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Response to Professor Rumboldt's reaction to our letter on hydroxyethyl starch use in managing aluminium phosphide poisoning

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We appreciate Professor Rumboldt's interest in our article and his caring comments (1). As he said, most published articles propose mitochondrial damage as the mechanism of phosphine toxicity; in fact, this hypothesis has been repeated in almost every medical article on aluminium phosphide (AlP) poisoning since the 1990s (2-4). To our knowledge, it has not been backed up by any studies in humans. Moreover, *in vitro* studies indicate incomplete inhibition of the mitochondrial function (5).

As we know, the main problem with severe AlP poisoning is refractory hypotension, which is almost always associated with severe refractory metabolic acidosis and fatal prognosis (6). There is a general consensus that the only possible management is supportive. However, despite advanced intensive care strategies, mortality rates vary between 24 and 66 % within the first few days (7, 8). This urged us to ask ourselves the following:

1. What really happens when phosphine is adsorbed by the gastric or pulmonary epithelium?
2. Is inhibition of cytochrome c oxidase really addressing the toxicity of AlP?
3. Considering the high mortality rate, are the current treatment protocols justified?

To answer these questions let us review the related pathological events. In our experience, accumulation of serous fluid in the pleural and peritoneal cavities is common. Literature reports congestion of the vital organs as the most prominent finding in autopsy examinations (9, 10). In our opinion, this points to the disruption of vascular integrity as soon as the absorbed phosphine enters the bloodstream. This condition can explain the rapid progress of hypotension, which is usually refractory to treatment with crystalloid solutions and vasopressors. Refractory hypotension leads to circulatory failure and consequently metabolic acidosis. In this condition, cell metabolism will decrease to enhance the chance of cell survival (11). Even though our hypothesis has not yet been tested, it explains every fact about AlP poisoning.

One such fact is that current treatment protocols are not addressing the problem. Almost all of them repeat the ancient errors and often fail to alleviate poisoning symptoms (12-14). We recently evaluated misconceptions such as using of charcoal, gastric lavage with $KMnO_4$ solution, and cardioactive steroids in managing AlP poisoning-induced heart failure (12-14) and decided not to follow these protocols in our patients.

Jaiswal et al. (6) report that 12 of the 14 patients presenting with hypotension died despite intensive care. In our experience, successful treatment of hypotension is usually associated with the improvement of lactic acidosis and patient survival. We propose Voluven® administration (6 % hydroxyethyl starch 130/0.4 in 0.9 % sodium chloride) at doses from 10 to 15 mL kg^{-1} body weight, without concomitant administration of additional doses of bicarbonate at arterial pH>7. However, we can not speak about "no need for administration of additional bicarbonate" at arterial pH <7, as none of our patients had an arterial pH below seven on admission. We would like to make clear that in addition to Voluven we administered normal saline in dosages as high as 4000-5000 mL over the first 24 hours to resuscitate the volume as well as other acceptable treatments such as magnesium sulphate, calcium gluconate, and N-acetyl cysteine. We would also like to make clear that when we as a referral hospital receive our patients, most of them have already received considerable doses of sodium bicarbonate and even vasopressors before admission.

We are agree with Professor Rumboldt that crystalloid solutions are better tolerated than colloidal, but disagree that "they are equally effective plasma expanders" in AlP poisoning treatment. In fact, considering that compromised vascular integrity is the main mechanism of phosphine-induced haemodynamic failure, only high molecular weight plasma expanders can remain in blood vessels.

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In his letter Professor Rumboldt has expressed concern about worsening the patients' prognosis, referring to the article by Hartog et al. "Concerns over use of hydroxyethyl starch solutions" (15). To address his concern, we read this and other articles arguing against the use of HES in critically ill patients (16-20). Most of the concerns raised refer to coagulopathy, acute kidney injury, and increased mortality. Jonville-Bera et al. (16) suggest that HES administration of more than 33 mL kg^{-1} day^{-1}, or the cumulative dose more than 80 mL kg^{-1} may be induce coagulopathy. In our patients, generally lower doses sufficed to overcome refractory hypotension. Therefore, this may not be an important issue. Rioux et al. (17) showed that administration of more than 14 mL kg^{-1} was associated with acute kidney injury in 10 % of patients treated with a 10 % Pentastarch solution (250 kDa/0.45) following cardiac surgery. Considering the high mortality of acute AlP poisoning, we believe that an even higher acute kidney injury rate may be acceptable if this treatment strategy saves the patient's life. Other studies compare 90-day mortality in severe sepsis patients receiving more than 2500 mL of HES *vs*. crystalloid solutions in the first four days of treatment. Myburgh et al. (18) found no significant difference in mortality rates between the treatments; Perner et al. (19) did; whereas Guidet et al. (20) reported that HES product needed less volume (generally more than 1000 mL) and stabilised the haemodynamics more rapidly than normal saline in severe sepsis patients at similar mortality rates. In contrast, administration of 500-1000 mL of Voluven within the first 6-12 hours sufficed to stabilise our patients.

It is only fair to admit, however, that our successful experience with HES solutions in AlP poisoning is limited to only five cases. Considering the poor prognosis of AlP; we believe that more remains to be learned from future randomised trials that would show the specific properties HES. If it proves successful, we could introduce this remedy as an antidote, even if its other uses are contraindicated.

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