Articles You Might Have Missed

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Dunn C, Bird S, Gaspari R. Intralipid Fat Emulsion Decreases Respiratory Failure in a Rat Model of Parathion Exposure. Acad Emerg Med. 2012 19(5):504–509.

Background: Organophosphate pesticide (OP) poisoning is a significant global toxicological problem, treatment has not significantly changed in the past 50 years, and mortality remains high.

Intralipid fat emulsion (IFE) has been used with varying levels of success as treatment for toxicity by lipophilic drugs. Many organophosphate pesticides are lipophilic and it is reasonable to believe that IFE may be an option in OP poisoning.

Research Question: Will intravenous fat emulsion decrease the respiratory depressant effects of a lethal dose of the lipophilic organophosphate agent parathion?

Methods: Using a rat model, parathion toxicity was achieved by instilling parathion directly into the stomach via gastric tube, following sedation with isoflurane. All rats were monitored for end-tidal CO₂, MAP, RR, minute ventilation, pulse rate, and pulse oximetry. Eighteen animals received parathion 54 mg/kg and were then divided into three treatment groups ($n=6$ each). Group 1 (control animals) received parathion alone. Group 2 received 15 ml/kg 20 % fat emulsion at 5, 25, and 45 min post-parathion exposure. Group 3 received the same dose of fat emulsion, but it was delayed until 20, 40, and 60 min post-parathion exposure.

Results: Group 1 control animals showed a steady rate of respiratory decline until apnea and cardiac arrest at 51 min. Group 2 showed a similar pattern with no difference in time to apnea or cardiac arrest (51 min; NS). Group 3 had a prolonged time period until apnea and cardiac arrest compared to controls (95 min; $p=0.002$). There was no difference in mortality among all three groups.

Conclusions: IFE administration at 20, 40, and 60 min after exposure to a lethal dose of parathion partially mitigates the respiratory depressant effects of parathion toxicity. Further research is required prior to concluding that IFE is a medical therapy for OP poisonings in the clinical setting.

Critique: This study is an important step forward in developing a new treatment for organophosphate toxicity. However, there are a few questions and concerns. It was interesting and counter-intuitive that animals with delayed treatment fared better than early treatment. As explained by the authors, this might be due to premature administration of IFE prior to accumulation of significant serum OP concentrations or, more worrisome, increased tissue distribution of the lipophilic OP via the fat emulsion. The authors did not check parathion concentrations before and after treatment with IFE. This may have provided information regarding the action of IFE in this study. Delayed treatment mitigated onset of apnea, but there was no statistical effect on mortality. The small sample size may have limited the ability to detect positive survival effects as the study was powered to demonstrate only a difference of 60 % between treatments. Additionally, the model may have been too severe as all control animals died. IFE is certainly worthy of additional scrutiny and future studies should also include standard therapies (atropine, oximes, and benzodiazepines) to assess how IFE might affect these antidotes.

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Implication for Toxicologists: This study presents the potential step forward in the treatment of OP poisoning with IFE. Organophosphate pesticide toxicity continues to be a significant global health problem and its treatment and management is an area requiring further research.

Pichon N, Dugard A, Clavel M, et al. Extracorporeal Albumin Dialysis in Three Cases of Acute Calcium Channel Blocker Poisoning with Life-Threatening Refractory Cardiogenic Shock. *Ann Emerg Med.* 2012 59(6):540–544.

Background: Calcium channel blocker (CCB) toxicity can be difficult to treat. CCBs are highly protein bound and not ideal candidates for extracorporeal removal via hemodialysis. Molecular Adsorbent Recirculating System (MARS) is a two dialysis membrane system, impregnated with albumin, which has been used to dialyze protein bound drugs. This system selectively filters protein-bound drugs and metabolites from the blood unlike standard hemodialysis.

Research Question: Is MARS effective in CCB overdose?

Methods: This is a case series consisting of three patients (two diltiazem, one verapamil) who presented in refractory cardiogenic shock from massive intentional CCB overdoses. All three cases presented with hypotension, bradycardia, and left ventricular dysfunction. All patients required intubation and mechanical ventilation and were treated with calcium salts, glucagon, and escalating doses of vasopressors. Two patients were treated with high-dose insulin as well. All three cases had metabolic acidosis, elevated lactate levels, and acute renal failure. MARS therapy was started within 12 h of presentation for a total of 4 or 6 h.

Results: The authors report improvements in MAP, lactate levels, and vasopressor requirements while on or following MARS therapy. There also was a decrease in the serum drug and metabolite concentrations. No complications were noted with MARS and all patients survived.

Conclusions: Albumin dialysis with MARS therapy may be clinically useful in patients with sustained hemodynamic instability from CCB toxicity.

Critique: The clinical improvement with MARS therapy in this report is intriguing, but can only be regarded as anecdotal evidence at this time. One limitation to the case series is the level of information given regarding medication dosing and temporality of clinical condition. Were patients truly maximally resuscitated prior to MARS? Some might regard the antidote and vasopressor doses as inadequate and no insulin dose is provided. Decreasing serum levels of parent drug and metabolites is a great metric, but it is unclear if MARS altered the natural toxicokinetic course for this case series. Dialysate drug levels to demonstrate actual drug removal during MARS therapy would be even more convincing.

Implication for Toxicologists: MARS therapy is FDA approved for drug poisonings and may be helpful as an adjunct in refractory CCB toxicity. MARS therapy also has practical hurdles: it is not readily accessible at many healthcare facilities, is costly, and requires special dialysis cartridges. With limited evidence, persuading a nephrologist to utilize MARS therapy may be difficult. Aggressive pharmacological management remains the first-line therapy CCB toxicity. Further research needs to be done on MARS therapy to determine its true efficacy and value.

Erdur B, Tura P, Aydin B, et al. A Trial of Midazolam Vs Diphenhydramine in Prophylaxis of Metoclopramide-Induced Akathisia. *Am J Emerg Med.* 2012 30:84–91.

Background: Metoclopramide is commonly used to treat nausea, vomiting, and headaches. While effective, akathisia is a common and noxious adverse effect. Concomitant diphenhydramine or benzodiazepine administration has been suggested to prevent akathisia, but there is limited evidence to support this recommendation.

Research Question: Does co-administration of diphenhydramine or midazolam with metoclopramide prevent akathisia?

Methods: This was a prospective, randomized, double-blinded controlled trial performed in an urban emergency department on adult patients who presented with nausea/vomiting or vascular type headaches. The primary outcome was the occurrence of akathisia. Secondary outcome was the occurrence of sedation. There were 225 enrollees, divided into three treatment groups ($n=75$ each). Group 1 received 10 mg metoclopramide plus 1.5 mg midazolam. Group 2 received 10 mg metoclopramide plus 20 mg diphenhydramine and group 3 received 10 mg metoclopramide and placebo. The Prince Henry Hospital Rating Score of Akathisia, a modified Ramsay Sedation Scale, and vital signs were performed at 0, 15, 30, 45, and 60 min posttreatment. Data were analyzed using standard deviations, percentages, χ^2 , and t tests.

Results: Midazolam, but not diphenhydramine, significantly decreased the incidence of akathisia (5 vs 21 %; $p=0.004$) compared to placebo. Both midazolam and diphenhydramine had significantly higher sedation scores than metoclopramide alone. There were no adverse hemodynamic or respiratory events that required intervention during this study. No patients returned to the ED with delayed or continued akathisia symptoms.

Conclusions: Co-administered midazolam, but not diphenhydramine, reduced the incidence of metoclopramide-induced akathisia compared to placebo.

Critique: This study was a well-designed randomized, blinded study with a large number of enrollees. However, there are potential issues with the study. For example: How were doses of the treatments selected? Many clinicians would

consider 20 mg of diphenhydramine subtherapeutic, thereby biasing this study arm to failure. Authors infer that there were no delayed adverse events, but the study did not include formal follow-up after discharge to fully substantiate that claim.

The study may have been strengthened by including formal follow-up after ED discharge. Follow-up may have allowed investigators to confirm a lack of delayed onset akathisia and broaden the scope of their study to examine for other treatment benefits. For example, dystonia, an EPS adverse drug effect, can occur up to 48 h after metoclopramide treatment. By extending the study to include follow-up, investigators would have the opportunity to evaluate for potential prophylactic benefit of diphenhydramine to prevent dystonia. Lastly, there is some evidence that the combination of metoclopramide and diphenhydramine improves headache outcome, so the combination therapy might have been of value as a treatment group in the study.

Implication for Toxicologists: This study supports the use of midazolam to decrease the incidence of metoclopramide-induced akathisia. Toxicologists may recommend midazolam to prevent akathisia, but any recommendation should also include monitoring for excessive sedation.

Reini SA, Forthergill DM, Gasier HG, et al. Propranolol's Potential to Increase Survival Time in a Disabled Submarine. *Aviat Space Environ Med.* 2012 83(2):131–135.

Background: In the event of a disabled submarine, rescue and survival time is limited in part because of carbon dioxide (CO₂) buildup that occurs following metabolic generation in an enclosed space. It is thought that crew members can survive at a CO₂ level of less than 6 % for 7 days with the assistance of CO₂ scrubbing canisters. There are no other current technical methods to reduce CO₂ accumulation in a closed setting. Propranolol has previously been shown to reduce CO₂ production (VCO₂) in work conditions and may be of value in the submarine accidents.

Research Question: Does twice daily administration of 40 mg propranolol over 72 h decrease resting metabolic VCO₂ in healthy men?

Methods: Eight healthy volunteer men participated in this randomized, placebo-controlled, double-blinded crossover study. Volunteers received 40 mg propranolol or placebo twice daily for 72 h; 96 h later, the process was repeated. Height, weight, resting heart rate, MAP, cardiac output, respiratory rate, VO₂, VCO₂, and respiratory exchange ratio (RER) were recorded twice daily. Linear regression and paired *t* tests were used to analyze data.

Results: Propranolol significantly reduced mean VCO₂, MAP, and HR when compared to placebo (*p*<0.001). Propranolol decreased mean resting VCO₂ by 6.5 %. No differences were noted in VO₂, RR, or RER between placebo and propranolol. Five out of the eight subjects reported feeling lethargic during the 72-h propranolol phase. No side effects were noted from placebo.

Conclusions: Investigators estimate that VCO₂ reduction in the propranolol group would add an additional 11 h to the crew member's survival time in a disabled submarine. Propranolol may offer a safe and practical method to increase survival and/or rescue time in a disabled submarine event.

Critique: This study demonstrates a potential benefit from a unique use of a well-known medication: improvement in survival time during a disabled submarine event. While this study showed a positive treatment effect, it has limitations. First, this study did not simulate actual conditions of a disabled submarine such as psychological stress, ambient temperature changes, and limited water access that would influence VCO₂ production. Importantly, VCO₂ was monitored at rest in the study subjects, not while they were exerting themselves as expected in a disaster situation. Secondly, potential treatment adverse effects might negatively impact crew members in a real emergency. Over half of the volunteers reported some amount of lethargy, likely a side effect of propranolol. Lethargy could reduce critical thinking and ability to perform manual labor that might be required to survive a disabled submarine event.

Implication for Toxicologists: This study is an interesting prospective on a potential use for propranolol in an emergency situation. Further research is indicated to elaborate the value of propranolol in this situation.