Let's Chew the Fat: Updates on the Use of Intravenous Lipid Emulsion

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- All preventive care including vaccinations, teeth cleaning and spay/neuter

It’s easier to tell you what we don’t cover:

- Pre-existing conditions
- Boarding
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- Tax
- Waste

Speaker Introduction

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What is Pet Poison Helpline?

- 24/7 animal poison control center
- Veterinary & human expertise
  - 20 DVMs, 35 CVTs
  - DABVT, DABT
  - DACVECC
  - DACVIM
  - 7 PharmDs
- Case fee of $49 includes
  - Unlimited consultation
  - Fax or email of case report

Educational center
- Free webinars (archived)
- Tox tools
  - Wheel of Vomit
  - Pot of Poisons (toxic plants)
- Textbook
- iPhone app
- Newsletters for vet professionals
- Free resources for clinics
  - Videos
  - Electronic material
  - Clings

Today’s topics
- ILE basics
- MOAs
- Dosing/administration
- Adverse effects
- Review of literature
  - Focus on 2014-2016

What is Intravenous Lipid Therapy?

http://ccm.ucdavis.edu/cpl/Histo%20Art/artery.jpg
Life saving fat!

- Intravenous lipid emulsion (ILE or IVLE)
- Intravenous fat emulsion (IFE)

Uses:
- Component for nutritional therapy (1960s)
  - PPN
  - TPN
- Vehicle for drug delivery (i.e., lipid emulsions)
  - Antidote for fat-soluble toxicant poisoning

Intravenous Lipid Basics

- Sterile, non-pyrogenic
- 10, 20, 30% solution
- Typically: soybean oil in water
  - Safflower oil, olive oil, fish oil
- Usually isotonic
- pH neutral
- USP requirements: pH of ILE between 6-9
- Shelf life up to 2 years
- pH decreases with aging
- Physical/chemical stress decreases shelf life

Historical experimental data

- Weinberg et al. (2003) with bupivacaine-induced cardiotoxicity in dogs (n=12).
  - Dose bupivacaine 10 mg/kg over 10 seconds
  - Circulatory collapse in mean of 7 min: HR <10 bpm, MAP <30 mmHg
  - All patients ventilated with O₂, internal cardiac massage X 10 minutes
  - ILE vs. saline (4 mL/kg; followed by 0.5 mL/kg/min X 10 min)
  - Saline: all died
  - ILE (all 6 dogs):
    - Normal sinus rhythm in 5 min
    - MAP >30 mmHg in 10 min
    - BP and HR @ baseline in 30 min
Multi-modal MOAs

• Toxin capture & release (intravenous partition)
  – Lipid "sink" vs "shuttle"
  – Transient capture in lipid-laden plasma
  – Rapid re-distribution to other organs

• Direct cardiac effects—improves cardiac output
  – Accelerate unbinding of drug from ion channels (i.e., bupivacaine)
  – Volume contributions & positive inotropic effect of ILE
  – Lipid metabolism, mitochondrial processing, nitric oxide modulation

• Increased toxicant metabolism
  – Increase in microsomal (e.g., hepatic) metabolism


ILE Dosing

• No optimal dosing regime established

• Traditional
  – 3.5 - 4 ml/kg IV bolus over 1-3 minutes, followed by 0.25 ml/kg/min IV, for 30-60 minutes
  – Adapted from human acute local anesthetic intoxication
  – Additional doses:
    – 1.5 ml/kg IV every 4-6 hours for the initial 24 hours.
    – Check for gross lipemia using capillary tubes prior to next dose
    – If after 3-5 doses of administration and no clinical response is seen, it can be discontinued

• What about ingested toxicants?
  – New suggestion from human literature (Fettiplace et al., 2015)
    – 2.25 mL/kg initial load
    – 0.025 mL/kg/min CRI for up to 6.5 hrs


Optimal dose of ILE?

• Perez et al. Determining optimal dose of ILE in rodent model of verapamil toxicity.
  – 18.6 mL/kg dose → greatest benefit to survival
  – 24.8 mL/kg → better improvement in MAP, BE, HR, but no added benefit to survival
  – Delivered at 2.48 mL/min.

• 4 mL/kg & 7 mL/kg boluses in canine studies

• Very wide variety in literature

• LD_{50} rat, IV = ~67 mL/kg during rapid infusion

ILE Administration & Handling

• Peripheral IV catheter
  • Ideally, dedicated catheter/line
  • No reported adverse effects with non-dedicated catheter
  • Consider 1.2 micron TPN filter
• Strict aseptic technique
  • Sterile gloves when preparing infusion/changing lines
• Refrigerate unused portion; discard after 24 hours

Which toxicants will respond to ILE?

• Lipid soluble toxicants!
  • LogP (AKA partition coefficient) > 1 or 2
  • The greater (more positive) the LogP, the more lipophilic/soluble in hydrophobic solutions
  • High volume of distribution (Vd)
  • The greater the Vd, the more the drug distributes into fat and muscle, away from the serum
  • These agents are less likely to be removed via hemodialysis
• Examples:
  • Verapamil: LogP = 3.8, Vd = 4.5
  • Bupivacaine: LogP = 3.4, Vd = 0.7
  • Ethanol: LogP = -0.1, Vd = 0.5

Reported Adverse Events

(causeality not always proven)

• People
  • Pancreatitis (Bucklin, 2013)
  • ARDS (Martin, 2014)
  • Fat overload syndrome (FOS) can lead to hyperlipidemia, hepatomegaly, fat embolism, icterus, & hemolysis.
  • Other: Anaphylaxis, fever, vomiting, tachypnea, dyspnea, acute lung injury, phlebitis.
• Rats: (Hiller et al, 2010)
  • Triglycerides were elevated immediately after infusion but returned to baseline by 48hrs.
  • Amylase, AST, BUN at all doses.
  • Histologic diagnosis of myocardium, brain, pancreas, and kidneys was normal at all doses.
  • Microscopic abnormalities in lung and liver were observed at 60 and 80 mL/kg; histopathology in the lung and liver was worse at 1 hr than at 4 and 24 hrs.
• Dogs:
  • Hemolysis in 1 dog (FOS?). Recovered after transfusion & supportive care (Gwaltney-Brant & Meadows, 2012)
Reported Adverse Effects
(causality not proven)

• Cats
  – Unilateral facial pruitis 10 h post ILE. Treated with chlorpheniramine, resolved in 8 hrs. (Peacock, et al., 2015)
  – Received other drugs in comb with ILE
  – Gross lipemia, transient (Peacock)
  – Gross lipemia >48 hrs (Seitz & Burkitt-Creedon, 2016)
  – Suspected corneal lipidosis (Seitz & Burkitt-Creedon, 2016)
  – 42 hrs after ILE, symmetrical, pannoreal white opacity
  – No uveitis, no aqueous flare. Fundic exam precluded.
  – ILE dose = 31.5 mL/kg over 120 min

Permethrin Literature

• Feline literature only
  • 7 articles with ILE, 2012-2016*
    – 6 case reports
    – 1 prospective, randomized study
  • Source: Most canine topical spot-on (~45% permethrin)
  • LogP of permethrin = 5.7-6.5

• Case reports
  – Wide variety of ILE dosing
    – 10-61 mL/kg (20% ILE)
  – Some with inappropriate initial management
    – Methocarbamol dosing too low
    – Only benzodiazepines given for tremors
  – Does not always/often stop tremors
  – Sometimes several hours until improvement
  – Some recurrence of signs/whospitalization

Permethrin/ILE Case Reports: Critique

• Some use permethrin with methocarbamol
  – LogP of methocarbamol = 0.55
• Other concomitant drugs (LogP)
  – Diazepam (2.82), midazolam (3.3), dexmedetomidine (2.8) (possibly helpful), phenobarbital (1.47), propofol (3.8)
• None have blood concentrations so cannot...
  – Confirm exposure
  – Confirm “lipid sink”
• Difficult to obtain meaningful data
• Clinical sign interpretation very subjective
Prospective, multi-center, randomized, controlled clinical trial
March, 2011-June, 2012
Western Australia (4 states)
- 1 vet school (Murdoch University)
- 12 private ERs
34 cats with suspected permethrin poisoning
Hypothesis: Clinical signs would improve with ILE vs saline control.

**Permethrin/ILE Clinical Trial**
(Peacock, et al. 2015)

Design clinical staging system, Stage A-F

- Inclusion criteria:
  - Direct application of permethrin spot-on by owner and stages C-F
- Exclusion criteria:
  - Previous treatment
  - Stage A or B (asymptomatic or very mild)
  - Body condition score 7-9 or diabetes mellitus, cardiac or renal disease
- Patient randomized to control or ILE. Not blinded.
- No significant difference between test & control group in:
  - Age, breed, sex, or weight
  - Time of application to presentation (median 14 and 13.5 hrs)
  - Clinical signs
Permethrin/ILE Clinical Trial
(Peacock, et al. 2015)

Treatment
- Tremors: Methocarbamol IV to effect (starting dose, 40 mg/kg)
- Seizures: Diazepam IV to effect (starting dose, 0.5-1 mg/kg)
- Then, dermal decontamination: Clip application site, bathe

Control Group (n = 14)
15 ml/kg, saline, IV over 60 min

Test Group (n = 20)
15 ml/kg, 20% ILE, IV over 60 min (equivalent to 0.25 ml/kg/min)

Allowed to use additional drugs or fluids as needed.

Additional agents given*

Control (n = 14)
- Methocarbamol (14)
- Diazepam (7)
- IV fluids (6)
- Alphaxone (1)
- Butorphanol (1)
- Midazolam CRI (2)

Test (n = 20)
- Methocarbamol (20)
- Diazepam (10)
- IV fluids (10)
- Alphaxone (3)
- Butorphanol (2)
- Acepromazine (1)
- Medetomidine (1)
- Phenobarbitone (1)
- Propofol (1)

*All doses listed in the article
* No statistical difference between groups

Permethrin/ILE Clinical Trial
(Peacock, et al. 2015)

- Significant results
  - ILE group had less severe signs (p < 0.001)
  - ILE group reached Stage A or B faster (p = 0.006)
    - 5.5 hrs (ILE) vs 16.2 hrs
- No significance
  - Duration of hospitalization (p = 0.087)
    - 19.4 hrs (ILE) vs 27.5 hrs

Relative frequency of distress signs or death compared to cats with permethrin poisoning in cats randomized to receive 0.9% saline (control) or intravenous lipid emulsion (ILE) treatment. The distribution of relative frequency between the two groups was significantly different (p < 0.001).
Permethrin/ILE Clinical Trial
(Peacock, et al. 2015)

• Significant results
  – ILE group had less severe signs (p = <0.001)
  – ILE group reached Stage A or B faster (p = 0.006)
    • 5.5 hrs (ILE) vs 16.2
• No significance
  – Duration of hospitalization (p = 0.087)
    • 19.4 hrs (ILE) vs 27.5 hrs

Relative frequencies of clinical stage at each time point in cats with permethrin toxicoses randomized to receive 0.9% sodium chloride (control) or intravenous lipid emulsion (ILE) treatment. The distribution of relative frequencies between the two groups was significantly different (P < 0.001).

Permethrin/ILE Clinical Trial
(Peacock, et al. 2015)

• Study limitations
  – Not blinded
  – No true exposure confirmation
  – No blood permethrin concentrations
  – Cannot determine if lipid “sink/shuttle” occurred
  – Cannot correlate clinical signs to blood concentrations
  – Cannot correlate doses of concomitant drugs to severity/resolution of signs
  – Cannot determine if ILE or any drugs were re-dosed
  – Cannot determine when other agents were given following T=0
• What can we learn?
  – ILE appears well tolerated in this cohort at 15 ml/kg over 60 min
  – It may hasten recovery when used as an adjunctive therapy
  – May be more economical (lipid is cheaper than methocarbamol)

Ivermectin – 20 cats

• Cats
  – 20 cats given 4 mg/kg ivermectin SQ for ear mites (20x overdose)
  – Log P = 5.83
  – 2 h post, all asymptomatic but treated with ILE
  – 1.5 mL/kg bolus (all cats) + 0.25 mL/kg/min CRI x 30 min for 4 Sphynx cats
  – 6 cats developed signs consistent with intoxication 14-48 h after overdose
  – Mydriasis, ataxia, incoordinated weakness, nystagmus, tremors, etc.
  – No serum concentrations measured

Ivermectin – 20 cats

<table>
<thead>
<tr>
<th>Day</th>
<th>Ivermectin dose</th>
<th>Clinical signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4 mg/kg SQ</td>
<td>No clinical signs</td>
</tr>
<tr>
<td>2</td>
<td>4 mg/kg SQ</td>
<td>No clinical signs</td>
</tr>
<tr>
<td>3</td>
<td>4 mg/kg SQ</td>
<td>No clinical signs</td>
</tr>
<tr>
<td>4</td>
<td>4 mg/kg SQ</td>
<td>No clinical signs</td>
</tr>
<tr>
<td>5</td>
<td>4 mg/kg SQ</td>
<td>No clinical signs</td>
</tr>
<tr>
<td>6</td>
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</tr>
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<td>7</td>
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<tr>
<td>8</td>
<td>4 mg/kg SQ</td>
<td>No clinical signs</td>
</tr>
<tr>
<td>9</td>
<td>4 mg/kg SQ</td>
<td>No clinical signs</td>
</tr>
</tbody>
</table>

ILE, intravenous lipid emulsion; CR, continuous rate infusion. Boli: 1.5 mL/kg. 4 mg/kg, 20x overdose.
Ivermectin – 20 cats

- Authors’ conclusions:
  - Incidence/severity of intoxication may have been higher if ILE were not preemptively given
  - Low BCS associated with increased severity
  - Feline half-life of ivermectin = 2.5 +/-2.2 days
    - Acknowledge that recovery time is as expected given half-life.
    - Maybe no effect on duration of recovery?
  - Call for laboratory analysis re: ILE/ivermectin


Ivermectin – 1 cat, case report

- Suspected ingestion of equine horse dewormer (unreported amount)
- PE: laterally recumbent, tachycardic, deepresp. excursions, hyperesthetic
- No response to supportive care after 24 hrs
- ILE x 2 doses
  - 30 min post = breathing deeper, more regular
  - 9 hr post = marked improvement in mention
  - Transient Spermia
- Discharged home on day 4 with mild ataxia
- Owner reports cat is normal by day 5
- Limitations
  - Unknown dose
  - No serum ivermectin testing
- Recovery time within realm of non-ILE cases


Ibuprofen

- Ibuprofen
  - 3 yo, 19 kg, mixed breed dog
  - 1,850 mg/kg Ibuprofen
    - Some pills present in emesis
  - Day 3-4: tachycardia, coma, cardiovascular instability
    - Transient coagulopathy, coagulopathy, clots, incoagulable, 1-2 hms/kg followed by 1L/1 of 5
    - 2 h post ILE, slight improvement level of consciousness
  - Day 2 = coarse ataxia, GI bleeding, icteric
  - Day 3-4 = Continued ICU care
  - Day 5 = discharged
- Serum Ibuprofen concentration
  - Baseline (pre ILE) = 190 mg/mL
  - 2 h after ILE dosing = undetectable
- Concern with results?
  - Serum toxicant concentration should increase due to “lipid sink” (i.e. drug moves into vesicles out of tissue) unless lipid partition was removed
  - Data do not support “lipid sink” theory
  - Where is ibuprofen?


Log P = 3.5-4.0
Naproxen

• Study pursued based on ibuprofen article
• $\text{LogP} = 3.18$
• Whole serum naproxen concentrations:

<table>
<thead>
<tr>
<th>Case</th>
<th>0 hour post, $\mu$g/ml</th>
<th>1 hour post, $\mu$g/ml</th>
<th>3 hours post, $\mu$g/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>73</td>
<td>12</td>
<td>7.2</td>
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<tr>
<td>2</td>
<td>99</td>
<td>19</td>
<td>7.2</td>
</tr>
<tr>
<td>3</td>
<td>84</td>
<td>21</td>
<td>18</td>
</tr>
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</table>

• Data do not support lipid sink theory
• PPH does not currently recommend ILE for most NSAID intoxications.

Summary

• Use ILE as adjunctive treatment only
• Not routinely recommended for asymptomatic patients, especially following ingestion
• Limited number of experimental studies and clinical trials. More evidence needed.
• Published studies require careful interpretation
• Adverse effects appear rare but may be under-reported

When in doubt, call
800-213-6680

• Something you’re not familiar or comfortable with
• Odd clinical signs
• Animals with preexisting disease
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Drs. Lynn Hovda, Ahna Brutlag, Robert Poppenga, Katherine Peterson

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- Carefully organized for ease of use in an emergency, with important toxicants arranged alphabetically within categories
- Details clinically relevant information on the most common toxicants encountered by small animals
- Presents a wealth of color photographs to aid in plant identification
- Includes 14 new topics to this edition covering cyclosporine A, sleep aids, tamrolimus, bath salts, synthetic marijuana, poisonous lizards, imidacloprid, spring bulbs, and sodium monofluoroacetate
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Comments? Questions? Email us! info@petpoisonhelpline.com

Permethrin Article References

- Kuo J and Olidamooy A. Adjunctive therapy with ILE and methocarbamol for permethrin toxicity in 2 cats. JVCC, 2013
- Bruckner M & Schwedes CS. Successful treatment of permethrin toxicosis in two cats with ILE. Tierarztliche Praxis Kleintiere, 2012
- Haworth MD & Smart L. Use of ILE in 3 cases of feline permethrin toxicosis. JVCC, 2012
Early human data

• Primarily case reports
• First case report 2006
  – Nerve block gone bad (bupivacaine and mepivacaine) → seizures and CPA
  – 20 minutes of CPR
  – 1.2 mL/kg of 20% ILE
  – Return of spontaneous circulation (ROSC) shortly after ILE bolus
  – Followed by CRI (0.5 mL/kg/min, IV, over 2 hours)
  – Survived (right coronary artery occlusion incidentally)


Human data

• Lethal dose of 2 meds:
  – Bupropion (monocyclic antidepressant)
  – Lamotrigine (Lamactil) (phenyltirazine derivative for seizures and bipolar disease)
  – 52 minutes of unsuccessful life support
  – Bolused 1.8 mL/kg of 20% ILE → immediate ROSC
  – Buproprion plasma levels revealed a peak plasma concentration post ILE, supporting lipid sink. No change in lamotrigine.

Veterinary data: experimental

• First ILE study in 1974 in rabbits
  – In-vivo and in-vitro
  – Chlorpromazine 30 mg/kg, IV
  – Control: All died
  – ILE: All lived
  – In-vitro:
    • ILE + rabbit blood → ↓ fraction of free chlorpromazine

• Similar study in rabbits with cyclosporine
  – ILE ↓ total body clearance and $V_d$

• Potential benefit for: bupivacaine, propranolol, thiopental, verapamil, beta-blockers, clomipramine, and chlorpromazine.

Veterinary data: experimental

- Weinberg et al. (1998) with bupivacaine-induced asystole in rats.
  - ILE ↑ dose of bupivacaine to produce asystole
  - ILE treated group: ↑ LD₅₀ by 48%
  - ↑ survival in rats


Veterinary data: clinical study

- Moxidectin toxicity
  - 16-week old Jack Russell terrier (3.2 kgs)
  - 10 hours after exposure, tx with ILE (Intralipid) at 2 mL/kg bolus IV, followed by 4 mL/kg/hour X 4 hours (0.07 mL/kg/min)
  - Repeated 25 hours after exposure at 0.5 mL/kg/min for 30 minutes
  - No blood levels evaluated