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Ethanol Pharmacokinetics in Neonates Secondary to Medication Administration

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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 9 blood samples per patient (± 6 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 as heel stick at the time of clinical laboratory collections or following a specific collection for study purposes. In addition, blood samples were collected as heel stick at the time of clinical laboratory collections or following a specific collection for study purposes. 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 on an average of 7.6 mg/L (range 1.3 to 21.5 mg/L) 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.

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

Ethanol Exposure

Distribution

Metabolism

Elimination

Ingestion

Absorption

Blood ethanol levels should not exceed the American Academy of Pediatrics recommendation following a single dose of an ethanol containing medication.

Sample Collection

- Approximately one third (131/390) of the blood alcohol levels were below the lower limit of quantification.
- Blood ethanol levels ranged from below detection to 85.4 mg/L.

Methods

Samples were collected from two populations:

- Study 1: Neonates (n=3) who received either oral phenobarbital (15% ethanol), oral dexamethasone (30% ethanol), or oral buprenorphine (15% ethanol, 21.5%) per standard of care were eligible for enrollment. A maximum of 9 blood samples per patient (± 6 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 as heel stick at the time of clinical laboratory collections or following a specific collection for study purposes. In addition, blood samples were collected as heel stick at the time of clinical laboratory collections or following a specific collection for study purposes. 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, 10% ethanol), or buprenorphine (n>14, control), or 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 (10uL) 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 on an average of 7.6 mg/L (range 1.3 to 21.35 mg/L) 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.

Endogenous Ethanol Production

- Endogenous blood ethanol levels ranged from below the LLOQ to 2.0 mg/L in neonates.
- Mean ± SD: 0.83 mg/L.
- Median ± SD: 0.84 mg/L.

For reference, previous studies have shown values below detection (0.05 mg/L) to 1.6 mg/L in adults.

Sample Collection

- Approximately one third (131/390) of the blood alcohol levels were below the lower limit of quantification.
- Blood 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 regimen.
- Ethanol levels do not exceed limits recommended for infants.
- Ethanol levels do not exceed limits recommended for infants.

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 ≥LOD).
- 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.