NIAID Studies on Thimerosal

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NIH, DHHS
NIAID Studies on Thimerosal

Scientific Questions

• Are the guidelines developed for methyl mercury (MeHg) appropriate for assessing the safety of thimerosal (sodium ethyl mercury thiosalicylate)?

• How are the distribution, metabolism, and excretion of thimerosal and MeHg related?
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Possibilities

• Thimerosal and MeHg are equivalent

• Thimerosal and MeHg are similar; MeHg guidelines offer additional/less margin of safety

• Thimerosal and MeHg are significantly different in distribution, metabolism, and excretion
## NIAID Studies on Thimerosal

<table>
<thead>
<tr>
<th>Thimerosal Exposure</th>
<th>MeHg Exposure/Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethyl mercury thiosalicylate</td>
<td>Methyl mercury in food</td>
</tr>
<tr>
<td>IM injection</td>
<td>Oral intake – food</td>
</tr>
<tr>
<td>Spaced intermittent exposure</td>
<td>Continuing exposure to reach steady state distribution</td>
</tr>
<tr>
<td>Infant exposure</td>
<td>Maternal and fetal exposure</td>
</tr>
<tr>
<td>Risk to infant</td>
<td>Risk from fetal exposure – most sensitive to damage</td>
</tr>
<tr>
<td>Measure levels directly</td>
<td>Extrapolate from maternal hair levels to fetal exposure and effects</td>
</tr>
</tbody>
</table>

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NIAID Studies on Thimerosal

• **Pilot clinical study and data** – University of Rochester

• **Follow-up clinical study** –
  University of Rochester, and Center for Toxicological Research (Argentina) and Children’s Hospital of Buenos Aires (Argentina)

• **Primate Studies** – University of Washington
  and University of Rochester
NIAID Studies on Thimerosal

Evaluation of mercury in infants after thimerosal-containing vaccines
(Univ. Rochester; The Lancet Vol 360 Nov 30, 2002)

• The blood half life of mercury from thimerosal-containing vaccines in infants appears to be shorter than the half life of methyl mercury in adults, possibly as short as 6 - 8 days.

• Infants excrete significant amounts of mercury in stool, unlike what is seen in rodent animal models of MeHg. This possibly accounts for the relatively short apparent half-life of ethyl mercury in this study.
NIAID Studies on Thimerosal

• Pilot clinical study and data – University of Rochester

• Follow-up clinical study –
  University of Rochester, and Center for Toxicological Research (Argentina) and Children’s Hospital of Buenos Aires (Argentina)

• Primate Studies – University of Washington and University of Rochester
Comparative Toxicokinetics of Methyl mercury (MeHg) and Thimerosal in Infant *Macca fascicularis*

Tom Burbacher and Danny Shen  
University of Washington  
Tom Clarkson  
University of Rochester

Funded by NIAID and NIEHS
Comparative Toxicokinetics of Methyl mercury (MeHg) and Thimerosal in Infant Macca fascicularis

Objective: Compare relative levels of mercury in blood and brain after exposure to mercury in the form of thimerosal or methyl mercury
## Mercury Exposure from Thimerosal in Typical Immunization Schedules

*(The Lancet Vol. 355 April 8, 2000)*

<table>
<thead>
<tr>
<th>Age</th>
<th>Vaccines</th>
<th>Hepatitis B (HB)</th>
<th>Mercury Dose (µg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Scheme A</td>
<td>Scheme B</td>
</tr>
<tr>
<td>Birth</td>
<td>BCG, OPV0</td>
<td>HB1</td>
<td></td>
</tr>
<tr>
<td>6 wks</td>
<td>DTP1, OPV1, Hib1</td>
<td>HB2</td>
<td>HB1</td>
</tr>
<tr>
<td>10 wks</td>
<td>DTP2, OPV2, Hib2</td>
<td>HB2</td>
<td></td>
</tr>
<tr>
<td>14 wks</td>
<td>DTP3, OPV3, Hib3</td>
<td>HB3</td>
<td>HB3</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BCG = bacille Calmette-Guerin          OPV = oral poliovirus
Hib = *Haemophilus influenzae* type b  DTP = diptheria-tetanus-pertussis
## Vaccine with Thimerosal and oral MeHg Dosing for Infant *M. fascicularis*

<table>
<thead>
<tr>
<th>Age</th>
<th>Vaccines</th>
<th>Hepatitis B (HB)</th>
<th>Mercury Dose (µg Hg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth</td>
<td>OPV0</td>
<td>HB1</td>
<td>20</td>
</tr>
<tr>
<td>1 wk</td>
<td>DTP1, OPV1, Hib1</td>
<td>HB2</td>
<td>20</td>
</tr>
<tr>
<td>2 wks</td>
<td>DTP2, OPV2, Hib2</td>
<td></td>
<td>20</td>
</tr>
<tr>
<td>3 wks</td>
<td>DTP3, OPV3, Hib3</td>
<td>HB3</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td><strong>Total</strong></td>
<td></td>
<td><strong>80 µg/kg</strong></td>
</tr>
</tbody>
</table>

**Scheme A**

OPV = oral poliovirus  
Hib = *Haemophilus influenzae* type b  
BCG = bacille Calmette-Guerin  
DTP = diptheria-tetanus-pertussis

Thimerosal was added to vaccines; MeHg given by oral gavage. Animals sacrificed 2, 4, 7 or 29 days after last exposure.
Body Weight (grams) at Dosing

Mean Body Weights (grams)

Days

0 10 20 30

Controls
Methylmercury
Thimerosal

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Blood Total Hg in Infant Monkeys During/Post Four Weekly Oral Doses of Methylmercury (20 \( \mu \)g Hg/kg)
Mean Blood Total Hg in Infant Monkeys During/Post Four Weekly Oral Doses of Methylmercury (20 µg Hg/kg)
One-Compartment Model Analysis of Mean Blood Total Hg Data from MeHg-Exposed Infant Monkeys (n = 17)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>V/F (L/kg)</td>
<td>1.62 ± 0.04</td>
</tr>
<tr>
<td>$k_a$ (day$^{-1}$)</td>
<td>1.87 ± 1.14</td>
</tr>
<tr>
<td>K (day$^{-1}$)</td>
<td>0.0283 ± 0.0014</td>
</tr>
<tr>
<td>$T_{1/2}$ (days)</td>
<td>24.5</td>
</tr>
<tr>
<td>Cl/F (ml/day/kg)</td>
<td>45.8</td>
</tr>
</tbody>
</table>

Analysis performed with SAAM II

NIAID, NIH, DHHS

IOM Feb 9, 2004
Blood Total Hg in Infant Monkeys During and Post Four Weekly IM Injections of Vaccine Thimerosal at 10 $\mu$g Hg/kg (N=4) and 20 $\mu$g Hg/kg (N=17)
Mean Blood Total Hg in Infant Monkeys During/Post Four Weekly IM Injections of Vaccine Thimerosal

Blood Hg (ng/ml)

- Thimerosal 20 ug/kg
- Thimerosal 10 ug/kg

Days

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Two-Compartment Model Analysis of Mean Blood Total Hg from Thimerosal-Exposed Infant Monkeys (n = 17)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>$k_a$ (day$^{-1}$)</td>
<td>3.24 ± 3.00</td>
</tr>
<tr>
<td>$k_{12}$ (day$^{-1}$)</td>
<td>0.081 ± 0.076</td>
</tr>
<tr>
<td>$k_{21}$ (day$^{-1}$)</td>
<td>0.177 ± 0.138</td>
</tr>
<tr>
<td>$k_{10}$ (day$^{-1}$)</td>
<td>0.148 ± 0.024</td>
</tr>
<tr>
<td>$T_{1/2,\alpha}$ (day)</td>
<td>2.13</td>
</tr>
<tr>
<td>$T_{1/2,\beta}$ (day)</td>
<td>8.62</td>
</tr>
<tr>
<td>$V_c/F$ (L/kg)</td>
<td>1.68 ± 0.30</td>
</tr>
<tr>
<td>$V_{ss}/F$ (L/kg)</td>
<td>2.45</td>
</tr>
<tr>
<td>$V_p$ (L/kg)</td>
<td>0.77</td>
</tr>
<tr>
<td>$C_l/F$ (ml/day/kg)</td>
<td>248</td>
</tr>
</tbody>
</table>

Analysis performed with SAAM II

NIAID, NIH, DHHS

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Washout of Total Hg in Blood and Brain after Four Weekly Oral Doses of Methyl mercury (20 µg Hg/kg)

- **Blood**: $y = 42.079e^{-0.0339x}$, $T_{1/2} = 20.4$ days
- **Brain**: $y = 116.42e^{-0.0118x}$, $T_{1/2} = 58.7$ days

Average Brain:Blood = 3.6 ± 1.3
Washout of Total Hg in Blood and Brain after Four Weekly IM Injections of Vaccine Thimerosal (20 mg/kg)  
(Corrected Slide Submitted to IOM May 3, 2004)

Average Brain:Blood Ratio = 4.5 ± 1.5

$y = 39.674e^{-0.0249x}$  
$T_{1/2} = 27.8$ days

$y = 12.617e^{-0.0894x}$  
$T_{1/2} = 7.8$ days

$\text{Days after Last Dose}$
### Data Summary

(Corrected Slide Submitted to IOM May 3, 2004)

<table>
<thead>
<tr>
<th></th>
<th>MeHg</th>
<th>Thimerosal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T1/2 Blood – Model</strong></td>
<td>24.5 days</td>
<td>T$_{1/2\alpha}$ 2.13 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T$_{1/2\beta}$ 8.62 days</td>
</tr>
<tr>
<td><strong>T1/2 Blood – Washout</strong></td>
<td>20.4 days</td>
<td>7.8 days</td>
</tr>
<tr>
<td><strong>T1/2 Brain - Washout</strong></td>
<td>58.7 days</td>
<td>27.8 days</td>
</tr>
<tr>
<td><strong>Brain: Blood</strong></td>
<td>3.6 ± 1.3</td>
<td>4.5 ± 1.5</td>
</tr>
</tbody>
</table>
Data Summary

(Corrected Slide Submitted to IOM May 3, 2004)

MeHg

0 10 20 30 40
0 7 14 21 28 35 42 49
Time (days)

Blood Total Hg (ng/ml)

Predicted
Observed

y = 116.42e^{-0.0118x}

y = 42.079e^{-0.0339x}

T1/2 = 58.7 days

T1/2 = 20.4 days

Thimerosal

0 10 20 30 40
0 5 10 15 20 25 30
Days after Last Dose

Concentration (ng/ml or ng/g)

Blood

Brain

Expon. (Blood)

Expon. (Brain)

y = 12.617e^{-0.0894x}

y = 39.674e^{-0.0249x}

T1/2 = 27.8 days

T1/2 = 7.8 days

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Conclusions-Monkey Study

(Corrected Slide Submitted to IOM May 3, 2004)

- Initial absorption and distribution of oral MeHg and Hg derived from i.m. thimerosal (in a vaccine vehicle) are similar.

- Blood Hg derived from thimerosal has a shorter terminal elimination half-life compared to MeHg in both blood (9 days vs 25 days) and the brain (28 days vs 59 days).

- Minimal accumulation of blood total Hg during weekly i.m. injections of thimerosal; continued accumulation of blood Hg occurred during weekly oral doses of MeHg.

- Although the brain-to-blood partition ratio of total Hg after thimerosal exposure (5.1) is higher than that for MeHg (3.4), it does not make up for the shorter half-life and much greater clearance of thimerosal-derived Hg from systemic circulation.
Thank you

• Tom Burbacher and Danny Shen – University of Washington

• Tom Clarkson and Elsa Cernichiari – University of Rochester

• Annette Kirshner and Cindy Lawler - NIEHS