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# Ethanol Pharmacokinetics in Neonates and Infants

Elizabeth Marek, PharmD*, Walter K. Kraft, MD

*Department of Pharmacology and Experimental Therapeutics, Thomas Jefferson University, Philadelphia, Pennsylvania*

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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 I 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,[5] 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.[6] 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[7] 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;[8] the United States considers 14 g to be 1 unit or standard

*Address correspondence to: Elizabeth Marek, PharmD, Department of Pharmacology and Experimental Therapeutics, Thomas Jefferson University, 132 S 10th St, 1170 Main Building, Philadelphia, PA 19107.
*E-mail address:* Elizabeth.marek@jefferson.edu (E. Marek).

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**Table I**
Ethanol content of select oral pediatric medications.

| Drug | Ethanol content (%) |
|---|---|
| Acetaminophen with codeine elixir | 7 |
| Chlorothiazide oral suspension | 0.50 |
| Cyproheptadine hydrochloride syrup | 5 |
| Dexamethasone oral solution | 30 |
| Diazoxide oral suspension | 7.25 |
| Digoxin oral solution | 10 |
| Ferrous sulfate oral drops | 0.20 |
| Griseofulvin oral suspension | 0.20 |
| Hydroxyzine hydrochloride syrup | 0.50 |
| Lasix oral solution | 11.50 |
| Maalox oral suspension | $<0.5$ |
| Metoclopramide oral solution | $<0.1$ |
| Nystatin oral suspension | $\leq 1$ |
| Phenobarbital elixir | 15 |
| Prednisolone oral solution | 2 |
| Propranolol hydrochloride | 0.60 |
| Ranitidine oral solution | 7.70 |
| Sulfamethoxazole and trimethoprim oral suspension | 0.26 |
| Zantac | 7.50 |

adult drink. The most commonly prescribed drugs containing ethanol included nystatin, ranitidine, furosemide, and morphine. Of 28 patients, 2 who had an intake of $>15$ UK units/wk (8.47 US units/wk) were both receiving oral morphine for weaning due to opioid abstinence. Since the study was completed, ethanol has been largely removed from oral morphine solutions for pediatric patients.

A second observational study in a UK neonatal intensive care unit (NICU) identified 38 preterm babies over a 1-year period with complete records that survived to discharge at a single hospital. Authors documented excipient intake rates from eight commonly used NICU medications. Two of these medications (iron and furosemide) contained ethanol as an excipient. Babies were exposed to 0.2 to 1.8 mL ethanol per week uncorrected for weight. Correlating to about 1 to 7 adult UK alcohol units/wk[9] or 0.57 to 4 US units/wk (ie, $>8$–56 g/wk), these intake rates are substantial when you consider that the US weekly recommended limits of alcohol in adults are 14 units/wk for men and 7 units/wk for women.[10]

## *Ethanol pharmacokinetics in adults*

### *Absorption*

Ethanol is a small molecule with both hydrophilic and lipophilic characteristics. It is rapidly absorbed in the stomach (20%) and intestines (80%) by simple diffusion. Ethanol absorption is largely dependent on gastric emptying rates because it is absorbed to a large degree in the duodenum.[11] In adults, delayed gastric emptying brought on by the ingestion of food reduces the absorption of alcohol independent of the relative macronutrient content of the meal.[12] This phenomenon is the basis for the commonly employed adage of "not drinking on an empty stomach." Differences in gastric emptying rates have an influence on the shape of the concentration time profile. Absorption rate is driven primarily by gastric motility, as evidenced by decreases in both $C_{max}$ and AUC at 30 minutes with cigarette smoking[13] and a reduced $C_{max}$ and delayed $t_{max}$ with aspirin administration.[14] Similarly, gastric bypass surgery[15] and use of promotility drugs[16,17] increase peak blood ethanol levels. Absorption differences can also be linked to the quantity, concentration, and speed at which ethanol is ingested.[18] For example, a drink with 10% to 30% ethanol is absorbed more rapidly than a more dilute drink; but drinks $>30\%$ ethanol are absorbed more slowly due to gastric irritation.[19] Ethanol is metabolized presystemically in the gastric mucosa at low ethanol doses (0.3g/kg or 0.15g/kg);[20,21] but the magnitude and importance of gastric first pass metabolism is debated.[22]

### *Distribution*

Following absorption, ethanol readily distributes into tissues and body fluids and does not exhibit any protein binding. Its volume of distribution is relative to water content, which is partially responsible for age- and sex-related differences in pharmacokinetic parameters.[23] In adults, total body water content depends on age, weight, and gender, and is approximately 50% to 60% of total body weight in men and 45% to 55% of body weight in women.[24] Ethanol crosses the blood–brain and placental barriers, due in part to its amphiphilic nature.[25] It has been described as following a 2-compartment model, with its distribution depending on elements that govern peripheral circulation, including vasoconstriction, hormone changes, muscular activity, temperature, and circulatory impairment.[23]

### *Metabolism*

Less than 10% of ethanol is excreted in the breath, sweat, and urine. The remaining fraction of ingested ethanol is metabolized to acetaldehyde by 1 of 3 systems: alcohol dehydrogenase (ADH), microsomal ethanol-oxidizing system (MEOS), or catalase. Acetaldehyde is subsequently oxidized to acetate by aldehyde dehydrogenase (ALDH). Acetate leaves the liver and is converted to acetyl-coenzyme A to ultimately produce carbon dioxide and water. A small fraction of ethanol is cleared by nonoxidative pathways and involves ethanol conjugation to endogenous substrates such as fatty acids, phospholipids, sulfate, or glucuronic acid to form fatty acid ethyl esters, phosphadityletheanol, ethyl sulfate, and ethyl glucuronide.[26,27] These metabolites have a longer half-life than ethanol and have been used as biomarkers of ethanol consumption and chronic ethanol use, although none are optimal for this purpose.[28]

A 70-kg adult can metabolize approximately 170 to 240 g of ethanol a day.[26] Ethanol clearance is easily saturated and is best described by Michaelis-Menton (saturation) kinetics. At high concentrations, ethanol is eliminated by zero-order kinetics at a rate of approximately 20 mg/dL/h depending on previous exposure and genetic differences.[29] Nontolerant individuals can eliminate ethanol at a rate of about 10 to 25 mg/dL/h,[23] whereas habitual drinkers can have elimination rates of $\geq 30$ mg/dL/h.[30] Ethanol elimination switches from zero-order to first-order kinetics when blood ethanol concentrations begin to drop below 1 to 3 mM (4.6–13.8 mg/dL).[31,32] Covariates that influence ethanol clearance include body weight, age, dissolved oxygen concentration,[33] and genetic polymorphisms (Table II).[34]

ADH accounts for the bulk of ethanol's oxidative metabolism. It has a wide spectrum of activity, oxidizing many primary and secondary alcohols.[26] ADH is primarily located in the liver, but can be found to a lesser extent in the gastrointestinal tract, kidneys, nasal mucosa, testes, and uterus.[26] Humans have 5 main classes of ADH enzymes (Class I–V), each with differing affinities for ethanol. Class I ADH is primarily found in the liver and contributes the most to ethanol metabolism.[26] Class I isozymes form hetero- or homodimers with $\alpha$, $\beta$, and $\gamma$ subunits, and are coded by *ADH1*, *ADH2*, and *ADH3* genes, respectively. All Class I ADH isoforms, except the $\alpha\alpha$ and relatively uncommon $\beta_3\beta_3$ isoforms, have Michaelis constant (Km) values $\leq 1$ mM and therefore become saturated quickly. The Km of $\alpha\alpha$ and $\beta_3\beta_3$ isoforms are about 4.2 and 24 mM, respectively.[26] Class II ADH is also located in the liver and helps in metabolizing higher ethanol concentrations due to its higher Km ($\sim$34 mM) for ethanol.[31] Class III ADH is distributed throughout the body, has a high Km for ethanol ($>2$ mM), and is important in metabolizing other alcohols.[26] Class IV ADH is