# Osmolality of Commonly Used Oral Medications in the Neonatal Intensive Care Unit.

Dhara D Shah

Andriy Kuzmov

Dana Clausen

Anita Siu

Christine A Robinson

*See next page for additional authors*



## Published In/Presented At

Shah, D. D., Kuzmov, A., Clausen, D., Siu, A., Robinson, C. A., Kimler, K., Meyers, R., & Shah, P. (2021). Osmolality of Commonly Used Oral Medications in the Neonatal Intensive Care Unit. *The journal of pediatric pharmacology and therapeutics : JPPT : the official journal of PPAG*, *26*(2), 172–178. https://doi.org/10.5863/1551-6776-26.2.172

Authors
Dhara D Shah; Andriy Kuzmov; Dana Clausen; Anita Siu; Christine A Robinson; Katelin Kimler PharmD, BCPPS; Rachel Meyers; and Pooja Shah

# Osmolality of Commonly Used Oral Medications in the Neonatal Intensive Care Unit

Dhara D. Shah, PharmD, Andriy Kuzmov, PhD, [...], and Pooja Shah, PharmD

## Abstract

### OBJECTIVE

The administration of hyperosmolar oral products in neonates has been associated with gastrointestinal complications. The American Academy of Pediatrics recommends a maximum osmolality of 450 mOsm/kg for formulas and enteral nutrition for term infants, and recent studies reported intolerance to enteral nutrition with osmolality above 500 mOsm/kg in low birthweight infants. The osmolality of medications administered to neonates is often not available in the literature or from manufacturers. The purpose of this study was to determine the osmolality of oral medications commonly administered to neonates in the NICU.

### METHODS

Fifty-two oral medications were chosen for this study, including solutions, suspensions, syrups, elixirs, and intravenous solutions administered orally. The osmolality of each medication was measured in triplicate by using freezing point depression.

### RESULTS

Thirty-seven of the 43 medications with measurable values (86.1%) had an osmolality greater than 500 mOsm/kg, and 6 medications (14%) had an osmolality less than 500 mOsm/kg. Nine medications did not result in a value.

### CONCLUSIONS

Our study provides osmolality data on oral medications commonly used in neonates with most oral medications having an osmolality greater than 500 mOsm/kg.

**Keywords:** neonates, osmolality, oral medications

## Introduction

Hyperosmolar oral products in neonates have been associated with the development of gastrointestinal complications such as feeding intolerance, delayed gastric emptying, and necrotizing enterocolitis (NEC).[1,2] The American Academy of Pediatrics recommends that the osmolality of formulas and enteral nutrition for normal infants should not exceed 450 mOsm/kg.[3] A recent systematic review demonstrated adverse gastrointestinal events occurring when the osmolality of formulas and enteral nutrition products exceeded 500 mOsm/kg in low birth weight infants.[4] Although no specific recommendations exist for the maximum osmolality of oral medications used in neonates, administration of hyperosmolar oral medications alone or in combination with enteral nutrition may increase the risk for gastrointestinal adverse events.[5,6]

Osmolality of medications is not readily available from the manufacturer or in standard drug information resources. Several previous studies, ranging in publication dates from 1983–2017, have tested the osmolality of oral medications in neonates.[7–12] In these studies, most oral medications evaluated had a mean osmolality >500 mOsm/kg: 82.7% (62/75),[7] 96.2% (25/26),[10] 94.8% (55/58),[11] and 60% (3/5).[12] Since the publications of these studies, medications used in the neonatal population have expanded and formulations have changed, creating a need for updated osmolality data. The purpose of this study was to determine the osmolality of oral medications commonly administered to neonates in the neonatal intensive care unit (NICU).

## Materials and Methods

Fifty-two oral medications that are commonly used in neonates were tested for osmolality, including suspensions, syrups, elixirs, and intravenous (IV) solutions that are administered orally. Oral medications that were not commercially available in a liquid form were compounded according to recipes supported in the literature, reconstituted with sterile water as recommended by the manufacturers, or prepared in accordance with institutional standards. Brand name, manufacturer, and concentration were documented for all medications studied. Investigational review board approval was not required because the research was not conducted in humans and did not include any patient information.

Osmolality was measured by the freezing point depression method using the Advanced Osmometer Model 3250 (Advanced Instruments, Norwood, Massachusetts). The instrument was calibrated with aqueous solutions of sodium chloride with known osmolalities of 100 mOsm/kg and 1500

mOsm/kg. Before samples were analyzed, the instrument's precision and accuracy were confirmed with a 900-mOsm/kg standard solution. The osmolality of all medications was measured in triplicate and the mean ± standard deviation was reported in mOsm/kg. Dilutions were performed for medications that measured outside of the instrument's calibration range of 100 to 1500 mOsm/kg.

## Results

Of the 52 medications that were tested, 43 medications resulted in a measurable osmolality with a range from 162 to 10,853 mOsm/kg. Six medications (14%) had a mean osmolality <500 mOsm/kg (Table 1). Thirty-seven medications (86.1%) had an osmolality >500 mOsm/kg: 2 medications (4.7%) had an osmolality between 500 and 1000 mOsm/kg (Table 2); 24 medications (55.8%) had an osmolality between 1000 and 5000 mOsm/kg (Table 3); and 11 medications (25.6%) had an osmolality >5000 mOsm/kg (Table 4).

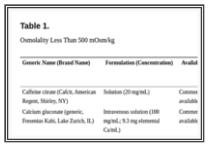

Table 1.

Osmolality Less Than 500 mOsm/kg

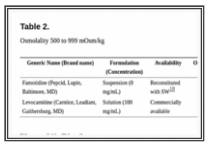

Table 2.

Osmolality 500 to 999 mOsm/kg

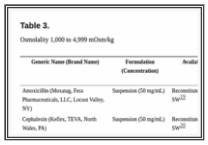

Table 3.

Osmolality 1,000 to 4,999 mOsm/kg

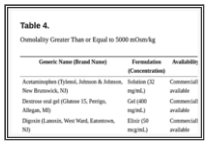

Table 4.

Osmolality Greater Than or Equal to 5000 mOsm/kg

Nine medications (17.3%) did not produce a result (Table 5). Five of these medications (55.6%) were suspensions whose particles settled on the bottom of the test tubes. The other 4 medications (44.4%) did not freeze adequately for measurement by the osmometer.

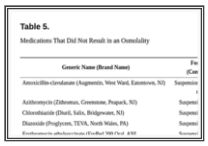

Table 5.

Medications That Did Not Result in an Osmolality

## Discussion

This study adds to previous data on the osmolality of oral medications used in the NICU. We included several medications that have not been previously reported, including cholestyramine, famotidine, hydrocortisone, oseltamivir, enalapril, clindamycin, metronidazole, multivitamins (AquADEKs, Actavis Pharma Inc, Parsippany, NJ), linezolid, sucrose 24%, phosphorus, cephalexin, potassium citrate-citric acid, and dextrose oral gel. Previous studies included extemporaneously compounded spironolactone that had a reported osmolality of 1780 mOsm/kg[10] and 3487 mOsm/kg.[9] We measured the recently commercially available spironolactone formulation demonstrating an osmolality <500 mOsm/kg. Several medications were previously reported, but concentrations varied, including clonidine, caffeine citrate, calcium gluconate, ursodiol, fluconazole, ferrous sulfate, dexamethasone, furosemide, and prednisolone.[9–11]

The osmolality of medications must be taken into consideration when administered alone or with enteral nutrition. Human breast milk has an approximate osmolality of 300 mOsm/kg but is closer to 400 mOsm/kg with the addition of human milk fortifiers, nutritional supplements, and medications.[4] Enteral formulas have an osmolality that ranges from 240 to 365 mOsm/kg and 293 to 459 mOsm/kg for 20-kcal/oz and 24-kcal/oz formulas, respectively.[9] The addition of oral medications to feeds increases osmolality and is associated with gastrointestinal complications such as NEC.[5,6] The clinical relevance of high osmolality feeds and medications, specifically the cutoff of 500 mOsm/kg, has not been elucidated in the clinical setting. The correlation of NEC and hyperosmolarity comes from limited data.[13] Based on the available literature, evidence to suggest that high osmolality is associated with delayed gastric emptying or development of NEC is inconsistent owing to variability and bias in study design.[4,5] Furthermore, owing to the unknown pathophysiology of NEC, it is difficult to attribute NEC development solely to osmolality. Delayed gastric emptying was observed with feed osmolality of 539 mOsm/L in human studies and greater than 624 mOsm/L in animal studies.[5] More research is needed in this area, and at this time efforts to reduce osmolality of medications is purely based on minimal clinical evidence. In addition, the effect of dilution of medications and formulas with gastric contents is unknown.

Our study confirms several commonly used oral medications prescribed in the NICU, such as ferrous sulfate, multivitamins, and electrolytes, have osmolalities above 3000 mOsm/kg. The practical reality of administering high-osmolality medications with feeds such as human breast milk with human milk fortifier translates into higher overall osmolality. For example, in a 1-kg premature infant a typical volume of a feed is 20 mL (with an osmolality of 400 mOsm/kg). If multivitamin is administered at a dose of 0.5 mL (with an osmolality of 10,853 mOsm/kg) and ferrous sulfate is administered at a dose of 3 mg (with an osmolality of 3117 mOsm/kg), the resulting total osmolality would be approximately 679 mOsm/kg (see Figure). Volume of gastric contents in a neonate is minimal and therefore does not significantly impact the overall osmolality. The osmolality of the gastric contents of a neonate has been found to be 266 to 294 mOsm/kg.[14] With an estimated gastric volume of 2 to 2.65 mL,[15] one could approximate a resulting total osmolality of 2016 mOsm/kg if the prior medications were administered in a fasting state or 632 mOsm/kg if administered with the above feed. Despite the anticipated dilution with the feeds and gastric contents, all of these situations still exceed the normally accepted limit of 450 to 500 mOsm/kg. This common medication regimen in combination with a feed exceeds the accepted osmolality limit, and patients often receive multiple oral medications that contribute to this calculation. As previously discussed, these high osmolality medications may be associated with the development of negative outcomes, such as NEC or delayed gastric emptying, although evidence to support this correlation is needed.

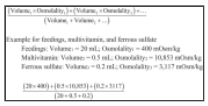

Figure.

Calculation of total osmolality of a solution.

Overcoming the high osmolality of medications is a clinical challenge with few solutions. Strategies suggested in previous studies to help lower the osmolality include diluting liquid medications with purified water in equal parts just prior to administration.[10,11] However, dexamethasone 0.5 mg/mL (osmolality of 4130 mOsm/kg) would need to be diluted 10 times for an acceptable osmolality. A limitation to this process is the need for large volumes to dilute medications with high osmolali-ties to achieve an acceptable osmolality. Large volumes are not practical in the clinical setting for neonates, especially preterm neonates. Additionally, there is an increased risk of medication errors due to further manipulation of the medication.

Dividing doses into multiple doses throughout the day is another method of overcoming high osmolality. Unfortunately, this leads to increased risk for error due to the increased number of doses that need to be prepared and administered. The administration time relative to feeding time may affect the clinical effect but the relevance of this is unclear. Intravenous forms are usually lower in osmolality owing to the absence of suspending agents, flavoring agents, and other vehicles; thus, they can be considered for use in enteral administration and this is a common mechanism used by NICUs. Examples that are used clinically include concentrated electrolytes and dexamethasone.

There are several limitations to consider when interpreting the osmolality results of our study. Foremost, there are scarce data[13] on the clinical effect o high osmolality, though many clinicians feel that it is clinically relevant and concerning, particularly for very premature infants. Since some liquid ora medications were compounded, there may be variations in extemporaneous preparations, based on the institution and drug reference. Additionally, depending on the extemporaneous preparation, variations in vehicles can contribute to differences in osmolality of the oral liquid medication. Furthermore, excipients in oral medications may vary by manufacturer, which may alter the osmolality. As noted in this study, formulations such as suspensions with large particle sizes may settle on the bottom or not adequately freeze and thus result in an inability to measure the osmolality.

In the future, routine availability of osmolality data from the manufacturers of oral medications and referenced in standard drug information resources would be helpful so that clinicians may have access to up-to-date information. In addition, reporting osmolality data for extemporaneous preparations would also be useful. Specific drug formulations need to be considered, especially in neonatal patients, to help improve care for this unique population.

## Conclusion

This study provides an updated list of osmolalities for oral medications commonly used in the NICU and identifies that most are hyperosmolar. The osmolality of all oral medications alone or in combination with enteral nutrition must be taken into consideration prior to administration in neonates, especially preterm neonates at higher risk of complications.

## Acknowledgments

Results were presented at Pediatric Pharmacy Advocacy Group Annual Meeting in Oklahoma City, OK, on April 12, 2019.

## ABBREVIATIONS

| | |
|---|---|
| IV | intravenous; |
| NEC | necrotizing enterocolitis; |
| NICU | neonatal intensive care unit |

## Footnotes

**Disclosure.** The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript. Catalent Pharma Solutions provided funding for the supplies required for this research. All authors have full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

**Ethical Approval and Informed Consent.** Given the nature of this study, the project was exempt from institution review board/ethics committee review.

## Article information

J Pediatr Pharmacol Ther. 2021; 26(2): 172–178.
Published online 2021 Feb 15. doi: 10.5863/1551-6776-26.2.172

PMCID: PMC7887878
PMID: 33603581

Dhara D. Shah, PharmD,✉ Andriy Kuzmov, PhD, Dana Clausen, BA, Anita Siu, PharmD, Christine A. Robinson, PharmD, Katelin Kimler, PharmD, Rachel Meyers, PharmD, and Pooja Shah, PharmD

✉Corresponding author.
Pharmacy Practice and Administration (AS, CAR, RM, PS), Ernest Mario School of Pharmacy, Rutgers, The State University of New Jersey, Piscataway, NJ; Department of Pharmacy (DDS), Montefiore Medical Center, Bronx, NY; Rutgers Pharmaceutical Industry Fellow at Catalent (AK), Rutgers, The State University of New Jersey, Piscataway, NJ; Biomedical Research Institute of New Jersey (DC), Morristown, NJ; Department of Pharmacy (AS), Jersey Shore University Medical Center, Neptune, NJ; Department of Pharmacy (DDS, CAR), Morristown Medical Center, Morristown, NJ; Department of Pharmacy (KK), Lehigh Valley Health Network, Allentown, PA; Department of Pharmacy (RM), Saint Barnabas Medical Center, Livingston, NJ; Department of Pharmacy (PS), Hackensack University Medical Center, Hackensack, NJ.
**Correspondence.** Dhara D. Shah, PharmD; dharashah6693@gmail.com

Received 2020 Feb 2; Accepted 2020 Jun 25.



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