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Elizabeth Marek, PharmD  
*Thomas Jefferson University*

Susan C. Adeniyi-Jones, MD  
*Thomas Jefferson University*

Lindsey Roke, PharmD  
*Thomas Jefferson University*

Tara E. DeCerbo, PharmD  
*Thomas Jefferson University*

Rebecca L. Cordell, PharmD  
*Thomas Jefferson University*

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Authors
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Ethanol Pharmacokinetics in Neonates Secondary to Medication Administration

Elizabeth Marek1, Susan C. Adeniyi-Jones2, Lindsey Roke3, Tara E. DeCerbo3, Rebecca L. Cordell4, Paul S. Monks4, and Walter K. Kraft1

1Department of Pharmacology & Experimental Therapeutics, Division of Clinical Pharmacology, Thomas Jefferson University, Philadelphia, PA; 2Department of Pediatrics, Thomas Jefferson University/Nemours Children’s Clinics, Philadelphia, PA; 3Department of Pharmacy, Thomas Jefferson University Hospital, Philadelphia, PA; 4Department of Chemistry, University of Leicester, Leicester, United Kingdom

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, however, 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 into heparin at the time of clinical laboratory collections or following a specific collection for study purposes. In addition, blood samples were collected after onset of anti-epileptic therapy, which included receiving oral buprenorphine (44% 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 (<100μL) 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 other medications. Ethanol levels were detectable in 38% (26/69) 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.

Conclusions: 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.

Methods

Samples were collected from two populations:

• Study #1: Neonates (n=3) who received either oral phenobarbital (15% ethanol), oral dexamethasone (30% ethanol), or both at 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 into heparin at the time of clinical laboratory collections or following a specific collection for study purposes. In addition, blood samples were collected after onset of anti-epileptic therapy. Blood samples were collected as soon as possible after onset of anti-epileptic therapy, which included receiving oral buprenorphine (44% 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 (<100μL) 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.

• Study #2: Neonates receiving sublingual buprenorphine (n=12), 30% ethanol, q8h or q12h, or oral nicotine (n=14), no ethanol for neonatal abstinence syndrome (NAS) from a separate clinical study (NCT01274786). Blood samples were collected as soon as possible after onset of anti-epileptic therapy. Ethanol levels were measured using a validated headspace gas chromatography mass spectrometry method utilizing micro-volume (<100μL) 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.

Sample Collection

• Approximately one third (1/3) of the blood alcohol levels were below the lower limit of quantification.

• Blood alcohol levels ranged from below detection to 85.4 mg/L.

Endogenous Ethanol Production

• Ethanol levels ranged from below the lower limit of quantification.

• Ethanol levels ranged from below detection to 85.4 mg/L.

Concentration-Time Profiles

• Ethanol is rapidly eliminated and does not accumulate with the current dosing regimens.

Future Directions

• Develop a population pharmacokinetic model to describe ethanol pharmacokinetics.

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.

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/L/dose ethanol.

• Neonates received the greatest amount of ethanol in a single dose from phenobarbital.

Patient Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value (±SD or Number)</th>
</tr>
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<tbody>
<tr>
<td>Sex</td>
<td>Male/Female</td>
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<tr>
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<tr>
<td>Female (n)</td>
<td>3/9</td>
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<tr>
<td>Postmenstrual Age (weeks gestation)</td>
<td>31.2 ± 5.0</td>
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<tr>
<td>Median Age (months)</td>
<td>3.5 ± 3.6</td>
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<td>Range Age (months)</td>
<td>1.0 to 12.0</td>
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<td>Sex by Age</td>
<td>Male: Female</td>
</tr>
<tr>
<td>Male (n)</td>
<td>5/7</td>
</tr>
<tr>
<td>Female (n)</td>
<td>3/9</td>
</tr>
</tbody>
</table>

Figure 1. Ethanol disposition in adults. The network includes pharmacological factors that have the potential to affect the absorption, distribution, metabolism, and excretion of ethanol in neonates who were treated with medications.

Figure 2. Recommended ethanol limits for pediatrics. The American Academy of Pediatrics, Food and Drug Administration, and European Medicines Agency have stated actions to either altering limits of ethanol content in medications or monitoring ethanol levels in neonates who were treated with medications.

Figure 3. Plasma sample collection. A plasma sample was collected at the time of the clinical laboratory collection or following a specific collection for study purposes. In addition, blood samples were collected from neonates in Study #2 who were on morphine. Patients did not receive medications that contained a sizable fraction of ethanol except 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 (<100μL) 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.

Figure 4. Endogenous ethanol production in neonates (n=26) was measured using a validated headspace gas chromatography mass spectrometry method utilizing micro-volume (<100μL) 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.

Figure 5. Ethanol levels ranged from below detection to 85.4 mg/L. Ethanol was rapidly cleared and did not accumulate with current dosing regimens.

Figure 6. Concentration-time profiles for buprenorphine only and controlled-release only medications. (A) Concentration-time profiles for all samples (below and below LLOQ). (B) Concentration-time profiles for buprenorphine and combination.

Figure 7. Concentration-time profiles for buprenorphine and combination. (A) Concentration-time profiles for all samples (below and below LLOQ). (B) Concentration-time profiles for buprenorphine and combination.

Figure 8. Ethanol content of oral medications that contained ethanol. Ethanol content was determined at Thomas Jefferson University/Nemours Children’s Clinic. Ethanol content of oral medications that contained ethanol ranged from 0.1 to 215 mg/L/dose ethanol.

Figure 9. Ethanol content of oral medications that contained ethanol. Ethanol content was determined at Thomas Jefferson University/Nemours Children’s Clinic. Ethanol content of oral medications that contained ethanol ranged from 0.1 to 215 mg/L/dose ethanol.

Figure 10. Ethanol content of oral medications that contained ethanol. Ethanol content was determined at Thomas Jefferson University/Nemours Children’s Clinic. Ethanol content of oral medications that contained ethanol ranged from 0.1 to 215 mg/L/dose ethanol.