Toxicology of High Priority Substances

Part 2: Metals

Metals

- Large, diverse class of elements
- Widely distributed in nature
- Humans are exposed to metals and metallic compounds from environmental and industrial sources
- Today:
  - Lead, Mercury, Arsenic and Cadmium

Each Metal has Multiple Forms

- Elemental
- Inorganic (minerals and salts)
- Organic (e.g., methyl-mercury, tetraethyl lead)

Toxic response depends on:

- Specific target tissues
- Concentration in target tissues, which will depend on the amount absorbed and the duration of exposure.
- Toxic potency of the specific metallic toxin

Toxic Metal Syndromes

- The particular syndrome associated with any particular metal depends largely on the tissues and organs where the metal is concentrated. Distribution depends on the specific chemical form of the metal: elemental, inorganic or organic.
  - Organic metal compounds are usually lipophilic, so can penetrate the blood-brain barrier more efficiently making them more likely to be neurotoxic.
  - Inorganic metal salts are often excreted through the kidneys making them more likely to be nephrotoxic.

Essential Elements

- Some metals are “essential” elements and required in some amount for normal body function.
  - Examples: Iron, Zinc, Manganese, Copper, and Selenium.
- However, when present in excess concentrations, even these will have toxic effects. The dose required for toxic effect is usually substantially (orders of magnitude) larger than the required dietary intake needed to prevent deficiency.

Toxic Metals

- Some metals have no physiologic role: Lead, Arsenic, Mercury, Cadmium are examples

Cell Injury Responses

- The principle toxic form of the metals is their free ion which binds to specific cell components
  - Enzymes
  - Cell structures (mitochondria, etc.)
  - DNA-related proteins
- Specific cell injury effects depend on concentration.
  - High concentrations produce immediate toxic effects with acute damage to exposed tissues.
  - Lower concentrations produce more subtle changes in cell function and a gradual decline in organ function and/or mutations/carcinogenesis.

Physiologic Responses

- Some metals have physiologic effects
  - Usually those with some essential physiologic role: for example: K, Na.
  - Others may mimic essential metals: for example, lithium.

Allergic Responses

- Immediate hypersensitivity (Pt, Be)
- Delayed hypersensitivity (Ni, Cr, Be, Zi)
- Bystander reactions and immune complex disease (Au, Hg)

Mutagenic Responses

- Carcinogenesis
  - Probably through interaction with DNA constituents.
  - Cr, As, Ni, Be, Cd

Teratogenic Responses

- Methyl mercury (Minamata disease)
- Lead (cognitive defects)

Residence Time

- Metals ions can remain in the body for a very long time.
  - In some cases (lead, for example), the metal can be incorporated into bone where it can remain sequestered. Circumstances that increase bone breakdown can release the metal and produce acute toxicity.

Metallothioneins

- Specific metal binding proteins in tissue and in the circulation.
- Sequester metal ions and provide protection against their toxic effects.
- Toxicity occurs when the binding capacity is exceeded or when the metal-protein complex is broken down in a cell and the metal ion released.

Excretion of Metals

- Since the toxic form is an element, metals cannot be removed by metabolism or biotransformation into other chemicals. The only way of removing metal toxins is by excretion.
- The kidney is the principal route of excretion. This subjects the kidney tubule cells to high levels of metal ions and, consequently, kidney injury is a common consequence of metal toxicity.

Chelation

- Techniques to increase the rate of excretion of metals
  - Administration of chemicals that form stable water-soluble complexes the metal ions and increase their rate of excretion
  - These chemicals are called “chelators”.
  - Some of these are toxic per se and some can actually increase the toxic effects of their metal ligand by mobilizing the metal.

Lead

- Ubiquitous
- Earliest documented toxic metal: plumbing
- Target tissues:
  - Brain and other nerve tissue
  - Liver
  - Kidney
- Multiple routes of cell injury
- Mutagenic through reduced DNA repair.
- Crosses the placenta: embryo/fetus at risk
- Half life: ~5-10 years

Lead: Toxic Responses

- Cell injury: Interferes with a wide variety of cellular processes
- Physiologic: none
- Allergenic: none
- Mutagenic: by reducing DNA repair, increases the net mutation rate
  - Carcinogenic
- Teratogenic: CNS effects

Elemental & Inorganic Lead

- Easily absorbed through inhalation and ingestion
- Primarily in the form of dusts and fume
- The NOAEL has not been defined and keeps getting lower.
- Acutely toxic with a wide variety of symptoms, none that are specific.
  - Abdominal pain
  - Neuropsychologic change: memory, cognition, personality
  - Peripheral nerve injury (weakness)
  - Blood lead levels diagnostic

Chronic Lead Toxicity

- Slow, insidious illness
- Recognition relies on suspicion and lead measurement
- No specific symptoms or signs
  - Abdominal pain
  - Neurologic injury
  - Reproductive toxicity (men and women)
  - Hypertension, gout
- Pregnancy can mobilize stored lead.
- OSHA standard
- CDC recommendations for childhood screening

Organic Lead

- Alkyl lead compounds
  - Tetraethyl lead
  - Tetramethyl lead
- Easily absorbed through skin
- Lipophilic and potent neurologic toxins
- Dwindling problem

Measuring and Managing Lead Exposure

- Lead levels
  - Variable relationship to toxic manifestations
  - Best in recent acute exposure
  - Less helpful in chronic exposure
- Zinc protoporphyrin levels
  - Measures lead effect in red blood cells
  - Useful is assessing unclear situations
- Medical removal from exposure
  - Pb> 60
  - Last three months > 50
  - "Increased risk" from lead exposure

Arsenic

- Ubiquitous, common element
- Relatively short half-life (hours)
- Forms
  - Elemental: non-toxic
  - Organic:
    - Dietary, non-toxic arsenobentaine and arsenocholine
    - Military: lewisite, very toxic
  - Inorganic forms are toxic
    - Pentavalent (arsenates)
    - Trivalent (arsenites)
    - Arsine gas (AsH_3)

Arsenic: Toxic Responses

- Cell injury: interfere with multiple processes
- Physiologic: none
- Allergenic: none
- Mutagenic: interferes with DNA repair
  - Carcinogenic: skin cancers, lung cancer, angiosarcoma
- Teratogenic: fetotoxic, congenital malformations

Target Tissues

- Absorbed through lungs or gi tract
- Distributed by red blood cells to liver, kidney, brain, muscle, skin and hair
- Acute responses
  - Arsine: red blood cells – hemolysis followed by kidney failure
  - Arsenic salts: intestinal cells, kidney, nervous system
- Chronic responses: neuropathy, chronic injury to kidney, liver and lung, skin changes, cancer

Measuring& Managing Arsenic Exposure

- Blood levels not helpful except early in acute toxic illness
- Arsenic can be measured in urine, but must be careful to eliminate non-toxic dietary arsenic
- Hair and nail arsenic can be measured
- Management
  - Removal from exposure
  - Chelation: BAL (dimercaprol); succimer

Mercury

- Forms
  - Elemental: toxic by inhalation, not by ingestion
  - Inorganic: mercury salts
  - Organic:
    - Aryl: oxidized to mercury salts
    - Alkyl: methyl mercury, ethyl mercury – extremely toxic
- Half-life about 2 months

Mercury: Toxic Responses

- Cell injury: interfere with multiple processes from divalent mercury ion
- Physiologic: none
- Allergenic: dermatitis
- Mutagenic: not known
  - Carcinogenic: none associated
- Teratogenic: Minamata Disease

Target Tissues

- Brain
  - Erethism: specific neuropsychologic changes
  - Loss of coordination
  - Dementia
  - Alkyl mercury has particular affinity for brain
- Kidney: acute renal injury
- Lung: acute inhalation injury
- Oral pathology

Measuring and Managing Mercury Exposure

- Measurement
  - Blood and urine
- Management
  - Removal
  - Chelation

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Break