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Magnesium sulfate and calcium channel blocking drugs as antidotes for acute organophosphorus insecticide poisoning – a systematic review and meta-analysis

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Abstract

Introduction: Treatment of acute organophosphorus or carbamate insecticide self-poisoning is often ineffective, with tens of thousands of deaths occurring every year. Researchers have recommended the addition of magnesium sulfate or calcium channel blocking drugs to standard care to reduce acetylcholine release at cholinergic synapses.

Objective: We aimed to review systematically the evidence from preclinical studies in animals exposed to organophosphorus or carbamate insecticides concerning the efficacy of magnesium sulfate and calcium channel blocking drugs as therapy compared with placebo in reducing mortality or clinical features of poisoning. We also systematically reviewed the evidence from clinical studies in patients self-poisoned with organophosphorus or carbamate insecticides concerning the efficacy of magnesium sulfate and calcium channel blocking drugs as therapy compared with placebo, in addition to standard therapy, in reducing mortality, atropine requirement, need for intubation and ventilation, and intensive care unit and hospital stay.

Methods: We performed a systematic review for articles on magnesium sulfate and calcium channel blocking drugs in organophosphorus or carbamate insecticide poisoning using PubMed and China Academic Journals Full-text (Medicine/Hygiene Series) databases and keywords: "organophosphorus or organophosphate poisoning", "cholinesterase inhibitor poisoning" OR "carbamate poisoning" AND "magnesium", "calcium channel blocker", or generic names of different calcium channel blocking drugs. Review of titles and abstracts revealed 2262 papers of potential relevance. After review of the

full papers, a total of 19 papers relevant to the question were identified: five preclinical studies, nine case reports or small case series, and five clinical studies and trials. We also obtained primary data from three unpublished clinical trials of magnesium sulfate, providing data from a total of eight clinical studies and trials for analysis. All studies were of organophosphorus insecticides; no studies of carbamates were found. No pre-clinical or clinical studies of calcium channel blocking drugs and magnesium sulfate in combination were found. We extracted data on study type, treatment regimens, outcome, and side effects. Pre-clinical studies: Two rodent studies indicated a benefit of calcium channel blocking drugs treatment on mortality if given before or soon after organophosphorus exposure, in addition to atropine and/or oxime. In poisoned minipigs, treatment with magnesium sulfate after organophosphorus insecticide poisoning reduced cholinergic stimulation and hypertension. Of note, magnesium sulfate further suppressed serum butyrylcholinesterase activity in one rat study. Observational clinical studies: Calcium channel blocking drugs and magnesium sulfate have been used to treat cardiac dysrhythmias and hypertonic uterine contractions in organophosphorus poisoned patients. A small neurophysiological study of magnesium sulfate reported reversion of neuromuscular junction effects of organophosphorus insecticide exposure. Comparative clinical studies: Only four of eight studies were randomized controlled trials; all studies were of magnesium sulfate, of small to modest size, and at substantial risk of bias. They included 441 patients, with 239 patients receiving magnesium sulfate and 202 control patients. The pooled odds ratios for magnesium sulfate for mortality and need for intubation and ventilation for all eight studies were 0.55 (95% confidence interval [CI] 0.32-0.94) and 0.52 (95% CI 0.34-0.79), respectively. However, there was heterogeneity in the results of higher quality phase III randomized controlled trials providing more conservative estimates. Although a small dose-escalation study suggested benefit from higher doses of magnesium sulfate, there was no evidence of a dose effect across the studies. Adverse effects were reported rarely, with 11.1% of patients in the randomized controlled trials receiving the highest dose of magnesium sulfate requiring their infusion to be stopped due to hypotension.

Conclusions: Both preclinical and clinical data suggest that magnesium sulfate and calcium channel blocking drugs might be promising adjunct treatments for acute organophosphorus insecticide poisoning. However, evidence is currently insufficient to recommend their use. Mechanistic and large multi-center randomized controlled trials testing calcium channel blocking drugs and magnesium sulfate are required to provide the necessary evidence, with careful identification of the insecticides ingested and measurement of surrogate markers of toxicity, including butyrylcholinesterase activity.

Keywords: Calcium channel blocking drugs; clinical trials; magnesium sulfate; pesticide; pre-clinical research.

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