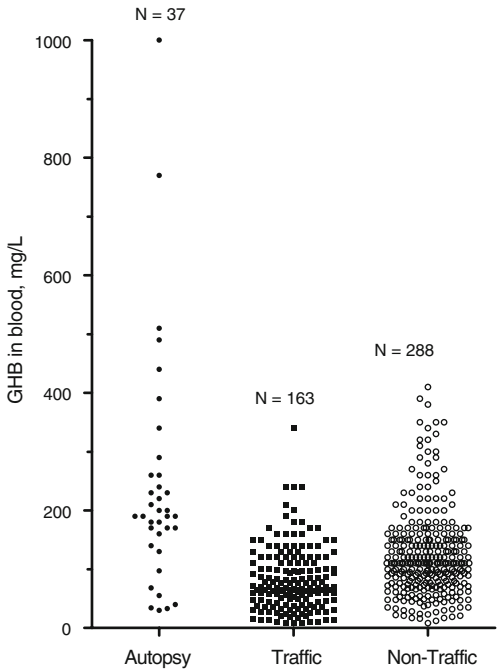

Fig. 2 Distributions of the concentrations of GHB in femoral venous blood taken at autopsy (N=37), compared with venous blood from impaired drivers (N=163) and people arrested for petty drug offences (N=288). One autopsy case (GHB 2,200 mg/L) is not plotted for clarity

related deaths arranged according to the highest concentration of GHB in blood or urine. One notices a high prevalence of multidrug intoxications, which is probably a significant factor in the cause of death. Blood concentrations of GHB were negative (<30 mg/L) in 12 cases (nr 38–49), and these are arranged after the highest concentration in urine. The urine-to-blood ratio of GHB (N=28) averaged 8.8:1 (median 5.2). In one case (nr 2), the urinary concentration (530 mg/L) was less than the blood concentration (1,000 mg/L), which might suggest that death occurred shortly after intake of GHB and before absorption and distribution in all body fluids were complete. In three other cases, the concentrations of GHB in vitreous humor were 78, 250, and 280 mg/L (data not shown in Table 2 in Electronic Supplementary Material) compared with concentrations in blood of 97, 180, and 210 mg/L.

According to the forensic pathologists, 77% of the deaths (N=38) were caused by some form of drug poisoning that involved GHB alone or together with other licit or illicit drugs. In 43% (N=22), the deaths were considered accidental, in 8% (N=4) as intentional, and in 24% (N=12) the intent was unknown. Clues as to the manner of death came from a close scrutiny of police reports, interviews with friends and relatives, and other circumstances, such as finding a farewell letter near the body. The remainder of the GHB-related deaths in Table 2 in Electronic Supplementary Material (N=11 or 22%) were suicides, homicides, or road traffic fatalities.

Ethanol was the drug most often seen together with GHB in 18 cases (blood alcohol concentration (BAC) range 0.10–2.1 g/L), followed by amphetamine in 12 cases (range 0.07–1.5 mg/L) and various combinations of licit and illicit drugs. Codeine and morphine were determined in nine and eight cases, respectively, and the presence of 6-acetylmorphine in two victims indicates heroin-related deaths.

Many of the deceased had prior drug-related offences, including impaired driving and/or use of illicit drugs (nontraffic cases). Of the 49 death cases, 36 (73%) were registered previously in our database a total of 172 times for drug-related offences (mean 3.4 times, median 1, range 1–28 times). One individual had 28 previous arrests before he died of a mixed-drug overdose.

Discussion

A number of compilations of therapeutic, toxic, and fatal concentrations of drugs in blood or serum are available, and these are useful when drug-related deaths are interpreted [21, 26–29]. One such compilation is available through The International Association of Forensic Toxicologists (TIAFT) via the website www.TIAFT.org. According to information from several sources, including the TIAFT list, 280 mg/L GHB in plasma or serum is considered sufficient to cause death. However, distinguishing a drug-related poisoning death from a drug-related death is not an easy matter as discussed in a recent review of postmortem clinical pharmacology [30].

Because of the high solubility of GHB in water and lack of binding to plasma proteins, one can expect that concentrations in whole blood are lower than in plasma or serum because of differences in water content. Indeed, the distribution ratio of GHB between serum and whole blood is probably similar to ethanol, namely 1.16:1 [31]. The fatal concentrations of GHB in plasma 250–280 mg/L is therefore expected to be ~16% lower in whole blood, owing to an uneven distribution of GHB between plasma and erythrocytes.

The concentrations of drugs determined in postmortem blood should always be interpreted cautiously because of many confounding factors, such as sampling site variations, condition of the body, extent of trauma and blood loss, whether decomposed, and the time delay between death and autopsy [32, 33]. Moreover, the presence of fluoride as preservatives and whether cardiac or femoral blood was analyzed are important considerations [34, 35]. In postmortem toxicology, pre-analytical variations often dominate over analytical uncertainty when drugs are analyzed and the concentrations interpreted [36].

In postmortem toxicology, blood from a femoral vein is preferred to cardiac blood as specimen for analysis of GHB. Some studies show appreciably concentrations of GHB in cardiac blood in deaths that were not considered to be drug-related [33, 37]. Distinguishing between antemortem ingestion of GHB and postmortem production is more problematic if cardiac blood is the specimen analyzed. Some investigators recommend a higher analytical cutoff concentration with cardiac blood, such as 50 mg/L [25]. Moriya and Hashimoto [24] reported 4.6±3.4 mg/L endogenous GHB in femoral venous blood from 23 autopsies and recommended a cutoff concentration of 30 mg/L. Elliott [23] found somewhat higher values, 12.3± 5.6 mg/L, in unpreserved blood from 38 deaths unrelated to GHB. Stephens et al. [34] reported a mean GHB concentration of 19 mg/L in autopsy blood (N=6) stored at 4°C compared with 20 mg/L in a subset of bloods stored at 25°C before analysis. The addition of sodium fluoride helps to prevent but does not eliminate formation of GHB in autopsy blood samples (unpublished work).

The police reports and circumstances of the death provide key pieces of information when investigating drug-related deaths. Autopsy findings might be unremarkable, although intoxication might be a reasonable conclusion as the cause of death when several drugs are used in combination. The concomitant use of other central nervous system depressants such as ethanol, benzodiazepines, or

barbiturates along with GHB represent a dangerous combination, owing to similar sites and mechanisms of action in the brain [38]. Previous use of centrally acting drugs is important to consider because of the development of tolerance. In the present study (see Table 2 in Electronic Supplementary Material), many of the deceased had been apprehended for abuse of drugs and are likely to have developed some tolerance.

The blood and serum concentrations of GHB in nonfatal cases have been relatively well characterized and might range from 45 to 295 mg/L with a median concentration of 180 mg/L in serum [39]. In nonfatal GHB cases admitted to hospital for emergency treatment in UK, the mean concentration in plasma was 245 mg/L (range 86–551 mg/L), and urine specimens contained 1,732 mg/L (range 5–5,581 mg/L) [40]. The mean, median, and highest GHB concentrations in blood in the present autopsy study were 294, 190, and 2,200 mg/L, respectively, and these overlapped with the concentrations in nonfatal cases [17].

After ingestion, GHB is distributed into the total body water and does not bind to plasma proteins so the amount of drug absorbed and distributed in body fluids might be calculated from the concentration in blood. Human dosing studies have shown that the volume of distribution of GHB is about 0.5–0.6 L/kg, and after sodium oxybate (4.5 g), the peak concentration in serum was 120 mg/L [12–14]. If the concentration of GHB in blood is taken to be 300 mg/L for a 70 kg body, a simple calculation shows that, in all body fluids and tissues at the time of death, there should be 10.5–12.6 g of GHB.

In a compilation of GHB-related deaths from Australia (N=10), a mean concentration in blood of 231 mg/L (range 77–370 mg/L) was considered sufficient to cause death [41]. A postmortem GHB concentration in blood of 345 mg/L was found in a man discovered dead at home, and also in this case, the blood-ethanol concentration was 116 mg/100 mL, and urine ethanol was 136 mg/100 mL [42]. In two other GHB-related deaths, there were 330 mg/L in femoral blood at autopsy [43] and 303 mg/L in heart blood [44]. The highest GHB concentration measured in cardiac blood was 2,937 mg/L, and the urine contained 33,727 mg/L giving a urine/blood ratio of 11.5:1 [45]. In another single case report, concentrations of GHB were 461 mg/L in femoral blood and 1,665 mg/L in urine (blood/urine ratio 3.6:1). This gives compelling evidence of a GHB fatality, although the manner of death was considered accidental [46].

In conclusion, most of the GHB-related deaths were young men, many of whom had prior arrests for use of illicit drugs as verified by the number of times they were identified in our database. GHB was analyzed in blood or urine but reported negative (<30 mg/L) in 93% of all cases, which speaks against the notion of an appreciable postmortem synthesis of GHB in femoral blood. Otherwise, many more cases would have been reported positive, and this supports the cutoff concentration of 30 mg/L used by our laboratory. The blood concentration of GHB leading to a fatal intoxication without concomitant use of other psychoactive substances is probably in excess of 300 mg/L.

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