Overcoming apathy in research on organophosphate poisoning

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High rates of pesticide poisoning in developing countries and increasing risk of nerve gas attacks in the West mean effective antidotes for organophosphates should be a worldwide priority

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Organophosphate pesticide poisoning is a leading cause of morbidity and premature loss of life in many developing countries of the Asia-Pacific region. The efficacy of current antidotes is largely unproved, and many other potential antidotes have been developed but are yet to be tested in humans. Meanwhile, preparation for the terrorist use of organophosphate nerve agents is leading to the stockpiling of large amounts of these unproved antidotes to treat mass poisoning. An international collaboration of academia, industry, and military is needed to make a concerted effort to develop and test new treatments that would benefit both groups of patients.

A problem shared is a problem halved?

Countries in the developed and developing world seem to have different priorities in dealing with the public health problem of poisoning. Yet both are making slow progress and ignoring common links. These common links indicate that a collaboration would be of immense benefit to both and that its lack is a needless wasted opportunity.

Western nations are most concerned about terrorist use of chemicals. The sarin nerve gas attack on the Japanese subway and the anthrax postal episode showed how vulnerable we are to terrorist (or military) attack using chemical or biological weapons. A great effort, involving expenditure of around $1bn (£550m, €800m) in the United States alone, is now underway to reduce the risks and consequences of future attacks.[1]

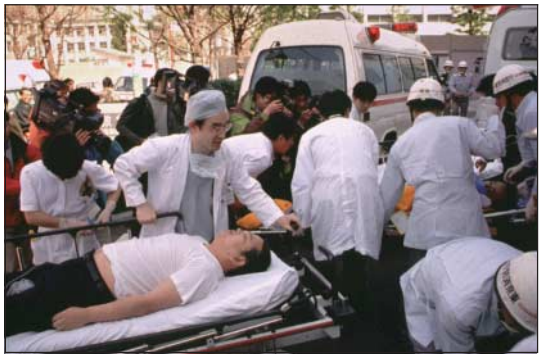
A major concern is the organophosphate chemical weapons or nerve gases, such as sarin, tabun, and VX, which were developed in the middle of the 20th century.[2] They are extremely toxic, with some causing death within minutes of exposure. The proportion of people who die in any future attack will depend on the gas used and the form and level of exposure. Large numbers of poisoned patients are likely to require intensive supportive care, high dose antidotes, and close observation over a prolonged time. These demands will stretch any available health services.

The reasons given for the lack of clinical research on preparing for such an attack have ranged from optimism to denial. Statements such as: "Standard, effective treatment methods for such acute effects are available. The prognosis for patients surviving the initial acute effects from most [organophosphate] nerve agents is very good, suggesting little incentive for research on treatments" show an amazing degree of complacency.[3] Others have argued, however, that the threat is such a concern that new antidotes for chemical weapons should be approved by the US Food and Drug Administration without human safety or efficacy data.[4] The few randomised controlled trials in organophosphate poisoning that have been done suggest that efficacy in animals does not translate into efficacy in humans.[5] Much of this massive expenditure on preparation for nerve agent attacks may be misplaced.

Meanwhile the developing world is coping with a largely hidden tragedy. Poisoning is seldom mentioned as a priority for health research in the developing world. Yet, in some Asian countries, poisoning is a leading cause of premature death.[6] Every year, hundreds of thousands of people are dying from pesticide poisoning.[7 8] Millions more are being treated in overstretched health services, and a substantial number are left with long term disability. Research or programmes to tackle the problem of poisoning in developing countries has been insufficient, particularly for pesticides.[9] Organophosphate poisoning is an important issue for developing countries, accounting for most deaths and disability after exposure to pesticides.[7]

Global failure of antidote development

Thus organophosphates are of worldwide interest. Their toxicity is well understood.[10] Current treatment



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The sarin attack in Japan produced many casualties

for organophosphate poisoning is to give atropine, an oxime such as pralidoxime, and benzodiazepines. However, no evidence exists that either oximes or benzodiazepines are effective at reducing morbidity or mortality in humans.[5] No good quality clinical research has been performed on these antidotes in humans.

Newer, more effective antidotes are needed. The currently recommended antidotes are the tip of a therapeutic iceberg that could be mobilised. Animal studies have shown many beneficial compounds, yet no new treatment has reached the bedside in the past 30 years, and no new treatment is in clinical trials. Potential new treatments identified in animal models include organophosphate hydrolases, which break down organophosphates and speed up reactivation of acetyl cholinesterase; reversible anticholinesterases (such as the carbamate pyridostigmine), which reduce re-inhibition of acetyl cholinesterase; and glutamate antagonists and agonists for adenosine and α-2 adrenergic receptors, which limit damage to the central nervous system.[11]

Information on these potential treatments has been available for years,[11] but neither the military nor the pharmaceutical industry has attempted to test them or develop new drugs. Arguments that new antidotes for organophosphate nerve agents should be approved without human safety or efficacy data have been heeded,[4] with the recent registration of pyridostigmine by the FDA without trials.[12] The controversy surrounding the role of pyridostigmine prophylaxis in Gulf war syndrome[13] shows the dangers of this approach.[13] Lack of human studies before wide scale use of pyridostigmine in military staff and the failure to gather prospective data during this experimental mass treatment make the association difficult to refute.[13]

Much of the research on treatment for nerve gas poisoning has concentrated on prophylaxis. However, in all recent reported exposures treatment, and usually diagnosis, of nerve gas poisoning has been delayed.[14 15] Thus the situation is similar to that faced with pesticide poisoning. Patients with pesticide poisoning require the same treatment as those poisoned by nerve gases.[10 11]Ample opportunity exists for clinical trials because at least two million people are poisoned by organophosphate pesticides each year in the developing world.[16 17] Yet little evidence exists to guide treatment.[5] The problems are compounded by the conditions in which most patients with pesticide poisoning are seen—in hospitals without sufficient doctors, nurses, ventilators, or antidotes to offer a good service.[17 18] This scenario may well be one that occurs in industrialised countries after a large scale chemical attack.

Collaboration and support are needed

The pharmaceutical industry has little incentive to develop new drugs for use primarily in developing countries. However, on humanitarian grounds alone, research into organophosphate pesticide poisoning in developing countries should become an international priority.[9 16] Although primary prevention by regulating pesticide availability and addressing social factors associated with self poisoning may improve outcomes,[19] the effect of these interventions is likely to be delayed.[17] Advances in antidote use, in particular research into currently available antidotes and the development of newer antidotes, are likely to result in a more immediate decrease in deaths.[9 17]

We believe that efforts must be directed towards clinical testing of treatments, towards getting new treatments, and reducing the number of pesticide deaths occurring each year. Priority should be given to treatments already in clinical use for organophosphate poisoning or being stockpiled as antidotes. In particular, randomised controlled trials are required to confirm the efficacy of antidotes and help rationalise scarce resources. International collaboration can assist this process, combining developed world resources and expertise in research with clinical experience in the developing world.[9] This approach will have the greatest initial benefit in developing countries, by reducing premature deaths. But it will also provide valuable information for the world as a whole. Academia, industry, and the military should therefore make a concerted effort to develop and test new treatments that would benefit both groups of patients.

Different incentives

There are many perspectives on the priorities for drug development for organophosphate poisoning. An international health perspective would prioritise finding out whether currently used treatments are safe and effective. The UK's Wellcome Trust is funding two large randomised controlled trials of activated charcoal and pralidoxime in Sri Lanka that will report in two or three years.[5] More recently, the Australian National Health and Medical Research Council has joined with the Wellcome Trust to support further collaborative research in Sri Lanka for other treatments for organophosphate poisoning by establishing a centre of excellence in clinical toxicology research.[9]

From a military perspective, treatments that are effective and safe as both preventive measures and after exposure in the field are ideal. Reversible anticholinesterases and organophosphate hydrolases seem the most promising from the animal data, but the absence of human data is a concern and much further preliminary work is required.

From a pharmaceutical industry perspective, the most attractive agents will be neuroprotective drugs. Such drugs would be useful in other forms of brain injury (such as ischemia or carbon monoxide poisoning) after their efficacy in organophosphate poisoning has been established.

Finally, from a developing world perspective, the possibility that interventions as cheap as bicarbonate and lactate might be effective requires study. The massive expenditure on unproved antidotes in the West provides a sound financial rationale for more research. The two million patients poisoned in Asia Pacific each year provide both a fertile ground within which to do this research and a moral imperative to do so.

It is possible that clinical research on organophosphate poisoning exists but is not being published. Military scientists may believe that wider dissemination of their results will result in loss of military advantage (although effective antidotes might also be a deterrent). Similarly, the pharmaceutical industry may not have published research for commercial reasons. However, it seems most likely that such research is simply not being carried out. Recent concerns by government

Summary points

Organophosphate poisoning is a major public health concern in both the developing and developed worlds

Atropine is the only clearly proved and moderately effective treatment.

Dozens of new drugs have been developed in animal studies and are potentially far more effective

No new antidotes have been tested in clinical trials in the last 30 years

Diverting money from stockpiling unproved antidotes to new drug development may benefit everyone

about having the means to respond to victims of chemical warfare and terrorist attacks mean that the time is ripe to break this drug development impasse.

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Is economic evaluation in touch with society's health values?

Joanna Coast

Health funding is increasingly based on the results of economic evaluation. But current methods fail to consider all society's health objectives and are too complex for policy makers to use

The technical expertise required for conducting economic evaluations and interpreting their results continues to increase. Current best practice includes cost effectiveness acceptability curves, net-benefit frameworks, and probabilistic modelling.[1] These methods are valuable, but by generating a pseudoscientific aura around economic evaluation, they camouflage critical weaknesses in current techniques. In this article, I describe the evolution of economic evaluation in health care (see box for terminology), explore the assumptions underlying current approaches and the resulting concerns, and suggest an alternative approach.

Why do we need economic evaluation?

People who are not economists often find it difficult to understand the importance of the theory behind the comparison of costs and effects. After all, if we compare two washing machines of equal cost and one works for 10 years and the other for 15, it is clear that the machine lasting 15 years is a better buy. The need for theory arises, however, because interpersonal rather than within individual comparisons are involved; in health care the question is not, generally, whether I choose the 10 or 15 year washing machine but whether I get the 10 year washing machine or you get the one lasting 15 years.

Welfare economics

Economic evaluation stems from Paretian welfare economics. It incorporates the principles that individuals are the best judges of their own wellbeing and that, if one person can be made better off without another being made worse off, there is global improvement in welfare. This value judgment is uncontroversial but, in policy terms, practically useless: few policies benefit some individuals without affecting others.

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