Published in final edited form as:

J Pediatr. 2015 June ; 166(6): 1533–1535. doi:10.1016/j.jpeds.2015.02.047.

Parenteral nutrition as an unexpected and preventable source of mercury exposure in preterm infants

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Abstract

Perinatal mercury exposure has neurodevelopmental consequences, which may be worse in preterm infants. In our cohort (N=60), maternal and infant prenatal exposures were low, but infant levels increased during hospitalization and correlated only with duration of parenteral nutrition. A non-negligible exposure resulted from the nutrition preparation on equipment shared with adult preparations.

Keywords

parenteral nutrition; mercury; preterm infant

Mercury (Hg) is a ubiquitous pollutant in the environment and can be found in various forms such as elemental mercury vapor, methyl mercury or mercuric chloride. Hg is most toxic developmentally in one of its organic forms known as methyl mercury (MeHg)¹⁻². When exposure to mercury occurs perinatally, it has toxic effects on the developing nervous system and may cause long-term deficits in cognition and behavior¹⁻⁵. Preterm infants have increased vulnerability to neurotoxic agents due to an immature blood-brain barrier and ongoing developmental processes. Non-occupational exposure to Hg is primarily dietary in nature via bioaccumulation of MeHg in the aquatic food chain, but iatrogenic exposures in the form of dental amalgam¹⁻², thimerosal-containing vaccines⁶ and blood transfusions⁷⁻⁸ have been reported. We investigated Hg exposures of preterm infants in the Neonatal Intensive Care Unit (NICU) of a tertiary care institution. We hypothesized that Hg levels in

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The authors declare no conflicts of interest.

neonates are related to maternal Hg levels and that infant Hg levels may rise if they are exposed to Hg through breast milk.

Methods

This was a prospective observational study of 60 maternal-infant dyads in the Vanderbilt NICU in Nashville, TN (January 1, 2010, through December 31, 2011). Infants of gestational age (GA) <30 weeks and birth weight < 1,500g were included in this study and those with prenatally diagnosed genetic or metabolic disorders excluded. Informed consent was obtained using Vanderbilt University Institutional Review Board approved forms (#090950).

Maternal hair samples were from the occipital scalp within two days of parturition, as described by Stokes-Riner et al in the Seychelles Child Development Study⁹ and indicate MeHg exposure during the last 3 months of pregnancy. MeHg was detected in all tested hair samples. Infant urine samples for total Hg were collected within the first week after birth and at 34-36 weeks postmenstrual age (PMA). Mercury levels were quantified using high-resolution inductively coupled plasma mass spectrometry. Urine levels were normalized against creatinine. These samples were analyzed in the University of Rochester laboratory used for Hg measurements in the Seychelles Child Development Study.⁹ Total parenteral nutrition (TPN) samples were from original preparation containers from separate infants at the bedside and individual components from the medical center pharmacy on the same day. We collected information on maternal source of drinking water through questionnaires and extracted data from infant's course from the medical record, with severe white matter injury (WMI) defined as intraventricular hemorrhage Grades III and IV or periventricular leukomalacia on cranial ultrasound at 30 weeks PMA. The following variables were determined between the 2 urine collection time points: days on ventilator, days on supplemental oxygen, days on TPN, number of blood transfusions and percent of infants feeding volume over the interval composed of expressed breast milk (vs. formula). When the study was conducted, use of donor breast milk (DBM) was not common practice in the NICU.

Infants were tested at 12 months chronologic age in the NICU Follow-Up clinic with the Developmental Assessment of Young Children (DAYC)¹⁰, a standardized assessment of motor, cognitive and communication and at 24 months with the Bayley Scales of Infant Development Third ed. (Bayley III)¹¹. Corrected age scores were reported.

To examine relationships between maternal characteristics and Hg levels we used a repeated measures analysis of variance with Huynh-Feldt correction for correlated errors occurring with violations of sphericity. Associations between continuous outcomes (DAYC and Bayley III scores) and infant Hg were examined using multivariable regression models adjusting for maternal education, GA and presence of severe WMI.

Results

Sixty infant-mother dyads participated in the study, with 12 part of a twin pair. Population race and ethnicity were representative of the Middle Tennessee Region. Most mothers consumed city water and only 3 drank well water. There were no correlations between water

source and either maternal hair MeHg levels or infant urine total Hg levels within the first week. Median length of stay in the NICU (80 days) was representative of preterm infants cared for in our nursery as was TPN duration and breast milk as the primary source of enteral nutrition (Table I). At second urine collection time, 12 infants had received one transfusion and 5 had received two.

Mean infant urine Hg levels during the first week of life were 0.60 µg/L (SD ± 0.30). At the second collection time point, mean infant urine Hg levels reached 1.1 µg/L (SD ± 0.40), a statistically significant rise ($p < 0.001$; Table II). Infants who received breast milk as their primary source of nutrition did not have higher Hg levels than infants fed primarily formula. The rise in Hg was also not associated with length of hospital stay, duration of respiratory support, mechanical ventilation or supplemental oxygen, or number of transfusions (all $p > 0.5$). Duration of total parenteral feeds was independently associated with an increase in infant urine Hg ($R^2 = 0.36$, $p < 0.05$).

TPN preparations with and without trace elements contained low but detectable levels of total Hg. Therefore, in an average study infant receiving 100 mL/kg/day of TPN for 3 weeks, the direct IV exposure to Hg was calculated as: $0.9 \text{ µg/L (TPN concentration)} \times 100 \text{ mL/kg/day} \times 1.0 \text{ kg} \times 21 \text{ days} = 1.890 \text{ µg}$ or 0.090 µg/day . Distributed in a blood volume of 78mL, this corresponds to a body burden of ~24.2 µg/L Hg.

Individual components of TPN had no detectable levels of mercury. The only potential contaminant source was shared mixing equipment with pediatric and adult preparations. Due to the large volumes and disparate composition of TPN for the entire hospital, it was not feasible to examine all components and mixtures.

To ensure that no adverse neurodevelopmental sequelae would follow this minimal but iatrogenic rise in Hg levels, these infants were followed in the developmental clinic until 24 months chronologic age. Two infants died prior to 1-year follow-up, neither of them with urine Hg levels above the median at any collection time. Upon 1- and 2-year follow-up of these infants, after adjusting for GA, WMI and maternal education, there were no significant correlations between outcomes and Time 2- or change in total Hg- levels. Infants in the highest quartile of urine Hg did not have worse outcomes than those with lower Hg. A limitation of the study with respect to interpretation of neurodevelopmental outcomes is the two year scope: many of the neurobehavioral effects of perinatal exposures to neurotoxins are not fully revealed until children reach their later preschool and early school-age years⁹.

Discussion

This study of low-exposure families neither confirmed a relationship between maternal MeHg hair levels and preterm infants early urine total Hg levels nor did it demonstrate an association between breast milk feeding and a rise in infant Hg levels. This was most likely due to the extremely low environmental exposure levels, different what we had initially hypothesized for our population. However, we identified TPN as a preventable source of Hg exposure in preterm infants. Infants showed increased levels of urinary Hg over their NICU

course correlated to duration of a TPN shown to have detectable Hg levels. Based on Hg concentrations found in TPN, daily IV Hg exposure for a 1 Kg infant were 0.09µg/kg/day, equivalent to 0.095µg/kg/day oral Hg, assuming 95% enteric absorption. Although this value is well below the minimal risk level proposed by the World Health Organization (0.3µg/kg/day) and the Agency for Toxic Substances & Disease Registry (0.23 µg/kg/day) it approximates the daily reference dose recommended by the Environmental Protection Agency (0.1µg/kg/day). Given the high vulnerability of the preterm infant brain to neurotoxic agents, such an exposure was concerning. However, there were no Hg-associated adverse neurodevelopmental consequences detected at 2 years in our cohort. The TPN for neonatal and pediatric purposes is now mixed on equipment that is not shared with adult preparations. Whether contamination of infant TPN with Hg is confined to our institution or is a universal phenomenon remains to be determined.

Acknowledgments

We would like to thank Gene E. Watson, MD (University of Rochester), for his support during the initial phases of this project.

Supported by the National Institute of Environmental Health Sciences (K12 ES 015955, R01 ES07331 and R01 ES ES020852).

Abbreviations

Hg	Mercury
MeHg	Methyl mercury
TPN	total parenteral nutrition
NICU	Neonatal Intensive Care Unit

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Table 1
Participant characteristics

Maternal Characteristics (n=54)	
Age (median, IQR)	26 (22,29)
Maternal ethnicity/race (N,%)	
Hispanic American	4 (6.6)
African American	22 (36.6)
Caucasian American	28 (51.8)
Source of maternal drinking water (N,%)	
City water	35(65)
Bottled water	16(30)
Well water	3 (5)
Infant characteristics (n=60)	
GA wks, median (IQR)	27 (26, 29)
Birth weight in g, median (IQR)	1,000 (810, 1150)
Female Sex (N, %)	27 (45)
White Matter Injury (severe) (N, %)	7 (11.7)
Length of NICU stay (median, IQR)	80 (53, 98)
Days ventilated* (median, IQR)	3 (1,18)
Days on supplemental oxygen* (median, IQR)	40.5 (9, 83.75)
Days on TPN* (median, IQR)	20.5 (14, 36.5)
Breast milk as primary nutrition* (N,%)	44 (73.3)
Number of transfusions* (median, IQR)	0 (0,1)
One year outcomes, DAYC corrected age scores (N = 51/58)	
Cognitive	107 (100,115)
Communication	109 (97,110)
Motor	102 (77,103)
Two year outcomes, Bayley corrected age scores (N =35/58)	
Cognitive Composite	95 (80,100)
Language composite	97 (77,103)
Expressive scaled score	9 (6,10)
Receptive scaled score	9 (6,10)
Motor composite	94 (85,107)
Gross motor scaled score	8 (6,10)
Fine motor scaled score	10 (9,12)

For both DAYC and Bayley III, standardized means are 100 and standard deviations 15

*
at second urine collection for Hg measurement

Table 2
Participant mercury collection and levels

	N	Values
MeHg in maternal hair µg/g, mean (SD)	54	0.15 (±0.18)
Total Hg in infant urine	60	
Time 1 collection	60	
Age in days, median (IQR)	60	1.0 (1, 2)
Total Hg µg/L, mean (SD)	60	0.60 (±0.3)
Time 2 collection	60	
Age in days, median (IQR)	60	47.5 (35, 58)
Total Hg µg/L, mean (SD)	60	1.1 (±0.40) **
Total Hg in TPN preparations at infant bedside µg/L, mean (SD)		
TPN with no trace elements	6	0.89 (±0.5)
TPN with trace elements	6	0.92 (±0.4)
Total Hg in TPN Individual Components From Pharmacy µg/L, mean (SD)		
Water base	3	0.03 (±0.0)
Amino acid solution	3	0
Heparin	3	0
Pediatric multivitamin	1	0
Pediatric trace elements	1	0

Reference levels for maternal hair MeHg 0.02 µg/g¹⁴

No references for infant urine; in vaccinated newborns <0.1 µg/L¹⁵; urine for children 10-11 year old without dental amalgams mean 0.27 µg/L¹⁶

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p <0.001 on paired t-test