K40 Clinical and Forensic Toxicology of Gamma - Hydroxybutyrate Closely Resembles That of Ethanol

A.W. Jones, PhD, DSc, National Lab Forensic Chemistry, 12 Artillerigatan, Linkoping, 58133, SWEDEN*

After attending this presentation, attendees learn about the clinical and forensic toxicology of two widely used recreational drugs, namely the legal drug ethanol and the illicit drug gamma-hydroxybutyrate (GHB). Both substances are highly soluble in water have low molecular weight and their pharmacological effects are similar to the major central nervous system depressants (general anesthetic gases, barbiturates and benzodiazepines).

This presentation will impact the forensic community by teaching the similarities and differences in clinical pharmacokinetics of ethanol and GHB, the analysis and stability of these substances in blood during storage, the distribution between serum and whole blood, and the effects of food and gender on concentration-time profiles. Moreover, the toxicity of ethanol and GHB are compared and contrasted based on the concentrations determined in blood from impaired drivers and medical examiner cases.

Ethanol and GHB are produced naturally in the body and are measurable in blood and urine at very low concentrations of ~1 mg/L. For recreational purposes both drugs are taken orally and are rapidly absorbed from the gut and distributed into the total body water (TBW) compartment. The distribution of ethanol and GHB between the plasma and erythrocyte fractions of whole blood is similar to that of water distribution, suggesting serum/whole blood ratios of 1.15:1 (range 1.10 to 1.20). Ethanol and GHB don't bind to plasma proteins and undergo extensive hepatic metabolism with only a small fraction (2-5%) of the dose being recoverable in the urine. The metabolism of ethanol and GHB occur by capacity limited kinetics and mathematically this can best be described by the Michaelis-Menten equation. Human dosing studies have shown that when the concentrations in blood pass 150 mg/L (ethanol) and 10 mg/L (GHB), the metabolizing enzymes are virtually saturated with substrate and zero-order kinetics applies. After moderate doses, the elimination rate of ethanol from blood is within the range 100- 200 mg/L/h compared with 10-20 mg/L/h for GHB. The terminal half- lives of ethanol and GHB are relatively short; being in the range 15-30 min. The apparent volumes of distribution (V_d) of both substances are

0.5-0.7 L/kg as expected for water-soluble, non-protein bound drugs that
distribute into the TBW. Concentration-time profiles of ethanol and GHB after moderate doses were similar for men and women in terms of C_{max}, t_{max} and area under the curve (AUC). The rate and extent of absorption is slowed considerably if ethanol or GHB are ingested together with or after a meal, owing to delayed gastric emptying and first-pass metabolism. Under these conditions, C_{max}, t_{max} and AUC are markedly diminished compared with the same dose of the drugs taken on an empty stomach.

Both ethanol and GHB can be determined in blood and urine by conventional gas-liquid chromatography with a flame ionization detector, either by direct injection or headspace technique. Methods are also available for analysis of these substances by GC-MS, which permits use of deuterium labeled analogues as internal standards for unequivocal identification. The concentrations of ethanol and GHB in specimens of whole blood from impaired drivers were remarkably stable during storage at 4°C for several months after sampling.

The mean and median blood-ethanol concentrations in impaired drivers were 1,700 mg/L (N = 29,000) and in some instances the concentrations exceeded 4000 mg/L. These results can be compared with mean and median GHB concentrations of 89 and 82 mg/L (N = 548) in impaired drivers, highest 340 mg/L. The concentrations of ethanol and GHB in blood from living subjects overlapped with concentrations seen in drug-related deaths. The mean and median blood-ethanol concentration (N = 800) was 3600 mg/L and 3500 mg/L, respectively compared with mean and median GHB (N = 37) of 294 mg/L and 190 mg/L, respectively.

Capacity limited pharmacokinetics of ethanol and GHB needs to be carefully considered when the concentrations in blood after toxic doses are interpreted. The terminal half-life should not be used to make predictions about times necessary to eliminate ethanol or GHB from blood or the amount ingested after large recreational or abuse doses are taken. Interpreting the concentration of ethanol and GHB in medical examiner in terms of toxicity and whether drug intoxication was a possible cause of death is complicated by concomitant use of other psychoactive substances.

Ethanol, GHB, Toxicology

Copyright 2009 by the AAFS. Unless stated otherwise, noncommercial *photocopying* of editorial published in this periodical is permitted by AAFS. Permission to reprint, publish, or otherwise reproduce such material in any form other than photocopying must be obtained by AAFS. ** Presenting Author*