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Efficacy and Safety of NBMI, a Novel Chelator for the Treatment of Childhood Lead Poisoning

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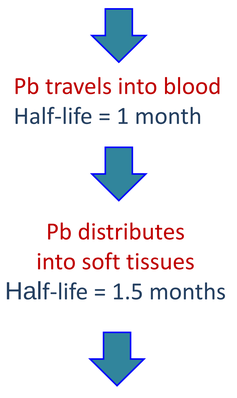
Opportunity

Introduction

Lead (Pb) is a heavy metal that exhibits numerous deleterious effects on the human physiology, especially in children. Pb exposure leads to developmental delays, disruption of blood synthesis, nephropathy, anorexia, and abdominal pain. More importantly, Pb is stored in bones and is released during life events (Figure 1), such as growth and pregnancy, posing life-long and transgenerational threats. Therefore, it is necessary to administer chelating agents that can bind and safely remove Pb from the body. However, current Pb chelators are not able to effectively penetrate into the bones (Table 1). N,N'-bis(2-mercaptoethyl)isophthalamide (Figure 2) is a novel thiol-containing lipid-soluble agent with the unique ability to cross the cell membrane and chelate heavy metals (including Pb) inside the cell. Here, I present a preclinical drug study that tests the efficacy and safety of NBMI for Pb-chelation therapy in rats. These results indicate that NBMI could potentially be a viable chelator for children with Pb-poisoning. In the future, we hope to present non-inferiority trials comparing NBMI to current chelators and help advance NBMI to clinical development for children with Pb-poisoning.

Chelator	Pros	Cons
CaNa2EDTA	• Effective against acute Pb exposure • Removes Pb from soft tissues	• Cannot pass through cell membrane • Severe hepatotoxicity • Mostly intravenous injection
DMSA	• Effective against acute Pb exposure • Removes Pb from soft tissues • Oral therapy is available	• Cannot pass through cell membrane • Neutropenia
Dimercaprol	• Can pass through cell membrane • Chelates Pb from the bones and tissues	• Only available as deep-muscular injections • Redistribution of Pb from bones to brain • Low therapeutic index
D-penicillamine	• Enhances urinary excretion of Pb • Oral therapy is available	• Severe nephrotoxicity • Cannot be used in children with penicillin allergy

Table 1: Currently Available Chelators

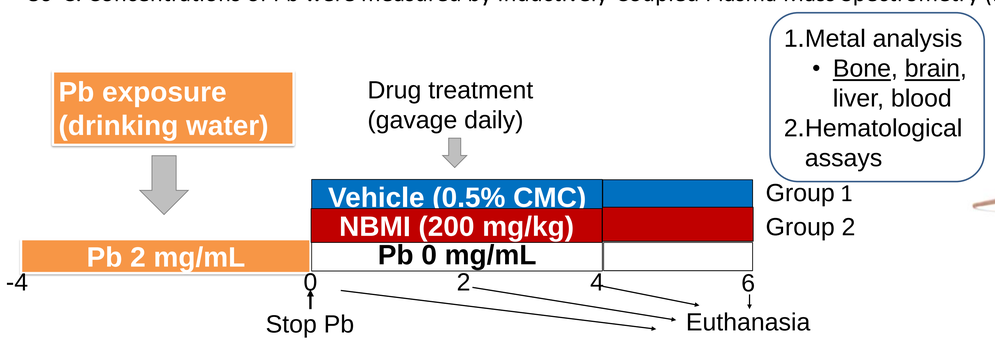


(Figure 1)

Approach

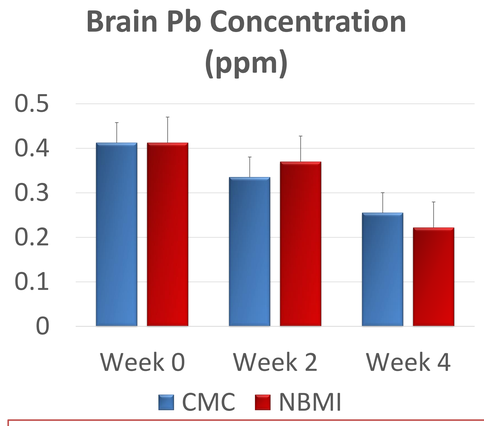
Method

We used 3-week-old weanling Female Sprague-Dawley rats in order to model the underdeveloped physiology of a human child. Rats were exposed to 2 mg/mL of lead acetate *via* drinking water for 4 weeks. At the end of 4 weeks, 6 rats were euthanized for the measurement of baseline tissue metal concentrations. For the rest of the rats, the Pb treatment ended and the water was replaced with regular facility water. On the same day, NBMI treatment (200 mg/kg body weight; administration volume 3 ml/kg) by oral gavage began and lasted for up to 2 weeks (n=3/group), 4 weeks (n=4/group), and 6 weeks (n=4/group). Vehicle group was administered with 0.5% Carboxymethyl Cellulose (CMC) without NBMI for up to 2, 4, or 6 weeks to serve as control. All rats were euthanized by the 6th week and all tissues were collected and frozen at -80^{o}C. Concentrations of Pb were measured by Inductively-Coupled Plasma Mass Spectrometry (Dartmouth University).

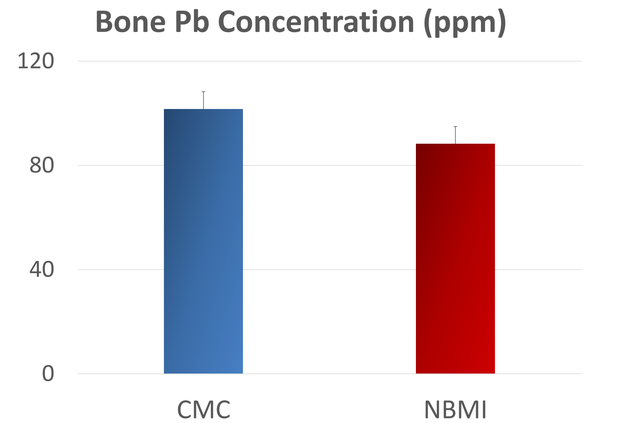


Sprague-Dawley rats
3-wk-old
Female

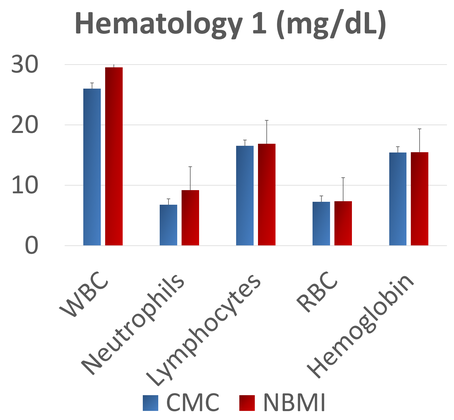
Results

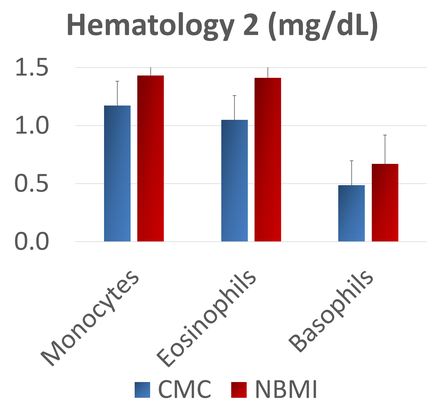


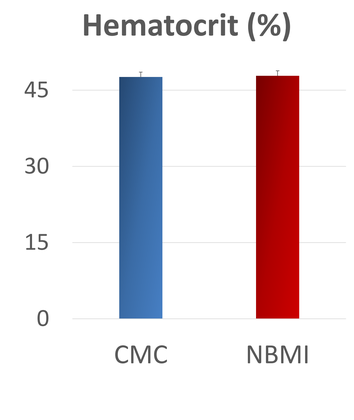
NBMI group trended towards having less Brain Pb content than vehicle group, suggesting possibility of brain chelation



NBMI group trended towards less bone Pb content than vehicle group ($p < 0.05$), suggesting bone chelation







Impact

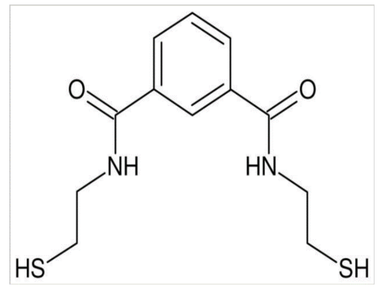
No significant differences in any hematological profiles including hematocrit comparing NBMI to vehicle group, proving NBMI's safety and tolerability

Value Proposition

- The unique feature about my innovation/research is the drug efficacy study design for a novel drug that may potentially be beneficial for lead poisoning.
- This addresses the problem of the lead Poisoning that is prevalent in children across the United States, such as in Flint, Michigan.

Future Studies

- More measurements of brain and bone chelation using ICP-MS
- Compare chelation efficacy of NBMI against conventional chelators, such as DMSA, and explore co-administration possibilities
- Explore roles of NBMI in chelation of other heavy-metals, such as chelation of copper which can help people with Wilson's Disease



(Figure 2): N,N'-bis(2-mercaptoethyl)isophthalamide

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Acknowledgement

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