Editorial:

Chewing the fat on veterinary toxicology: the path to discovery

Last year approximately 15% of the published articles in this Journal related to the field of toxicology. It is not surprising that toxicology should feature so prominently in a journal devoted in Emergency Medicine. Many toxins cause severe injury and even death if left untreated and most require immediate action. In cases of possible or suspected toxin exposure, conventional therapy dictates that efforts should be made to limit absorption of substances that were ingested by inducing emesis and following this by the administration of activated charcoal. In regards to activated charcoal administration, there are recommendations that the addition of cathartics to activated charcoal, such as sorbitol, or repeated dosing are indicated in case that the toxins undergo enterohepatic circulation. These principles have remained unchanged and unchallenged for many years. The problem is then how do we know if there are better ways to manage intoxicated patients? Are there additional treatments that should become part of standard protocols? Are there interventions (eg, repeat dosing) that have little impact of course of disease? Many of these questions are difficult to address, especially when these involve clinical patients.

One approach is to use experimental models whereby animals are subjected to known doses of toxicants, and interventions are evaluated in their ability to reduce some measure – either the presence of the toxin or the clinical sign associated with intoxication. Such an approach is described in this issue by Koenigshof et al, whereby different methods of activated charcoal use are tested against a placebo

treatment group.[1] The authors sought to evaluate whether the addition of sorbitol to activated charcoal or repeat administration of activated charcoal indeed improved clearance of a toxin (in this case carprofen) known to cause severe injury in dogs. It is worthwhile to note that in this experiment,[1] blood concentration of the toxin was the endpoint and not any measure of the clinical manifestation of intoxication with carprofen. The key findings of this study[1] should lead to some rethinking (and likely further investigation) to what has become standard recommendations; the use of repeat dosing of activated charcoal when the toxin is believed to undergoes enterohepatic recirculation. While there were clear benefits associated with the addition of sorbitol to activated charcoal and repeat dosing when compared to placebo, there was limited improvement noted in the treatment groups, which raises the question whether much is gained by the addition of sorbitol or repeating administration of activated charcoal, at least in the context of the experimental design.[1]

Although there are a number of advantages to carrying out experimental toxicological studies, it could take a number of years before clinical applications can be tested and shown to improve patient care. A case in point was that it took 8 years for the first successful clinical application of intravenous lipid therapy as a treatment for bupivacaine toxicity[2] to be reported following the seminal publication by Weinberg et al[3] on an experimental rodent model of lipid infusion therapy in 1998. Since then an entire new field of toxicology revolving around intravenous lipid therapy has been spawned, and the literature includes various veterinary reports that have been recently reviewed.[4] There are now over 100 hundred

publications related to intravenous lipid therapy including experimental animal studies, clinical case studies and review articles. Given that intravenous lipid therapy is becoming more widely practiced based as evidenced by various case studies and recommendations by various veterinary poison centers, one could question why there is a need to publish further examples where such therapy may have a role in managing patients with toxicities. The simple answer is that there is still much to learn and understand about intravenous lipid therapy and although studies (be they experimental or case reports) have their flaws, they can still offer valuable information. Despite the large number of studies on the subject, the exact mechanism by which intravenous lipid therapy "rescues" patients remains incompletely understood.[5] Theories have been put forth and continue to evolve as more data is generated. A recent shift in our understanding is that it is perhaps more appropriate to describe the main mechanism as a "lipid shuttle" rather than a "lipid sink" as the substance bound to lipid is simply surrounded and transported to a different organ (eg, liver, kidney, muscle) for detoxification or elimination.[5] An important aspect that must be recognized is that the body must be able to cope with the toxic substance somehow, as intravenous lipid can only compartmentalize, transport and delay the interaction between the toxic substance and its target tissue. The lipids themselves cannot degrade the toxic substance.

In this issue of the Journal there are number of new studies that offer some additional insights relating to intravenous lipid therapy in the context of toxicology. In contrast to the study mentioned previously by Koenigshof et al,[1] where ingestion of toxic doses of non-steroidal anti-inflammatory drugs are treated with different

activated charcoal therapies, the case series by Herring et al[6] describe the use of intravenous lipid therapy as an adjunct treatment to standard approach of inducing emesis, repeat administration of activated charcoal with and without sorbitol in cases of ingestion of toxins.[6] The maximal possible dose ingested in these cases (range 61-207 mg/kg of naproxen) would have certainly led to severe toxicities, yet these patients did not experience any major sequelae.[6] It is perhaps worthy of mention that intravenous lipid therapy was used *before* the onset of any clinical signs, and so in this study, intravenous lipid therapy was used to mitigate the development of toxic injury. However, the lack of a control (eg, standard therapy without intravenous lipid therapy) prevents the true assessment whether lipids offered additional protection in these cases. Nevertheless, the authors did document a dramatic decrease in plasma concentrations of naproxen following intravenous lipid therapy in these cases that cannot be attributed to any other intervention as gastrointestinal decontamination does not alter plasma concentration of substances. This case series was highly suggestive that lipid therapy prevented the development of the expected morbidity given the doses of naproxen ingested, and that lipid therapy was associated with rapid reduction in plasma concentrations of naproxen given its predicted plasma half-life.

The administration of intravenous lipid therapy to prevent or mitigate the development of toxic signs as opposed to treat following the development of clinical signs is debatable as all interventions carry some risks. Offering some potential insights or perhaps an opportunity to refine our questions, the case study by Jourdan et al[7] does allows us to explore this point, albeit with various limitations.

Although one would probably not design a prospective study in this manner, the authors faced a unique clinical situation whereby 20 cats from a cattery were simultaneously presented following accidental 20-fold overdose of ivermectin. At presentation, no cat showed signs of intoxication. Each cat was treated with at least one infusion of intravenous lipid emulsion, however, 4 cats received additional treatment with intravenous lipids in the form of constant rate infusion for 30 minutes. In the event a cat developed clinical signs following this initial approach, additional boluses and infusions of intravenous lipid emulsions were planned. The interesting observations were that asymptomatic cats that were treated with a bolus followed by a 30-minute infusion (n=4) appeared to be 'protected' from the toxic effects of the ivermectin overdose, as compared to 6 of 16 cats treated with an initial single bolus of intravenous lipid that went on the development clinical signs and require further treatment. Additional observations included that body condition scores (a measure of body fat) may influence the risk for developing clinical signs associated with ivermectin toxicity and that an initial bolus followed by a 30-minute infusion of intravenous lipid may reduce the risk of toxicity.[7] Although these findings need to be confirmed with carefully designed prospective controlled studies, this clinical report makes a compelling case that this protocol is worth considering.

In regards to investigating the effects and potential benefits of intravenous lipid therapy in cats with a similar toxin, permethrin, Peacock et[8] al report the largest randomized controlled trial in cats. In this trial, investigators chose to evaluate the impact of intravenous lipid therapy on course of clinical signs associated with

permethrin toxicity. For this, investigators needed to develop a grading scheme to stratify patients into various stages of the disease based on semi-objective criteria and then reassess cats following an infusion of intravenous lipid emulsion or a placebo. The main findings of this study were that an intravenous lipid infusion appeared to reduce the time required to recover from intoxication.[8] Entry criteria required cats to display advanced signs of intoxication before treatment and so this study excluded cases that were asymptomatic at presentation or presented at the early stages of intoxication.[8] Although the study findings does support the use of intravenous lipid therapy in cases of permethrin toxicity in cats, further studies are required to evaluate optimal dosing and treatment protocols.

It would be fair to say that recent interest and application of intravenous lipid therapy in veterinary toxicology has been very exciting, although we still have much to learn. The fact that we have reached the point where we now have prospective, randomized, placebo-controlled clinical trials in relation to intravenous lipid therapy does not necessarily mean that we cannot learn from individual case reports and retrospective studies. In order to formulate the right questions, design and carry out prospective studies, we do rely of having ample descriptive data about the clinical presentation, the course of progression and outcome of animals affected by various toxins. So contributions such as those made by Hickey et al,[9] DuHadway et al[10] and Katzenbach et al[11] each provide needed data to improve our understanding of the toxicities presented and the clinical course of intoxications. It is with these types of information that we can one day evaluate efficacy of novel treatment protocols. If there is one thing we have learned from our experience with

intravenous lipid therapy is that we don't know where the next breakthrough will emerge and that progress does occur if you ask the right questions and pursue various lines of enquiry.

Daniel L. Chan, DVM, DACVECC, DECVECC, DACVN, MRCVS
Professor of Emergency and Critical Care Medicine and Clinical Nutrition
Section of Emergency and Critical Care
Department of Clinical Science and Services
The Royal Veterinary College
University of London, United Kingdom

The author declares no conflict of interest

References

1. Koenigshoft AM, Beal MW, Poppenga RH, et al. Effect of sorbitol, single, and multidose activated charcoal administration on carprofen absorption following experimental overodose in dogs. J Vet Emerg Crit Care 2015; 25(5):xx-xx

2. Rosenblatt MA, Abel M, Fischer GW, et al. Successful use of a 20% lipid emulsion to resuscitate a patient after a presumed bupivacaine-related cardiac arrest. Anesthesiology 2006;105(1):217-8

3. Weinberg G, VadeBoncouer T, Ramaraju G, et al. Pretreatment or resuscitation with a lipid infusion shifts the dose-response to bupivacaine-induced asystole in rats. Anesthesiology 1998;88(4):1071-5.

4. Fernandez AL, Lee JA, Rahilly L, et al. The use of intravenous lipid emulsion as an antidote in veterinary toxicology. J Vet Emerg Crit Care 2011;21(4):309-20.

5. Fettiplace MR, Weinberg G. Past, Present, and the Future of Lipid Resuscitation Therapy. JPEN J Parenter Enteral Nutr 2015;39(1 Suppl):72S-83S.

6. Herring JM, McMichael MA, Corsi R, et al. Intravenous lipid emulsion therapy in three case of canine naproxen overdose. J Vet Emerg Crit Care 2015;25(5):xx-xx

7. Jourdan G, Boyer G, Raymond-Letron I, et al. Intravenous lipid emulsion therapy in 20 cats accidentally overdosed with ivermectin. J Vet Emerg Crit Care 2015;25(5):xx-xx

8. Peacock RF, Hosgood G, Swindells KL, et al. A randomized, controlled clinical trial of intravenous lipid emulsion as an adjunctive treatment for permethrin toxicosis in cats. J Vet Emerg Crit Care 2015;25(5):xx-xx

9. Hickey MC, Son TT, Wismer T. Retrospective evaluation of methionine intoxication associated with urinary acidifying products in dogs: 1525 cases (2001-2012). J Vet Emerg Crit Care 2015;25(5):xx-xx

10. DuHadway MR, Sharp CR, Meyers KE, et al. Retrospective evaluation of xylitol ingestion in dogs: 192 cases (2007-2012). J Vet Emerg Crit Care 2015; 25(5):xx-xx

11. Katzenbach JE, Foy DS. Retrospective evaluation of the effect of antivenom administration on hospitalization duration and treatment cost for dogs evenomated by *Crotalus viridis*: 113 dogs (2004-2012). J Vet Emerg Crit Care 2015;25(5):xx-xx