Medical and legal confusion surrounding gamma-hydroxybutyrate (GHB) and its precursors gamma-butyrolactone (GBL) and 1,4-butanediol (1,4BD)

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Summary

Background: Gamma-hydroxybutyrate (GHB) is used as a recreational drug, with significant associated morbidity and mortality; it is therefore a class C drug under the Misuse of Drugs Act (1971). However, its precursors gamma-butyrolactone (GBL) and 1,4-butanediol (1,4BD) remain legally available despite having similar clinical effects.

Aim: The aim of this study was to determine whether the relative proportions of self-reported ingestions of GHB or its precursors GBL and 1,4BD were similar to those seen in analysis of seized drugs.

Design and methods: Retrospective review of our clinical toxicology database to identify all cases of self-reported recreational GHB, GBL and 1,4BD use associated with ED presentation in 2006. Additionally all seized substances on people attending local club venues were analysed by a Home Office approved laboratory to identify any illicit substances present.

Results: In 2006, there were a total of 158 ED presentations, of which 150 (94.9%) and 8 (5.1%) were GHB and GBL self-reported ingestions respectively; 96.8% (153) were recreational use. Of the 418 samples seized, 225 (53.8%) were in liquid form; 85 (37.8%) contained GHB and 140 (62.2%) contained GBL. None of the seized samples contained 1,4BD and there were no self-reported 1,4BD ingestions.

Conclusions: Self-reported GHB ingestion was much more common than GBL ingestion, whereas GBL was more commonly found in the seized samples. These differences suggest that GBL use may be more common than previously thought and we suggest that there should be further debate about the legal status of the precursors of GHB.

Introduction

Gamma-hydroxybutyrate (GHB) is a naturally occurring endogenous compound, related to the inhibitory neurotransmitter, gamma-aminobutyric acid (GABA). It was synthesized for use as an anaesthetic agent in the 1960s, but it did not become an established agent due to adverse effects including nausea, vomiting and seizure-like activity.¹² Over the next few decades, GHB first became abused by...
bodybuilders due to reported beneficial effects on growth hormone concentrations, and then by ‘clubbers’ and recreational drug users, who reported stimulant, euphoric and pro-sexual effects.3,4 Several case reports and case series in the 1990s highlighted the potential adverse effects of recreational use of GHB and its precursors, including seizures, drowsiness and coma, and associated respiratory compromise.5–12 Due to these reports, GHB was listed as a DEA Schedule I drug in 2000 in the US (although it is classified as a DEA Schedule II agent for medicinal prescription as Xyrem®). In the UK, the legislation concerning the possession and/or dealing of GHB was changed in June 2003, and it was classified as a Class C controlled substance under the Home Office Misuse of Drugs Act (1971).

The precursors of GHB, gamma-butyrolactone (GBL) and 1,4-butanediol (1,4BD), are chemically very similar to GHB. Both of these compounds are widely used in the chemical industry, as solvents in paints and cleaning products or in the production of rubber and plastics. GBL is a component of nail varnish remover pads. Both GBL and 1,4BD are rapidly broken down in vivo to GHB.13 Since 1,4BD is broken down by the same pathways as ethanol, co-ingestion of ethanol may lead to an inhibition of 1,4BD metabolism to GHB and therefore delayed onset of toxicity.14 Previous reports have noted clinical features of toxicity that is identical to that seen following GHB ingestion, following both GBL and 1,4BD ingestion.15–19 Despite these reports of similar patterns of toxicity, and the change in legal status of GHB in the UK, both GBL and 1,4BD remain legally available and potentially could be used recreationally instead of GHB.

It has been reported that there is high use of GHB, as well as other recreational drugs of abuse, amongst homosexual men.4,20–23 There are several large clubs used by the ‘gay’ or men who have sex with men (MSM) community within the catchment area of our inner-city Emergency Department (ED). These offer prolonged clubbing promotions, which cover the majority of the weekend (Friday evening to Tuesday lunchtime). There have been suggestions in the medical and general press that there has been a shift amongst GHB users to GBL and other precursors such as 1,4BD, due to the disparity in the current legislation.24–27 However, there are no published data to confirm or refute this. Therefore, we collected clinical and demographic data on patients presenting to our ED with GHB, GBL or 1,4BD toxicity, and compared their self-reporting of the drug ingested with analysis of drugs seized on the ‘club scene’.

Methods

Data on all patients presenting to our large inner-city ED with acute poisoning (recreational, deliberate or accidental) are collected prospectively on a dedicated clinical toxicology database. Retrospectively we searched this database to identify all cases of self-reported recreational use of GHB, GBL and 1,4BD associated with presentation to the ED between 1 January 2006 and 31 December 2006 inclusive. Basic demographic data were collected on the sex, date and time of presentation and clinical data including initial presenting Glasgow Coma Score (GCS), disposition from the ED and outcome/length of stay were collected. In addition self-reported co-ingested substances (ethanol, other recreational drugs or other over the counter/prescription medications) were also recorded. Routine toxicology screening is not currently undertaken in the UK as part of standard clinical practice and so all drugs ingested are purely on the basis of the patients’ self-report.

All people attending the MSM club venues in our ED catchment are routinely searched by door staff prior to entry to the venue. Any suspected recreational drugs or opened bottles of any description, which are often used to covertly carry GHB and its precursors into clubs, are seized and placed into a Metropolitan police locked and secured ‘drug collection’ bin. All of the seized samples and bottles are then transported by the Metropolitan Police to the Home Office approved drugs of abuse storage and screening laboratory at St George’s University of London, therefore maintaining a documented chain of custody. Samples are then analysed in batches to identify any illicit substances present, as described previously.28

Results

Emergency department presentations

Number of presentations and characteristics

There were a total of 420 drugs of abuse-related presentations to our inner-city hospital Emergency Department (ED) in the study period, of which 158 (37.6%) were related to GHB (150; 94.9%) and GBL (8; 5.1%) ingestion, as reported by the patient. There were no cases of self-reported 1,4BD ingestion. The majority of these presentations (96.8%) were self-reported recreational use, although there were 4 (2.5%) cases of attempted deliberate self-poisoning (3 GHB, 1 GBL) and one (0.7%) case of accidental ingestion (GHB). Basic presenting clinical parameters of patients on arrival in the ED are
summarized in Table 1. There was significant variation in the time of presentation to the ED, with the majority of patients presenting outside of normal working hours (08:00–18:00) (Figure 1). The majority of patients were male (93.4%) and the largest number of presentations was in the 20–34 year age group (Table 1 and Figure 2).

### Table 1 Clinical parameters on arrival in the ED

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Number of presentations</th>
<th>Percentage of presentations</th>
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<tbody>
<tr>
<td>&lt;20</td>
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<td>6.8</td>
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<tr>
<td>20–24</td>
<td>30</td>
<td>22.6</td>
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<tr>
<td>25–29</td>
<td>37</td>
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<td>30–34</td>
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<td>22.6</td>
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<td>4</td>
<td>3.0</td>
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<tr>
<td>Heart rate (b.p.m)</td>
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<td>&lt;60</td>
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<tr>
<td>60–100</td>
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<td>13</td>
<td>8.6</td>
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<tr>
<td>Respiratory rate</td>
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<tr>
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<tr>
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<tr>
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</tr>
<tr>
<td>Other</td>
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<td>3.3</td>
</tr>
</tbody>
</table>

**Figure 1.** Time of presentation following self-reported GHB/GBL ingestion, demonstrating those presenting during normal ‘working hours’ (striped bars) and those presenting outside ‘normal working hours’ (filled bars).

Severity on presentation, outcome following presentation and length of stay

Glasgow coma score (GCS) on presentation was used as one marker of severity of poisoning (Figure 3). The majority of patients had significant drowsiness; 24 (15.8%) had a GCS on presentation of $\leq 8/15$ and 72 (47.4%) had a GCS of $\geq 8$ (59.3%). Despite this large proportion of patients with a reduced GCS on presentation, 92.2% of patients were discharged directly or self-discharged from the ED or required only a short period of observation in the ED observation ward (Figure 4). Of 12 (7.8%) that required admission to hospital, the majority (91.7%) were admitted to a critical care facility, usually because of significant neurological and respiratory compromise, resulting in the need for airway protection with endotracheal intubation. Median (interquartile range) length of stay was greater in those people requiring admission to ‘higher care facilities’, being 2.4 (1.7–3.0) h, 5.6 (3.6–8.6) h, 15.6 h and 18.7 (10.1–39.2) h for those discharged/self-discharging directly from ED, admitted to an ED observation ward, to a general medical ward and a critical care (HDU/ITU) facility respectively. The overall median (interquartile range) length of stay in the ED and/or hospital for
all patients was 2.8 (1.9–4.0) h and those presenting with a low GCS (≤8/15) had a statistically significantly longer length of hospital admission [3.4 (2.4–7.5) h, chi-squared analysis, $P = 0.038$].

There was one fatality amongst those people who self-reported recreational GHB use. A 25-year-old male was found collapsed at home following attending a nightclub venue, where he was reported to have ingested GHB, ketamine and MDMA. On arrival of the Ambulance Service, he was in cardio-respiratory arrest, with a prolonged ‘down time’ of >20 min. Despite successful resuscitation out of hospital, he suffered significant hypoxic brain injury and was declared dead 2 days later. The coroner’s listed the cause of death as death by accident/misadventure, and the death certificate listed the cause of death as ‘Mixed drug overdose (MDMA and GHB toxicity) with associated lower respiratory tract infection’.

**Co-ingested drugs**

34.4% of patients reported that they had ingested GHB or GBL alone (Table 1). The remainder self-reported co-ingestion of one or more recreational drug of abuse/ethanol, of which the most common were ethanol (34.0%) and MDMA (32.0%) (Table 1). Co-ingestion of other drugs with GHB and/or GBL was not associated with an increased incidence of lower GCS (≤8) ($P = 0.9$) or an increased length of stay ($P = 0.33$).

**GHB/GBL in seized recreational drugs**

Between 28 August 2006 and 14 January 2007, there were 418 samples seized from clubbers attending MSM club venues in the catchment area of the ED, of which 225 (53.8%) were in liquid form. Analysis of these 225 liquid samples demonstrated that 85 (37.8%) contained GHB and 140 (62.2%) contained GBL. No samples were found to contain 1,4BD. In addition none of the non-liquid seizures were found to contain GHB powder.

**Comparative proportions of GHB and GBL**

The proportion of GHB self-reported in patients presenting to the ED was 94.9% (ratio of GHB:GBL was 0.05) compared to 37.8% in seized drugs from people attending club venues within the catchment area of the ED (ratio of GHB:GBL was 1.65).

**Discussion**

In this study, we have demonstrated that the majority of patients presenting to our inner-city hospital emergency department with suspected gamma-hydroxybutyrate (GHB), gamma-butyrolactone (GBL) or 1,4-butanediol (1,4BD) toxicity, self-report ingestion of GHB rather than its two precursors (GBL and 1,4BD). However, analysis of drugs seized from people attending the same club venues in our catchment area, show that there is significantly more GBL than GHB being seized. There were no self-reports of 1,4BD ingestion and no 1,4BD seizures in this study.

Patients who presented to the hospital in our study had very similar clinical presentations and outcomes to those reported in other large case series from the USA, Spain and Switzerland.9,11,12 These other studies, whilst not reporting duration of hospital stay have shown that there was a positive correlation between low Glasgow Coma Score on arrival to the ED, and an increased duration of coma/time to recovery.9,11 In a small study of patients with severe GHB poisoning, defined as a GCS of <8, serum concentrations of GHB were shown not to correlate with either the presenting GCS or time to recovery.29 The co-ingestion of recreational drugs varied between these studies and our retrospective study, although ethanol was the most commonly reported co-ingested substance. Similar to our findings, lone ingestion of GHB was seen in the minority of cases.9,12

Both GHB and its precursors have a steep dose–response curve, with rapid onset of symptoms, and previous studies appear to suggest that there is no difference between the clinical effects of GHB or its precursors.15–19,30 In addition, there have been several reported deaths not only relating to ingestion of GHB, but also to its precursors GBL and 1,4BD.19,31–33 Our study demonstrated that a much higher proportion of people attending the ED self-reported ingestion of GHB rather than GBL, particularly when compared to the analysis of seized compounds, which suggests a higher availability of GBL than GHB. One limitation of our study is that
the time periods of data collection for the seized drugs analysis and the clinical cases were not identical, however the peak frequency of presentation for the clinical cases was during the overlapping time period. There was insufficient information available on whether there is a difference between doses ingested, in terms of amount and number, between users of GHB and GBL who present to the ED with toxicity. It is our clinical impression that many individual users do not differentiate between GHB and GBL when obtaining either one of them and, therefore, assume that they had ingested GHB when self-reporting what was ingested.

The legislation concerning the possession and/or dealing of GHB in the UK was changed in 2003, when it was classified as a Class C controlled substance under the Home Office Misuse of Drugs Act (1971). Since then, the legal status of its precursors GBL and 1,4BD has remained unchanged and, therefore, it is legal to possess and supply both of these compounds. This disparity in the legal status of GHB and its precursors, is similar to that in other countries such as Switzerland, Australia and New Zealand. In the United States, over the counter sale of GHB was banned in 1990, and in 2000 it was listed as a DEA Schedule I drug (although it is classified as a DEA Schedule II agent for medicinal prescription as Xyrem®). In addition, in view of the unique properties of GBL and 1,4BD (they can be readily converted into GHB either following ingestion or by simple chemical reactions) and the fact that they have legitimate industrial use, a new paragraph was added to the Controlled Substances Act, in which both were recognized as ‘Controlled Substance Analogues’, whereby diversion for human consumption is tantamount to diversion of a Schedule 1 controlled substance.

It is difficult to determine whether the change in legal status of GHB has meant that previous users have shifted to using to either GBL or 1,4BD instead, which remain legal. First, and most important, there is currently no readily available toxicological test to differentiate between the presence of GHB, GBL or 1,4BD in patients presenting with self-reported ingestion of one of these drugs. Therefore, all studies looking at use of GHB and its precursors are based on self-reported ingestions. Studies from Switzerland suggest that since the change in legislation (GHB became a controlled substance in December 2001), there has been an increase in the frequency of hospital presentations with self-reported GBL ingestion. In 2001 there were no cases of self-reported ingestion of GBL, but in 2002 and 2003 self-reported GBL ingestion comprised 26% and 57% of GHB/GBL presentations to the ED respectively. Although patterns of use for ‘GHB’ have been previously reported, there are no epidemiological data from other countries, such as Australia, New Zealand and the USA differentiating patterns of GHB, GBL and 1,4BD use, and whether this relates to changes in the relevant legislation.

There is a need for further work to determine whether GBL is associated with morbidity and mortality similar to GHB; one potential explanation of our finding is that the majority of club seizures are GBL, whereas the majority of ED presentations are self-reported GHB, is that GHB is associated with greater clinical toxicity. Although there have been no studies directly comparing the two agents we do not feel that it is likely that this is the case, as GBL is rapidly converted to GHB after ingestion in equimolar ratios. Previous studies looking at the comparative pharmacokinetics of GHB and GBL were done many decades ago. It is possible that, with newer analytical techniques, more detailed studies would allow the identification of a potential metabolic product or by-product of GBL that would allow differentiation of GBL and GHB ingestion. This would allow further studies to be undertaken to differentiate analytically between patients presenting with poisoning with GHB or its chemical precursors and therefore confirm the findings in our study that are based on self-reported ingestion.

Further studies are also needed to confirm whether GHB/GBL dealers are trying to switch to GBL due to differences in its legal status, and whether users truly know the difference between GHB, GBL and 1,4BD, or view all of these agents as equivalent to ‘GHB’ in terms of recreational use. There are limited data available on the source of GHB/GBL ingested by users. Since GHB is classified under the Misuse of Drugs Act (1971), it can either be bought from dealers or manufactured at home for personal use from GBL. Conversely, the precursors GBL and 1,4BD are widely used in the chemical industry within the UK. Large amounts of GBL and 1,4BD are imported into the UK each year. The majority of these imports are used by a small number of companies, as ‘consumptive chemicals’ (i.e. chemicals that are consumed in the production of other chemicals, but do not form any part of the final product), solvents in paints and cleaning products or in the production of plastics and rubber, such as Spandex®. As there are no realistic alternatives to either of them available for these current uses, there has been resistance to the reclassification of the precursors under the Misuse of Drugs Act (1971). Currently all ‘large’ imports have to specify the ‘end user’ and there is a voluntary code to minimize misdirection as recreational drugs of abuse. In addition to misdirected imported supplies, users may either obtain the
precursors from products freely available on sale in the UK, which contain them, or directly from suppliers overseas and import them in small quantities to circumvent the current voluntary legislation.

Studies looking at adverse effects of GHB precursors in comparison with GHB and epidemiological data on current supply routes for GHB, GBL and 1,4BD used within the recreational drugs scene in the UK, would allow a more informed debate about the current legal disparity of GHB and its precursors. Confirmation that GBL and 1,4BD possess a similar adverse effect profile to GHB, and findings from this study demonstrating that GBL is abused as a recreational drug (together with the possibility that 1,4BD is used recreationally), strongly suggests that current UK legislation is unlikely to be effective in significantly reducing morbidity and mortality associated with these substances.

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Conflict of interest: D.M.W. and P.I.D. have acted as scientific advisers to the UK Advisory Council on Misuse of Drugs (ACMD) and the European Monitoring Centre for Drugs and Drugs Abuse (EMCDDA).

References


