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# Fatalities associated with the use of $\gamma$ -hydroxybutyrate and its analogues in Australasia

David G E Caldicott, Fiona Y Chow, Brian J Burns, Peter D Felgate and Roger W Byard

**G**amma-hydroxybutyrate (GHB) is an endogenous water-soluble tetra-carbon neurotransmitter. It was first synthesised in 1961 and used to model GABAergic pathways in the brain. As the metabolically active end-product of a family of recreational substances, including  $\gamma$ -butyrolactone and 1,4-butanediol, it was first used illicitly in the late 1980s and early 1990s.

GHB was initially marketed as a health food supplement, ostensibly as a sleep aid and body-building supplement. Because it occurs naturally in the body, GHB has been considered erroneously as a "safe" natural high. Concerns about its adverse effects were first expressed in the United States,<sup>1,2</sup> and were given high profile with the erroneous association with the death of the actor River Phoenix in 1993. Warnings regarding the potential harm associated with its use were first issued by the Food and Drug Administration in 1990, but since then its illicit use has not only continued but increased considerably. Between 1994 and 2001, US emergency departments reported that attendances of people who had used GHB increased nearly sixfold,<sup>3</sup> while deaths in people taking GHB are well documented in the international medical literature.<sup>4-6</sup>

We report here the first case series from Australia and New Zealand of fatalities associated with GHB and its analogues, and review some of the problems with the recreational use of this family of drugs.

## METHODS

Deaths associated with GHB were identified from four sources:

- *The database of coronial reports at Monash University National Centre for Coronial Information.*

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## ABSTRACT

**Objective:** To identify deaths in Australasia associated with overdose of  $\gamma$ -hydroxybutyrate (GHB) and its precursors ( $\gamma$ -butyrolactone and 1,4-butanediol).

**Design:** A retrospective search of medical and scientific information sources, as well as popular newsprint, for the period January 2000 – August 2003, with formal clinical, toxicological and forensic evaluation of retrieved data.

**Main outcome measure:** Death associated with forensic data implicating GHB or its analogues.

**Results:** Ten confirmed GHB-associated deaths were identified, with eight considered to be directly attributable to GHB. Only two of these eight cases were positive for ethanol toxicology.

**Conclusions:** Our study supports the existing evidence that GHB overdose is associated with fatalities, and that fatal overdoses occur in the context of isolated use.

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- *State and territory forensic toxicology laboratories.* For cases with confirmed positive toxicological results for GHB or its precursors, clinical and coronial details were requested and reviewed by two of us (D G E C and R W B).

- *The NexisLexis newsprint search engine.* Articles from the Australasian region were sought, using the search terms "gamma hydroxybutyrate" or "gamma hydroxybutyric acid" AND "death" or "overdose" or "fatality". The results were manually searched for articles relating to mortality or morbidity. (NexisLexis is the largest newsprint search engine in the world, covering more than 36 000 individual "news" publications not searched in traditional MEDLINE searches.)

- *Personal knowledge of the authors.* Cases in which our expert opinion had been sought regarding cause of death.

The records of all deaths associated with GHB were reviewed by a state forensic pathologist (R W B).

Ethical considerations were discussed with the South Australian State Pathology Service, and ethical approval was obtained from the Royal Adelaide Hospital Ethics Committee.

## RESULTS

For the search period 1 January 2000 to 31 August 2003, 10 deaths confirmed to be associated with GHB were identified: four through the National Centre for Coronial Information, one through personal knowledge, and the remainder through individual state forensic laboratories. Two deaths reported in the popular press as being associated with GHB were also investigated, but postmortem analysis revealed no evidence to substantiate the suggestion that GHB or its analogues were involved. Details of the 10 cases are summarised in Box 1.

The average age at death was 33.1 years (median, 28.75 years; range, 22–42 years), and eight of the 10 were men.

From the review of the records of all the deaths, eight were considered to be directly attributable to GHB, while GHB was thought to be incidental in one, and possibly contributory in the remaining death. One of the deceased suffered from mild asthma, but there were no other comorbid findings or postmortem pathological findings, apart from those described in Box 1. The two cases in which death could not be directly attributed to GHB had correspondingly lower GHB blood levels. Of the other

**1 Summary of 10 cases in which death was associated with intake of  $\gamma$ -hydroxybutyrate (GHB)**

Case no.	Year	Age and sex	Cause of death	Summary of circumstances (if known)	Levels of GHB	Other substances
1	2000	26M	Mixed drug toxicity	Found dead in car; hose attached to exhaust	Postmortem: blood, 10 mg/L; urine, 90 mg/L	Blood: carboxyhaemoglobin level, 21% saturation; fluoxetine, 0.17 mg/L; nortriptyline, 0.28 mg/L
2	2001	38M	GHB toxicity	Found dead in apartment	Postmortem: blood, 77 mg/L	Nil
3	2001	22M	Respiratory arrest secondary to GHB	Brain dead on arrival at hospital	Antemortem: blood, 220 mg/L; serum 250 mg/L (both tests on admission to hospital 4–5 hours after ingestion of 1,4-butanediol $\pm$ GHB)	Nil
4	2001	31F	Mixed drug toxicity	Drugs found at scene and tested	Postmortem: blood, 50 mg/L	Blood: cannabis; cocaine, 0.28 mg/L
5	2001	24M	Multiple injuries while under the influence of GHB	Fall from height; history of depression; containers of 1,4-butanediol found at scene	Postmortem: blood, 40 mg/L	Urine: traces of cannabinoids
6	2001	24M	Respiratory arrest associated with combined GHB ("fantasy") and alcohol misuse	Consumed "fantasy" at home	Postmortem: blood, 370 mg/L	Blood alcohol level, 0.2 g/100 mL
7	2002	42F	GHB and alcohol toxicity	Passenger on a cruise ship; died soon after sexual intercourse. Previous history of asthma	Postmortem: blood, 210 mg/L; liver fluid, 120 mg/L; stomach contents, 6300 mg/L	Blood alcohol level, 0.127 g/100 mL
8	2002	35M	Respiratory arrest secondary to GHB	Ingestion of 30 mL GHB. No pulse or respiration when ambulance arrived, but regained pulse after electrocardioversion and cardiopulmonary resuscitation. Life support terminated 2 days later.	Antemortem: blood, 210 mg/L; urine, 230 mg/L	Antemortem urine: cocaine metabolites and MDMA (3 mg/L); none in blood
9	2003	35M	Multiple drug toxicity, in particular GHB	Consumption of alcohol and "fantasy". Collapsed outside hotel	Postmortem: blood, 230 mg/L; urine, 8.2 g/L	Postmortem blood: MDMA (< 1 mg/L); phentermine, 0.1 mg/L
10	2003	21M	Respiratory arrest leading to hypoxia causing cardiac arrest and thereafter brainstem death	At nightclub, ingested unspecified amount of "liquid E" 1 hour before presentation	Postmortem: serum, 150 mg/L; urine, 82 mg/L	Antemortem blood: alcohol, 0; methamphetamines, 0.3 mg/L; amphetamines, < 0.1 mg/L

MDMA = 3-4-methylenedioxyamphetamine.

eight, GHB blood levels ranged from 77 mg/L to 370 mg/L (mean, 231 mg/L). Only two of these eight cases were positive for ethanol toxicology.

## DISCUSSION

Our study supports existing evidence that GHB overdose is associated with fatalities, and that death can occur when GHB is the only substance taken.

There are a number of limitations inherent in our study. Case identification depends on suspicion being raised of GHB involvement in a death, and we have only included cases in which positive toxicological find-

ings were reported. Analysis of tissue for the presence or absence of GHB and its analogues has traditionally not been part of the toxicological work-up for autopsy, although this is changing. In the most recent series, which was reported from Holland,<sup>6</sup> analysis for GHB was only done in response to specific information or requests, as it is not part of routine testing in hospitals and forensic institutes. It is possible that deaths caused by GHB and its analogues have been overlooked because evidence of GHB in tissue had not been specifically sought. There are many countries in the South-East Asia and Oceania regions where the facilities for analysis of GHB do not exist. Further-

more, GHB is metabolised very quickly — after ingestion of 1–3 g, GHB can only be detected for 8 hours in blood and 12 hours in urine.<sup>7–9</sup> This makes it difficult to trace if not anticipated and actively pursued. In all probability, the number of deaths reported in this series is an underestimate of actual deaths over the same period.

It has been reported that GHB levels can increase after death, and concern exists that this might be used to confound forensic investigations.<sup>10</sup> However, tissue levels between those endogenously produced and those found in significant overdose appear to be at least an order of magnitude different. GHB levels in overdose have been well

**Important points**

- Overdose of  $\gamma$ -hydroxybutyrate (GHB) and its analogues *can and does* cause death in the prehospital setting.
- Users of  $\gamma$ -hydroxybutyrate incorrectly differentiate overdose and “g-ing out”. Unconsciousness after using this drug is an overdose.

described. In one series, serum levels ranged from 45 mg/L to 295 mg/L, with a median of 180 mg/L.<sup>11</sup> GHB levels associated with death are less frequently described. The average level in the cases in our series in which GHB was thought to have definitely contributed to death was 231 mg/L, with a range of 77–370 mg/L. This compares with other mean postmortem levels of 112.3 mg/L,<sup>5</sup> and isolated GHB overdose levels of 345 mg/L.<sup>12</sup>

The levels found in our patients were very high, even compared with levels of GHB reported in other cases in the medical literature. This may support the hypothesis that there is little understanding of the potential hazards of this drug by the community that uses it, a fact reflected in its continuing popularity among young Australians.<sup>13</sup>

The precursor chemicals,  $\gamma$ -butyrolactone (GBL) and 1,4-butanediol (1,4-BD), have been marketed to bypass the current near-universal ban on GHB, but have been shown to be equally dangerous.<sup>14,15</sup> GBL has been banned in many countries,<sup>16</sup> but, with a multimillion-dollar value in trade on the international industrial chemical market, legislation to control the distribution of 1,4-BD is proving more problematic. Both GBL and 1,4-BD are endogenously converted by the body into GHB by peripheral lactonases and alcohol and aldehyde dehydroge-

nases,<sup>14</sup> respectively. In a case published elsewhere,<sup>15</sup> 1,4-BD was not identified in postmortem tissue, but analysis of samples from the scene was highly suggestive of 1,4-BD being the cause of death. Because of the restrictions in obtaining GHB, it is probable that most of the “GHB” being consumed in Australia is now in the form of GBL or 1,4-BD.

GHB and GHB-like drugs are taken to induce a euphoric feeling, an effect that occurs at a dose not much lower than that required to induce unconsciousness. In an Australian series of 76 GHB users,<sup>17</sup> half had experienced a GHB overdose in which they had lost consciousness. More worryingly, some of these users did not see loss of consciousness as a negative outcome, many reporting that they had received reassurance from the Internet that “GHB overdose was not in itself a dangerous thing”. The information provided by such sources is notoriously unreliable<sup>18</sup> and partisan towards drug use. Those who had overdosed felt that over 90% of other users of GHB were similarly likely to overdose at some stage.<sup>19</sup>

As might be expected for an unregulated, illicitly produced and covertly distributed substance, it is difficult to estimate the incidence of GHB use in Australia. Press reporting aside,<sup>20-22</sup> most indicators suggest that its use is increasing. The Australian Customs Service reported 39 detections between 1 January and 16 April 2002 — more than in the previous 4 years combined.<sup>23</sup> Further information regarding trends in use can be obtained from the Illicit Drug Reporting System. In 2000, less than 1% of party drug users interviewed reported ever having used GHB; this proportion increased to 23% in 2001 and 35% in 2002. Similarly, reports of recent use increased relative to previous years.<sup>24</sup>

GHB is rarely taken in isolation, with most users tested having another substance in their bloodstream.<sup>25-27</sup> Self-reporting users also report polydrug use; 7% of users in one series reported usually using GHB when they took ecstasy.<sup>24</sup> Aficionados and purists claim that it is this combination that is dangerous, rather than GHB on its own. Our series (and others) show quite clearly that GHB can be fatal in isolation. One might speculate that significantly increased morbidity and mortality would be associated with drugs that can act as sedatives and respiratory depressants, such as alcohol and opiates. In our series, only two of seven cases were shown to have detectable ethanol levels in their blood (Box 1), and none of the other drugs found were at levels normally associated with death (Box 2).<sup>28</sup>

The lessons from our report are stark: overdose of GHB and its analogues *can and does* cause death in the prehospital setting. These deaths are probably generally due to cardiorespiratory depression and loss of airway, but may also be associated with injury associated with diminished judgement. We have been unable to detect any reports in the international medical literature of deaths from GHB that have occurred “in-hospital”, apart from a patient who was already in full cardiac arrest. Users and advocates of this drug incorrectly differentiate overdose and “g-ing out” — unconsciousness after using this drug is an overdose. If further deaths are to be avoided, measures that serve to discourage hospital attendance, whatever the motivation, and whoever initiates them, should be strenuously rejected.

As all deaths occur in the prehospital arena, it is unlikely that any measures other than those involving harm reduction will have a significant impact on deaths from this group of drugs.

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**COMPETING INTERESTS**

None identified.

**2 Reported fatal levels of drugs, other than  $\gamma$ -hydroxybutyrate (postmortem findings), compared with levels in our series**

Drug	Drug concentrations in postmortem blood (mg/L)	
	Previously reported <sup>28</sup>	Our series
Phentermine	1.5–7.6 (mean, 4.0)	0.1 (Case 9)
Fluoxetine	1.3–6.8 (mean, 3.8)	0.17 (Case 1)
Cocaine	0.9–21 (mean, 5.3)	0.28 (Case 4)
		Metabolites only (Case 8)
MDMA [3-4 methylenedioxymethamphetamine]	0.6–2.8 (mean, 1.8)	Urine only, none in blood (Case 8)
		< 1 (Case 9)
Methylamphetamine	0.09–18 (mean, 0.96)	0.3 (Case 8)
Nortriptyline	0–26 (mean, 11.0)	0.28 (Case 1)

## REFERENCES

- 1 Adornato BT, Tse V. Another health food hazard — gamma-hydroxybutyrate-induced seizures. *West J Med* 1992; 157: 471.
- 2 Chin MY, Kreutzer RA, Dyer JE. Acute poisoning from gamma-hydroxybutyrate in California. *West J Med* 1992; 156: 380-384.
- 3 DAWN. Trends in drug-related emergency department visits, 1994-2001. At a glance. Rockville, MD: US Department of Health and Human Services, Substance Abuse and Mental Health Services Administration, 2002. Available at: dawninfo.samhsa.gov/pubs\_94\_02/short-reports/filesTDR\_EDvisits\_glance\_1994\_2001.pdf (accessed Aug 2004).
- 4 Gamma hydroxy butyrate use — New York and Texas, 1995-1996. *MMWR Morb Mortal Wkly Rep* 1997; 46: 281-283.
- 5 Timby N, Eriksson A, Bostrom K. Gamma-hydroxybutyrate associated deaths. *Am J Med* 2000; 108: 518-519.
- 6 Bosman IJ, Lusthof KJ. Forensic cases involving the use of GHB in The Netherlands. *Forensic Sci Int* 2003; 133: 17-21.
- 7 Fieler EL, Coleman DE, Baselt RC. Gamma-hydroxybutyrate concentrations in pre- and postmortem blood and urine. *Clin Chem* 1998; 44: 692.
- 8 Elliot S. The presence of gamma-hydroxybutyric acid (GHB) in postmortem biological fluids. *J Anal Toxicol* 2001; 25: 152.
- 9 Elian AA. Determination of endogenous gamma-hydroxybutyric acid (GHB) levels in antemortem urine and blood. *Forensic Sci Int* 2002; 128: 120-122.
- 10 Sakurada K, Kobayashi M, Iwase H, et al. Production of gamma-hydroxybutyric acid in post-mortem liver increases with time after death. *Toxicol Lett* 2002; 129: 207-217.
- 11 Sporer KA, Chin RL, Dyer JE, Lamb R. Gamma-hydroxybutyrate serum levels and clinical syndrome after severe overdose. *Ann Emerg Med* 2003; 42: 3-8.
- 12 Jones C. Suspicious death related to gamma-hydroxybutyrate (GHB) toxicity. *J Clin Forensic Med* 2001; 8: 74-76.
- 13 Pollard R. The \$5 rush with a fatal sting. *The Sydney Morning Herald* 2003; 26-28 December: 23.
- 14 Zvosec DL, Smith SW, McCutcheon JR, et al. Adverse events, including death, associated with the use of 1,4-butanediol. *N Engl J Med* 2001; 344: 87-94.
- 15 Theron L, Jansen K, Skinner A. New Zealand's first fatality linked to the use of 1,4-butanediol (1,4-B, Fantasy): no evidence of coingestion or comorbidity. *N Z Med J* 2003; 116: U650.
- 16 Department of Justice, Drug Enforcement Administration. Placement of gamma-butyrolactone in List I of the Controlled Substances Act (21 USC 802(34)). *Federal Register* 2000; 65(79): 21645-21647.
- 17 Degenhardt L, Darke S, Dillon P. GHB use among Australians: characteristics, use patterns and associated harm. *Drug Alcohol Depend* 2002; 67: 89-94.
- 18 Boyer EW, Shannon M, Hibberd PL. Web sites with misinformation about illicit drugs. *N Engl J Med* 2001; 345: 469-471.
- 19 Degenhardt L, Darke S, Dillon P. The prevalence and correlates of gamma-hydroxybutyrate (GHB) overdose among Australian users. *Addiction* 2003; 98: 199-204.
- 20 Pollard R, Beaumont L. 'Tis the season to be wasted, probably on "G". *The Age* (Melbourne) 2003; 27 Dec.
- 21 Berry J. Twelve GHB overdoses at dance festivals. *The Age* (Melbourne) 2004; 9 Mar.
- 22 Five hospitalised by party drug. *Sunday Herald Sun* (Melbourne) 2004; 23 May.
- 23 Australian Customs Service. Annual report 2001-2002. Canberra: Office of the Attorney General, 2003.
- 24 White B, Breen C, Degenhardt L. NSW party drugs trends 2002: findings from the Illicit Drug Reporting System (IDRS) Party Drugs Module. Sydney: National Drug and Alcohol Research Council, 2003.
- 25 Li J, Stokes SA, Woeckener A. A tale of novel intoxication: seven cases of gamma-hydroxybutyric acid overdose. *Ann Emerg Med* 1998; 31: 723-728.
- 26 Chin RL, Sporer KA, Cullison B, et al. Clinical course of gamma-hydroxybutyrate overdose. *Ann Emerg Med* 1998; 31: 716-722.
- 27 Garrison G, Muller P. Clinical features and outcomes after unintentional gamma hydroxybutyrate (GHB) overdose [abstract]. *J Toxicol Clin Toxicol* 1998; 26: 503-504.
- 28 Baselt RC. Disposition of toxic drugs and chemicals in man. 6th ed. Foster City, Calif: Biomedical Publications, 2002.

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