State-of-the-Art-Review

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The use of intravenous lipid emulsion as an antidote in veterinary toxicology

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Abstract

Objective – To review the use of IV lipid emulsion (ILE) for the treatment of toxicities related to fat-soluble agents; evaluate current human and veterinary literature; and to provide proposed guidelines for the use of this emerging therapy in veterinary medicine and toxicology.
Data Sources – Human and veterinary medical literature.
Human Data Synthesis – Human data are composed mostly of case reports describing the response to treatment with ILE as variant from mild improvement to complete resolution of clinical signs, which is suspected to be due to the variability of lipid solubility of the drugs. The use of ILE therapy has been advocated as an antidote in cases of local anesthetic and other lipophilic drug toxicoses, particularly in the face of cardiopulmonary arrest and unsuccessful cardiopulmonary cerebral resuscitation.
Veterinary Data Synthesis – The use of ILE therapy in veterinary medicine has recently been advocated by animal poison control centers for toxicoses associated with fat-soluble agents, but there are only few clinical reports documenting successful use of this therapy. Evidence for the use of ILE in both human and veterinary medicine is composed primarily from experimental animal data.
Conclusions – The use of ILE appears to be a safe therapy for the poisoned animal patient, but is warranted only with certain toxicoses. Adverse events associated with ILE in veterinary medicine are rare and anecdotal. Standard resuscitation protocols should be exhausted before considering this therapy and the potential side effects should be evaluated before administration of ILE as a potential antidote in cases of lipophilic drug toxicoses. Further research is waranted.

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Keywords: antidotes, cardiopulmonary resuscitation, critical care, toxicology, toxicology general

Intralipid therapy developed for overdose of local anesthetics in human medicine
Additional drugs that have had reports of lipid-responsiveness:
Bupivicaine
Clomipramine
Verapamil
Bupropion
Mepivacaine
Ropivacaine
Haloperidol
Quetiapine
Doxepin
Carvedilol
Carbamazepine
Flecanide
Hydrocloroquine

Amlodipine
Propranolol
Moxidectin

Soybean oil used most frequently
Categorized based on mean droplet size
- Macro (MDS >1.0 micrometer)
- Mini (1.0-0.1 micrometer)
- Micro (<0.1micrometer)

Size correlates to safety
- Droplets >1um are phagocytized by reticuloendothelial activation system and induce inflammation and microvascular embolization

Emulsifier will reduce size of droplets
- Will also reduce liposome content of solution (i.e. the higher the emulsifier content, the lower the liposome content)
- Liposome catabolism forms lipoprotein-X (LP-X)
- Higher LP-X can cause hypercholesterolemia

Lipid emulsifications are not stable for long periods
- pH will slowly decrease over shelf life
- Liposomes will destabilize
- Keep them at constant temperatures without physical stresses
- Refrigerate and discard 24 hours after opening

Adverse Effects
- Contamination
    - Less likely with ILE than PN
- Reaction
    - Acute pyrogenic reactions “colloid reaction”
        - <1% of human cases
    - Anaphylactoid-like signs
        - Fever, nausea, vomiting, dyspnea, tachypnea, cyanosis, arrhythmias, hypotension, cardiovascular collapse
    - Hypersensitivity to egg phospholipid or soybean oil
- Delayed or subacute reactions
    - “Fat overload syndrome”
    - Overwhelming endogenous lipid clearance
    - FOS can result in fat embolism, hyperlipidemia, hepatomegaly, icterus, splenomegaly, thrombocytopenia, increased clotting times, hemolysis
    - Neuro effects have been reported
    - Pulmonary compromise is also possible
    - Hypertriglyceridemia
        - Possible increased risk of pancreatitis
- Specific product reactions

- Intralipid - slight increased HR and decreased in arterial pH
- Medialipide or PUFA - reduction in myocardial contractile performance
    - Not recommended

MOA

- Lipid sink effect
    - Lipophilicity of a drug is related to its log P value where P represents partition coefficient
        - Solubility of compound between hydrophilic (water) compound and hydrophobic one (octanol)
        - The higher the log P value, the more lipophilic a drug is
        - Log P only accurate at neutral pH!
        - Drugs considered lipophilic if their log P >1.0
- improved myocardial performance
    - Either reversal of toxicosis or benefit of lipids on myocardium
        - Cardiac myocytes can use FFAs for energy
        - Can also increase intracellular calcium

Animal studies

Mostly experimental

- Benefit to ILE in local anesthetic induced cardiac arrest
- Benefit in verapamil (calcium channel blocker) toxicosis
- Scattered case reports

Table 2: Pharmacologic drugs whose side effects may be potentially reversed by administration of intravenous lipid emulsion (ILE), with the Log *P* listed

Drug	Log *P* value
Amlodipine	1.90
Baclofen	1.30
Bupivacaine	3.64
Bupropion	3.47
Carbamazepine	2.30
Carprofen	4.13
Chlorpheniramine	3.17
Chlorpromazine	5.35
Clomipramine	3.30
Cyclosporine	3.00
Dexamethasone	1.83
Diazepam	2.82
Digoxin	1.26
Diltiazem	2.80
Indomethacin	4.27
Itraconazole	5.90
Ivermectin	3.50
Ketoprofen	3.12
Lidocaine	2.26
Loratadine	5.20
Metoprolol	1.88
Moxidectin	4.10
Naproxen	3.18
Nicotine	1.17
Nifedipine	3.22
Nifedipine	2.50
Promethazine	2.85
Trazodone	1.80
Verapamil	3.83
Vinblastine	3.69

Dosing recommendations (extrapolated from experimental studies and human literature)
1.5ml/kg IV over 1 minute (1.5-4 ml/kg)
0.25ml/kg/min (15 ml/kg over 1 hour)
Additional individual bolus aliquots can be administered slowly at up to 7 mL/kg
CRI doses of 0.05 mL/kg/h can be continued until clinical signs improve (not to exceed 24 h)

Other considerations:
Heparin can alter lipid metabolism and possibly reduce likelihood of adverse effects, but not is not recommended

Questions

What is the current recommended dose of intralipid for intoxication with a drug that has is lipophilic:

1) Initial bolus of 1.5ml/kg over 1 hour, followed by 15ml/kg over 24 hours
2) 1.5ml/kg bolus over 10 minutes, repeat as necessary
3) CRI of 15ml/kg/min until signs resolve up to 24 hours
4) Bolus of 1.5ml/kg over 1 minute followed by 15ml/kg over 1 hour

True/False: Based on research with intravenous lipid emulsification therapy for drug toxicoses, a drug is considered ‘lipophilic’ if its Log P value is <1.0

What are the two proposed mechanisms of ILE therapy in treating local anesthetic induced cardiotoxicosis?

Answers

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True/**False**: Based on research with intravenous lipid emulsification therapy for drug toxicoses, a drug is considered 'lipophilic' if its Log P value is <1.0

Should be >1.0

What are the two proposed mechanisms of ILE therapy in treating local anesthetic induced cardiotoxicosis?

Lipid sink and direct provision of fatty acids to heart for energy source