Peer reviewed article

γ-hydroxybutyrate (GHB) and γ-butyrolactone (GBL): analysis of overdose cases reported to the Swiss Toxicological Information Centre

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Summary

We analysed 141 cases of γ-hydroxybutyric acid (GHB) and γ-butyrolactone (GBL) intoxication reported by physicians to the Swiss Toxicological Information Centre between 1995 and 2003. GHB and GBL intoxication are associated with considerable morbidity. Multiple drug use is common. Overdosing frequently results in non-reactive coma, which accounts for the severity of the intoxication and the costs occasioned by management.

Key words: intoxication, GHB, GBL, gamma-hydroxybutyrate, gamma-butyrolactone, liquid ecstasy

Introduction

γ-hydroxybutyrate (GHB) and its precursor γ-butyrolactone (GBL) are emerging as substances of abuse in Europe. GHB is produced clandestinely and sold in the street and via the Internet under names such as "liquid ecstasy". GHB first gained popularity in the 1980s as a sleep aid, a dietary supplement and, among bodybuilders, a purported growth hormone stimulator. Recreationally, GHB is said to cause euphoria and to increase sensuality and disinhibition [1, 2]. During the 1990s the number of poisonings with GHB and GBL in patients taking these drugs for recreational purposes increased dramatically to several thousand per year in the USA [1]. In Europe, GHB is a relatively new drug of abuse. While several cases of GHB intoxication have been reported from 1997 onwards [3, 4], systematic data on the adverse effects of GHB are rare. Chin et al. described the clinical course of GHB toxicity in a series of 88 patients seen in an emergency department in San Francisco, USA [5]. Miró et al. analysed a series of 104 GHB intoxications from an emergency department in Barcelona, Spain [6]. We are not aware of any other large series or of any systematic data analysis in connection with reports to poison centres in Europe. We analysed all well-documented cases of GHB and GBL intoxication reported by doctors to the Swiss Toxicological Information Centre (STIC) between January 1995 and December 2003. The goal of this study was to define the clinical features of GHB-like drug toxicity with a view to improving management of intoxication and avoiding unnecessary treatment. Our aim was also to provide epidemiological data on this new medical problem in Switzerland.

Methods

The study was approved by the ethics committee of Zurich University Hospital. The STIC collects detailed clinical reports from physicians and hospitals treating poisoning cases by means of an in-house computer-based and structured data-recording and analysis system (TOXI) [7]. A search of the TOXI database yielded 285 calls related to GHB or GBL use. Only well documented cases with a report from the attending physician were analysed further. For every case the information in the data base was verified on the basis of the archived original reports and supplemented by information from discharge letters and laboratory where available. There were 141 cases of acute GHB or GBL intoxication and 7 of GHB withdrawal-related problems. The causal relationship between GHB or GBL intoxication and symptoms and clinical course was rated probable in all these cases. Probable causality included an appropriate temporal relationship between drug ingestion and toxic reaction, and the absence of other drugs or diseases that could explain the symptoms. Laboratory confirmation of GHB use was not available for any

The present study was supported by the Swiss Federal Office of Public Health (BAG).

of the patients since toxicology screens do not include GHB and there was no assay for the rapid detection of GHB at the time of the study. In the majority of cases patients reported having used GHB or GBL after regaining consciousness or appropriately labelled bottles were found on comatose patients. Data were analysed using STATISTICA (StatSoft™) for Windows. Where distributions were skewed, medians are reported and Mann-Whitney U-tests conducted. In comparisons between groups χ^2 or simple T-tests were calculated as appropriate. The criterion for significance was set at $p < 0.05$.

Results and discussion

There were only occasional cases of GHB intoxication in Switzerland until 1999, when the number of reported cases began to rise dramatically (Figure 1). In December 2001 GHB use was prohibited in Switzerland. We found that from from 2002 onwards reports of GBL intoxication began to replace GHB cases. It thus appears that GBL is now sold as a substitute for GHB.

Epidemiological and clinical data for the 141 patients with well-documented GHB or GBL intoxication are shown in Table 1 and compared with those from all larger published studies. Among the 141 patients toxicity was rated as severe in 64 (45%), moderate in 54 (38%) and minor in 22 (16%) according to the Poisoning Severity Score [8]. Some clinical features appear to be typical of GHB and GBL intoxication and include deep coma with sudden awakening, bradycardia, hypoventilation and agitation. Most patients are reported to present with reduced levels of consciousness. Of the total of 141 cases, 86 (61%) were comatose and 39 (28%) somnolent. A Glasgow Coma Scale score (GCS) of 3 corresponding to non-reactive coma was recorded in 9 of 51 patients (18%) with GHB mono-intoxication, in 10 of 31 patients with alcohol co-use (32%), and in 10 of 26 poly-drug-users (38%) who took more than two drugs including GHB. These differences, however, were not significant. Bradycardia was significantly associated with a GCS of 8 or below ($\chi^2 = 4.76$; $p < 0.05$) and all patients with hypotension also had a low GCS of 3–5. Transient agitation or combativeness was frequent in GHB mono-intoxicated patients (13 of 51 or 25%), and was not associated with concomitant drug use. Seizure-like activity, mainly myoclonic jerking, was reported in 18 of all patients (13%). In four of these cases seizures were reported but not directly observed by hospital personnel. While GHB has been used in an animal model of absence seizures, EEG studies in humans failed to document epileptiform changes [9]. Vomiting occurred in 4 of 51 patients (8%) with GHB mono-intoxication. We found that vomiting was significantly more frequent in patients with GHB intoxication and alcohol consumption (10 of 31 or 32%) than in patients without concomitant alcohol use (12 of 110 or 11%, $\chi^2 = 8.37$; $p < 0.05$). Aspiration as a possible fatal consequence of coma and vomiting may therefore be lessened by reducing co-use of alcohol.

Respiratory insufficiency was reported in 12 patients, seven of whom were consequently intubated. An additional 11 patients were intubated in view of a depressed level of consciousness and an assumed risk of aspiration. The proportion of patients who received mechanical ventilation was similar to that in the USA [5, 10], but considerably higher compared with more recent data from Spain [6]. Mechanical ventilation may be necessary, but the benefit of intubating patients with GHB intoxication is unclear since aspiration has also been reported during in- and extubation [10]. Further investigation is needed to study the benefits and risks of intubating patients with GHB intoxication.

The median duration of symptoms was 2 hours (range 20 min–10 h). Coma rarely lasted longer than four hours in non-intubated patients, a finding consistent with those from other case series [5, 6, 10]. Accordingly, if coma lasts longer than ap-

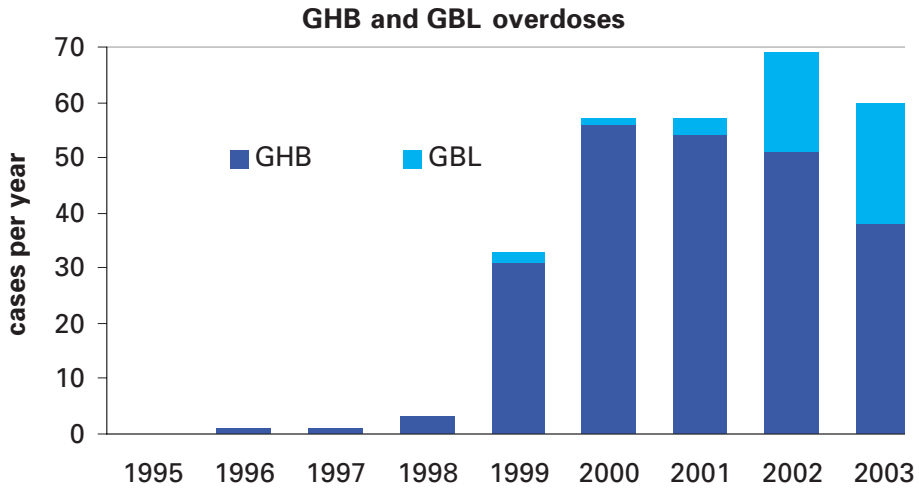

Figure 1

Figure 1 shows the number of γ-hydroxybutyric acid (GHB) and γ-butyrolactone (GBL) intoxications reported to the STIC per year. GHB use was prohibited in Switzerland in December 2001. Note the rise in reported GBL overdose cases in 2002 while GHB cases began to decline.

Table 1

Epidemiological and clinical data of patients with GHB or GBL intoxication.

	Present series (n = 141)	Miró et al. [6] (n = 104)	Chin et al. [5] (n = 88)
Place	Switzerland	Barcelona	San Francisco
Setting	Cases reported to poison centre	Emergency department	Emergency department
Epidemiological data			
Age (mean ± SD) (years)	24 ± 7	23 ± 5	28 ± 6
Gender male (%)	73	66	69
Weekend (Fr 17:00 – Mo 8:00) (%)	52	92	NR[a]
Late night (22:00 – 9:00) (%)	49	67	NR
Coingestion of alcohol (%)	22	73	39
Coingestion of illicit drugs (%)	34	86	28
Amphetamine derivative (%)	21[b]	43	31
Marijuana (%)	16	8	2
Cocaine (%)	8	25	5
Opiates (%)	5	1	2
Sedative (%)	1	3	2
Ketamine (%)	1	11	0
Clinical data			
GCS = 3 (%)	23	17	28
GCS < 9 (%)	40	50	60
Mechanical ventilation (%)	13	3	13
Hypothermia (<36 °C) (%)	NR	28	69
Bradycardia (<55/min) (%)	30	20	35
Hypotension (SBP<95mmHg) (%)	8	7	11
Seizure-like activity (myoclonus) (%)	13	6	2
Agitation (%)	19	5	NR
Vomiting (%)	16	23	30
Laboratory data			
Hypokalaemia (<3,5 mmol/l) (%)	9	27	NR
Elevated creatine kinase (>140 U/L) (%)	12	29	NR

[a] NR: not reported,
[b] including ecstasy (10.6% of all cases)

prox. 4 hours, other or additional causes of coma need to be reconsidered and computed tomographic scans of the brain performed. At present there is no rapid drug screen for GHB-like drugs. Detection of GHB in both blood and urine is possible only by gas chromatography-mass spectroscopy in specialised laboratories. Elimination half-life is, on a dose-dependent basis, between 27–35 min [11]. GHB levels decrease rapidly over several hours and are undetectable in blood within 4–8 hours of administration and in urine after a maximum of 12 hours [10, 11].

Multiple drug use is common among GHB users [2, 5, 6], and physicians should therefore be aware of medical problems related to co-ingested drugs which may change the relatively uniform presentation of GHB or GBL intoxication. Currently the drugs most frequently used with GHB in Switzerland are alcohol and amphetamine derivatives, including ecstasy. Use of GHB with other drugs was reported to induce more severe adverse events than use of GHB alone [2]. In our study, use of other drugs in addition to GHB did not significantly affect the level of consciousness compared with GHB use alone, but there was a tendency to more pronounced coma in patients using GHB and alcohol.

There were seven reports of chronic GHB users experiencing withdrawal-related symptoms. All had used GHB every day over at least some weeks, mainly as a sleep aid or to calm down. Patients presented within one day after discontinuing drug intake with tachycardia (5), tremor (4), agitation (4), hypertension (3), anxiety (2), insomnia for several days (2), and hallucinations (1). GHB and GBL dependence has only recently been described [2, 12]. GHB or GBL discontinuation may result in severe withdrawal symptoms similar to alcoholic delirium tremens, with varying degrees of autonomic dysfunction and possibly severe agitation. Due to the short half-life of GHB, dependence has only been described in patients taking high and multiple doses every day (typically more than 20 g/day) [2]. Given the popularity of the drug, physicians need to be aware of the signs of GHB withdrawal. Such patients need treatment in a critical care setting and should not be transferred to psychiatric services.

In summary, the results of the present study are consistent with the clinical findings of retrospective case series [5, 6] and of a recent small prospective series of patients with confirmed GHB intoxication [10]. By including data from many hospitals in Switzerland, we also wish to convey an impression of this new epidemic and what it involves. We confirm considerable morbidity due to GHB and GBL use in Switzerland. Special attention should be focused on GHB dependence and withdrawal-related symptoms. Management of patients with GHB intoxication included mechanical ventilation and hospitalisation in ICU services in up to a third of all patients, thus generating elevated treatment costs in each of these cases. It needs to be investigated whether less aggressive management is appropriate. Further epidemiological investigation is also required to address the true frequency of GHB use and possible preventive measures.

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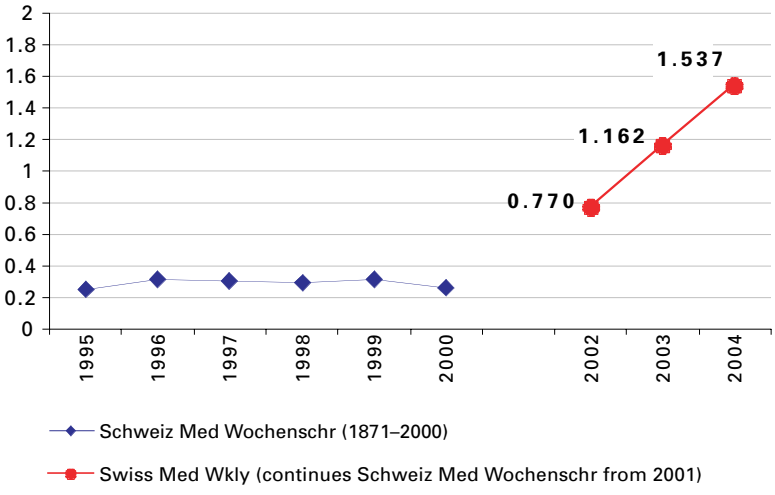

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