Clinical Pharmacology & Toxicology Pearl of the Week

~Lead Toxicity~

NOTE: Blood lead levels > 0.5 umol/L from an occupational exposure are a notifiable disease in Alberta. The ordering provider must notify Occupational Health & Safety within 7 days of identifying the lead level. The Notifiable Occupational Diseases form for Alberta can be found on the Alberta Open Government Portal and then searching for "Notifiable Occupational Diseases" in Publications.

Introduction

- Lead is a heavy metal with both acute and chronic toxicity.
- Environmental lead exposure has been progressively decreasing since the 1970s due to public health measured to remove lead from residential paint, plumbing, and gasoline.
- Lead has no physiologic role in the body and lead levels as low as 0.17 umol/L have been associated with decreased IQ in young children. For this reason, there is no lead level which is considered "safe."

Pathophysiology

- There are three primary ways in which lead causes toxicity:
    1. Binding to proteins which affects the structure and function of several enzymes, receptors, and structural proteins.
    2. Mimicking other divalent cations (e.g. Ca^{2+}, Mg^{2+}) causing interference with calcium signalling and enzymes requiring calcium or magnesium co-factors.
    3. Altering DNA replication due to impaired DNA methylation.
- Lead causes multi-organ dysfunction with neurologic, hematologic, and gastrointestinal manifestations being most common.
    1. Disrupted calcium signalling impairs neurotransmission and adversely effects brain development.
    2. Inhibition of several enzymes involved in heme synthesis leads to impaired RBC production. Increased membrane fragility and hemolysis further contributed to anemia.
    3. Impaired GI motility leads to constipation, colicky abdominal pain, and anorexia.
- Chronic lead exposure is also associated with chronic kidney disease and interstitial fibrosis.

Clinical Manifestations

- Symptoms of mild lead toxicity are non-specific and include fatigue, difficulty concentrating, impaired cognition, irritability, anhedonia, headaches, impaired fertility, and hypertension.
- More severe symptoms are typically only seen with lead levels > 3.38 umol/L. Symptoms include:
    - Encephalopathy (Altered mental status, seizures, papilledema, optic neuritis, coma)
    - Motor predominant peripheral neuropathy (Wrist drop, foot drop)
    - Colicky abdominal pain
    - Microcytic Anemia
    - Acute renal dysfunction, Fanconi-like syndrome

Diagnostic Testing

- Whole blood lead level is the preferred measure of lead exposure. Blood lead levels are generally most reflective of the last 3 to 6 months of exposure, but do not reflect cumulative lifetime exposure.
    - Obtaining a lead level is recommended for any patient with a significant exposure history or symptoms potentially attributable to lead.
    - Lead level screening is recommended every 6 months for patients with high-risk occupations.
    - For patients with retained bullets, lead level screening is recommended monthly for the first three months after the injury, followed by annually once levels are stable.
- Blood lead level reference values are listed below. The lower reference range for young children is due to evidence of impaired neurologic development in children with lead levels ≥ 0.17 umol/L.

Demographic	Reference Range
Age < 6 years	< 0.17 umol/L
Age > 6 years	< 0.50 umol/L

- Complete blood count, electrolytes, creatinine, liver enzymes, and urinalysis are recommended in patients with an elevated lead level to assess for end-organ injury.
- Radiographs are indicated if an ingested foreign body or retained bullet is suspected.
- Any patient with lead toxicity and an altered level of consciousness or seizures should have neuroimaging to assess for signs of cerebral edema.

Management

- Most adults with lead levels < 3.38 umol/L and children with lead levels < 2.17 umol/L are expected to have mild or no symptoms. In these patients, chelation is generally not recommended. Management consists of identifying the source of lead, reducing further exposure, and trending lead levels.
    - Patients should undergo a thorough review of potential lead exposures.
    - In Alberta, patients with occupational exposures must be reported to Occupational Health & Safety as a notifiable occupational disease.
    - Anyone with an occupational or hobby exposures should be encouraged to use appropriate personal protective equipment and behavioural safety measures (see below) to minimize lead exposure.
    - Lead levels > 1.5 umol/L should be repeated monthly until < 1.5 umol/L, followed by every 3 months until < 0.5 umol/L. Routine lead level screening should continue every 6 months if patient continues to work with lead.
- For symptomatic patients, adults with a lead level > 3.38 umol/L, or children with a lead level > 2.17 umol/L, chelation may be considered on a case-by-case basis.
    - Patients should be assessed in hospital to expedite investigations, lead exposure identification, decontamination if necessary, and initiation of treatment.
    - All cases should be reviewed with a Medical Toxicologist to determine the need for chelation and the most appropriate treatment regimen.
    - Severe manifestations of lead encephalopathy including seizures and increased intracranial pressure are managed as per standard seizure and ICP management guidelines in addition to chelation therapy.
- Special Circumstances:
    - <u>Gastrointestinal Lead Foreign Body</u>
        - Expedited removal of the foreign body from the GI tract is recommended. All patients should be assessed in hospital and have lead levels trended until the foreign body is removed.
        - Whole bowel irrigation and/or endoscopic removal should be considered on a case-by-case basis.
    - <u>Retained Bullets</u>
        - Release of lead from retained bullets generally decreases over time as the bullet becomes encapsulated in fibrous tissue.
        - Lead levels should be trended monthly for the first three months and annually thereafter.
        - If lead levels are rising, surgery should be consulted to consider removal.

Safety Measures to Reduce Lead Exposure	
Personal Protective Equipment	Modifiable Behaviours
Appropriate PPE to prevent lead exposure will depend on the tasks being performed, but should generally include: • Protective clothing such (e.g. coveralls) • Respiratory Protection • Gloves (were appropriate)	• Switch to non-lead-based products if possible • Use designated work clothes that are changed and laundered at work • Immediately change clothes and shower after returning home from work • Separately store and launder any clothes worn to and from the workplace • Do not bring eat, drink or smoke in any workspace which could be contaminated • Wash hands thoroughly before eating, drinking, or smoking

Summary

- Chronic lead exposure is associated with non-specific neurocognitive symptoms and impaired cognitive development in children.
- Acute lead toxicity is characterized by encephalopathy, cerebral edema, seizures, gastrointestinal symptoms, and microcytic anemia.
- Most asymptomatic patients with elevated lead levels can be managed with identification of the lead source, removal from the exposure, and trending of lead levels.
- Chelation is generally recommended for patients with severe symptoms, adults with a lead level > 3.38 umol/L, or children with a lead level > 2.17 umol/L. The decision to proceed with chelation and most appropriate chelation regimen should be made in consultation with Medical Toxicology.

References

1. Garcia RC, Snodgrass WR. Lead toxicity and chelation therapy. Am J Health Syst Pharm. 2007 Jan;64(1):45-53.
2. Kershner AK, Tobarran N, Chambers A, Wills BK, Cumpston KL. Retained bullets and lead toxicity: a systematic review. Clin Toxicol. 2022 Oct;60(10):1176-1186.
3. Marcus AH. Multicompartment kinetic models for lead: linear kinetics and variable absorption in humans without excessive lead exposures. Environ Res. 1985 Apr;36(2):459-72.
4. St Clair WS, Benjamin J. Lead intoxication from ingestion of fishing sinkers: a case study and review of the literature. Clin Pediatr. 2008 Jan;47(1):66-70.

The Clinical Pharmacology (CP) physician consultation service is available Mon-Fri, 8am-5pm, excluding stat holidays. The on-call physician is listed in ROCA on the AHS Insite page. CP consultations are also available through Netcare e-referral, Specialist Link, and RAAPID. You can also find us in the Alberta Referral Directory (ARD) by searching "Pharmacology" from the ARD home page. Click HERE for more details about the service.

The Poison and Drug Information Service (PADIS) is available 24/7 for questions related to poisonings. Please call 1-800-332-1414 (AB and NWT) or 1-866-454-1212 (SK). Information about our outpatient Medical Toxicology Clinic can be found in Alberta Referral Directory (ARD) by searching "Toxicology" from the ARD home page.

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