How much is too much when the pediatric minimal **alcohol** dose for **toxicity** is unknown?

FDA PEDIATRIC GUIDELINES

1. The FDA has set a maximum **limit of 0.5% ethanol** in oral over-the-counter products intended for children younger than age **6 years**[1]

2. The American Academy of Pediatrics Committee on Drugs has recommended that the amount of ethanol contained in any preparation **should not be able to produce a blood concentration >25 mg/dL** after a single dose[2]

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Alcohol level leading to **toxicity** in pediatrics is unknown[1]

Ethanol Pharmacokinetics in Neonates and Infants

- Pharmacokinetics, pharmacodynamics, and safety of ethanol **in this vulnerable population** have not been well characterized[3]
- There remains a lack of evidence of the adverse events of ethanol in the developing brain of infants. Due to the lack of evidence on how ethanol affects developing brains, clear recommendations are impossible at this time, but it seems reasonable for clinicians to minimize the use of ethanol-containing solutions in neonates whenever possible.[3]

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Ethanol Pharmacokinetics in Neonates and Infants

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ABSTRACT

Introduction: Ethanol has been used for years in neonatal and infant liquid medications, yet the pharmacokinetics, pharmacodynamics, and safety of ethanol in this vulnerable population have not been well characterized. The purpose of this review is to raise awareness of ethanol use as an excipient in neonatal and infant medications and to provide insight, based on the available evidence, into clearance rates of ethanol in babies. We also discuss ethanol pharmacokinetics in adults, theoretical pharmacokinetic changes in neonates and infants as it may apply to ethanol disposition, and case reports involving ethanol exposure in neonates and infants.

Materials and methods: This study was a narrative review in which relevant papers were selected using databases and scientific search engines such as PubMed with the key words *ethanol, infant,* and *newborn infant.*

Results: It remains unclear what ethanol exposure is safe for neonates and infants. The Food and Drug Administration and American Academy of Pediatrics have both taken action, by either setting limits of ethanol content in over-the-counter medications or by recommending restricted exposure to ethanol-containing pediatric formulations.

Conclusions: Until the short- and long-term health effects of chronic ethanol administration can be further characterized, ethanol-containing medications should be used with caution.

Introduction

Ethanol, also known as alcohol or ethyl alcohol, has been used medicinally and recreationally for centuries, and its pharmacokinetic properties have been studied widely for medical, legal, and forensic purposes. Ethanol serves as a solvent and a microbial preservative in oral liquid medications and is the second most commonly used solvent in liquid formulations following water.[1,2] Often used to dissolve water-insoluble ingredients, it can be found in medicinal solutions, elixirs, and spirits. Table 1 shows some examples of commonly prescribed oral ethanol-containing medications in the United States, and their respective ethanol contents. Ethanol can also be found in parenteral formulations and functions as a co-solvent.

Despite widespread use of ethanol in medications for neonates and infants, the pharmacokinetics and safety of this pharmacologically active agent are not well described. There is limited information on the physiologic effects of ethanol in pediatric populations except in acute poisonings when signs of ethanol exposure can include hypoglycemia, acidosis, tachycardia, hypothermia, hyporesponsiveness, and disorders of consciousness.[3,4] The Food and Drug Administration has set a maximum limit of 0.5% ethanol in oral over-the-counter products intended for children younger than age 6 years (21 CFR P328 2013). The American Academy of Pediatrics Committee on Drugs has recommended that the amount of ethanol contained in any preparation should not be able to produce a blood concentration >25 mg/dL after a single dose,[3] whereas the European Medicines Agency recently proposed that blood ethanol levels should not exceed 1 mg/dL after a single dose (or a dose of 6 mg/kg) in children younger than age 6 years.[4] These limits are intended to serve as safety standards, although they are not based on specific scientific evidence.

Ethanol intake secondary to medication administration can vary widely in pediatric patients. A pilot study of pediatric intensive care unit patients aged 26 weeks to 15 years in the United Kingdom found that 26 of 28 patients were prescribed an ethanol-containing medication with a daily intake of 0.006 to 2.18 mL uncorrected for weight. Authors estimated that these intakes were equivalent to about 0.07 to 15.2 adult UK alcohol units per week[5] or 0.04 to 8.68 US alcohol units per week (ie, >0.5–121 g/wk). The United Kingdom considers 8 g to be 1 unit, or standard adult drink;[6] the United States considers 14 g to be 1 unit or standard

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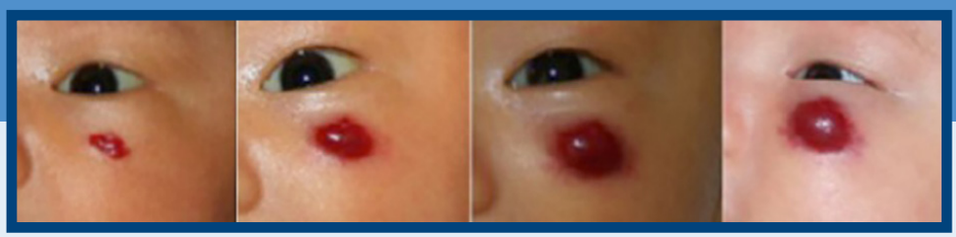
Since the activity of alcohol dehydrogenase is immature, clearance of ethanol is reduced and, as a consequence, after administration, its accumulation is largely observed in the plasma[4]

Newborns, infants, and children are not able to metabolize ethanol as efficiently as adults; as a consequence, they may be at higher risk of both acute and chronic alcohol-related toxicities.[4]

- The use of ethanol in pediatric pharmaceutical preparations raises some concerns since it can be harmful either for possible acute toxicity after accidental overdose or for potential chronic toxicity, with prolonged medicinal exposure for treatment of pediatric chronic diseases[4]

References: 1. Food and Drugs administration. Code of federal regulations. Drug of human use. Over-the-Counter Drug Products Intended for Oral Ingestion That Contain Alcohol; 21.CFR 328.10. Mar. 13, 1995 **2.** American academy of pediatrics. Ethanol in liquid preparations intended for children. Committee on drugs- pediatrics. 1984; 73 (3): 405–407. **3.** Marek E, Kraft WK. Ethanol pharmacokinetics in neonates and infants. *Curr Ther Res Clin Exp.* 2014 ; (76) : 90–97./ **4.** Zuccotti GV, Fabiano V. Safety issues with ethanol as an excipient in drugs intended for pediatric use. *Expert Opin Drug Saf.* March 2011; 10(4):499-502. Accessed on May 5, 2022.

Proliferating Infantile Hemangioma Won't Wait



HEMANGEOL® (propranolol hydrochloride) oral solution is indicated for the treatment of proliferating infantile hemangioma requiring systemic therapy.

Important Safety Information

CONTRAINDICATIONS
HEMANGEOL® (propranolol hydrochloride) is contraindicated in the following conditions:
• Premature infants with corrected age <5 weeks • Infants weighing less than 2 kg
• Known hypersensitivity to propranolol or any of the excipients • Asthma or history of bronchospasm • Heart rate < 80 beats per minute, greater than first-degree heart block, or decompensated heart failure • Blood pressure < 50/30 mmHg
• Pheochromocytoma

WARNINGS AND PRECAUTIONS
HEMANGEOL® prevents the response of endogenous catecholamines to correct hypoglycemia and masks the adrenergic warning signs of hypoglycemia, particularly tachycardia, palpitations, and sweating.

HEMANGEOL® can cause hypoglycemia in children, especially when they are not feeding regularly or are vomiting; withhold the dose under these conditions. Hypoglycemia may present in the form of seizures, lethargy, or coma. If a child has clinical signs of hypoglycemia, parents should discontinue HEMANGEOL® and call their health care provider immediately or take the child to the emergency room. HEMANGEOL® may cause or worsen bradycardia or hypotension. Monitor heart rate and blood pressure after treatment initiation or increase in dose. Discontinue treatment if severe (<80 beats per minute) or symptomatic bradycardia or hypotension (systolic blood pressure <50 mmHg) occurs. HEMANGEOL® can cause bronchospasm; do not use in patients with asthma or a history of bronchospasm. Interrupt treatment in the event of a lower respiratory tract infection associated with dyspnea and wheezing. HEMANGEOL® may worsen circulatory function in patients with congestive heart failure or increase the risk of stroke in PHACE syndrome patients with severe cerebrovascular anomalies. Investigate infants with large facial infantile hemangioma for potential arteriopathy associated with PHACE syndrome prior to HEMANGEOL® therapy. HEMANGEOL® will interfere with epinephrine used to treat serious anaphylaxis.

ADVERSE REACTIONS
The most frequently reported adverse reactions to HEMANGEOL® were sleep disorders, aggravated respiratory tract infections, diarrhea, and vomiting. Adverse reactions led to treatment discontinuation in fewer than 2% of treated patients. Adverse events such as cardiac disorders, urticaria, alopecia, hypoglycemia, and bradycardia occurred in less than 1%. Safety and effectiveness for infantile hemangioma have not been established in pediatric patients greater than 1 year of age.

Please see accompanying Full Prescribing Information or visit www.hemangeol.com

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