From Mad Hatters to Thimerosal: the Truth about Mercury Poisoning

Brian J Hall MD
The University of Utah School of Medicine adheres to ACCME Standards regarding industry support of continuing medical education.

Speakers are also expected to openly disclose intent to discuss any off-label, experimental, or investigational use of drugs, devices, or equipment in their presentations.

This speaker has nothing to disclose.
Goals for the talk

1. Understand common exposure sources of mercury
2. Appreciate some of the clinical features of acute and chronic mercury poisoning
3. Know the different tests available for mercury here at ARUP and other labs
4. Gain knowledge regarding treatments available for acute and chronic toxicity
Mercury

- Chemical symbol is Hg
- Atomic number is 80
- Also known as quicksilver or hydrargyrum
  - hydr = water or runny
  - argyros = silver
- At or near liquid at room temperature and pressure
History

- Egyptian tombs - 1500 BC
- In China and Tibet
  - thought to prolong life, heal fractures and maintain good health
  - Qin Shi Huang died from drinking mercury taken to prolong his life
- Ancient Greeks, Egyptians and Romans
  - Ointments and cosmetics
History

“Mad as a hatter”
- coined from mercury poisonings in the 18th and 19th centuries in the felt hat industry

Hunter-Russel syndrome
- Mercury poisonings found among workers in a seed-packing factory in Norwich, England - late 1930s
Forms of mercury

- Elemental
- Inorganic
  - Mercury chloride and other salts
- Organic
  - Methylmercury (MeHg)
  - Dimethylmercury
  - Ethylmercury (Thimerosal)
Elemental mercury

- Also known as quicksilver or liquid metallic mercury
  - poorly absorbed by ingestion and skin contact (<0.01% absorbed through an intact GI tract)
- ~80% of inhaled vapor absorbed through respiratory tract
- Chronic exposure by inhalation can cause
  - tremors, impaired cognitive skills, and sleep disturbance in workers
Common sources of elemental mercury

- Thermometers
- Amalgam
- CFLs
- Occupational
Many mercury thermometers are still used today in meteorology.

The typical "fever thermometer" contains between 0.5 to 3g of elemental mercury.

Swallowing the mercury poses little harm.
- Inhalation of the vapor can cause health problems.
Mercury and thermometers

- Many countries have banned them outright from medical use
- The AAP and EPA recommend the use of alternative thermometers in the home
- Manufacturers now often use galinstan, a liquid alloy of gallium, indium, and tin as a replacement
Mercury and amalgam

- Most commonly used dental restorative material used for dental fillings
- Mixture of mercury and one other metal
- Used for its low cost, strength, durability, ease of application and bacteriostatic effects
- Composite resin which is a tooth colored quartz-like material is also now used
Amalgam fillings

- Thousands of people have fillings removed out of fear of mercury toxicity
  - dental amalgams have been blamed for: coronary artery disease and multiple sclerosis
- Public Health Service concluded that dental amalgams do not pose a serious health risk
Compact Fluorescent Lamps (CFLs)

- CFLs contain a very small amount of mercury sealed within the glass tube
  - on average 4 mgs vs older bulbs that contained up to 500 mgs
- In the past year mercury content has dropped in CFLs by approximately 20%
- Some manufacturers have dropped content to 1.4-2.5 mgs per bulb
Contaminated air

- The background of mercury in outdoor air is generally between 10 and 20 ng/m³

- Occupational Air exposure
  - Medical, dental, and other health services
  - Chemical, metal processing, electrical equipment, automotive, building, and other industries
  - In areas where mercury might have been spilled
Inorganic mercury

- Occurs as salts such as mercury chloride
- Primarily affects the GI tract and kidneys
- Can cause severe kidney damage
- Neurologic damage requires continuous or heavy exposure
Common sources of inorganic mercury

- Cosmetics
- Ova and Parasite kits
- Eye drops
- Batteries
- Occupational
Cosmetics

- Ancient Egypt and even today
- Used in cosmetic industry as a preservative, usually as phenylmercury salts and thimerosal
- Most manufacturers have phased it out
  - still added to eye products as a preservative and germ-killer
- Federal law allows eye products to contain up to 65 parts per million of mercury
Minnesota - first state ban on mercury in cosmetics

- In January 2008 Minnesota
  - first state to ban intentional addition of mercury to cosmetics
- Fines up to $700 for Retailers
- Fines up to $10,000 for Manufacturers
Case report

- Family of four from Lithuania recently moved to the US presented with diarrhea
- Parasites were suspected
  - Family was given ova and parasite collection kits
  - Misunderstood the instructions and drank the contents
- Family presented next day with severe abdominal cramping
Inorganic mercury as a preservative

- 4% mercuric chloride was used
- 5 year old went into renal failure within hours, 4 year old followed the next day
  - Both transferred to a major medical ICU
  - Treated with succimer, dialysis, plasma exchange, supportive care
  - Mercury blood levels as high as 1480ug/L and 1020ug/L (normal <10ug/L)
Organic Mercury compounds

- Compounds of mercury often more toxic
- Can cause brain and liver damage
- Dimethylmercury
  - the most dangerous
Common sources of organic mercury

- Vaccines
- Food
- Occupational
Minamata disease

- Methylmercury poisonings in Japan - 1950s from industrial run-off
- 1,784 deaths as of March 2001
- Children with severe developmental disabilities

The Basra Incident

- Mass methylmercury poisoning September 1971 in Basra, Iraq
- Shipments of American barley and Mexican wheat intended as seed grain
  - had been treated with antifungal methylmercury to prevent rot
- Stolen from the docks and sold as food to the local population
The Basra Incident

- 1973 American reporter found evidence of 6,530 cases of mercury poisoning treated in local hospitals
- Officially 459 deaths have been admitted, but it has been estimated at many more

Dimethylmercury exposure - case

- August 14, 1996 a 48 y/o female chemistry professor at Dartmouth
  - Spilled one to several drops (~0.1 to 0.5mL) of dimethylmercury on a glove
- Three months later, episodes of nausea and vomiting
- Five months after exposure
  - ataxia (difficulty with balance), dysarthria (slurred speech), loss of vision and hearing
Dimethylmercury cont

- Whole blood mercury
  - 4,000 ug/L (normal <10ug/L)
- Symptoms progressed rapidly to cognitive deficits and coma in final 3 weeks
- Despite chelation therapy, the patient did not improve

Organic Mercury - Ethylmercury

- This is the form found in thimerosal which is used in vaccines as a preservative and as a topical antiseptic.
Thimerosal

- An ethylmercury containing preservative
  - has been used in vaccines since the 1930s
- Contains 49.6% Hg by weight
- Normal dose in vaccines is 12.5-25ug Hg per 0.5mL
- Local hypersensitivity had been observed, but no other adverse affects in recommended doses
- Concern that some infants receiving multiple doses could exceed federal guidelines

Ethylmercury

- Effects of high dose EtHg thought to be similar to high-dose MeHg, but low dose effect unclear
- MeHg crosses blood brain barrier by AA transport system
- EtHg is larger and decomposes faster and is thought not to have as active a transport system as MeHg
CDC and AAP press release
July 9, 1999

- Thimerosal should be removed from all vaccines
- Birth dose of the HepB vaccine should be delayed in children not at risk for hepatitis
- “Parents should not worry about the safety of vaccines. The current levels of thimerosal will not hurt children, but reducing those levels will make safe vaccines safer . . . we have an opportunity to increase our margin of safety.”

On August 26, 2004, Governor Arnold Schwarzenegger banned thimerosal containing influenza vaccines in California.

Many states have followed suit.
Studies

Bernard et al 2001
- Hypothesized autism spectrum disorder is a mercurial syndrome

Nelson and Bauman 2003
- Major difference in neuropathology of autism and Hg poisoning

Ball et al 2001
- No evidence of adverse effects by vaccines except well-known hypersens. response

More studies

- In 2004 two studies in the United Kingdom studied thimerosal in vaccines and neurodevelopmental or psychological problems.
  - neither showed that thimerosal was harmful.
- A recent study in 2007 published in JAMA looked at outcomes in 7-10 year olds exposed to thimerosal.
  - No evidence of neurologic problems in children was found.

The cost of “increasing the margin of safety”

- After the July 1999 announcement 10% of hospitals suspended Hep B vaccine of all newborns
  - 3 month old born to a Hep B positive mother died of overwhelming infection

- In August 2005
  - 5 year old autistic boy died from an arrhythmia caused by injection of EDTA
  - belief that thimerosal had caused his autism

After effects

- About 10,000 autistic children in the United States receive mercury chelating agents every year
- Thimerosal has been removed from most vaccines in the US
  - Some preparations of influenza vaccines still contain it
Harms outside of medicine

➢ As of February 1, 2009

• over 5,600 cases alleging a causal relationship between vaccines and autism filed, no compensations on any claims

• Vaccine Injury Compensation Program launched in 1988 to protect vaccine makers from frivolous lawsuits

Autism - the true cause

- Strong underlying genetic component
  - clustering within families of relatives with Autism
  - number of known causes of autism that are genetic (10-15% of cases a specific genetic cause can be identified)
  - 70% concordant rate among monozygous (identical) twins
Organic Mercury - Methylmercury

- Main biologic source of organic mercury
- Inorganic Hg deposits in aquatic environments
  - methylated by bacteria, fungi and phytoplankton into MeHg
- Accumulates in the environment, increases as it goes up the foodchain
- Larger species such as tuna and swordfish have higher levels
Figure 1. Accumulation of mercury in the food chain.

(Reprinted from Clean the Rain, Clean the Lakes: National Wildlife Federation, 2000)
<table>
<thead>
<tr>
<th>Fish/Shellfish</th>
<th>Mean mercury level in parts per million (ppm)</th>
<th>Omega-3 fatty acids (grams per 3-oz. serving)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canned tuna (light)</td>
<td>0.12</td>
<td>0.17–0.24</td>
</tr>
<tr>
<td>Shrimp</td>
<td>ND*</td>
<td>0.29</td>
</tr>
<tr>
<td>Pollock</td>
<td>0.06</td>
<td>0.45</td>
</tr>
<tr>
<td>Salmon (fresh,frozen)</td>
<td>0.01</td>
<td>1.1–1.9</td>
</tr>
<tr>
<td>Cod</td>
<td>0.11</td>
<td>0.15–0.24</td>
</tr>
<tr>
<td>Catfish</td>
<td>0.05</td>
<td>0.22–0.3</td>
</tr>
<tr>
<td>Clams</td>
<td>ND*</td>
<td>0.25</td>
</tr>
<tr>
<td>Flounder or sole</td>
<td>0.05</td>
<td>0.48</td>
</tr>
<tr>
<td>Crabs</td>
<td>0.06</td>
<td>0.27–0.40</td>
</tr>
<tr>
<td>Scallops</td>
<td>0.05</td>
<td>0.18–0.34</td>
</tr>
</tbody>
</table>

From the American Heart Association website
From the FDA

- For pregnant women, women planning to be pregnant, nursing women and children:
  - Should limit consumption of all fish with mercury levels <1 ppm (about 12 ounces per week or 3 to 4 servings)

- People other than pregnant women or young children
  - May eat 14 ounces a week of fish with mercury levels that average 0.5 ppm
From the National Resources Defense Council (NRDC) and FDA

LEAST MERCURY

Enjoy these fish:

Anchovies
Butterfish
Catfish
Clam
Crab (Domestic)
Crawfish/Crayfish
Croaker (Atlantic)
Flounder*
Haddock (Atlantic)*
Hake
Herring
Mackerel (N. Atlantic, Chub)

Mullet
Oyster
Perch (Ocean)
Plaice
Pollock
Salmon (Canned)**
Salmon (Fresh)**
Sardine
Scallop*
Shad (American)
Shrimp*
Sole (Pacific)
Squid (Calamari)
Tilapia
Trout (Freshwater)
Whitefish
Whiting

*Fish in danger
**Farm raised salmon that may contain unsafe levels of Polychlorinated Biphenyls (BCPs)
More from the NRDC and FDA

- MODERATE MERCURY
  Eat six servings or less per month:
  - Bass (Striped, Black)
  - Carp
  - Cod (Alaskan)*
  - Croaker (White Pacific)
  - Halibut (Atlantic)*
  - Halibut (Pacific)
  - Jacksmelt (Silverside)

- Lobster
- Mahi Mahi
- Monkfish*
- Perch (Freshwater)
- Sablefish
- Skate*
- Snapper*
- Tuna (Canned chunk light)
- Tuna (Skipjack)*
- Weakfish (Sea Trout)

*Fish in danger
HIGH MERCURY
Eat three servings or less per month:

- Bluefish
- Grouper*
- Mackerel (Spanish, Gulf)
- Sea Bass (Chilean)*
- Tuna (Canned Albacore)
- Tuna (Yellowfin)*

HIGHEST MERCURY
Avoid eating:

- Mackerel (King)
- Marlin*
- Orange Roughy*
- Shark*
- Swordfish*
- Tilefish*
- Tuna
- (Bigeye, Ahi)*

*Fish in danger
Key to previous slides

- Least mercury: Less than 0.09 parts per million
- Moderate mercury: From 0.09 to 0.29 parts per million
- High mercury: From 0.3 to 0.49 parts per million
- Highest mercury: More than .5 parts per million
Fish consumption

- A recent study of children in the Seychelles Islands (near Madagascar)
- Analysis of brain mercury concentrations in infants who died of unrelated causes
- Found no neurotoxicity or excessive brain mercury levels attributable to fish ingestion

Toxicity

➢ All toxic presentations, whether acute, chronic, or subacute, are difficult diagnoses

- Multiple organ systems are affected (e.g., CNS, kidney, mucous membranes) and disease can mimic a variety of other diseases
Acute Toxicity

- Usually related to inhalation of elemental mercury or ingestion of inorganic mercury
Acute Toxicity

- **Inhalation of elemental mercury**
  - fever, chills, shortness of breath, metallic taste, and pleuritic chest pain
  - Also stomatitis, lethargy, confusion, and vomiting

- **Inorganic mercury orally or through GI tract**
  - Ashen-gray mucous membranes, hematochezia, vomiting, severe abdominal pain, hypovolemic shock
  - Symptoms usually begin several hours postingestion, may last several days
Chronic inorganic exposure

- Usually from occupational exposure to elemental Hg converted to the inorganic form
- Can present with renal failure, dementia, and acrotdynia
- Acrodydna or Pink Disease
  - Considered a mercury allergy, not present in everyone exposed
  - Erythema of the palms and soles, edema of the hands and feet, desquamating rash, hair loss, pruritus, diaphoresis, tachycardia, hypertension, photophobia, irritability, anorexia, insomnia, poor muscle tone, and constipation or diarrhea.
Exposure to organic mercury usually leads to chronic toxicity, but rarely acute toxicity.

Classic triad of chronic toxicity:
- tremors, gingivitis, erethism

Erethism:
- constellation of neuropsychiatric findings
- includes insomnia, shyness, memory loss, uncontrolled perspiration, blushing, emotional instability, depression, anorexia, and vasomotor disturbance
Organic mercury poisoning

- Usually from ingestion of contaminated food
- Onset of symptoms is usually delayed
  - days to weeks after exposure b/c it targets enzymes and requires their depletion
- Symptoms include:
  - Visual disturbance (e.g., visual field constriction), ataxia, paresthesias (early signs)
  - hearing loss, dysarthria, mental deterioration, muscle tremor, movement disorders, and, with severe exposure, paralysis, and death
Mechanisms

- 90-100% of methylmercury is absorbed through the GI tract where it enters the bloodstream and distributes throughout the body
  - Readily binds sulfhydryl groups and is transported across the blood-brain barrier by an AA carrier and readily accumulates in the brain
  - Amount of MeHg in fetal blood is thought to be proportional to the mother’s
At risk populations

- Pregnant women
- The unborn fetus
- Young children
- Occupational
The unborn fetus

- All forms of mercury are toxic to the fetus
- Methylmercury most readily passes through the placenta
  - Even with an asymptomatic patient, maternal exposure can lead to spontaneous abortion or retardation
From the EPA for women and young children

1. Do not eat Shark, Swordfish, King Mackerel, Tilefish

2. Eat up to 12 ounces a week of a variety of fish and shellfish that are lower in mercury

3. Check local advisories about safety of fish in local lakes, rivers, and coastal areas
   - If no advice eat up to 6 ounces per week but no other fish the rest of the week
Diagnosis

- Really depends on lab testing
- Normal mercury levels are considered to be less than 10 ug/L in the blood and urine
- In persons chronically exposed to methylmercury the earliest signs of intoxication (paresthesia, sensory disturbances) occurred when levels in blood and hair exceeded 200 ug/L and 50 ug/g respectively
## Lab testing

<table>
<thead>
<tr>
<th>Forms</th>
<th>Clinical time frame (reference range)</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood Total mercury</td>
<td>Acute exposure (&lt;10 mcg/g)</td>
<td>DMA, ICPMS</td>
</tr>
<tr>
<td>Urine Inorganic mercury</td>
<td>Chronic exposure (&lt;10 mcg/g)</td>
<td>ICPMS</td>
</tr>
<tr>
<td>Hair Total mercury</td>
<td>Chronic exposure (&lt;2mcg/g)</td>
<td>ICPMS</td>
</tr>
<tr>
<td>Nails Total mercury</td>
<td>Chronic exposure (none)</td>
<td>ICPMS</td>
</tr>
<tr>
<td>Breast milk Total mercury</td>
<td>Real time (none)</td>
<td>ICPMS</td>
</tr>
<tr>
<td>Stool Organic mercury</td>
<td>(none)</td>
<td>ICPMS</td>
</tr>
</tbody>
</table>
Lab testing: limitations

- Stability
- External contamination
Direct Mercury Analyzer

- Controlled heating is used to liberate mercury from solid and aqueous samples
- The sample is then thermally and chemically decomposed within a decomposition furnace
- The products are then carried to the catalytic section of the furnace
- Oxidation is completed and then the products are carried to an amalgamator that selectively traps mercury
- The amalgamator is then rapidly heated, releasing mercury vapor
- An atomic absorption spectrophotometer measures the absorbance of the mercury vapor
Inductively coupled plasma mass spectrometry (ICPMS)

- The specimen is diluted with yttrium and the blood is then centrifuged for 25 minutes to concentrate the solids at the bottom of the sample tube
- Urine is not centrifuged
- The sample is aspirated into an inductively coupled plasma-mass spectrometer (ICP-MS) which has been calibrated for Hg testing
- The aspirant is atomized in the instrument “spray chamber,” and then ionized in the argon plasma
- The generation of the plasma is by means of a series of concentric glass tubes referred to as a “torch,” through which argon gas flows
ICPMS cont

- Up to 2.5 kW of radio frequency power can be applied to a drive coil which surrounds the outlet end of the torch.
- This power sustains a plasma discharge in the argon at a temperature of 6000 K.
- Cations of Hg are filtered by the quadrupole, transduced from Hg cations into electrons and magnified by the ion multiplier.
- Cations are counted and summed.
- Quantitation is achieved by a calibration curve established from ratios between increasing amounts of Hg in each calibrator and a constant amount of Y internal standard.
- The Hg concentration in the sample is computed from the curve.
Figure 1. Schematic of an ICP-MS system showing the location of the plasma torch and radio frequency (RF) power supply.
Treatment

- Immediate supportive care is most important
  - Inhalation of elemental Hg and ingestion of inorganic mercury can cause airway obstruction and respiratory failure
- Gastric lavage for organic ingestion
- Activated charcoal binds inorganic and organic forms
Chelating agents can be used in symptomatic patients such as Penicillamine, Dimercaprol, EDTA and Succimer.

Hemodialysis is used in severe cases of toxicity when renal function has declined.

Neostigmine (cholinesterase inhibitor) may help motor function in chronic methylmercury toxicity which often leads to acetylcholine deficiency.
Prognosis

- In a study by He et al in Singapore in mercury refinery workers demonstrated that prognosis was promising following the removal of chronic exposure and chelation therapy even in severe cases

- Ova and parasites kids recovered
Summary

- The route as well as the form of mercury are very important in any suspected exposure.
- It is important to understand which species of fish have the highest levels of mercury.
- Monitoring is important in at risk populations.
- Media attention has caused a heightened fear of mercury and its common uses.
Clinical diagnosis is difficult because signs and symptoms affect multiple organs and acute or chronic exposure can mimic other diseases