DR. DOLITTLE'S DILEMMA: WHAT ANIMALS TELL US ABOUT ANTIDOTES

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Regulatory toxicology animal studies in two species are usually required before drugs can be given to humans for the first time. However, well-designed animal models of poisoning can also provide important information on efficacy for both current and novel antidotes. It is important that such studies are designed with clinical treatment as the focus, with information from patients guiding animal model and study design, and the aim of results being taken back into humans. The models should be similar to human poisoning to be useful. Rodent studies are often not designed from a clinical perspective; furthermore, these species respond to poisons very differently to humans. Translation of rodent results into human trials has proven difficult and resulted in an interest in developing highly relevant large animal models. We first developed a minipig model of dimethoate organophosphorus (OP) insecticide poisoning that showed many of the cardiotoxic and neurotoxic effects seen in poisoned humans. As expected, pralidoxime was poorly effective. However, the model is very different from human poisoning in one major aspect – it shows relatively few features of muscarinic toxicity. This has prevented translational studies of treatments for muscarinic toxicity despite good progress with relevant studies of oximes, novel nicotinic blockade, and solvents. An intravenous pig cyanide model was then developed to compare the efficacy of two current antidotes and a new antidote. This model again showed similarity to human poisoning: the lethal cyanide dose was similar to human poisoning, blood lactate concentrations were markedly raised, and death occurred from cardiovascular shock. The model was set up to give antidotes the best possible chance for effect; unfortunately, neither dicobalt edetate nor hydroxocobalamin was effective at twice a survivable dose (10.0 vs 5.25 mg/kg). The novel antidote was itself highly toxic in this model. We also established a model of paracetamol poisoning that was difficult due to the effect of paracetamol metabolites on methemoglobin production, requiring slow intravenous administration to prevent clinically relevant methaemoglobinaemia. We are now setting up a model of colchicine poisoning that will be used to study the efficiency of anti-colchicine Fab before their use in clinical practise. Each of these models has strengths and weaknesses that needed to be accounted for in study design, but each was able to provide information useful for clinical practice. Large animal models can provide us with important data that often cannot be collected from interventional human studies. It is important that their design is drawn from clinical practice and their results are judged against this perspective.