

Heavy Metals

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LEAD



History

- Most widely used nonferrous metal
- US annual production averages 1.1 million tons
- Use- waterproofing, electrical and radiation shielding properties, smelting, printing industry, solder, ammunition, bronze/brass, plating, paint, glazes
- In US-electric storage batteries (2/3 use)



Epidemiology

- Lead poisoning rates higher among black (11.2%) and Mexican-American (4.0%) vs. white children (2.3%)
- 8.0% of low-income children are lead poisoned compared with 1.9% (middle) and 1.0% (high income) children
- 1.2% of rural children age 6 months to 5 years have levels > than 30mg/dL compared to 19% of urban children



Epidemiology

- Mean blood lead level for Americans aged 1 - 74 continue to decline
 - 12.8 mg/dL in 1976-1980
 - 2.9 mg/dL in 1988-1991 to
 - 2.3 mg/dL in most recent data



Epidemiology

- Children living in pre-1946 housing had 8.6% rate of lead poisoning;
- 4.6% 1946-1973
- 1.6% of those in post 1973 housing



Sources of Lead

- Household paint
- Dust
- Soil
- Air
- Exotic
- Food
- Water
- Leaded Gasoline



Lead Pharmacodynamics

- Absorption affected by age
 - adults absorb 5-10%
 - children 40-50%, retain 20-25%
- Spontaneous excretion <50mg/24hr
- Distribution in two major compartments
 - Bone: $t_{1/2}$ 20years
 - Soft tissue: $t_{1/2}$ 20-30 days



Mechanism of Lead Toxicity

- High affinity for sulfhydryl groups in structural and enzymatic proteins
- Chemically similar to calcium inhibiting membrane-bound Na,K-ATPase
- Inhibits ferrochelatase leading to elevated erythrocyte protoporphyrin (EP)
- Most sensitive tissues are kidneys, hematopoietic system and nervous system



Lead Pathophysiology

- Range of toxic effects
 - decreased stature
 - decreased hearing acuity
 - inability to maintain steady posture
 - impairment of biosynthesis of active Vit D metabolism
 - reduced gestational age birth weight related to maternal and cord elevated lead level
 - reduced reproductive potential



Lead Pathophysiology

Neurobehavioral/cognitive

- Noted at levels as low as 10-15 mcg/dL
- Lead in early stages of development may produce life-long decrements in intelligence, possibly reversible



Lead Pathophysiology

Neurobehavioral/cognitive


- Average decline of 2-4 IQ points
- Impairment of reading skills
- Impairment of academic success
 - 7-fold increase in failure to graduate from high school



Pathophysiology

Neurobehavioral/cognitive


- Lower class standing
- Greater absenteeism
- Deficits in vocabulary
 - fine motor skills
 - reaction time
 - hand-eye coordination



Pathophysiology

Neurotoxicity


- Classically manifests as acute encephalopathy
- More subtle neurotoxic effects are less well understood
 - altered neurotransmitter function
 - morphologic changes in developing brain in utero



Pathophysiology

Other System Effects

- Peripheral nervous system
- Hematologic
- Renal
- Reproductive System
- Endocrine system
- Skeletal
- GI
- Cardiac




Clinical Presentation in Children

- Asymptomatic lead level > 10
 - CNS: Impaired cognition, behavior
 - PNS: Impaired fine motor coordination
 - Misc: Impaired hearing, growth
- Mild to Moderate lead level > 50 - 70
 - CNS: Hyperirritability, lethargy, decreased interest in play, “difficult child”
 - GI: Intermittent vomiting, abdominal pain, anorexia




Clinical Presentation in Children

- Severe lead level > 70 - 100
 - CNS: Encephalopathy (coma, altered sensorium, seizures, incoordination, loss of developmental skills; papilledema, cranial nerve palsy, signs of increased ICP)
 - GI: Persistent vomiting
 - Heme: Pallor (anemia)



Clinical Presentation in Adults

- Mild lead levels > 40
 - CNS: Fatigue, moodiness, falls asleep easily, decreased interest in leisure activities
 - MISC: Impaired psychometrics, reproduction; elevated blood pressure
- Moderate lead levels > 80 ug/dL
 - CNS: Headache, memory loss, decreased libido, insomnia
 - GI: Metallic taste, abdominal pain, anorexia, constipation
 - Renal: Nephropathy with chronic exposure



Clinical Presentation in Adults

- Severe lead levels > 100 - 150
 - CNS: Encephalopathy (coma, seizures, obtundation, delirium, focal motor deficits, headache, papilledema, signs of increased ICP)
 - PNS: Foot drop, wrist drop
 - GI: Abdominal colic
 - Heme: Pallor (anemia)
 - Renal: Nephropathy



Clinical Diagnosis

Differential Diagnosis

- Anemia
- Seizures
- Mental retardation
- Severe behavioral effects
- Colicky abdominal pain
- Cerebral and abdominal sickle cell crises
- Infectious encephalitis



Clinical Diagnosis

- Screening lead levels, iron levels
- X-rays of long bones and abdomen
- Complete blood count and smear
- (FEP) free erythrocyte protoporphyrin levels
- Ca disodium EDTA mobilization test/UA



Normal Value for Blood Lead?

- No “normal” lead levels
- Lead serves no physiologic function
- “Acceptable” level in children by CDC criteria - 0 to 9 mg/dL
- Effect on enzymatic processes at 10-15mg/dL



Treatment of Lead Poisoning

- Environmental inspection/ hazard reduction
- Nutritional supplementation
- Chelation therapy



Treatment

Nutrition

- Check for adequate iron and calcium intake
- Iron supplementation
- Supplementation of other trace metals such as copper and zinc in the form of a multivitamin with minerals



Treatment

Chelation Therapy

- British Anti-Lewisite (BAL)
- CaNaEDTA
- D-Penicillamine
- Dimercaptosuccinic acid (DMSA)



Indications for Chelation Therapy

- Evidence that blood lead level is not declining after abatement
- The age of child
- Elevated EP level
- Assumption that therapy will reverse some neurodevelopmental changes



Prevention

- Routine lead screening
- Universal lead screening
- Who should be screened?
 - Virtually all children should be screened for lead poisoning



Screening

AAP Recommendations

- Children in high-risk groups at age one and two
- Once for ages 36-72mo, if not previously tested
- Targeted Screening based on identification of risk factors



Recommended Actions

- 10-14 Retest in 3 mo; education
- 15-19 Retest in 2 mo; education; if 15-19 occurs twice refer for case management
- 20-44 Clinical evaluation; education; environmental investigation



Recommended Actions

- 45-69 Clinical evaluation and case management within 48 hr; education; environmental investigation; chelation
- ≥70 Hospitalize child; chelation now; education, environmental evaluation



MERCURY



Available Forms

- **Elemental**
 - quicksilver
- **Inorganic salts**
 - corrosive sublimate
 - calomel
- **Organic compounds**
 - methyl mercury
 - ethyl mercury



Sources of Mercury

- **Elemental** - batteries, thermometers, dental amalgams
- **Inorganic** - fireworks, fur hat processing, tattooing inks, photography
- **Organic** - insecticides, embalming agents, wood preservatives



Mercury Toxicokinetics

	Elemental	Inorganic	Organic
Primary Route	Inhalation	Oral, cutaneous	Oral
Distribution	CNS, kidney	Kidney	CNS, kidney, liver
Elimination	Renal, GI	Renal, GI	Fecal, renal



Mercury Pathophysiology

- Covalently binds to sulfur, replacing hydrogen ion of sulfhydryl groups
- Reacts with phosphoryl, carboxyl, and amide groups as well
- Results in widespread dysfunction of enzymes, transport mechanisms and structural proteins



Mercury Clinical Presentation

	Elemental	Inorganic	Organic
CNS	Tremor	Erethism, tremor	Minamata Disease
Pulmonary	+++	-	-
GI	+	+++	-
Renal	+	+++	+
Acrodyvnia	+	+	-



Mercury Treatment

- Supportive Care
- Decontamination
 - removal of vapors
 - washing exposed skin
 - Spill decontamination
 - GI (AC, protein lavage, WBI)
- Chelation
 - BAL (contraindicated for organic toxicity)
 - DMSA



Parental Chelation

(British Anti-lewisite)

- Developed during WWII to counteract chemical warfare agent lewisite
- Used for inorganic mercury, arsenic, and lead toxicity
- BAL permits ring-formation with the metal, increasing stability



Parenteral Chelation

(British Anti-lewisite)

- Administered intramuscularly only
- Dose and duration depends on metal being chelated and severity
- Adverse effects
 - HTN, fever, N/V, salivation, headache,
 - Hemolysis in G6PD deficient patients
- Peanut allergy is a contraindication to the use of BAL



Parenteral Chelation

Calcium Disodium Edetate

- Capable of chelating many metals, but used primarily in lead toxicity
- Given with BAL for severe toxicity (BAL must precede EDTA by 4 hours)



Parenteral Chelation

Calcium Disodium Edetate

- Adverse effects
 - nephrotoxicity
 - max dose 1g children/ 2g adults
 - monitor renal function closely
 - malaise, headache, anorexia, anemia, transient hypotension
 - depletion of endogenous metals (Cu, Zn, Fe, Mn)



Oral Chelators

D-Penicillamine

- Used for lead and arsenic toxicity
- Role in lead intoxication has been replaced
- Iron decreases absorption by 65%
- Course of therapy is normally 2 -6 months, compliance issues



Oral Chelators

D-penicillamine

- **Adverse effects include**
 - N/V, rash
 - leukopenia, thrombocytopenia
 - hemolytic anemia
 - Stevens-Johnson syndrome
- **Indicated in the event of both DMSA and EDTA failure**



Oral Chelators

Dimercaptosuccinic Acid (DMSA)

- **An analogue of BAL, the first oral agent approved for lead intoxication (1991)**
- **Used in lead, arsenic, and organic and inorganic mercury poisoning**



Oral Chelators

Dimercaptosuccinic Acid (DMSA)

- **Approved for use in children with lead levels > 45 mg/dL**
- **Efficacy shown with children having lead levels of 25 - 45 mg/dL**



Oral Chelators

Dimercaptosuccinic Acid (DMSA)

- **Major advantages**
 - less toxic
 - orally active and highly effective
 - relatively specific chelator
 - hemolysis is not of concern with G6PD-deficient patients
 - can be used concomitantly with iron



Oral Chelators

Dimercaptosuccinic Acid (DMSA)

- **DMSA therapy reduces mean blood lead levels by 70% - 80%**
- **Rebound occurs in 2 -4 weeks; repeated administrations may be necessary**
- **Adverse effects**
 - N/V/D
 - abdominal gas/pain
 - transient elevations in LFTs
 - rash, pruritus




IRON TOXICITY



Iron Poisoning Incidence

- 75% Occur in Children < 6 Years Old
- 84% Considered Accidental
- 50% Treated in Health Care Facility
- 4% Moderate to Severe Symptomatology
- 2 Deaths

1996 AAPCC Annual Report




Iron Poisoning Pathophysiology

- Corrosive Action on GI Mucosa
Nausea, Vomiting, Diarrhea
Hemorrhagic Gastritis
Intestinal Necrosis
Perforation/Peritonitis
Strictures, Fibrosis, Scarring




Iron Poisoning Pathophysiology

- Systemic Effects
Hemodynamic Effects
Metabolic Effects
Central Nervous System Effects
Hepatotoxic Effects




Iron Poisoning Systemic Effects

- Hemodynamic Effects
Postarteriolar Dilatation, Venous Pooling
Capillary Leakage
Reduced Tissue Perfusion
Lactic Acidosis
Cardiac Failure, Shock
- Direct Myocardial Damage




Iron Poisoning Systemic Effects (Cont.)

- Inhibit Krebs Cycle/Oxidative Processes
Buildup Organic Acids
Hyperglycemia
- Leukocytosis
- Mild Obtundation to Profound Coma
- Hepatotoxic
Catalyst of Lipid Peroxidation
Cirrhosis/Necrosis



Iron Poisoning Time Course of Intoxication


<u>Phase</u>	<u>Onset</u>	<u>Symptoms</u>
I	0-3 Hours	Vomiting, Diarrhea Lethargy, Restless, Abdominal Pain, Hemetemesis
II	Up to 12 Hours	Quiescent Period
III	12-48 Hours	Shock, Acidosis, Coma, Seizures, Pulmonary Edema, Hypoglycemia,
IV	2-4 Weeks	Coagulation Defects GI Scars/Strictures



Iron Poisoning

Assessment of Toxic Potential


- Early GI Effects May Limit Absorption
- Assess *Elemental Iron* Content
- Consider *Rapid vs Sustained Release*
- Consider Time Course



Iron Poisoning

Assessment of Toxic Potential

- Symptoms *Always* Take Precedence Over Estimation of Ingested Dose
- If Patient Remains Asymptomatic for 6-8 Hours Further Intervention Usually Not Required
- Other Useful Assessments:
Abdominal Radiography
Serum Iron (TIBC ??)




Iron Poisoning

Assessment of Toxic Potential

Ingestion*	Toxic Potential
< 20 mg/kg	Little Risk of Toxicity
20-60 mg/kg	Moderate Risk Requires Intervention at Home (Ipecac) or Health Care Facility Follow for Symptoms, Chelation May Be Necessary
> 60 mg/kg	High Risk Requires Hospital Visit and GI Decontamination Usually Require Chelation


* mg/kg Elemental Iron



Iron Poisoning

Elemental Iron Content


Salt Form	Percent Elemental Iron
Ferrous Sulfate	20
Ferrous Fumarate	33
Ferrous Gluconate	12
Ferrocholate	12
Ferrous Chloride	28
Ferroglycine Sulfate	16
Ferrous Succinate	35
Ferric Phosphate	37
Ferric Chloride	20
Ferric Ammonium Citrate	16



Iron Poisoning

Serum Iron/TIBC Assessment

- Toxicity Occurs with Free Circulating Iron (Except GI Symptoms)
- Serum Iron > 350 mcg/dl Considered Toxic
 > 500 mcg/dl Aggressive Therapy
 300-500 mcg/dl Possible Chelation
 150-350 mcg/dl GI Symptoms Only
- Levels Obtained 4-6 Hours After Ingestion



Iron Poisoning

Treatment

- Supportive Care Most Important
- Monitor For:
GI Hemorrhage, Excessive Fluid Loss
Abnormal/Rapid Changing Vital Signs
Acidosis, Electrolyte Imbalances
Coagulation Profile, Liver Function
- Level of Intoxication Determines Aggressiveness



Iron Poisoning

Gastrointestinal Decontamination

- Choice Depends on Estimation of Ingestion Symptoms, Abdominal Radiograph
Whole Bowel Irrigation
Surgical Removal
- Follow-Up Radiograph Warranted in Certain Cases



Iron Poisoning

Lavage Solutions

- Use of Bicarbonate, Phosphate, Deferoxamine Lavage Solutions Controversial with No Concrete Evidence of Efficacy
- Some Evidence For Enhancement of Absorption



Iron Poisoning

Deferoxamine

- Binds 9 mg Elemental Iron per 100 mg Free Serum Iron
Ferritin, Hemosiderin
- Cytochrome Systems, Hemoglobin, Transferrin Minimally Affected



Iron Poisoning

Deferoxamine

- Ferrioxamine Complex Formed
Dependent on pH > 6
- Antidote MOA:
Limit Distribution Volume
Protection of Mitochondrial Function
Enhance Renal Elimination



Iron Poisoning

Deferoxamine Challenge Test

- 50 mg/kg (1 Gram Maximum) Given IM
- Theoretically If Free Iron Present Ferrioxamine Imparts "Vin Rose" Urine
- Complex pH and Concentration Dependent
- Many False-Negative Tests Reported
- Delay of 1-3 Hours Common



Iron Poisoning

Deferoxamine

- Pregnancy Not Considered a Contraindication
- Acute Hypotension Seen With Rapid Bolus
Probably Due to Histamine Release
- IV Route Now Preferred
- Dose:
15 mg/kg/hr IV



Iron Poisoning

Discontinuing Chelation Therapy

- Disappearance of "Vin Rose" Urine
Absence of Free Iron ??
False Negatives ??
Useful When Serum Iron Not Available
Discontinue Therapy in 24 Hours
- Serum Iron Level < 100-150 mcg/dl
- Guidelines Assume Absence of Symptoms



ARSENIC POISONING



Arsenic Poisoning

Source Of Exposure

- Common Ingredient
Rodenticides
Insecticides
Herbicides
Special Paints
Folk Remedies
Glass and Metal Production
- Seafood, moonshine, contaminated well water



Arsenic Poisoning

Source Of Exposure

- Estimated 1.5 Million Exposures Per Year
Most Common Acute Metal Poisoning
Second Only To Lead In Chronic Toxicity
- Arsine Gas Formed In Metal Processing



Arsenic Poisoning

Mechanism of Toxicity

- Intracellular Toxin
- Two Forms Encountered
Trivalent (Arsenite) - Rapid GI
Absorption; Toxic Effects Directed
At Cellular Level

Pentavalent (Arsenate) - Less Toxic
Of Two Forms; Converted To
Trivalent Form



Arsenic Poisoning

Mechanism of Toxicity

- Combines With Sulfhydryl Groups On
Enzymes and Proteins
Interferes With Krebs Cycle
Interferes With Oxidative Phosphorylation
- Substitutes For Phosphate In Cellular Reactions
With Resultant Loss Of High Energy Bonds
- Elimination
Primarily Renal With Biphasic Curve
Small Amounts: Bile, Feces, Saliva



Arsenic Poisoning Clinical Presentation

Phase	Symptoms
Early	Onset 0.5-2 Hour Violent Gastroenteritis With Profuse Diarrhea and Colicky Abdominal Pain; Rapid Progression To CV Collapse, Dysrhythmias, CNS Depression
Intermediate	Severe Capillary Damage With Massive Third Spacing; ARDS, Proteinuria, Renal and Liver Failure



Arsenic Poisoning Clinical Presentation (Cont.)

Phase	Symptoms
Delayed	Equivalent To Chronic Exposure Symmetrical Polyneuropathy (Sensory and Motor); Wernicke-Like Encephalopathy, Palmer Hyperkeratosis, Exfoliative Dermatitis, Mee's Lines, Anemia, Leukopenia, Thrombocytopenia, Edema, Alopecia, Stomatitis



Arsenic Poisoning Assessment

- Follow Fluid/Electrolyte Balance Closely
- Baseline EKG
- Anticipate Multi-Organ System Failure
- Baseline Chest X-Ray
- Blood Indices/Clotting Studies



Arsenic Poisoning Assessment

- Diagnosis Rests of History and Presentation
- Serum/Urine Levels Not Readily Available
- May Show on Abdominal Radiograph
- Garlic-Like Odor
- Serum Levels Confirmation Only
- Monitor Course With 24 Hour Urine Levels



Arsenic Laboratory Evaluation

- Acute
 - radiopaque on X-ray
 - 24-hour urine collection
 - levels < 50 ug normal (or < 50ug/L spot level)
 - levels > 100 ug is abnormal
 - when seafood is ingested, can see levels 200-1700 ug/L



Arsenic Poisoning Management

- Vigorous Fluid/Electrolyte Resuscitation
- Early Initiation of Chelation Therapy
- Lavage, Activated Charcoal
- Dermal Decontamination If Arsenic Gas



Arsenic Poisoning Chelation Therapy

- **BAL (Dimercaprol)**
3-5 mg/kg IM Loading Dose
2.5-3.0 mg/kg IM Q 4-6 Hours; Day 1-2
2.5-3.0 mg/kg IM Q 8-12 Hours Thereafter
Peanut Oil Vehicle; IM Administration Only
- **D-Penicillamine**
100 mg/kg/Day (Maximum 1-2 Grams/Day)
Four Divided Oral Doses



Arsenic Poisoning Chelation Therapy

- Duration Of Initial Therapy Depend On Severity
Mild: 5-7 Day Course
Severe: 10-14 Day Course
- DMSA (Chemet)



Arsenic Poisoning Management

- Repeat Courses Until 24 Hour Urine Level Falls Below 50 mcg/L/24 Hours
- Hemodialysis In Presence Of Renal Failure
- Hemolysis Due To Arsenic Gas Unresponsive To BAL Therapy; Exchange Transfusion Possibly Effective
- Alkalinize Urine With Significant Myoglobinuria



Arsenic Treatment

- **Investigational therapies**
 - DMPS
 - Monoesters of DMSA
 - NAC
 - Antibodies to arsenic
 - DTE
 - Sulfo-adenosyl-L-methionine



Arsenic Poisoning Arsenic Gas Exposure

- Latent Period Up To 24 Hours Seen
- Initial Symptoms
 - Abdominal Pain
 - Headache
 - Weakness
 - Malaise
 - Nausea/Vomiting
 - Hemolysis
 - Renal Failure
 - Hyperkalemia
 - Anemia



**Florida Poison
Information Center
Network**



1-800-222-1222