REPURPOSING TO SPEED CHEMICAL AND BIOLOGICAL MEDICAL COUNTERMEASURE DISCOVERY AND DEVELOPMENT

The Effect Of Time And Sequence On Organophosphate And Opioid Antidote Administration After Exposure To Organophosphates

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Drug-drug interactions occur when one drug alters the pharmacological effect of another causing additive or antagonistic interactions. The net result of a drug interaction may be a response that is greater than anticipated, a decrease in the effectiveness of one or both drugs, or the appearance of an unanticipated adverse effect. For drugs that require a rapid response (i.e. treatment for nerve agent or opioid poisoning) knowing the optimal timing and sequence of treatment with multiple antidotes is critical to obtain maximum efficacy and to avoid adverse drug-drug interactions. Organophosphate (OP) and opioid poisoning can often present similar symptoms which can confound the decision for proper treatment when the exposure agent is unknown. Therefore, co-administration of antidotes for both organophosphate and opioid poisoning could be advantageous for the patient. However, it is unclear if co-administration of the two treatments will have additive or antagonistic results for one or more of the drugs. Additionally, the timing and sequence of administration for optimal efficacy has not been investigated. In this study the pharmacokinetics and therapeutic efficacy of concomitant administration of atropine/2-pyridine aldoxime methyl chloride (2-PAM) and naloxone, used for the treatment of nerve agent exposure and opioid exposure, respectively, was evaluated in guinea pigs. Pharmacokinetic parameters for all drug combinations showed no observable difference in the plasma PK curves due to the addition of naloxone suggesting no discernible drug-drug interactions. There was, however, a 58% decrease in the distribution half-life of naloxone when administered together with the OP antidotes. When evaluating the timing and sequence of antidote administration animals treated with 2-PAM/atropine/midazolam displayed the best survivability after OP exposure. The presence of naloxone did not appear to effect survivability in any of the treatment groups. Studies are ongoing to assess the effects of timing and sequence of antidote administration after opioid exposure.

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