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

Sayed Mahdi Marashi, Mohammad Majidi, Mehran Sadeghian, Reza Abdi, Hassan Sarhaddi, Zeynab Nasri Nasrabadi

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 (PH₃), 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 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 PH₃ from the plasma compartment to cure AlP poisoning. We believe it is possible for this novel extracorporeal technique to become an efficient method for PH₃ 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. In fact AlP is a grain fumigant and phosphine gas (PH₃), 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. After inhalation of the phosphine gas or ingestion of the aluminum phosphide compound, PH₃ is absorbed through the mucosal surface of the gastrointestinal tract or the respiratory system, respectively. The exact mechanism of action at the cellular level is obscure; however, cytochrome c oxidase inhibition, oxidative stress, correlative effects and loss of vascular integrity are proposed as possible mechanisms of action.

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%.

As Chugh et al. demonstrated that survivors have PH₃ blood levels less than 1.067 ± 0.16 mg%, it is surmised that the possible toxic levels are concentrations above these limits. 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. Unfortunately, because it is not known (i) the extent to which activated charcoal binds AlP and (ii) the efficacy of inhibition of PH₃ release by such binding, the administration of oral activated charcoal or charcoal hemoperfusion in the treatment of AlP poisoning has not yet been ascertained in clinical trials.

Catalytic decomposition of PH₃ over CoCe-promoted carbon nanotubes Phosphine is a nucleophile and therefore has reducing properties, tending to form coordinate bonds with metals. Li et al. have recently reported on the catalytic decomposition of PH₃ 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 AIP 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 AIP 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$^1$. Therefore, all cases of acute AIP 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%$^1$.

Some authors consider gastric lavage with potassium permanganate followed by activated charcoal and vegetable oil as the first interventions$^{11,111}$. However, others consider that gastric lavage would not be of use and that it may increase toxicity$^{12}$. Furthermore, it is not known to what extent activated charcoal binds AIP$^9$ or the likely efficacy of inhibition of PH$_3$ release by binding AIP 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 AIP 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$^{12}$. The most commonly used adsorbent to treat poisoning is activated charcoal, which can remove soluble toxins with molecular weights ranging from 10 to 40,000 daltons to a significant extent$^{13}$. 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 AIP 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$_3$. We don't know if PH$_3$ could be carried back to the lungs.

**CONCLUSION** The advantages of establishing an effective technique for acute AIP 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 AIP poisoning, which would also improve the outcome for patients after this lethal toxicity.

**CONFLICTS OF INTEREST** Authors declare no conflicts of interest.

**ABOUT THE AUTHORS** Sayed Mahdi Marashi is a forensic medicine and clinical toxicology specialist from the legal medicine research center in Tehran, Iran. He is currently the supervisor of medical commissions of Sistan and Baluchestan province in cooperation with Reza Abidi and Hassan Sarhadi. Mohammad Majidi is also a forensic medicine and clinical toxicology specialist who is working in a toxicology ward of Urmia University of Medical Sciences. Mehran Sadeghian and Zeynab Nasiri-Nasrabadi are residents of forensic medicine and pediatrics, respectively, at Tehran University of Medical Sciences, who are both working with Dr. Sayed Mahdi Marashi to propose novel treatment strategies in the management of acute aluminum phosphate poisoning.

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