

Iatrogenic exposure to mercury after hepatitis B vaccination in preterm infants

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Thimerosal, a derivative of mercury, is used as a preservative in hepatitis B vaccines. We measured total mercury levels before and after the administration of this vaccine in 15 preterm and 5 term infants. Comparison of pre- and post-vaccination mercury levels showed a significant increase in both preterm and term infants after vaccination. Additionally, post-vaccination mercury levels were significantly higher in preterm infants as compared with term infants. Because mercury is known to be a potential neurotoxin to infants, further study of its pharmacodynamics is warranted. (*J Pediatr* 2000;136:679-81)

The mercury content of drugs and vaccines is being scrutinized, given the potential effects of exposure to mercury through diet and the environment.¹⁻³ Thimerosal, an organic mercury compound, is used for the enhancement of product stability in several drugs and vaccines. Most neonates received hepatitis B vaccine, which contained thimerosal. The recommended dose of pediatric hepatitis B vaccine contained

thimerosal 1:20,000, or 0.25 ppm (12.5 µg of mercury). At our institution the hepatitis B vaccine (at the time of this study) was given within the first week of life, regardless of the mother's hepatitis status. To our knowledge, and according to both manufacturers of the vaccine, no study has examined total mercury levels in newborn infants after inoculation with hepatitis B vaccine. The goal of this study was to evaluate

iatrogenic exposure to mercury in preterm infants receiving their initial dose of hepatitis B vaccine in comparison with term infants.

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and p. 599.

METHODS

The study protocol was approved by the Emory Institutional Review Board, and informed written consent was obtained from a parent or guardian for every newborn infant (n = 23) enrolled in the study from Grady Health System's Neonatal Intensive Care Unit between August 1997 and March 1998. All intravenous fluids and medications administered were mercury-free. The inclusion criteria included a birth weight of ≤1000 g, 5-minute Apgar score of 7 or greater, mother who was seronegative for hepatitis B, and hepatitis B vaccine inoculation in the first week of life after consent had been obtained. The control group was composed of 5 term infants whose inclusion criteria differed only by weight of ≥3500 g. Control subjects were not selected from the normal nursery because healthy babies would have been discharged before the post-vaccination levels could be obtained. In the group of 18

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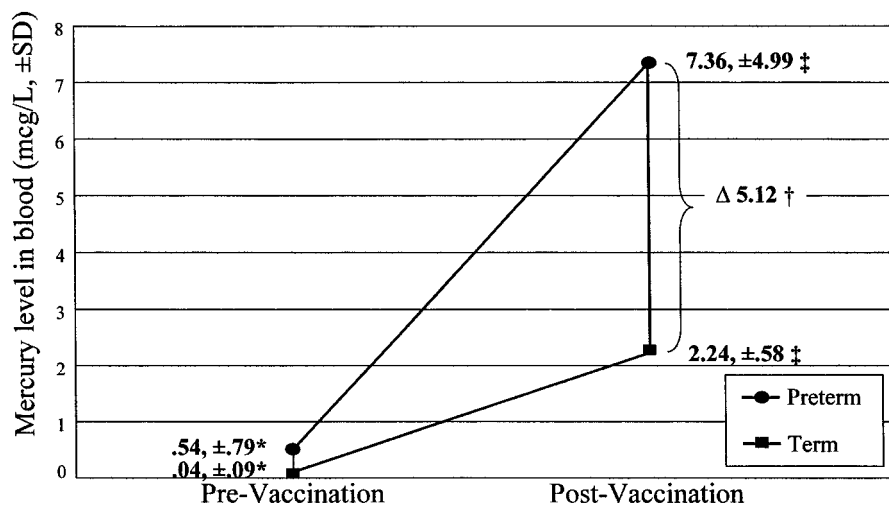


Figure. Difference in mean mercury levels (in micrograms per liter) between preterm and term infants. † $P < .01$; ‡ $P < .01$; * $P = .2$.

Table. Patient demographics

Primary variables	Preterm infants (n = 15)	Term infants (n = 5)	Mean difference	P value
Mean gestational age (wk)	25.5	39	13.5	.001*
Mean birth weight (g)	748	3588	2840	.001*
Mean length (cm)	31	40	9	.107

*Indicates statistical significance at 95% CI.

preterm infants enrolled in the study, post-vaccination mercury levels could not be obtained for 3 infants; therefore, 15 subjects were assessable (Table).

All infants had a baseline mercury level determined before vaccination. Mercury measurements required 0.3 mL of blood collected in EDTA tubes. Blood mercury levels were measured with the ELAN 6000 Inductively Coupled Plasma Mass Spectrometer (Perkin-Elmer, Norwalk, Conn).⁴ After baseline mercury levels were determined, all participants received an initial dose of hepatitis B vaccine, (Engerix, 10 $\mu\text{g}/0.5$ mL [Smith Kline Biologicals, Rixensart, Belgium]) injected intramuscularly. Determination of mercury levels was conducted 48 to 72 hours after vaccination. Statistical analysis was performed by using Kruskal-Wallis 1-way analysis of variance to evalu-

ate the differences within and between groups.

RESULTS

There were no differences between preterm and term infants with respect to mean pre-vaccination mercury levels ($P = .2$) (Figure). When the differences between pre- and post-vaccination mercury levels were compared within each of the 2 groups, the post-immunization mercury levels were significantly increased in both groups of infants ($P < .01$) (Figure). Comparison of post-vaccination mercury levels between groups showed a higher mean mercury level for the preterm group (mean \pm SD, 7.36 ± 4.99 $\mu\text{g}/\text{L}$; range, 1.3-23.6 $\mu\text{g}/\text{L}$) compared with the term group (mean \pm SD, 2.24 ± 0.58 $\mu\text{g}/\text{L}$; range, 1.4-2.9 $\mu\text{g}/\text{L}$).

This difference in post-vaccination mercury levels between the 2 groups of infants is significant ($\Delta = 5.12$ $\mu\text{g}/\text{L}$, $P < .01$) (Figure). Nine of 15 preterm infants had mercury levels above the range of term infants (ie, >2.9 $\mu\text{g}/\text{L}$).

DISCUSSION

This study demonstrates that elevated mercury levels after a single dose of hepatitis B vaccine were detected in both preterm and term infants. Hepatitis B vaccine was studied because newborns receive this vaccine in the first days of life. No dosing adjustment is made for hepatitis B vaccine on the basis of birth weight; thus, preterm infants are exposed to relatively more mercury than term infants. Although Department of Health and Human Services guidelines suggest a normal blood mercury level is 5 to 20 $\mu\text{g}/\text{L}$,⁵ there are discrepancies in published literature regarding what are considered normal versus toxic levels.⁶⁻⁸ Furthermore, these data were derived entirely from adults with occupational exposure to mercury.

The available evidence indicates that the metabolism and toxicity of organic (eg, ethyl-, methyl-) mercury is similar for humans and animals.^{9,10} Mercury is oxidized to the divalent inorganic cation in the red blood cells, lungs, and liver of both humans and animals. Once mercury is oxidized and degraded to the inorganic form (ionic Hg^{+2}), penetration across the blood-brain barrier has been shown to be minimal.^{11,12} It is concentration of and duration of exposure to unoxidized mercury that lead to toxicity. Newborns, especially preterm infants, may have decreased ability to both oxidize and eliminate mercury.

In our study, preterm infants had a greater than 10-fold higher mean mercury level at baseline compared with term infants, although this difference was not statistically significant. The presence of mercury at baseline in both groups would suggest maternal expo-

sure; however, maternal mercury levels were not measured in this study. A possible explanation for the difference in baseline mercury levels between groups could be that preterm infants, because of their immature livers, are not able to synthesize a metal-binding protein, metallothionein.¹³ This decreased production of metallothionein, along with a decreased hepatic processing and renal elimination of mercury, could result in increased plasma levels.^{14,15} Post-vaccination mean mercury levels in preterm infants were 3 times higher than those in term infants, a difference that was statistically significant. In addition to their decreased ability to metabolize and eliminate mercury, premature infants have a smaller volume of distribution than term infants. All these factors could contribute to the higher concentrations of mercury found in the preterm group.

Iatrogenic mercury exposure should raise concern because little is known about mercury's effect on the preterm neonate. Several major studies in the last 25 years have examined the effects of both prenatal and postnatal mercury exposure on infants and children.¹⁶⁻²² These studies used varying methodologies and reported conflicting findings about neurodevelopmental outcomes. The results must be compared and interpreted with caution; however, it appears that mercury in high levels during critical developmental periods may be neurotoxic. Although we studied only a small number of subjects and did not examine outcomes, our study is unique in reporting blood mercury levels in the preterm population. Preterm infants are at risk for neurologic disorders even without mercury exposure. Because we found a statistically significant rise in total mercury levels in these infants after vaccination, we are concerned about the possibility of compounding the neurologic risk for these infants. However, no information is currently available to suggest such a

causal link with immunizations. Until thimerosal-free hepatitis B vaccine is universally available, there are few practical alternatives in those situations in which the mother is seropositive for hepatitis B. Further studies are needed to assess the pharmacodynamics of mercury over the first days and weeks of life after hepatitis B immunization.

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