Role of IV lipid emulsion antidote

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The first animal reports suggesting an increased rate of recovery from barbiturate-induced CNS depression with lipid infusion were published in 1962[1].

Encouraging results of animal studies, and successful use in human case reports, have demonstrated lipid emulsion has a potential role in the treatment of lipophilic molecules intoxications[2].

Background

Image: Fotolia/Sherry Young.

Lipid emulsion – also referred to as intravenous lipid emulsion (ILE), lipid resuscitation therapy, intravenous lipid emulsion rescue and intravenous fat emulsion – is known as a component of parenteral nutrition (ILE 30 per cent). It is also used as a carrier for lipid soluble drugs, such as propofol, etomidate and diazepam[3,4].

ILE is an injectable oil in water emulsion mixing long-chain and medium-chain triglycerides, or a combination of both, purified egg phospholipids as emulsifiers, anhydrous glycerol for the adjustment of tonicity, water for injection (with a pH of six to nine) and contains no preservatives[3,4].

ILE is available in concentrations ranging from 10 per cent to 30 per cent. Although purified

soybean oil is most commonly used as the major source of triglycerides, other sources are also used (such as olive oil and fish oil)[3,4].

The United States Pharmacopeia and the European Pharmacopoeia standards have established a globule size distribution limit for all lipid emulsions where the mean droplet size must be lower than 500 nanometres, and the percentage of fat larger than 5µm must be lower than 0.05 per cent[5]. ILE stability may be compromised by divalent and trivalent cations, or a pH less than five[6].

Pharmacokinetics

ILE follows similar metabolic pathways as natural chylomicrons. The exogenous fat particle is taken up by the low-density lipoprotein receptors7. Circulating lipoprotein lipase enzyme hydrolyzes triglycerides, releasing the free fatty acids then taken up by muscles and used as an energy substrate[7].

Dog studies have demonstrated after infusion of a lipid emulsion, significant amounts of lipid emulsion were removed by skeletal muscle (47 per cent), splanchnic viscera (25 per cent), myocardium (14 per cent) and subcutaneous tissue (13 per cent), with no removal observed in the liver[8]. A rapid elimination of ILE droplets occurs. The half-life has been reported between 5.34 minutes and 6.51 minutes[9].

Mechanism of action

An ILE bolus provides an expanded intravascular lipid phase that sequesters lipid soluble compound from the target tissues, decreases free drug levels and thereby lessens toxic effects[4,5,7]. The “lipid sink” effect is dependent on the lipophilicity of a drug[3,4,7]. The higher the lipophilicity, the greater the effectiveness of ILE as an antidote is expected.

The lipophilicity of the drug is related to its logarithm octanol/water partition coefficient (logP) value. A drug with a logP greater than 1.0 is considered to be lipophilic. ILE containing fatty acids, major substrate of cardiac myocytes, may augment cardiac muscle function by increasing myocardial mitochondrial adenosine triphosphate synthesis[10]. ILE could also have a positive inotropic effect on hearts intoxicated by increasing contractility in cardiac myocytes via action on voltage-dependent calcium channels[3,11].

Indications

In veterinary medicine, lipid-soluble toxicants successfully treated with ILE are in Table 1[12-32]. Use of ILE has been advocated by animal poison control centres, such as the Veterinary Poisons Information Service (VPIS) and the American Society for the Prevention of Cruelty to Animals Animal Poison Control Center[33].

Faster recovery time has another advantage for pet owners beyond seeing their pet return to normal, reducing the time spent in the veterinary clinic. However, the use of ILE is considered extra-label and informed consent is needed before its use. In human medicine, severe toxicosis, which has been reported as potentially responsive to treatment with ILE, includes local anaesthetics, beta-blockers, calcium channel blockers, antidepressants, anti-psychotics, anti-epileptics, barbiturates, anti-malarial, cocaine and herbicides[3]. ILE is also effective to treat cardiac arrest and in amelioration of perturbed haemodynamic parameters, failing conventional therapy, attributable to overdose of lipophilic drugs[3,4].

Contraindications

A VPIS position statement indicates “ILE is not suitable for lipophilic compounds, such as vitamin D compounds and anticoagulant rodenticides”. ILE pretreatment also does not alter the median lethal dose, 50 per cent (LD50) in a murine model of paraoxon, a metabolite of parathion (organophosphate insecticide)[34]. Contraindications to ILE include severe fat metabolism disorders (such as renal insufficiency and liver damage)[8].

Toxicity

The LD50 of 20 per cent soy-based ILE in rats is 67ml/kg[35]. A wide safety margin exists for further increases in ILE dose for lipophilic drug toxicosis[3].

Adverse reactions

Rapid ILE infusion induces fat overload syndrome, characterised by sudden elevations in serum triglycerides, dyspnoea, fever, respiratory distress, hepatic function and coagulation disturbances, seizures and coma[3,4]. Pancreatitis can occur if a patient has received multiple doses or a prolonged infusion of ILE[3,4].

Lung injury has also been reported[3,4]. ILE interferes with laboratory measurements (such as albumin, amylase, bilirubin, creatine kinase and glucose)[36]. Centrifugation (1,200rpm to 1,500rpm for 10 minutes) of blood samples reduces laboratory interferences[36].

Dose/administration

The following dosage recommended for dogs and cats is adapted from human literature. Administration of an initial ILE 20 per cent IV bolus 1.5ml/kg over one minute, followed by a continuous rate infusion of 0.25ml/kg/min
for the next 30 to 60 minutes.

In non-responsive patients, additional intermittent bolus can be given IV slowly at up to 7ml/kg[37]. If

clinical signs do not improve after 24 hours, discontinue ILE. ILE 20 per cent preparations are isotonic and can be given by a peripheral vein or in a central catheter using aseptic techniques to prevent bacterial contamination risk[3,8].

Storage and handling

ILE should not be stored above 25°C, not be frozen and has a two-year shelf life. Emulsions showing signs of discolouration, phase separation and leakage should not be used. Emulsions should be used immediately after the overwrap is removed[8].

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