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Abstract

Purpose:
Ethanol serves as a solvent and microbial preservative in oral liquid medications and is the second most commonly used solvent in liquid medications following water. Despite widespread use of ethanol in liquid medications for neonates, the pharmacokinetics and toxicity of ethanol in young children are not well described. The aim of the current study is to quantify blood ethanol levels in neonates secondary to oral ethanol containing medications.
Methods:
Neonates who received either oral phenobarbital (15% ethanol) and/or oral dexamethasone (30% ethanol) per standard of care were eligible for enrollment. A maximum of 6 blood samples per patient (4.5 mL total) were taken over the study period. Blood samples were collected via heel stick at the time of clinical laboratory collections or following a specific collection for study purposes. In addition, blood samples were collected from neonates receiving sublingual buprenorphine (30% ethanol) for neonatal abstinence syndrome from a separate clinical study. Blood ethanol levels were measured using a validated headspace gas chromatography-mass spectrometry method utilizing micro-volume (~100uL) plasma samples. The limit of detection and lower limit of quantification for the assay were 0.1 mg/L and 0.5 mg/L respectively.
Results:
A total of 39 plasma samples from 15 neonates who were on ethanol containing medications were collected over the study period. Four neonates were exposed to phenobarbital and/or dexamethasone, while eleven neonates were exposed to buprenorphine alone or in combination with phenobarbital. Patients were exposed to an average of 71.6 mg/kg (range 13.1 to 215 mg/kg) of ethanol after a single dose of an ethanol containing medication. Blood ethanol levels were detectable in 98% (38/39) of samples, quantifiable in 67% (26/39) of samples, and ranged from below detection to 85.4 mg/L. Ethanol was rapidly cleared and did not accumulate with current dosing regimens.
Conclusion:
Ethanol intake secondary to medication administration varied widely. Blood ethanol levels in neonates were low and ethanol was eliminated rapidly after a single dose of oral medications that contained a sizable fraction of ethanol.

Background

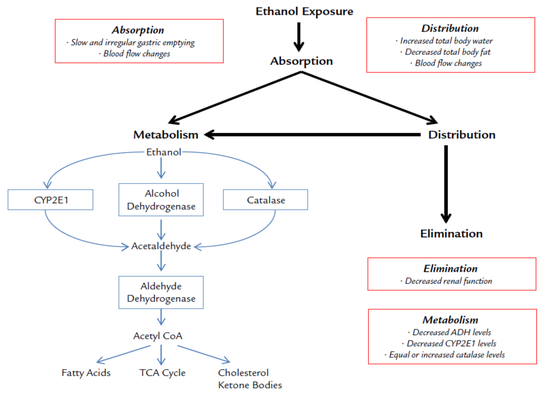


Figure 1. Ethanol disposition in adults. The red boxes indicate physiologic factors that have the potential to affect the absorption, distribution, metabolism, and excretion of ethanol in neonates when compared to adults.
Figure reproduced from: Marek E, Kraft WK. Ethanol pharmacokinetics in neonates and infants. Curr Ther Res Clin Exp. 2014 Oct 22;76:90-7.

Organization	Year	Recommendation
American Academy of Pediatrics[1]	1984	Blood ethanol levels should not exceed 250mg/L following a single dose of an alcohol containing medication
Code of Federal Regulations, 21 CFR 328	1995	Any over the counter product shall not contain >0.5% alcohol as an inactive ingredient in children <6 years
European Medicines Agency[2]	2014	Blood ethanol levels should not exceed 10mg/L in children <6 years of age

Figure 2. Recommended ethanol limits for pediatrics. The American Academy of Pediatrics, Food and Drug Administration, and European Medicines Agency have all taken action, by either setting limits of ethanol content in over-the-counter medications or by recommending restricted exposure to ethanol containing pediatric formulations.

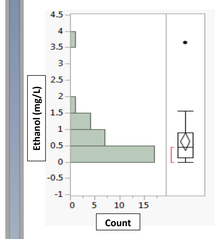
1. Ethanol in liquid preparations intended for children. Pediatrics. 1984 Mar;73(3):405-7.
2. Committee for Human Medicinal Products (CHMP). Questions and answers on ethanol in the context of the revision of the guideline on 'Excipients in the label and package leaflet of medicinal products for human use' (CPMP/463/00).

Methods

Samples were collected from two populations:

- Study #1: Neonates (n=3) who received either oral phenobarbital (15% ethanol, q12hr) and/or oral dexamethasone (30% ethanol, q12hr) per standard of care were eligible for enrollment. A maximum of 6 blood samples/patient were taken over the study period. Blood samples were collected via heel stick at the time of clinical laboratory collections or following a specific collection for study purposes.
  - Inclusion Criteria: age <1 year, on any oral ethanol containing medication
- Study #2: Neonates receiving sublingual buprenorphine (n=12, 30% ethanol, q8hr) or morphine (n=14, control, no ethanol) for neonatal abstinence syndrome (NAS) from a separate clinical study (NCT01452789).
  - Inclusion Criteria: ≥37 weeks gestation, exposure to opiates in utero, signs and symptoms of NAS requiring treatment
- Blood ethanol levels were measured using a validated headspace gas chromatography-mass spectrometry method utilizing micro-volume (~100uL) plasma samples. The limit of detection (LOD) and lower limit of quantification (LLOQ) for the assay were 0.1 mg/L and 0.5 mg/L respectively.

Endogenous Ethanol Production



- ***Endogenous blood ethanol levels ranged from below the LLOQ to 3.65 mg/L in neonates***
  - *-Mean: 0.63 mg/L*
  - *-Median: 0.44 mg/L*
- *For reference, previous studies have shown levels below detection (0.05 mg/L) to 1.6 mg/L in adults[1]*

- *80% of the samples had detectable blood ethanol levels (≥LOD)*
- *43% of the samples had quantifiable blood ethanol levels (≥LLOQ)*

Figure 3. Endogenous ethanol production in neonates (n=30 samples from 14 neonates). Samples were obtained from neonates in Study #2 who were on morphine. Patients did not receive any ethanol containing medications.

1. Jones AW, Mårdh G, Anggård E. Determination of endogenous ethanol in blood and breath by gas chromatography-mass spectrometry. Pharmacol Biochem Behav. 1983;18 Suppl 1:267-72.

Sample Collection

- ***Approximately one third (13/39) of the blood alcohol levels were below the lower limit of quantification***
- ***Blood ethanol levels ranged from below detection to 85.4 mg/L***

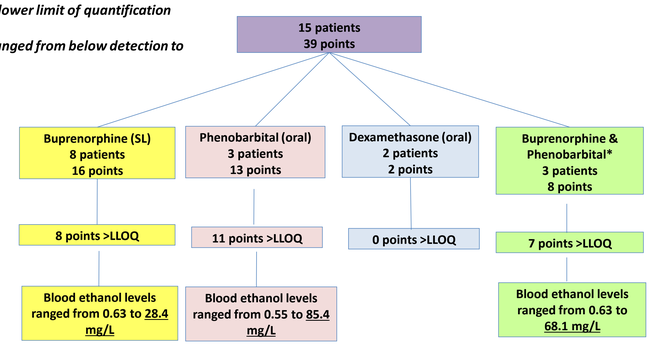


*Figure 8: Plasma sample collection. A total of 39 plasma samples from 15 neonates were collected over the study period. *Eliminated from further analysis due to overlapping medication administration times.*

Patient Baseline Characteristics

Characteristic	Mean ± SD or Number
	Phenobarbital or Dexamethasone "Ethanol" (n=3)
Birth weight (g)	1858 ± 1540.1
Gestational age (wk)	31.1 ± 5.9
Postnatal age (day)	28.3 ± 2.1
Postmenstrual age (wk)	35.2 ± 5.6
Sex	
Male/Female	2/1
Race	
Black/White	3/0

Figure 4. Patient baseline characteristics (at first blood draw) in Study #1.

Characteristic	Mean ± SD or Number	
	Morphine "Control" (n=14)	Buprenorphine "Ethanol" (n=12)
Birth weight (g)	2900.8 ± 453.2	2935.5 ± 361.4
Gestational age (wk)	39.1 ± 1.2	38.9 ± 1.4
Postnatal age (day)	13.3 ± 5.0	12.2 ± 5.5
Postmenstrual age (wk)	41.1 ± 1.3	40.7 ± 0.4
Sex		
Male/Female	7/7	5/7
Race		
Black/White	0/14	3/9

Figure 5. Patient baseline characteristics (at first blood draw) in Study #2.

Ethanol Intake

- ***Patients were exposed to a wide range of ethanol after a single dose of an ethanol containing medication***
  -Range 13.1 to 215 mg/kg/dose ethanol
- ***Neonates received the greatest amount of ethanol in a single dose from phenobarbital***

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	≤ 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

Figure 6. Ethanol content of select oral pediatric medications available at Thomas Jefferson University. Ethanol content is expressed as w/v.
Figure reproduced from: Marek E, Kraft WK. Ethanol pharmacokinetics in neonates and infants. Curr Ther Res Clin Exp. 2014 Oct 22;76:90-7.

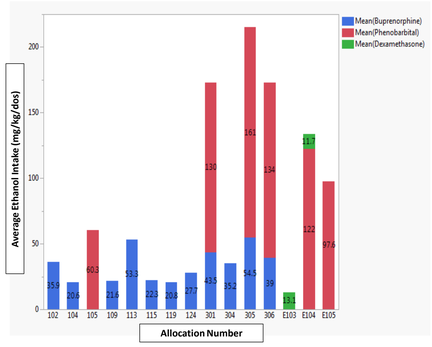


Figure 7. Mean ethanol intake (mg/kg/dose) over the duration of sample collection. Four neonates were exposed to phenobarbital and/or dexamethasone, while eleven neonates were exposed to buprenorphine alone or in combination with phenobarbital.

Concentration-Time Profiles

- ***Ethanol is rapidly eliminated and does not accumulate with the current dosing regimens***

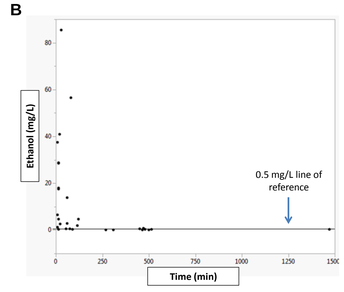
A

Concentration (mg/L)	Occurrence
0-0.5	12
0.5-1.0	3
1.0-5.0	6
5.0-10.0	1
10.0-20.0	3
20.0-30.0	2
30.0-40.0	1
40.0-50.0	1
50.0-60.0	1
60.0-70.0	0
70.0-80.0	0
80.0-90.0	1
Total	31

Total: 31 points from 12 patients

19 points >LLOQ from 9 patients

B



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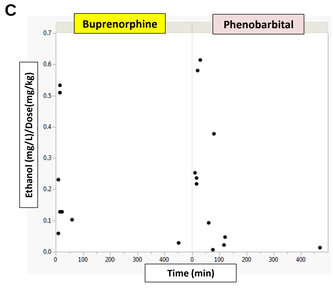

Figure 9: Concentration-time plots for buprenorphine only and phenobarbital only neonates. (A) Breakdown of samples. (B) Concentration time profile for all samples (above and below LLOQ). (C) Dose normalized concentrations of buprenorphine and phenobarbital.

Conclusion & Future Directions

Conclusions

- Ethanol intake secondary to medication administration varied widely, but was generally low
- Endogenous ethanol generation is present in non-ethanol treated infants (43% of samples ≥LLOQ)
- Blood ethanol levels in neonates were low and ethanol was eliminated rapidly after a single dose of oral medications that contained a sizable fraction of ethanol
  - All blood ethanol levels were below the American Academy of Pediatrics recommendation following a single dose of an ethanol containing medication
  - Approximately one third of blood ethanol levels were above the European Medicines Agency recommendation following a single dose of an ethanol containing medication

Future Directions

- Develop a population pharmacokinetic model to describe ethanol pharmacokinetics

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