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USE OF INTRAVENOUS LIPID EMULSION TREATMENT IN VETERINARY TOXICOLOGY

Introduction

The use of intravenous lipid emulsions (ILE) in human clinical toxicology has become a common practice as life-saving treatment for cardiotoxicity after local anaesthetics overdose. Because of the favourable safety profile of ILE much research is performed to determine the potential antidotal properties in intoxications caused by other lipophilic cardiotoxic substances. Human case reports indicate ILE may be useful in the resuscitation from toxicity induced by various tricyclic antidepressants (TCA), lipophilic β blockers and calcium channel blockers. In veterinary toxicology ILE has been primarily described as an antidote in the management of long-lasting neurotoxicity, like in permethrin intoxications in cats and ivermectin intoxications in dogs. In this lecture an overview of the current knowledge concerning the use of ILE in veterinary practice is provided [1], as well as practical treatment guidelines [2,3].

ILE characteristics

Lipid emulsions have been used for years as a component of parenteral nutrition. They are oil-in-water solutions based on neutral triglycerides. The ready to use fluids can be administered via a peripheral catheter as they are isotonic. Concentrations of 10 to 30% are marketed but primarily the 20% is used as an antidote.

Mechanism of action

The mechanism of the antidotal effect of ILE is still not completely elucidated. Infusion of lipid emulsion provides a compartment for lipophilic drugs in the blood compartment, making them unavailable to act on their target organs. The lipophilic drug inside the lipid emulsion compartment is subsequently metabolized together with the liposomes in the liver and muscle tissue, and thus cleared from the body. This so-called lipid sink/shuttle is thought to be a major antidotal mechanism in neurotoxicity. Other mechanisms have been postulated to explain the antidotal effect on cardiac function, such as a direct effect on myocardial cells improving cardiac output.

Quality of data and cases

The veterinary literature on the efficacy of ILE therapy consists primarily of case reports and case series. This unfortunately limits interpretation as they represent low-quality evidence. Therefore these data should be evaluated with caution. Most case studies describe a clinical improvement after the initial standard therapies were unsuccessful, i.e. a marked reduction in the severity of neurological symptoms, tremors and convulsions became less or disappeared, animals awakened from their comatose state, shortly after ILE administration. In some studies measurements of blood drug concentrations before, during and after ILE treatment have been done during intoxication with ivermectin, naproxen, ibuprofen and lidocaine and provide a more objective assessment. Transient increase followed by a subsequent decrease in lipophilic drug blood concentration has been reported, suggestive of a successful utilisation of the lipophilic properties of the ILE. In general, the use of ILE may lead to a quicker recovery of the animal and a shorter, less intense admission period. However, often antidotes other than ILE are available with a more proven effect on the intoxication. Therefore, with current knowledge, ILE should not be considered first choice treatment. Currently its use in permethrin and avermectin poisoning may be considered in an early stage of treatment in case of severe poisoning.

Dosing protocols

Current dosing protocols are derived from protocols used for the treatment of local anaesthetic systemic toxicity in man; although these protocols seem safe, it remains obscure if these are the optimal dosing protocols in animals. For severe, protracted neurotoxicity, and potentially life-threatening cardiotoxicity, the following dosing protocols are proposed in Box 1 and Box 2 [3].

Safety considerations, side effects and adverse effects

Patients may demonstrate a hypersensitivity reaction to ILE but from experience with parenteral feeding this is a rare occurrence. The sensitivity is directed against soya bean oil or chicken egg proteins. Caution should be taken in the presence of serious disturbances of fat metabolism and liver failure. The administration of ILE can potentially limit the therapeutic effect of regular lipophilic drugs that are administered at the same time. The use of ILE induces transient hyperlipidaemia, this can interfere

with optic measuring techniques, such as used to determine levels of haemoglobin, glucose, electrolytes (e.g. magnesium), lactate dehydrogenate, bilirubin, urea, bile acids and coagulation parameters for several hours. Pancreatitis has been suggested as a complication of chronic hyperlipidaemia; the association of increased plasma amylase concentrations and the risk for pancreatitis with the use of ILE is currently unclear. Excessive amounts of lipid can induce a 'fat overload syndrome' however, with normal, currently advocated dosing protocols this has not been described in small animals.

Box 1
Dosing protocol of intravenous lipid emulsions (20%) with severe, protracted neurotoxicity caused by (strong) lipophilic substances

Sufficient response to standard therapy in a severe poisoning
- Yes: Use of ILE is not indicated.
- No: Consider the use of ILE.

Considerations before using ILE
- Check liver, pancreas, and kidney function, especially if organ function was compromised before.
- Correct electrolyte disturbances, especially hypokalemia, hypophosphatemia, and hyponatremia.

Dosing with neurotoxicity
1. Administer one intravenous bolus injection (peripheral or central) of 1.5 mL/kg in 1 to 2 minutes.
2. Start a CRI at 0.25 mL/kg/min (ie, 15 mL/kg/h) for 30 to 60 minutes or
3. If there is a risk of volume overload
   a. Consider temporarily stopping all infusions.
   b. Consider a reduced rate at 0.07 mL/kg/min (4 mL/kg/h) for 4 hours.
4. Monitor for pyrogenic and allergic responses (especially in the first 20 minutes), and stop CRI if they occur.

Evaluate patients 4 to 6 hours after stopping the ILE administration.
1. With insufficient or no clinical improvement, repeat the dose once or twice as soon as the plasma/serum is (macroscopically) no longer lipemic and there are no signs of hemolysis. Stop if there is little or no effect.
2. With distinct clinical improvement do the following:
   a. Keep patients under observation for at least 12 hours.
   b. Consider measuring plasma/serum triglyceride concentrations to track fat elimination.
3. Patients can be discharged if the clinical status permits.
4. The maximum total dose of ILE is 16.5 mL/kg in 60 minutes.

Abbreviation: CRI, continuous rate infusion.

Derived from Robben et al. 2016

References

1. Dijkman MA, Van Rhijn N, De Vries I, Meulenbelt J, Robben JH. Intraveneuze vetemulsie als antidotum in de veterinaire praktijk. Deel 1: een literatuuroverzicht. Tijdschr Diergeneeskd. 2015:5,24-8.
2. Dijkman MA, Van Rhijn N, De Vries I, Meulenbelt J, Robben JH. Intraveneuze vetemulsie als antidotum in de veterinaire praktijk. Deel 2: Praktische richtlijnen. Tijdschr Diergeneeskd. 2015:6,22-7.
3. Robben JH, Dijkman MA. Lipid therapy for intoxications. Vet Clin Small Animals; 2016; early online.

Box 2
Dosing protocol of intravenous lipid emulsions (20%) with severe, potentially life-threatening cardiotoxicity by (strong) lipophilic substances

1. Administer one intravenous bolus injection of 1.5 mL/kg in 1 minute.
2. Immediately follow it by a CRI of 0.25 mL/kg/min (ie, 15 mL/kg/h).
3. After 5 minutes the clinical condition of patients is evaluated.
   - If necessary, a second bolus of 1.5 mL/kg can be administered in 1 minute. A final third bolus injection may be administered again 5 minutes later. A maximum of 3 bolus injections can be given.
   - The CRI can be increased to 0.5 mL/kg/min (30 mL/kg/h).
4. As soon as heart function and circulation are restored, the CRI has to be continued for at least 10 minutes or until the maximum dose for 30 minutes has been reached.
5. The maximum total dose of ILE is 10 to 12 mL/kg in 30 minutes.

Abbreviation: CRI, continuous rate infusion.

Derived from Robben et al. 2016