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CASE REPORT

Gamma-hydroxybutyrate and cocaine intoxication in a Danish child

Victoria Elizabeth de Knegt[1], Torben Breindahl[2], Kirstine Moll Harboe[3], Gitte Leth Møller[1] & Malene Landbo Børresen[1]

[1]Department of Pediatrics, Hvidovre University Hospital, Hvidovre, Denmark
[2]Department of Clinical Biochemistry, Vendsyssel Hospital, Aalborg University, Aalborg, Denmark
[3]Department of Clinical Pharmacology and Danish Poison Information Center, Bispebjerg Hospital, University of Copenhagen, Copenhagen, Denmark

Correspondence
Victoria Elizabeth de Knegt, Department of Pediatrics, 460, Hvidovre Hospital, Kettegård Alle 30, 2650 Hvidovre, Denmark.
Tel/Fax: +45 50469429;
E-mail: victoriadeknegt@gmail.com

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Key Clinical Message

GHB intoxication must be considered in children with coma and a suspicion of drug intoxication. Furthermore, mixed intoxication with several substances and the possibility of unpredictable symptom profiles should be anticipated to ensure optimal symptomatic treatment of patients.

Keywords

gamma-hydroxybutyrate, gamma-hydroxybutyric acid, GHB, cocaine, pediatric, child, intoxication.

Introduction

Gamma-Hydroxybutyrate (GHB) is an endogenic gamma-aminobutyric acid analog originally used in the 1960s as an anesthetic drug. It was revoked due to side effects but later reintroduced as a drug for treatment of narcolepsy. In the 1980s GHB was promoted as a bodybuilding and weight loss aid due to its purported growth hormone stimulatory effects [1, 2]. After it was banned in the US in 1990, its use in body building [3] and as a recreational drug [4] expanded. GHB reached the UK in the mid 1990s [5] and shortly thereafter Denmark as a substance of abuse [6]. The prevalence of GHB use in Scandinavia is considered to be low, but the proportion of intoxications with GHB relative to other drugs-of-abuse is high and numerous fatalities have been described [7].

Gamma-butyrolactone (GBL) and 1,4-butanediol (BD) are prodrugs of GHB. Both substances are accessible as pure industrial solvents (>98%) and purchasing opportunities as well as recipes for converting these prodrugs into GHB are easily available [8]. The legal status of GBL and BD vary and only a few countries have classified the compounds as controlled substances.

GHB, GBL, and BD intoxication in children has been described. Accidental ingestion of GBL solvents [9–11], ingestion of BD coated toy beads [12–15], and cases of children and adolescents unintentionally drinking GHB laced soft drinks have been reported [16, 17]. We report a case of a 3-year-old boy ingesting GHB from a fluid container found in a fitness center. To our knowledge, GHB intoxication in children as a result of the substance's supposed growth hormone stimulatory effects and misuse among bodybuilders has not been reported before.

Case

A 3-year-old Danish boy was admitted to hospital with sudden onset lethargy, vomiting, and unconsciousness. The child was with his father in a fitness center, where he was left unsupervised in a children's play area. Shortly after, the child came up to his father and said that he had drunk something from a fluid container left on a nearby

table. Approximately 40 min later, when the family was eating at a nearby restaurant, the child suddenly became lethargic and distant and was rushed to hospital.

Upon arrival the patient was cyanotic and unconscious with a Glasgow Coma Score (GCS) of 8 and a saturation of 84%. All other vital parameters were normal. Initial blood sugar was 5.2 mmol/L. The patient exhibited equally dilated pupils that had slow response to light bilaterally. The patient woke up after 10 min and after another 15 min was fully awake with a GCS of 15. Active charcoal was given. Initial blood tests including hemoglobin, capillary blood gas, kidney, electrolyte, liver enzyme, and infection parameters were normal. Plasma ethanol was below 3.0 mmol/L. Since the hospital did not have a pediatric department, the patient was transferred to an appropriate hospital for observation.

Approximately 90 min after time of ingestion, the patient again suddenly became bradycardic and desaturated to 60%. The patient exhibited dilated pupils and increased tonus in his hands and arms, but showed otherwise no signs of cramping. The patient improved spontaneously within 3 min with normal pulse and saturation but fell into deep sleep. Cerebral CT was normal. Continuous ECG monitoring showed sinus rhythm. A urine sample was acquired by bladder puncture. A urine toxicology screening (immunoassay panel test) was negative for amphetamines, benzodiazepines, cocaine metabolites, cannabis, cannabis metabolites, methadone, and opiates. A urine sample was saved for further testing. The patient was stabilized without ABC problems, but with continued lowered GCS. He was transferred to the intensive care unit where repeated blood tests were normal. Approximately 6 h after ingestion, the patient woke up and presented no further symptoms.

The patient's father was aware of GHB use in the fitness center. On the basis of the symptoms as well as the history, we suspected GHB intoxication. Isocratic high-performance liquid chromatography with tandem mass spectrometry (LC-MS/MS) was used to determine GHB and prodrugs with a method adopted from Wood et al. [18] using a Symmetry C18 column, 2 × 100 mm (3.5 μm) from Waters. The GHB concentration in the patient's urine sample retrieved 1.5–2 h after ingestion was 186 μg/mL. GBL was 15 μg/mL and BD was not detected. The urinal cut-off concentration used to distinguish exogenous GHB ingestion from endogenous levels is 10 μg/mL.

Discussion

The urine GHB concentration found in this case report (186 μg/mL) was 18 times higher than the maximum endogenous level. In comparison, a study of 8 healthy adult volunteers who were administered a single 25 mg/kg dose of GHB showed peak urine concentrations of 230 ± 86.3 μg/mL 60 min after ingestion [19]. Another study of 12 adult volunteers ingesting the same dose of GHB reported peak concentrations in the range 32.6–161.3 μg/mL (average 67.6 μg/mL) [20]. In a study of 16 adult volunteers, doses of 50 mg/kg resulted in peak urine concentrations averaging 150–200 μg/mL in samples collected 0–3 h after drug administration [21]. Due to insufficient urine sample volume, it was not possible to determine the creatinine level of our patient's urine sample. We are, therefore, unable to comment on the degree of urinal dilution. We can, however, conclude that the urine GHB concentration in this case report corresponds to levels found in adults who are administered GHB doses of 25–50 mg/kg.

Our case demonstrates previously described symptoms of GHB toxicity. These are vomiting, lethargy, somnolence, respiratory distress, bradycardia, and CNS depression. The patient showed sudden onset of symptoms and spontaneous remission – two very characteristic traits of GHB intoxication [22]. One symptom that did not fit the profile of GHB intoxication, however, was the dilation of the patient's pupils.

The patient's symptom pattern exhibited a biphasic profile. Sedative symptoms with affected GCS appeared twice, initially 40 min after ingestion and then again 1.5–2 h after ingestion. GHB is known to show a mixed stimulant-sedative pattern where psychostimulant effects appear first and sedative effects appear later [23]. A double-peaked sedative effect, however, has not been described previously. It is known that elimination of GHB from the body is biphasic. The first phase follows linear, zero-order kinetics where the rate of elimination is independent of the drug concentration. Remaining elimination follows a inversely proportional, concentration-dependent first-order kinetic rate of elimination [19, 24, 25]. A biphasic symptom profile should, therefore, not be possible.

The biphasic clinical presentation of symptoms raises the suspicion of the possible involvement of other toxic agents. The observed dilated pupils support this suspicion but at the same time could have been the result of parasympathetic effects caused by vomiting and a fall in blood pressure, pulse, and respiration frequency. Subsequent comprehensive urine drug screening was, therefore, carried out to determine the possible presence of other drugs not detected in the immunoassay panel test. A low concentration of benzoylecgonine – a metabolite of cocaine – estimated to 20 ng/mL was found by LC-MS/MS. The combination of GHB and cocaine is well-known in the world of fitness and bodybuilding, where the stimulatory effects of cocaine are used to counteract the

sedative effects of GHB. The presence of cocaine in conjunction with GHB in our patient was, therefore, not surprising.

Initial urine analysis by immunoassay was false negative for cocaine. Screening tests for benzoylecgonine have cut-off concentrations between 150 and 300 ng/mL and concentrations less than this remain undetectable. Since the amount of cocaine in the urine sample was below the limit of quantification and because the patient received active charcoal within the appropriate time interval, we believe that this treatment may have terminated further absorption of cocaine.

Another factor that needs to be considered is the effect of food on the symptom profile of GHB and cocaine. The patient had eaten a meal shortly after ingesting the unknown fluid. Food could have played a role in the absorption rate of both GHB and cocaine and may have contributed to the biphasic symptom profile seen.

Another plausible cause of the biphasic profile seen in our patient may be ingestion of a mixture of GHB, GBL and/or BD. It is known that both prodrugs of GHB have the same toxic effects as GHB but GBL has more rapid absorption, greater lipid solubility, higher serum concentration, and more prolonged hypnotic effects than GHB [26–28]. The concentration of GBL and GHB in urine is, however, inconclusive with regard to GBL ingestion due to the dynamic equilibrium that exists between GHB and GBL *in vitro* [29].

Hence, it remains speculative whether a mixture of GBH, GBL and/or BD could produce the symptom profile observed in our patient or if it may have been caused by food ingestion or by the presence of other drugs that were not detected. On the basis of our patient's clinical presentation and resolution of symptoms and a confirmatory high urine level of GHB, we conclude that GHB was the most likely cause of our patient's symptoms.

Conclusion

GHB intoxication must be considered in children with coma and a suspicion of drug intoxication. Furthermore, mixed intoxication with several substances and the possibility of unpredictable symptom profiles should be anticipated to ensure optimal symptomatic treatment of patients. The use of GHB and cocaine in the world of bodybuilding and our account of a new child victim demonstrates a new area of concern.

Consent

Written informed consent was obtained from the parents of the patient for publication of this case report. A copy of the written consent is available for review by the Editor of this journal.

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Conflict of Interests

The authors declare that they have no competing interests. There are no relevant financial relationships that should be disclosed. There are no conflicts of interest.

References

1. Takahara, J., S. Yunoki, W. Yakushiji, J. Yamauchi, and Y. Yamane. 1977. Stimulatory effects of gamma-hydroxybutyric acid on growth hormone and prolactin release in humans. J. Clin. Endocrinol. Metab. 44:1014–1017.
2. Galloway, G. P., S. L. Frederick, F. E. Staggers, M. Gonzales, S. A. Stalcup, and D. E. Smith. 1997. Gamma-hydroxybutyrate: an emerging drug of abuse that causes physical dependence. Addict. Abingdon. Engl. 92:89–96.
3. Myrenfors, P.. 1996. [Ten cases of poisoning with gamma hydroxybutyrate. An endogenous substance used by body builders]. Läkartidningen 93:1973–1974.
4. From the Centers for Disease Control. 1991. Multistate outbreak of poisonings associated with illicit use of gamma hydroxy butyrate. JAMA 265:447–448.
5. Stell, J. M., and J. M. Ryan. 1996. Ecstasy and neurodegeneration. Gamma-Hydroxybutyrate is a new recreational drug that may lead to loss of consciousness. BMJ 313:424.
6. Engelsen, J., and H. R. Christensen. 1999. [Gamma-hydroxybutyrate–an endogenous substance and a new central nervous system stimulant. Clinical aspects of acute poisoning]. Ugeskr. Laeger 161:6903–6907.
7. Knudsen, K., J. Greter, and M. Verdicchio. 2008. High mortality rates among GHB abusers in Western Sweden. Clin. Toxicol. Phila. Pa. 46:187–192.
8. Sanguineti, V. R., A. Angelo, and M. R. Frank. 1997. GHB: a home brew. Am. J. Drug Alcohol. Abuse 23:637–642.
9. Rambourg-Schepens, M. O., M. Buffet, C. Durak, and M. Mathieu-Nolf. 1997. Gamma butyrolactone poisoning and its similarities to gamma hydroxybutyric acid: two case reports. Vet. Hum. Toxicol. 39:234–235.
10. Piastra, M., R. Barbaro, A. Chiaretti, A. Tempera, S. Pulitanò, and G. Polidori. 2002. Pulmonary oedema

caused by «liquid ecstasy» ingestion. Arch. Dis. Child. 86:302–303.
11. Savage, T., A. Khan, and B. G. Loftus. 2007. Acetone-free nail polish remover pads: toxicity in a 9-month old. Arch. Dis. Child. 92:371.
12. Ortmann, L. A., M. W. Jaeger, L. P. James, and S. M. Schexnayder. 2009. Coma in a 20-month-old child from an ingestion of a toy containing 1,4-butanediol, a precursor of gamma-hydroxybutyrate. Pediatr. Emerg. Care 25:758–760.
13. Runnacles, J. L. M., and J. Stroobant. 2008. [gamma]-Hydroxybutyrate poisoning: poisoning from toy beads. BMJ 336:110.
14. Gunja, N., E. Doyle, K. Carpenter, O. T. Chan, S. Gilmore, G. Browne, et al. 2008. Gamma-hydroxybutyrate poisoning from toy beads. Med. J. Aust. 188:54–55.
15. Suchard, J., S. Nizkorodov, and S. Wilkinson. 2009. 1,4-Butanediol content of aqua dots children's craft toy beads. J. Med. Toxicol. Off J. Am. Coll. Med. Toxicol. 5:120–124.
16. Suner, S., C. S. Szlatenyi, and R. Y. Wang. 1997. Pediatric gamma hydroxybutyrate intoxication. Acad. Emerg. Med. Off J. Soc. Acad. Emerg. Med. 4:1041–1045.
17. Shannon, M., and L. S. Quang. 2000. Gamma-hydroxybutyrate, gamma-butyrolactone, and 1,4-butanediol: a case report and review of the literature. Pediatr. Emerg. Care 16:435–440.
18. Wood, M., M. Laloup, N. Samyn, M. R. Morris, E. A. de Bruijn, R. A. Maes, et al. 2004. Simultaneous analysis of gamma-hydroxybutyric acid and its precursors in urine using liquid chromatography-tandem mass spectrometry. J. Chromatogr. A 1056:83–90.
19. Brenneisen, R., M. A. Elsohly, T. P. Murphy, J. Passarelli, S. Russmann, S. J. Salamone, et al. 2004. Pharmacokinetics and excretion of gamma-hydroxybutyrate (GHB) in healthy subjects. J. Anal. Toxicol. 28:625–630.
20. Brailsford, A. D., D. A. Cowan, and A. T. Kicman. 2012. Pharmacokinetic properties of γ-hydroxybutyrate (GHB) in whole blood, serum, and urine. J. Anal. Toxicol. 36:88–95.
21. Haller, C., D. Thai, P. Jacob, and J. E. Dyer. 2006. GHB urine concentrations after single-dose administration in humans. J. Anal. Toxicol. 30:360–364.
22. Chin, R. L., K. A. Sporer, B. Cullison, J. E. Dyer, and T. D. Wu. 1998. Clinical course of gamma-hydroxybutyrate overdose. Annu. Emerg. Med. 31:716–722.
23. Abanades, S., M. Farré, M. Segura, S. Pichini, D. Barral, R. Pacifici, et al. 2006. Gamma-hydroxybutyrate (GHB) in humans: pharmacodynamics and pharmacokinetics. Annu. N. Y. Acad. Sci. 1074:559–576.
24. Abanades, S., M. Farré, M. Segura, S. Pichini, A. Pastor, R. Pacifici, et al. 2007. Disposition of gamma-hydroxybutyric acid in conventional and nonconventional biologic fluids after single drug administration: issues in methodology and drug monitoring. Ther. Drug Monit. 29:64–70.
25. Palatini, P., L. Tedeschi, G. Frison, R. Padrini, R. Zordan, R. Orlando, et al. 1993. Dose-dependent absorption and elimination of gamma-hydroxybutyric acid in healthy volunteers. Eur. J. Clin. Pharmacol. 45:353–356.
26. Kohrs, F. P., and W. H. Porter. 1999. Gamma-Hydroxybutyrate intoxication and overdose. Annu. Emerg. Med. 33:475–476.
27. Lettieri, J., and H. L. Fung. 1978. Improved pharmacological activity via pro-drug modification: comparative pharmacokinetics of sodium gamma-hydroxybutyrate and gamma-butyrolactone. Res. Commun. Chem. Pathol. Pharmacol. 22:107–118.
28. Roth, R. H., J. M. Delgado, and N. J. Giarman. 1966. Gamma-butyrolactone and gamma-hydroxybutyric acid. II. The pharmacologically active form. Int. J. Neuropharmacol. 5:421–428.
29. Ciolino, L. A., M. Z. Mesmer, R. D. Satzger, A. C. Machal, H. A. McCauley, and A. S. Mohrhaus. 2001. The chemical interconversion of GHB and GBL: forensic issues and implications. J. Forensic Sci. 46:1315–1323.

