WHAT CAN WE LEARN FROM THE MANAGEMENT OF OP INSECTICIDE POISONING TO OPTIMIZE TREATMENT FOR NERVE AGENT POISONING?

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Background: Effectiveness of antidote therapy in nerve agent poisoning cannot be assessed in human beings for ethical reasons. Clinical course of poisoning by organophosphate (OP) pesticides follows the same principles as by nerve agents. Accordingly, it appeared rational to follow antidote effects as close as possible in OP pesticide-poisoned patients and assess, whether the findings correspond to those derived from experimental studies, thus allowing rational extrapolation to nerve agent poisoning. Methods: In a clinical trial, obidoxime was administered to severely OP-poisoned patients in addition to atropine as early as possible and as long as reactivatability of acetylcholinesterase (AChE) was anticipated. Red blood cell (BRC)-AChE activity, reactivatability of patient's RBC-AChE (incubation of diluted patient's RBCs with 100 µmol/l obidoxime in vitro), plasma level of obidoxime, and neuromuscular transmission were monitored. The data were compared with results derived from reactivation experiments on phrenic-diaphragm preparations of mice as well as human RBC-AChE exposed to various Ops and various oximes. From these results a strategy for oxime treatment and monitoring of nerve agent poisoning was derived. Furthermore, atropine amounts used were registered as well as its pharmacokinetics during poisoning and correlated with the cholinesterase status of the patients. Results: In OP-poisoned patients, inhibited non-aged RBC-AChE could be reactivated by obidoxime concentrations found to be effective in experimental studies. The degree of reactivation achieved in the patients correlated well with theoretical values, derived from calculations basing on plasma levels of obidoxime, paraoxon, RBC-AChE activity in vivo and reactivatability of patient RBC-AChE. Reactivation (RBC-AChE) and improvement of neuromuscular function in the patients correlated well and, when RBC-AChE activity exceeded some 30 % of normal, neuromuscular transmission was hardly impaired. Comparably, in phrenic-diaphragm preparations paraoxon-induced neuromuscular failure was antagonized by oximes, when an increase of muscle AChE activity exceeding roughly 40 % of normal was achieved. This close correlation of neuromuscular function and AChE activity of muscle and RBCs points to RBC-AChE as a suitable surrogate parameter. Accordingly, effectiveness of oximes in nerve agent poisoning may be predicted from in vitro studies with human RBC-AChE, thus preventing from misinterpretations due to species differences of AChE. Studies conducted with nerve agents and human RBC-AChE revealed that the experimental compound HLö7 appears to be the most appropriate reactivator (broadest spectrum, best reactivation properties), followed by HI 6, which also is not yet licensed and available on the common market. Generally, from the commercially available oximes obidoxime appears to be superior to pralidoxime in poisoning by most nerve agents and OP pesticides, especially when used at doses recommended in the product information sheets. Conclusion: Therapeutic benefit of oximes, namely reduced need of artificial ventilation in a mass casualty situation, may be anticipated when effective doses are administered early and long enough. Due to fast ageing of some nerve agents (e.g. soman), oxime therapy has to be initiated as early as possible, at best by administration of autoinjectors by first aid personnel (e.g. fire brigades) when first signs and symptoms arise. Since during a terrorist attack or on a battlefield intoxication is expected to evolve mostly from small amounts of poison, e.g. rarely exceeding 2-5 times LD50, compared to mega-doses used in suicide poisoning, a single i.m. oxime injection may be sufficient. However, several nerve agents that do not show fast ageing may be released after absorption over a longer time from the tissue (e.g. VX) requiring oxime therapy over a longer period. In such cases oximes should be administered by infusion. To assess the time-frame over which oxime treatment is necessary a simple test system could be helpful. To this end reactivatability of RBC-AChE as well as inhibitory activity of patients

plasma could be used. Oxime therapy should be maintained (i) as long as inhibited RBC-AChE is reactivatable. This can be tested in vitro by incubation of patient's plasma with HI 6 (100 µmol/l, 30 min incubation time, 37°C)resulting in reactivation. (ii) Oxime therapy should be maintained as long as inhibitory activity is present in the plasma. Weaning from artificial ventilation should be taken into account when RBC-AChE activity is higher than 30 % of normal, indicating unimpaired neuromuscular transmission. Neuromuscular transmission can be assessed by repetitive stimulation of the ulnaris nerve and recording the muscle compound action potentials at the hypothenar. Generally, huge amounts of atropine are not necessary, but dosing should follow a protocol warranting an early sufficient atropinization e.g. by using a starting dose of 2 mg i.v. followed by an observation period of 5 min. If there is no effect, this dose may be doubled every 5 minutes until muscarinic symptoms relieve. If no reactivation can be achieved atropine infusion at a rate $\leq$ 2 mg/h may maintain sufficient atropinization.