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Please cite this article as:

Sayed Mahdi Marashi et al., Removal of phosphine from the bloodstream using hemoperfusion device consisting of metal-promoted carbon nanotubes. *Hypothesis* 2013, **11**(1): e6, doi:10.5779/hypothesis.v11i1.345

Removal of phosphine from the bloodstream using hemoperfusion device consisting of metal-promoted carbon nanotubes

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Received: 2013/05/08; Accepted: 2013/09/24;
Posted online: 2013/12/13

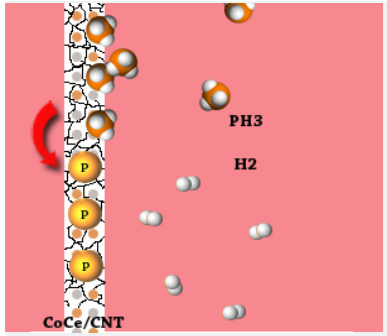

Illustration provided by Authors

ABSTRACT Aluminum phosphide (AlP) self-poisoning leads to severe toxicity with a high mortality rate in developing countries. No effective methods to treat severe AlP poisoning have been identified to date. It is surmised that toxic levels are blood concentrations above 1.067 mg%. In some instances of toxic exposure, charcoal hemoperfusion is an effective way to remove the poisonous substances from the circulation. However, it seems that adsorption of phosphine gas (PH_3), the toxic ingredient of AlP, by activated charcoal is not adequate and, therefore, it is unlikely that charcoal hemoperfusion would be effective in treating AlP poisoning. Carbon nanotubes (CNTs) are appropriate for supporting metal nanoparticles. Cobalt (Co) and cerium (Ce) nanoparticles supported on CNTs (CoCe-CNTs) have catalytic properties in the phosphine decomposition reaction. We hypothesize that the substitution of charcoal with CoCe alloy supported on CNTs in hemoperfusion cartridges can be used to remove PH_3 from the plasma compartment to cure ALP poisoning. We believe it is possible for this novel extracorporeal technique to become an efficient method for PH_3 removal, enhancing the patient's chance of survival.

INTRODUCTION ***Aluminum phosphide poisoning*** Because of the accessibility, severe toxicity and low price of aluminum phosphide (AlP), AlP self-poisoning as a method of suicide is on the rise, with a high mortality rate in developing countries[1]. In fact AlP is a grain fumigant and phosphine gas (PH_3), the toxic ingredient, can easily be released from its weak bonds in the aluminum-based compound by contact with air moisture or acidic stomach contents[1,2]. After inhalation of the phosphine gas or ingestion of the aluminum phosphide compound, PH_3 is absorbed through the mucosal surface of the gastrointestinal tract or the respiratory system, respectively[1]. The exact mechanism of action at the cellular level is obscure; however, cytochrome c oxidase inhibition, oxidative stress, corrosive effects and loss of vascular integrity are proposed as possible mechanisms of action[3,4,5,6].

Acute AlP poisoning is a serious medical emergency. At the present time, medical toxicologists have no effective treatment protocol to overcome severe AlP poisoning and its mortality rates range from 37% to 100%[6,7]. As Chugh *et al.* demonstrated that survivors have PH_3 blood levels less than 1.067 ± 0.16 mg%, it is surmised that the possible toxic levels are concentrations above these limits[1,8]. Decreases in systemic absorption or enhanced elimination methods would be effective ways to alleviate systemic toxicity.

Enhance elimination and extracorporeal blood removal techniques Oral administration of activated charcoal can reduce the systemic absorption of many toxins from the gastrointestinal tract via irreversible binding. Charcoal hemoperfusion clearance exceeds that of other extracorporeal elimination methods (such as hemodialysis or exchange transfusion) if the toxin is not bound by plasma proteins and is adsorbed to a significant extent by activated charcoal[9]. Unfortunately, because it is not known (i) the extent to which activated charcoal binds AlP[10] and (ii) the efficacy of inhibition of PH_3 release by such binding, the administration of oral activated charcoal or charcoal hemoperfusion might not be of use. In addition, the efficacy of oral activated charcoal or charcoal hemoperfusion in the treatment of AlP poisoning has not yet been ascertained in clinical trials[11,12].

Catalytic decomposition of PH_3 over CoCe-promoted carbon nanotubes Phosphine is a nucleophile and therefore has reducing properties, tending to form coordinate bonds with metals[2,13]. Li *et al.*[14] have recently reported on the catalytic decomposition of PH_3 using cobalt (Co) and cerium (Ce) nanoparticles supported on carbon nanotubes (CoCe/CNTs). In a catalytic activity test they showed that cobalt phosphide (CoP) is the only, and the most active, phase formed on

CoCe-promoted carbon nanotubes. In fact phosphorus atoms migrate onto the CoCe nanoparticles dispersed on CNTs. Moreover, the CoCe/CNTs remained unwavering during the PH_3 decomposition reaction.

HYPOTHESIS Based on this background, we hypothesize that CoCe/CNTs hemoperfusion could be used to eliminate PH_3 from the circulation. Adding the CoCe/CNTs-containing cartridge to the hemodialysis machine circuit will allow it to combine with and remove PH_3 from the bloodstream. This novel extracorporeal elimination method could be used in the first hours of severe AlP poisoning. We believe that CoCe/CNTs hemoperfusion can successfully remove the poison from the circulation to alleviate systemic toxicity.

SUPPORTING ARGUMENTS Despite advances in human knowledge, the toxicokinetics of AlP and PH_3 are not clearly defined. We don't know how rapid absorption or transportation of PH_3 occurs. Nonetheless, there are some data supporting the possible correlation of blood PH_3 levels with the severity of clinical toxicity[1]. In fact, all vital organs may be affected. Development of cardiac dysrhythmia and refractory shock coinciding with metabolic acidosis of increasing severity occurs within the first few hours, and is associated with poor prognosis[1,6]. Therefore, all cases of acute AlP poisoning should receive medical care as serious emergencies. There is no effective treatment protocol or specific antidote and, despite advances in critical care, mortality ranges from 37% to 100%[7].

Some authors consider gastric lavage with potassium permanganate followed by activated charcoal and vegetable oil as the first interventions[1,11,15]. However, others consider that gastric lavage would not be of use and that it may increase toxicity[2,16]. Furthermore, it is not known to what extent activated charcoal binds AlP[10] or the likely efficacy of inhibition of PH_3 release by binding AlP to activated charcoal. Marashi *et al.* recently published their opinion that administration of oral activated charcoal is not of benefit[12].

Although we don't know the exact toxicokinetics of PH_3, clinical experiments support rapid absorption via the respiratory system or gastrointestinal tract to reach the circulation. These experiments suggest that, in acute AlP poisoning, scavenging PH_3 from the bloodstream may enhance the chance of achieving more desirable results from treatment.

Hemoperfusion involves the circulation of anticoagulated blood through an adsorbent-filled column[17]. The most commonly used adsorbent to treat poisoning is activated charcoal, which can remove soluble toxins with molecular weights ranging from 100 to 40,000 daltons to a significant extent[9,18]. The molecular weight of PH_3 is about 34 daltons; therefore, it is not adsorbed efficiently with charcoal hemoperfusion.

As mentioned above, CoCe-promoted CNTs effectively catalyze the PH_3 decomposition reaction. Thus, utilizing CoCe/CNTs as adsorbent particles within a hemoperfusion device is technically possible. After removal of PH_3 from the bloodstream, we would expect alleviation of the symptoms of AlP poisoning. After removal of PH_3 from the plasma compartment, a positive gradient may develop for the discharge of PH_3 from organ tissues to the plasma. However, we have no evidence about organs that may concentrate PH_3.

CONCLUSION The advantages of establishing an effective technique for acute AlP poisoning treatment in humans are great and could save certain critically poisoned patients. However, a number of challenges are present. The safety of CoCe/CNTs hemoperfusion and its effects on the cellular matrix of blood and plasma electrolytes need to be explored further. Our hypothesis would reveal a new path to clinical toxicologists for the treatment of acute AlP poisoning, which would also improve the outcome for patients after this lethal toxicity.**H**

CONFLICTS OF INTEREST Authors declare no conflicts of interest.

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