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Development of next generation medical countermeasures to nerve agent poisoning

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Abstract

Medical countermeasures provide a key role in the UK integrated approach to chemical defence and are aimed at preventing or mitigating the effects of exposure to nerve agents. It is UK policy that medical countermeasures will be licensed products. Demonstration of efficacy relies on extrapolation of animal-derived data to man which means that species selection is extremely important. For the foreseeable future it is likely that a combination of pretreatment and therapy will be required to provide protection against nerve agent poisoning. There is a longer-term aspiration to develop a post poisoning-therapy which would reduce the reliance on pretreatment, prevent or mitigate the effects of exposure to all nerve agents and decrease the requirement for three autoinjectors. Immediate therapy comprising physostigmine (0.2 mg/kg), hyoscine hydrobromide (4 mg/kg) and HI-6 (93.6 mg/kg) protected all animals against the lethal effects of a supralethal dose of GD, when given 1 min after nerve agent poisoning in the absence of any pretreatment. In contrast when hyoscine hydrobromide was replaced with hyoscine methyl nitrate most of the animals died within 24 h, whereas when an equal mixture of hyoscine hydrobromide and hyoscine methyl nitrate was used all the animals survived. None of these animals had an intussusception. It would not be possible to deliver these doses of HI-6 to a human from a single autoinjector device. Recent studies have shown that a lower dose of HI-6 (7 mg/kg) which can be delivered via an autoinjector, in combination with physostigmine and hyoscine hydrobromide provides good protection against the lethal effects of a supralethal dose of GD. A number of animals died between 6 and 24 h and had an intussusception. The surviving animals did not begin to regain weight until 48 h after poisoning. In contrast when a mixture of hyoscine hydrobromide and hyoscine methyl nitrate was used, one animal died within 15 min, the other animals all survived, regained weight from 24 h and did not have an intussusception. These studies will now be extended to include other agents and will be taken forward to studies in non-human primates where the incidence of intussusception will be closely monitored.

Keywords: Guinea-pig; Nerve agent; Incapacitation; Lethality; Intussusception; Therapy

1. Introduction

Nerve agents are organophosphate compounds, which act by irreversibly inhibiting peripheral and central acetylcholinesterase (AChE), which is responsible for terminating the action of the neurotransmitter acetylcholine. Inhibition of this enzyme results in a build up of acetylcholine causing over-stimulation of muscarinic and nicotinic receptors producing the characteristic signs of nerve agent poisoning including hypersecretion, convulsions, respiratory distress, coma and death.

Medical countermeasures provide a key role in the UK integrated approach to chemical defence and are

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aimed at preventing or mitigating the effects of exposure to nerve agents. It is UK policy that medical countermeasures will be licensed products and that they must be effective, acceptable, practicable and affordable. There are important differences between the Chemical Defence community and the 'mainstream' pharmaceutical industry in that there are no opportunities to demonstrate efficacy in human subjects. The emphasis for efficacy relies on extrapolation of animal-derived data to man which means that species selection is extremely important. Previous studies have shown that the guinea-pig is the best non-primate model for predicting the efficacy of treatment for nerve agent poisoning in primate species (Dirnhuber et al., 1979; Berry and Davies, 1970; Gordon et al., 1978; Inns and Leadbeater, 1983). It is important that medical countermeasures do not compromise military performance and that they are safe from a regulatory standpoint. Medical countermeasures must be appropriate for use which means that drugs recommended for self- or buddy-aid administration must be easily administered by non-medical service personnel. Medical countermeasures must be affordable with respect to the cost of development and licensing. The deterrent value of good medical countermeasures should not be underestimated and it is important for the morale of service personnel to know that the in-service medical countermeasures are effective.

In the development of medical countermeasures to nerve agent poisoning it is acknowledged that different nerve agent administration routes are likely to have different requirements for effective treatment. There is a limited window of opportunity for the administration of immediate therapy following inhaled agent. The signs of poisoning develop within minutes and if therapy is administered on signs of poisoning and at 15 min intervals, if signs of poisoning persist, it is likely that therapeutic levels of the drugs will remain in the bloodstream after the agent has been absorbed. In contrast, following poisoning by the percutaneous route, the onset of signs will be slower and may not appear for some hours. If therapy is taken on signs and at 15 min intervals thereafter it is likely that the agent will continue to be absorbed after the drug levels have fallen below therapeutic levels and further medical aid and management will be required.

The current UK medical countermeasures for nerve agent poisoning were developed over a number of years. Earlier treatments consisting of P2S pretreatment and P2S and atropine therapy were less effective against poisoning by soman and tabun than other agents (Gordon and Leadbeater, 1977). The P2S tablets were large and would have been difficult for an incapacitated man to swallow. In the 1980s the P2S tablets were withdrawn and P2S was incorporated into an autoinjector with atropine. Later a diazepam tablet was placed in the cap of the autoinjector. At about the same time oral pyridostigmine pretreatment was being developed for issue to the UK services. The concept of carbamate pretreatment for protecting against organophosphate poisoning was introduced by Koster (1946) and the effectiveness of atropine and carbamate pretreatment against soman poisoning was demonstrated later in a number of species (Berry and Davies, 1970). Early studies with pyridostigmine included P2S in the pretreatment; however, in 1976 the decision was made, based on animal studies, to discontinue P2S pretreatment and to develop pyridostigmine as a pretreatment for the UK Services. Pyridostigmine, unlike P2S, was formulated in convenient small tablets that were easier to swallow and were issued to the UK services in 1981. In 1990 diazepam was replaced by the water-soluble prodrug, avizafone, so that all the components of the therapy could be given as a single injection.

The UK services are currently issued with pyridostigmine pretreatment (30 mg) to be taken every 8 h in anticipation of a nerve agent attack and immediate therapy with up to three ComboPens containing atropine sulphate (2 mg) (a muscarinic antagonist), pralidoxime mesylate (30 mg) (P2S; an oxime) and avizafone (10 mg) (a water-soluble prodrug of the anticonvulsant diazepam). The current doctrine for the use of therapy is to administer the first ComboPen on signs of poisoning and at 15 min intervals if signs persist. This combination of pretreatment and therapy protects guinea-pigs (Leadbeater et al., 1985) and non-human primates (Dirnhuber et al., 1979) against the lethal effects of nerve agent poisoning although it is less effective against incapacitation.

For the foreseeable future it is likely that a combination of pretreatment and therapy will be required to provide protection against nerve agent poisoning (Aas, 2004). Refinements to both the pretreatment and therapy are likely to improve the effectiveness of medical countermeasures. The superior efficacy of pretreatment with physostigmine and hyoscine in protecting against nerve agent-induced incapacitation and mortality has been demonstrated in the absence (Wetherell et al., 2002) and presence of immediate therapy (Leadbeater et al., 1985). Inns and Leadbeater (1983) also assessed the efficacy of a number of bispyridinium compounds containing both oxime and other substituents, synthesised by Hagedorn and her colleagues (Oldiges and Schoene, 1970). The inclusion of oximes like HI-6 as part of immediate therapy further enhances protection against a range of agents (Dawson, 1994). In the UK it is proposed to replace the in-service medical countermeasures with