Organ mercury levels in infants with omphaloceles treated with organic mercurial antiseptic

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SUMMARY Samples of fresh and fixed tissues from infants with exomphalos treated by thiomersal application were analysed for mercury content. The results showed that thiomersal can induce blood and organ levels of organic mercury which are well in excess of the minimum toxic level in adults and fetuses. The analysis of fresh and fixed tissues must be carefully controlled against normal tissues in order to interpret mercury levels accurately.

The introduction of the application of 0.1% tincture of Thimerosal (thiomersal)* in the treatment of exomphalos is generally attributed to Grob (1957). No unequivocal cases of organic mercury poisoning have been reported after its use in patients with exomphalos though several cases of 'pink disease' have been reported (Schippan and Wehran, 1968; Stanley-Brown and Frank, 1971), as well as a case of 'mercury intoxication' (Leenders et al., 1974). This is thought to be an idiosyncratic reaction unrelated to excessive dosage and should be distinguished from true poisoning.

Analysis of fresh tissue samples obtained at necropsy from an infant with exomphalos treated by thiomersal application who died unexpectedly showed raised tissue levels of mercury. This prompted us to search the records at the Hospital for Sick Children, Toronto, for other mercury-treated cases of exomphalos and carry out organ mercury analysis.

Materials and methods

Between 1969 and 1975 there had been 13 cases of exomphalos treated by thiomersal application. 10 had died and 9 of these had necropsy examinations. Formalin-fixed wet tissues were available from 6 of the 9. Mercury assays had been carried out in 1972 on fresh tissues from 2 of these 6 cases by the Public Health Division of the Department of Health, Toronto, using similar methods to those described below.

We performed organ mercury assays on three sets of fresh tissue samples and six sets of formalin-fixed tissues. Cold vapour atomic absorption was used to measure total mercury in blood (Magos and Clarkson, 1972). Solid tissues were weighed and homogenized in 0.9% w/v sodium chloride solutions (1.0 g tissue to 9 ml sodium chloride solution). Aliquots from the homogenate were treated and measured as described for hair samples by Giovanoli-Jakubczak et al. (1974). Samples of the mercury-contaminated omphalocele sac were not stored or transported in the same container as any of the analysed samples.

Results

Table 1 shows that all 3 cases in which fresh tissue analysis was performed had absorbed an excessive load of mercury ranging from 65 to 2700 times the normal tissue levels. The fresh organ levels in Cases 2 and 3 suggest that the blood levels were similar to or, perhaps in Case 3, even higher than the level of 1340 ppb (parts per billion) found in Case 1. Mercury assays were repeated on the formalin-fixed tissues of the 3 cases in which fresh tissue assays had been performed, and the results are shown in Table 2 with those from the other fixed and stored samples.

These results show a general increase in mercury concentration after fixation which appears to be related more to the duration of storage than to the total dose administered. The mercury content of the formalin fixative was negligible, <6 ppb. Although analysis of all the samples indicated an excessive load...
Table 1  Concentrations of total mercury on fresh necropsy tissues and data from published reports on normal and toxic tissue levels. All concentrations of Hg are expressed in ng/ml and ng/g (ppb) fresh tissue.

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Analysis on fresh necropsy tissue</th>
<th>Normal levels</th>
<th>Levels in fatal cases: published reports</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Case 1</td>
<td>Case 2*</td>
<td>Case 3*</td>
</tr>
<tr>
<td>Liver</td>
<td>15 500†</td>
<td>11 800</td>
<td>26 600</td>
</tr>
<tr>
<td>Kidney</td>
<td>2 360</td>
<td>3 700</td>
<td>4 600</td>
</tr>
<tr>
<td>Brain</td>
<td>650†</td>
<td>5 100</td>
<td>2 800</td>
</tr>
<tr>
<td>Blood</td>
<td>1 340‡</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

*Data kindly supplied by Dr. G. J. Stopps, Ontario Dept. of Public Health.
†Liver beneath omphalocoele membrane.
‡Sample taken from cerebellum. Levels from other regions of the brain ranged from 460–1140 ng/g.

Table 2  Mean organ total mercury concentration showing the effects of fixation and storage.

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Mean* organ total Hg concentration (in ppb)</th>
<th>Duration of storage (m)</th>
<th>Number of 0.1% thiomersal applications</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fresh tissues</td>
<td>Fixed tissues</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>5 152</td>
<td>7 920</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>6 870</td>
<td>12 220</td>
<td>45</td>
</tr>
<tr>
<td>3</td>
<td>11 330</td>
<td>15 780</td>
<td>45</td>
</tr>
<tr>
<td>4</td>
<td>—</td>
<td>34 350</td>
<td>48</td>
</tr>
<tr>
<td>5</td>
<td>—</td>
<td>56 650</td>
<td>66</td>
</tr>
<tr>
<td>6</td>
<td>—</td>
<td>131 300†</td>
<td>54</td>
</tr>
</tbody>
</table>

*This value is the mean of 4 samples of tissue, liver, kidney, spleen, and heart muscle or skeletal muscle as available. The values in individual tissues moved erratically, and the mean showed the trend most clearly.
†Samples of Case 6 showed evidence of drying at some time during storage.

Discussion

Whether the levels reported in Table 1 are acutely toxic or capable of producing chronic neurological damage in the newborn infant exposed perinatally as opposed to the fetus, older child, or adult, is unclear. Intrauterine exposure to methyl mercury (Study Group of Minimata Disease, 1968; Swedish Expert Group, 1971; Amin-Zaki et al., 1974a) causes damage in newborn infants at mercury levels similar to those associated with both acute and chronic neurological damage in older children and adults (Jailili and Abbasi, 1961; Damluji, 1962; Bakir et al., 1973; Suzuki et al., 1973; Rustam and Hamdi, 1974). The clinical notes of the 6 cases studied, showed that 3 had developed unexplained vomiting, acidosis, or convulsions, but none of these findings alone is specific or indeed unusual in neonates.

We traced one of the survivors of this therapy. Full neurological examination at 10 years of age failed to show any evidence of the signs of minimal mercury damage such as visual field narrowing or glove and stocking paraesthesia. We are unable to comment on his intellectual development, though the school re-

of mercury had been absorbed, extrapolation to fresh tissue levels was not immediately possible. Complex factors appear to be involved, and any attempt at interpretation of mercury levels in fixed and stored tissues must be carefully controlled with other normal tissues fixed for a similar period in similar fixatives. A more detailed report will be published elsewhere.
ports that he is restless, easily distracted, and not interested in schoolwork.

The use of mercurial antiseptics in the treatment of exomphalos appears to be declining rapidly, despite its recent advocacy (Venugopal et al., 1976), undoubtedly because of the introduction of effective surgical procedures and a growing appreciation of the toxicity of organic mercurials.

Since it is clear that treatment of exomphalos by the application of alcoholic mercurial antiseptics can produce blood and tissue levels of mercury well above the threshold at which damage occurs in all other age groups, it is extremely unlikely that these infants escape neurological damage, which may be subtle. We therefore suggest that treated survivors should be examined neurologically and psychologically as a matter of urgency.

Organic mercurial antiseptics should be heavily restricted or withdrawn from hospital use, as the fact that mercury readily penetrates intact membranes and is highly toxic seems to have been forgotten. Equally effective and far less toxic broad-spectrum antifungal and antibacterial topical antiseptics are currently available.

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References


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