# ALCOHOL: A PHARMACEUTICAL AND PHARMACOLOGICAL POINT OF VIEW DURING LACTATION

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## ABSTRACT

### Background
A safe amount of alcohol that can be ingested by suckling infants is not known. As a result, alcohol consumption by lactating mothers during this crucial time can potentially harm infants.

### Objective
This article provides an overview of alcohol pharmacokinetics and pharmacodynamics in breast milk.

### Methods/Discussion
This paper reviews literature on alcohol exposure as it relates to suckling infants. Intended and unintended alcohol exposure through breast milk may occur by skin contact, inhalation and by use of alcohol co-formulated drugs. A method for calculating the time to alcohol elimination from breast milk is also discussed.

### Summary
As there is no evidence on a safe amount of alcohol in breast milk, alcohol exposure throughout lactation should be avoided, to ensure the welfare of suckling infants.

**Key Words:** *Alcohol, lactation, breastfeeding, pharmaceutical exposure*

Alcohol made of honey, water and yeast is probably the oldest alcohol beverage known to mankind, as it was first produced 8000 years ago. Beer was known since 5400 before Christ, and the first recipes for wine were found in 3500 before Christ in Egypt, on papyrus rolls. The first recipes for distilled alcohol came from the ancient Chinese, Romans and Greeks. However, the Arabs claim to have the first recipe for distilled alcohol. In the Middle Ages, beer was used as a substitute for clean drinking water. Distilled alcohol was expensive and not available for most people.

This changed in the 17th century when it was discovered that distilled alcohol could be produced using corn and beets, which were available at lower costs. See https://en.wikipedia.org/wiki/History_of_alcoholic_beverages for a complete overview of the history of alcoholic beverages. Alcohol has been widely used to extract active ingredients from plants, and is usually removed from the pharmaceutical preparation after extraction. In pharmaceutical practice, alcohol had been widely used in various preparations. It has been used in elixirs and tinctures mainly to dissolve herbal ingredients, preserve finished products, delay the crystallization of active ingredients and mask the unpleasant taste of active ingredients. Nowadays, the use of alcohol in pharmaceutical preparations is limited, retaining its use mainly in herbal medicine and homeopathic medicines. A list of

alcohol containing drug preparations can be found on different internet sites, and patients should be aware of drugs co-formulated with alcohol with up to 15% volume of alcohol in water, such as: acetaminophen, dextromethorphan, antihistamines, risedronate, belladonna extracts, atropine, laxatives, opioids and opium like tinctures, isosorbidenitrate, NSAIDs for topical use, (pseudo)ephedrine, furosemide, metoclopramide, prednisolone, theophylline, iron-preparations and digoxine.

In pharmaceutical practice, 70% volume of alcohol in water solutions have been used in clean rooms to disinfect working benches, for packaging pharmaceutical preparations such as ampoules and for hand glove sterilization prior to working in clean rooms.

Also, hand wash preparations used in sterile areas or in direct patient care settings, often contain alcohol. Direct contact of alcohol with the pharmaceutical preparation is not allowed. Therapeutic uses of alcohol today are limited, although its use in the past has been broad. It was used for pain control for ocular, neuralgia[1], trigeminal neuralgia and inoperable malgnincies.[2]

Furthermore, alcohol was used to treat methanol, methyl alcohol and ethylene glycol toxicities[2], to inhibit preterm labor[3], and to minimize the size of thyroid nodules.[5]

**Pharmacology**

Ethanol has effects on a number of physiological systems. It has a dose-dependent depressive effect on the central nervous system (CNS), varying from mild anxiolytic effects, to sedation and respiratory depression.[2] Clinical effects are related to the dose taken, age, body composition, intrinsic clearance capacity for alcohol, diet, and interacting agents. Other drugs that potentiate the effects of alcohol are benzodiazepines, barbiturates, opiates, antidepressants and vice versa.[2] The impact of ethanol on the cardiovascular system depends on dose, length and frequency (chronic or acute use).[2] The symptoms may vary between a mild coronary vasodilatation to persistent increase in diastolic and systolic blood pressure, supraventricular tachyarrhythmia's, atrial fibrillation, and cardiomyopathy.[2] At high doses, alcohol prolongs the QT interval and ventricular repolarization.

Other drugs may interact and potentiate the cardiovascular effects of alcohol, such as tricyclic antidepressants and sodium channel antagonists. An overview of pharmacodynamic interactions with alcohol is given in Table 1. Extreme chronic alcohol abuse may lead to decreased lower esophageal sphincter pressure, disruption of the gastrointestinal epithelial architecture and barrier function. This increases the risk for Barrett's esophagus, adenocarcinoma, pancreatitis, fatty liver, hepatitis, and cirrhosis.[2]

**Pharmacokinetics**

After oral ingestion, ethanol is completely absorbed from the gastrointestinal tract by passive diffusion, with the concentration gradient as the most important driving force. Therefore, the rate of absorption of ethanol correlates with the concentration of alcohol consumed. The absorption rate of alcohol is much higher in the duodenum and jejunum, as compared with the absorption in the stomach. The gastric emptying rate is an important factor in regulating the rate of ethanol absorption from the gastrointestinal tract. This is the primary reason why meals with high fat content can decrease the rate of absorption and possibly the extent of pre-systemic metabolism of ethanol.[2]

Ethanol undergoes extensive pre-systemic metabolism and its elimination generally follows Michaelis–Menten kinetics. The metabolic capacity for ethanol, including the extent of pre-systemic metabolism, varies depending upon nutritional status, diet, ethnicity, genetics, the type and quality of concurrent food intake, as well as the frequency and amount of ethanol consumed.[2]

The primary metabolic pathway for ethanol is oxidation by alcohol dehydrogenase (ADH) in the liver, but extrahepatic ADH enzymes are also present in the gastrointestinal tract, kidneys, nasal mucosa, testes, and uterus. ADH is highly saturable since their Michaelis-Menten constant (Km) for ethanol is approximately 1 mmol/L.[2] In addition to ADH, cytochrome P450 (CYP) 2E1 is another important enzyme responsible for the metabolism of ethanol.

It is estimated that the contribution of ethanol oxidation by CYP2E1 at lower blood alcohol concentrations is about 10–20%. However, when the blood alcohol concentration reached 0.8 % (pro mille), the contribution of CYP2E1 could be more than 50%.[2]

Therefore, the role of CYP2E1 on ethanol metabolism is of more importance in patients intoxicated with alcohol. The CYP2E1 enzyme can be induced by chronic ethanol use, fasting, obesity, and diabetes mellitus.[2] Also, blood alcohol concentrations differ between the sexes. For women who have a lower volume of distribution and lower gastric ADH, this results in a decreased first-pass metabolism and an increased bioavailability, which may lead to higher levels of toxicity.[2] Drug-alcohol interactions may occur at any pharmacokinetic level. For an overview *see Table 2.*

**TABLE 1** Pharmacodynamic interactions of drugs with alcohol, derived from reference[17]

| **DRUG** | **EFFECT OF INTERACTION WITH ALCOHOL** |
|---|---|
| Acetaminophen | Increased risk of hepatotoxicity |
| Amitriptyline | Sedation |
| Acetylsalicylic acid | General intoxication, flushing |
| Diazepam | Increased motor impairment, sedation |
| Efavirenz | General intoxication |
| Felodipine | Hypotension, tachycardia |
| Gabapentine | Tachycardia |
| Lorazepam | Increased motor impairment, decreased memory recall, sedation |
| Methamphetamine | Increased heart rate, decreased systolic blood pressure |
| Methylphenidate | Stimulation (in general), euphoria |
| Nifedipine | Tachycardia |
| Opioids | Increased respiration and CNS depression |
| Triazolam | Increased psychomotor impairment |
| Verapamil | General intoxication |
| Zolpidem | Increased psychomotor impairment, sedation |
| Zopiclone | Increased psychomotor impairment |

**TABLE 2** Pharmacokinetic interactions with alcohol, derived from reference[17]

| | **Drug** | **Effect of interaction with alcohol** |
|---|---|---|
| **Effect of alcohol on concomitant drug** | Acetaminophen | ↑of NAPQI |
| | Amitryptiline | ↑ AUC and Cmax |
| | Acetylsalicylic acid | ↓Cmax |
| | Abacavir | ↑Cmax; ↑AUC; ↓T1/2 |
| | Chlordiazepoxide | Depending on chronic or acute alcoholic intake, kinetic parameters may differ |
| | Diazepam | Depending on chronic or acute alcoholic intake, kinetic parameters may differ |
| | Erythromycin | ↑Tmax; ↓AUC |
| | Fluvoxamine | ↑Ka |
| | Morphine | Chronic alcohol intake a decrease in formation of alcohol glucuronides |
| | Nifedipine | ↑AUC |
| | Procainamide | ↑Cl; ↓T1/2; ↑*N*-acetylation |
| | Tetracycline | ↑Cmax; ↑AUC |
| **Effect of concomitant drug on alcohol** | **Drug** | **Effect of interaction with alcohol** |
| | Acetylsalicylic acid | ↑Cmax; ↑AUC |
| | Cimetidine | ↑Cmax |
| | Disulfiram | ↓Cl; ↑AUC |
| | Fomepizol | ↓Cl; ↑AUC |
| | Maraviroc | ↑AUC |
| | Oxycodone | Decrease in breath alcohol concentration |
| | Verapamil | ↑Cmax; ↑AUC |

**Alcohol and lactation**

Alcohol transfers to breast milk with a milk:plasma ratio of about 1, which means that breast milk levels are equal to plasma levels of the mother, with a relative infant dose of 16%.[6] The rate of detoxification of alcohol in infants, especially in their first month of life, is half the rate of adults. Consequently, there is no safe dose of alcohol for infants.[6] Some anecdotal reports exist that beer can enhance the taste and increase the breast milk production: however it has been shown that the consumption of breastmilk was 23% lower among those infants.[7] Heavy maternal alcohol intake reduces the absolute amount of breast milk. As well, excessive maternal alcohol intake may lead to neonatal drowsiness, aberrant sleep pattern, and even Cushing Syndrome. A sleepy study performed on 23 infants exposed to ethanol in human milk at 3-5 months of age revealed that 19 infants have significantly less active sleep within 3.5 hours of exposure to alcohol as compared to alcohol free breastmilk.[8] The absolute infant dose depends on the actual amount of alcohol ingested by the mother and the time to breastfeeding after the last drink.[7] A team at The Motherisk program has developed an algorithm with pharmacokinetic modeling to calculate the time needed for the complete alcohol elimination from breastmilk.[9] Moreover there is a mobile app (Feedsafe) available for downloading which calculates the time to complete alcohol elimination from breast milk [http://www.feedsafe.net/]. Exposure to alcohol on the skin is negligible because alcohol is not absorbed. Breastfed children of health care workers and people working in clean rooms are not at risk, when exposed to alcohol in this way. The relationship between ethanol concentration in inhaled air and duration of exposure were linear to the blood levels and concentrations of ethanol in the exhaled air of the exposed individuals.[11] An air alcohol concentration of 1000 ppm, leads to blood concentrations of about 2 ppm after 4 hours of exposure.[11] Simulations of working in alcohol contaminated air performed by 12 minutes of a bicycle ride every hour, for example, may increase plasma alcohol concentrations with a factor 2-3.[11] Occupational exposure to alcohol through the air is regulated, allowing a range between 500 to 1000 ppm, depending on the particular country's laws .[12]

From the study of Dumas-Campagna, it was shown that 4 hours of exposure to 1000 ppm, leads to a plateau blood alcohol concentration of 2 ppm (0.002 per mille).[11] The total amount of alcohol inhaled following 8 hours of work, at 1000 ppm alcohol air limits, equates to 10-11 grams of pure alcohol ingested. This corresponds to drinking 1 alcoholic drink.[12] Thus, breastfeeding mothers should avoid working in places with air alcohol concentrations between 1 and 1000 ppm or higher to prevent their babies from exposure to alcohol.[12]

The human body, in absence of alcohol exposure or intake, produces alcohol itself (in the gut) which leads to alcohol concentrations of approximately of 1 ppm in blood. This corresponds to 0.01 gram of alcohol intake, or alcohol consumption of 0.001 drink per day.[13]

Another potential exposure to alcohol is usage of drugs co-formulated with alcohol. For most drugs, alternatives are available, so it is easy to avoid exposure during lactation. However, the digoxine formulary for neonates may serve as exclusion. In this case, a risk benefits assessment should be performed and discussed with the parents and caregivers. The long term pediatric outcomes of alcohol exposure during breastfeeding are significantly understudied and inconclusive.

Along with the above mentioned neonatal effects of drowsiness, abhorrent sleep patterns and Cushing Syndrome, a study of Little et al (1989) found that ethanol ingested through breast milk has a slight but significant detrimental effect on motor development, but not mental development, in 12 month old breast-fed infants.[16] However, Little was not able to replicate these results when children reached 18 months of age.[15] Magnus et al. (2014) found that there were no increased risks of asthma as a result of maternal alcohol consumption during breastfeeding.[14]

Therefore, given the controversial reports, more research is needed to support the reported findings.

## CONCLUSION

In conclusion, alcohol exposure may be intentional, unintentional or occupational. Careful consideration should be given for drugs co-formulated with alcohol that may be required for the treatment of various medical conditions. The existing knowledge regarding the safe amount of alcohol during lactation is not yet known. The literature of long term pediatric outcomes is very limited and controversial. Considering pharmacokinetic properties, a breastfeeding schedule should account for the time needed for complete alcohol clearance from the breast milk, to ensure that infants are not exposed to alcohol, as alcohol can potentially harm their development. If the mother is willing to breastfeed while consuming alcohol, it is reasonable to use trough levels to calculate the time to immediate elimination from the breast milk. Since there is no defined amount of alcohol that can be consumed while lactating, mothers are advised to avoid alcohol products while breastfeeding.

**Conflict of Interest**

None to declare.

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