Straight Tox

1,4-Butanediol & GHB

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"I thought he was going to die. I didn't want to tell my kids that, of course, but I thought he was going to die." Those were the words of Shelby Esses, whose son Jack quickly fell unconcious after swallowing a handful of Spin Master Aqua Dots.(1)

If you have been following the news, you are likely familiar with what happened here. For those who may have missed this story, this is the latest chapter in "toxic toys" from China, Aqua Dots® . Aqua Dots® is a toy that consists of small beads coated with a water-activated adhesive. The idea is to arrange the colored beads into the desired design then spray them with water to cause them to fuse together. However, a problem seems to lie in the adhesive. The adhesive is intended to contain 1,5-pentanediol, which is considered to be non-toxic, but somehow the Aqua Dots® that little Jack Esses was playing with, as well as others on store shelves, contained instead 1,4-butanediol. Whether the substitution of 1,4-butanediol for 1,5-pentanediol, which cost approximately 5 times that of 1,4-butanediol, was simply a mistake or a calculated attempt to save money in production costs is a matter of speculation at this point.(1) What is known is that Aqua Dots® were quickly pulled from store shelves throughout the United States.

It has long been known that 1,4-butanediol (BD) is an analog to the popular recreational and "date-rape" drug, gamma-hydroxybutyrate (GHB). In fact BD is more than an analog, it is a pro-drug to GHB; rapidly metabolizing to GHB in the body. As such, understanding the pharmacodynamics of GHB are imperative to understanding BD intoxication.

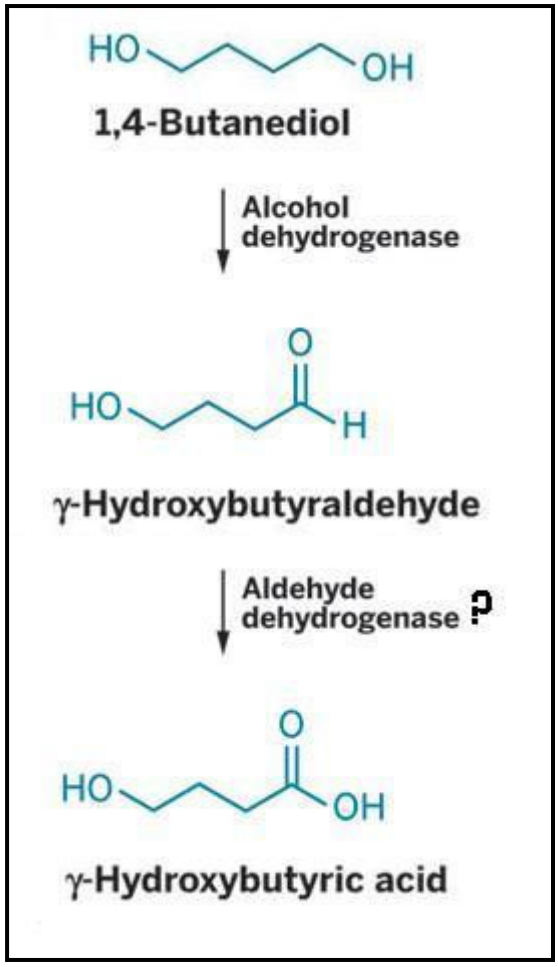
Pharmacodynamics:

The clinical effects of BD are essentially indistinguishable from those of GHB and may be solely due to the GHB produced by BD's rapid metabolism. The effects of GHB are dizziness, alcohol-like inebriation, and sleep induction. At higher concentrations vomiting, myoclonus, respiratory depression, coma and death may occur. The effects of GHB are short-lived and often resolve abruptly within a matter or a few hours. This along with its relative safety and widespread availability make it particularly well-suited as a date rape drug.(2)

However, because two metabolic steps are required to convert BD to GHB, the pharmacokinetics of BD differ somewhat from GHB and therefore merit special attention.

Pharmacokinetics:

In a very recent study involving 8 healthy adult volunteers administered a 25 mg/kg dose of BD, the following was observed: The average maximum concentration (Cmax) for BD was 3.8 mg/L, approximately one tenth of that of GHB at 45.6 mg/L. For five of the eight subjects, measurable plasma GHB levels were present at the first specimen collection, 5 minutes after dosing. All subjects had measurable plasma levels of GHB 30 minutes after dosing. The elimination half-life for BD was 39.3 ± 11.0 min and 32.3 ± 6.6 min for GHB. Plasma concentrations of both BD and GHB were below the limit of quantitation of 1 mg/L by 4 hours after dosing.



Extensive conversion of BD to GHB was demonstrated, indicating that ingestion of BD is essentially equivalent to GHB intake. The prompt appearance of GHB in the plasma indicates rapid absorption and metabolism of BD occurs after oral ingestion. Compared to a previous study of GHB by the same authors, the time to maximum concentration (Tmax) for GHB was somewhat greater than that observed for GHB due to the metabolism of administered BD in this study (57.2 ± 12.5 versus 39.4 ± 11.2 min, respectively). This may be due to the fact that GHB is a carboxylic acid with greater polarity than the neutral aliphatic alcohol, BD, and hence gastrointestinal absorption of GHB is likely to be slower than that of BD.

The rate of metabolism of BD was found to be variable and to correlate with the ADH-IB genotype. Four subjects had high GHB:BD AUC ratios of 80-100, indicative of rapid metabolism of BD to GHB, and four subjects had low AUC ratios ranging from 8 to 17. Three of the four individuals with lower GHB:BD AUC ratios were Asian, suggesting possible genetic-based differences in BD metabolism. Genotyping for a well-known ADH-IB G143A single nucleotide polymorphism was performed which revealed an interesting correlation. Three of four subjects with variant alleles (GA and AA) had greater Cmax and lower CL/F values for BD than subjects with wild-type (CG) variants. This finding is

discordant with the well-described association of G143A variant genotype with 40-fold increase in ethanol metabolism.

The authors suggest several possibilities for this observation. Variant ADH enzymes may have altered substrate affinity for diols such as BD, which can cyclize, versus straight-chain alcohols. Although ADH-mediated metabolism is rate limiting in ethanol metabolism, it may be that the second step conversion of γ-hydroxybutyraldehyde to GHB is the rate-limiting step for BD. It is also possible that another pathway exists for the elimination of BD. Support for this hypothesis comes from some animal data showing that metabolism of BD to GHB occurs in brain tissue independent of both ADH and aldehyde dehydrogenase. Furthermore, although ethanol blocks BD from metabolism by ADH in liver cells, aldehyde and disulfiram failed to block the second step of the conversion of γ-hydroxybutyraldehyde to GHB, suggesting that aldehyde dehydrogenase may not be involved in the formation of GHB from BD. This would suggest that the metabolic pathway of BD metabolism may not be identical to ethanol, as previously hypothesized.

Summary:

As long assumed, it appears the clinical effects of BD are indistinguishable from those of GHB, and are likely to be solely the result of metabolic production of GHB from BD. However, the pharmacokinetics for BD are not yet fully understood. The data would suggest that the Tmax for GHB when derived from the ingestion of BD is shorter than when ingesting GHB alone, perhaps due to more rapid absorption of BD from the GI tract. Furthermore, because the first step in the metabolic process of converting BD to GHB, conversion of BD to γ-hydroxybutyraldehyde, is mediated by ADH, the concomitant use of ethanol may slow the onset and extend the clinical symptoms of GHB intoxication.(3)

1. Harris, Peggy, Mom: Son passed out after eating toy beads. Associated Press, November 9, 2007
2. Mason, P.E., Kerns, W.P.II, Gamma Hydroxybutyric Acid (GHB) Intoxication. *Acad. Emerg. Med.* 9,730-739 (2002)
3. Thai, D., Dyer, J.E., Jacob, P., Haller, C.A., Clinical Pharmacology of 1,4 Butanediol and Gamma-hydroxybutyrate After Oral 1,4-Butanediol Administration to Healthy Volunteers. *Clinical Pharmacology & Therapeutics*, 81:2, 178-184 (2007)