Concentration-Time Profiles of Gamma-Hydroxybutyrate in Blood After Recreational Doses are Best Described by Zero-Order Rather Than First-Order Kinetics

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Abstract

The recreational drug gamma-hydroxybutyrate (GHB) has a short plasma elimination half-life ($t_{1/2}$) reported to be about 30–50 min. However, this represents a terminal half-life and therefore might not necessarily apply after large (abuse) doses are taken. Clinical studies with sodium oxybate (sodium salt of GHB) suggest that zero-order rather than first-order kinetics are more appropriate to describe post-peak concentration-time (C-T) profiles. We report the case of a 23-year-old male found unconscious by the police and a blood sample contained 100 mg/L GHB and 0.14 g% ethanol. On regaining consciousness the man admitted drinking alcohol about 6 h earlier but claimed that his drink must have been spiked with GHB. The police wanted to know how much GHB had been administered to account for the man’s clinical condition. A back-calculation for 6 h, assuming a GHB half-life of 40 min, gives a very high concentration in blood of ~900 mg/L, which would probably have proven fatal. Back-calculating using zero-order kinetics and a proposed elimination rate of 18 mg/L per hour leads to a GHB concentration of 208 mg/L, which is much more realistic. Toxicologists should not arbitrarily apply the principles of first-order kinetics after abuse doses of drugs, when zero-order or saturation kinetics (Michaelis-Menten) are more appropriate.

Introduction

The elimination half-life ($t_{1/2}$) of a drug is an important concept in clinical pharmacology because it expresses the rate of change in concentration in blood or plasma in units of time (1). For drugs metabolized according to first-order kinetics, the half-life represents the time necessary for the drug concentration in plasma, or the amount of drug in the body, to decrease by half or 50%. After five half-lives ~97% of a drug is eliminated from the body (2). The concentration versus time (C-T) profile in the post-peak phase for drugs with first-order kinetics is an exponential function ($dc/dt = -kC$), where $k$ is the elimination rate constant having the units of reciprocal time (1). The elimination half-life is easy to calculate directly from the rate constant; $t_{1/2} = \ln 2/k$ or $t_{1/2} = 0.693/k$.

Information about plasma elimination half-lives of drugs is widely available in clinical pharmacology text books as well as in compilations of therapeutic and toxic concentrations (3, 4). According to the reference book Disposition of Toxic Drugs and Chemicals in Man, the $t_{1/2}$ of GHB is between 0.3 and 1.0 h, and the volume of distribution ($V_d$) is 0.4 L/kg (5). These pharmacokinetic parameters are derived from controlled dosing studies with healthy volunteers or hospital patients as the subjects. For ethical and safety reasons, the amount of drug administered in such studies are kept relatively low, and the concentrations in plasma are within the therapeutic interval.

In real-world situations, such as recreational drug use much larger doses of drugs are taken, which suggest that metabolizing enzymes become saturated with substrate. Under these conditions elimination occurs by capacity limited processes so that zero-order or Michaelis-Menten kinetics are more appropriate to describe C-T data rather than first-order kinetics. Obviously the pharmacokinetic model used has implications when drug concentrations are interpreted as exemplified here for GHB.

Case History

A 23-year-old male was found unconscious at 5:30 a.m. after
earlier suffering from seizures. He was taken by the police to a local hospital for observation and treatment and a blood sample was taken at 6:10 a.m. Analysis of the blood sample at our laboratory showed that it contained 100 mg/L GHB and 0.14 g% ethanol. After awakening at the hospital and when questioned by the police, the man admitted drinking alcohol with friends between 10:00 and 12:00 p.m. before suddenly “blacking-out” and losing consciousness. The man maintained that someone must have spiked his drink with GHB. The police requested an expert opinion about the amount of GHB administered to account for the man’s clinical condition, seizures and loss of consciousness.

To answer these questions, we reviewed the scientific literature concerning GHB and looked at articles dealing with pharmacokinetics and pharmacodynamics of this recreational drug (6–8). Table I presents pharmacokinetic parameters of GHB obtained during human dosing studies with pharmaceutical product Xyrem® (Jazz Pharmaceuticals, Palo Alto, CA), which is the sodium salt of GHB (sodium oxybate). The information was obtained from the product monograph of Xyrem, a drug indicated for treatment of cataplexy in patients suffering from narcolepsy (9). An extensive toxicology literature also exists on sodium oxybate and GHB, including a number of comprehensive review articles (10–12).

**Methods**

Venous blood was taken with the aid of evacuated tubes (2 × 10 mL), which contained a mixture of sodium fluoride (100 mg) and potassium oxalate (25 mg) as preservatives. The man’s skin was swabbed with soap and water or a non-alcoholic disinfectant and two evacuated tubes were filled with blood in rapid succession.

Ethanol was determined in blood by headspace gas chromatography (HS-GC) and flame-ionization detection (FID) as described in more detail elsewhere (13). Two technicians each made a single determination working independently with different sets of equipment. Aliquots of blood (100 µL) were diluted 11 times (1 + 10) with n-propanol as internal standard and transferred into glass vials (22 mL) that were made air-tight with crimped on aluminum caps. The coefficient of variation of this method of analysis was less than 1% at a mean ethanol concentration of 0.05 g%, and the limit of quantitation (LOQ) for forensic purposes was 0.01 g% (14).

GHB was determined in blood by GC and FID as described in more detail elsewhere (15). An aliquot of blood (0.5 mL) was treated with acetone to precipitate proteins and centrifuged, and the resulting supernatant was removed and acidified with sulfuric acid. This reaction converts GHB into gamma-butyrolactone (GBL), so our method determines total GHB + GBL. The GBL was back-extracted with dichlormethane, the volume of organic solvent reduced by evaporation under nitrogen, and the aliquot analyzed by the GC–FID instrument. The cut-off concentration for reporting GHB positive in blood from living subjects was 8 mg/L, which therefore serves as the LOQ of the method. The analytical precision (coefficient of variation) of this GC–FID method was 3.9% at a GHB concentration of 8 mg/L and 7.9% at 200 mg/L.

**Table I. Summary of Pharmacokinetic Parameters of Xyrem (sodium oxybate) According to Information from Jazz Pharmaceuticals**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
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<tbody>
<tr>
<td><strong>Absorption and bioavailability</strong></td>
<td>Rapidly absorbed after oral administration, $t_{\text{max}} = 0.5–1.25$ h post-dosing and oral bioavailability ≤25%</td>
</tr>
<tr>
<td><strong>Dose-proportionality</strong></td>
<td>Non-linear kinetics, doubling the dose from 4.5 to 9.0 g increased area under the curve (AUC) 3.8-fold and $C_{\text{max}}$ increased 2.4–2.9-fold.</td>
</tr>
<tr>
<td><strong>Distribution</strong></td>
<td>Distributes into the total body water, $V_d = 0.19–0.38$ L/kg and ~1% of the drug is bound to plasma proteins.</td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td>Approximately 95% metabolized to the end-products carbon dioxide and water, primarily via the Krebs cycle, and no active metabolites are known.</td>
</tr>
<tr>
<td><strong>Elimination</strong></td>
<td>Approximately 2–5% of the dose is excreted unchanged in urine, terminal plasma $t_{\text{1/2}} = 40–60$ min after the first and second doses and $t_{\text{1/2}}$ tends to increase with the dose.</td>
</tr>
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**Results and Discussion**

The clinical and forensic toxicology of GHB resembles, in many respects, the legal drug ethanol (16). Both substances are rapidly absorbed from the gut, distribute into the total body water compartment, and show negligible binding to plasma proteins (11,17). Trace amounts of ethanol and GHB are produced naturally in the body and the endogenous concentrations in blood are ~1 mg/L (18,19). Ethanol and GHB easily pass through the blood-brain barrier to interact with GABA neurotransmission and depress the central nervous system (CNS) (20). Both the legal drug ethanol and GHB undergo extensive hepatic metabolism (95–98%) to produce $\text{CO}_2$ and $\text{H}_2\text{O}$ as end-products. For both drugs, only about 2–5% of the dose administered is excreted unchanged in the urine (21,22). Furthermore, gram quantities of ethanol and GHB are ingested, and the metabolizing enzymes become saturated with substrate, which means that the C-T profiles are best described by non-linear kinetics rather than first-order kinetics (6,23).

Figure 1 shows mean C-T profiles for GHB in a study with Xyrem (sodium oxybate) involving 18 men and 18 women each of whom received an oral dose of 4.5 g. This graph was redrawn
from the clinical study by Borgen et al. (7), and the hockey-stick nature of the plasma GHB profile at 90 min post-dosing is strikingly obvious. This verifies that non-linear saturation kinetics operates and the C-T data might be fitted to the Michaelis-Menten equation as reported elsewhere for ethanol (24–26). Figure 1 suggests that when the concentration of GHB in plasma exceeds 25–30 mg/L, the major metabolizing enzyme are saturated with substrate and zero-order kinetics operate (27).

The zero-order elimination rate constant derived from the C-T data in Figure 1A was 18 mg/L/h and seemed to be independent of sex. The semi-logarithmic C-T plots (Figure 1B) show average curves, and the terminal plasma elimination half-life for GHB was ~40 min. The oral dose of sodium oxybate (MW 127) administered by Borgen et al. (7) was 4.5 g, which corresponds to 3.68 g GHB (MW 104). In the same study, plasma Cmax was 86 mg/L, the tmax was 1 h (median), and the terminal half-life was 0.63 h (38 min).

In the forensic case described here, the concentration of GHB in blood was 100 mg/L at 6:10 a.m. A back-calculation to 12 p.m. (~6 h) assuming first-order elimination kinetics (t½ = 40 min) gave an estimated GHB concentration of ~900 mg/L, which, according to a recent autopsy study, is sufficient to cause death (28). A back-calculation assuming zero-order kinetics (k0 = 18 mg/L/h) resulted in a GHB concentration of 208 mg/L at 12 p.m., which is much more realistic (29). This is also a dangerously high concentration of GHB, considering that the man’s blood alcohol concentration was 0.14 g% because both drugs act as CNS depressants (30). The time of sampling blood in the case report and the time the man was found unconscious by the police are unequivocal. However, the time of administration of GHB is based on information gleaned from police reports and questioning of the victim and his companions.

The mean and median concentrations of GHB in blood of impaired drivers were 89 and 82 mg/L, respectively (N = 548) and the highest concentration was 340 mg/L (31). By comparison, the mean and median GHB concentrations in medical examiner cases (N = 39) were 281 and 190 mg/L, respectively (28). The pharmacokinetics of drugs in overdose is a subject barely mentioned in the forensic toxicology literature. For ethanol and GHB, large amounts are taken compared with other psychoactive substances, and this makes it more realistic to assume zero-order kinetics rather than first-order kinetics when back extrapolation and other pharmacokinetic calculations are made.

Converting the concentration of GHB in blood into the amount of drug absorbed and distributed in all body fluids and tissues has not received a lot of attention. This type of calculation is valid and well proven for ethanol by use of the Widmark equation (32)

\[ A = BAC \times \text{body weight (kg)} \times \text{rho factor (L/kg)} \]

where A is amount of alcohol (g) absorbed and distributed in all body fluids and tissues, kg is body weight of the subject, and rho is Vd of ethanol 0.5–0.7 L/kg (33).

The close similarity between ethanol and GHB in terms of solubility in water, distribution in body fluids, negligible binding to plasma proteins, and non-linear saturation kinetics supports the notion of converting plasma GHB concentration into the amount of drug absorbed and distributed in body fluids. If the man’s body weight was 70 kg, Vd for GHB 0.4 L/kg (Table I), a GHB concentration in blood of 208 mg/L corresponds to 5.8 g of the drug absorbed and distributed in all body fluids and tissues. Because bioavailability of GHB after oral ingestion is fairly low (Table I), considerably more than 5.8 g must have been ingested to account for the man’s clinical condition. Whether the man’s drink was spiked with GHB or the drug was taken voluntarily remains an open question.

After recreational use and abuse of drugs that have capacity limited pharmacokinetics, such as ethanol and GHB, the C-T profiles are best described by zero-order kinetics rather than first-order kinetics. This should be remembered when pharmacokinetic calculations, such as back extrapolation, are made.

Acknowledgment

There was no external funding for this study.
References


Manuscript received March 20, 2009; revision received May 8, 2009.