

Keynote: Good, Bad And Ugly Designs For Phase II Clinical Trials

Buckley NA (1,2). 1. South Asian Clinical Toxicology Research Collaboration;
2.University of NSW, Sydney, Australia

Pesticide poisoning kills hundreds of thousands of people each year. There is no high-quality evidence for benefit from any antidote, although there is universal acceptance that atropine in anti- cholinesterase poisoning results in immediate and obvious benefits.

There is an urgent need for better evidence on the effects of current treatments and also newer, more effective, antidotes. Animal studies have revealed many compounds offering clear benefits in particular for organophosphorus pesticides and paraquat, yet no new treatment has been generally adopted in clinical practice during the last thirty years.

There have been a number of small trials of a number of antidotes including magnesium, pralidoxime, bicarbonate, fresh frozen plasma and clonidine (for OP poisoning) and immunosuppression and antioxidants (paraquat). In general, these have been quite small trials (n=25 to 250) being used for indications where there was little or no preceding human data supporting the use of the antidote or the preferred dose. Yet many have not used typical Phase II trial methodology, and their results are often over-stated and thus viewed with skepticism. They are also of limited value for other researchers who wish to pursue these antidotes further.

Successful drug development involved more than doing one definitive trial. Phase II is critical in terms of designing future definitive (Phase III) trials for:

1.Selecting the preferred dose/duration based on safety and likely efficacy. 2.Selecting an appropriate primary clinical outcome. 3.Selecting secondary clinical outcomes. 4.Selecting biomarker outcomes and timing that provide causal evidence. 5.Determining the sample size and power. 6.Determining the timing and outcomes for interim analyses.

Examples from various trials conducted over the last decade (e.g. 1-6) show that some playing the drug- development game have attempted to 'hit a six' and been clean bowled, while others demonstrate that a better strategy is to carefully work the scoreboard along with ones and twos. **References** : 1. Wong A, Sandron CA, Magalhaes AS, Rocha LCS. Comparative efficacy of pralidoxime vs sodium bicarbonate in rats and humans severely poisoned with O-P pesticide. Clin.Toxicol. 2000; 38(5):554- 5. 2. Lin JL, Lin-Tan DT, Chen KH, Huang WH. Repeated pulse of methylprednisolone and cyclophosphamide with continuous dexamethasone therapy for patients with severe paraquat poisoning. Crit Care Med. 2006;34(2):368-73. 3. Pajoumand A, Shadnia S, Rezaie A, et al. Benefits of magnesium sulfate in the management of acute human poisoning by organophosphorus insecticides. Hum.Exp.Toxicol. 2004; 23(12):565-9. 4. Hong SY, Yang JO, Lee EY, Kim SH. Effect of haemoperfusion on plasma paraquat concentration in vitro and in vivo. Toxicol.Ind.Health. 2003;19(1):17-23. 5. Guven M, Sungur M, Eser B. The effect of plasmapheresis on plasma cholinesterase levels in a patient with organophosphate poisoning. Hum.Exp.Toxicol. 2004;23(7):365-8. 6. Pawar KS, Bhoite RR, Pillay CP, et al. Continuous pralidoxime infusion versus repeated bolus injection to treat organophosphorus pesticide poisoning: a RCT. Lancet. 2006; 368(9553):2136-41.