Propofol: NEW Insights
Physical Chemistry & Pharmacology

Propofol Infusion Syndrome PRIS:
Separating Facts from Fiction

Dr. David Goodale
Executive Clinical Director
DBG Pharma LLC
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No Conflicts
Propofol (molecule) Chemistry

Propofol is a yellow oil liquid, Immiscible in Water

“Insoluble in Water” PubChem Nat’l Library of Medicine
Toxico[https://toxnet.nlm.nih.gov/cgi-bin/sis/search2/f/?./temp/~R1wVSx]

Greater potency means greater lipophilicity
Induction of Anesthesia: Drug equilibrium between blood & brain

Propofol bolus dose
Short Duration of Action:
Intralipid pulls propofol out of brain

Bolus dose of lipid returning to the brain ~2 min after induction
Short-acting: Propofol with Lipid

Longer-acting: Propofol with water


Propofol tolerance: Increasing dose requirements with repeated dosages

**INDUCTION Doses**

**MAINTENANCE Doses**

Intralipid \textit{‘active’} Vehicle

Lipophilic-Drug Sink in Blood

Hyperlipidemia

\begin{itemize}
\item [↑] Dosage Creep
\item [↓] Efficacy: Propofol $^{1,2}$
\end{itemize}

Brain

Tissue Distribution: Blood

Lipids Bind Propofol

Blood

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1 Brimacombe, J Resistance to Anesthetic Agents, Anaesthesia and Intensive care 22:236, 1994
Intralipid ‘active’ Vehicle
Lipophilic-Drug Sink in Blood

Hyperlipidemia

↑ Dosage Creep

↓ Efficacy:
- Propofol ¹,²
- Anesthetics Analgesics ²
- NMJ Blockers ?
- Warfarin ³,⁴

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- Propofol ¹,²
- Anesthetics Analgesics ²
- NMJ Blockers ?
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Tissue Distribution: Blood
Lipids Bind
- Propofol

1 Brimacombe, J Resistance to Anesthetic Agents, Anaesthesia and Intensive care 22:236, 1994
Blood Lipids:
Reduced Efficacy of Lipid Soluble Inhaled Anesthetics

<table>
<thead>
<tr>
<th>ANESTHETIC</th>
<th>MAC (%)</th>
<th>λ(oil:gas)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrous oxide</td>
<td>104</td>
<td>1.4</td>
</tr>
<tr>
<td>Desflurane</td>
<td>6</td>
<td>19</td>
</tr>
<tr>
<td>Sevoflurane</td>
<td>2</td>
<td>51</td>
</tr>
<tr>
<td>Enflurane</td>
<td>1.7</td>
<td>98</td>
</tr>
<tr>
<td>Isoflurane</td>
<td>1.4</td>
<td>98</td>
</tr>
<tr>
<td>Halothane</td>
<td>0.75</td>
<td>224</td>
</tr>
<tr>
<td>Methoxyflurane</td>
<td>0.16</td>
<td>960</td>
</tr>
</tbody>
</table>

The potency of an anesthetic increases as its liposolubility increases.
Blood Lipids:
Reduced Efficacy in Piperidine Analgesics
Hydrophilic vs Lipophilic

Fig. 1. Structures of the opioids and piperidine-type narcotics.
Blood Lipids:

May reduce efficacy of Lipophilic NMJ Blockers
Propofol can be administered to:

- Egg Sensitive patients
- Soy Sensitive patients

- **Intralipid** approved over 55 years ago  
  No Contraindications

- U.S. Food Allergen Labeling & Consumer Protection Act exempts highly refined oils from warnings about allergic reactions  
  [https://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/Allergens/ucm106187.htm](https://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/Allergens/ucm106187.htm)

- Grocery Store Soy Oil & Peanut Oil  
  No Contraindications  
  *J Allergy Clinical Immunol.* 76:242-5, 1985

- **“No evidence for contraindications to the use of propofol in adults allergic to egg, soy or peanut.”**  

- DIPRIVAN Clinical database at AstraZeneca: contains egg allergic pts w no reactions
DIPRIVAN anesthetic ... Summary

Propofol is a **yellowish liquid oil** that is immiscible with water.

The more **Lipophilicity** a substance is the more **Potency**.

**Intralipid** vehicle: is *pharmacologically “active”* drug.

**No Contraindications** needed for Egg or Soy Sensitive Patients.
PRIS *Linked* to Mitochondrial Disease

3 PRIS myths scientifically corrected

Five Separate Scientific Links

*Davld Goodale*

Executive Clinical Director

*DBG Pharma LLC*
Propofol (molecule) is **not** toxic to Mitochondria

*In Vitro* studies: Tissue in **Water**-based buffer

**Propofol oil:**  **Octanol : Water** is 6761 : 1

<table>
<thead>
<tr>
<th>Propofol</th>
<th>Sedation</th>
<th>Concentration</th>
<th>Blood + Lipid</th>
<th>Mitochondria Experiment</th>
<th>Mitochondria Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Branca 1991</td>
<td>Rat liver mitochondria</td>
<td>0-75 umol</td>
<td>Water</td>
<td>No effect on ATP,</td>
<td></td>
</tr>
<tr>
<td>Branca 1991</td>
<td>Rat liver mitochondria</td>
<td>0-100</td>
<td>Water</td>
<td>Small Membrane potential</td>
<td></td>
</tr>
<tr>
<td>Rogoulet '96</td>
<td>Rat liver mitochondria</td>
<td>25-400</td>
<td>Water</td>
<td>Inhibits Complex 1 &amp; H⁺ leak</td>
<td></td>
</tr>
<tr>
<td>Schenkman 2000</td>
<td>Guinea pig heart</td>
<td>50, 100, 200</td>
<td>Water/ albumin</td>
<td>No mitochondria studied</td>
<td></td>
</tr>
<tr>
<td>Sumi 2018</td>
<td>H neuroblast &amp; Myoblast</td>
<td>25, 50, 100</td>
<td>Water</td>
<td>Inhibits Complex I, II, III</td>
<td></td>
</tr>
</tbody>
</table>

**Cardiac**

| Zhou, 1997 | Rat cardiomyocytes | 10 25 50-200 | Water | Rapid ↓ Contractility | |
| Hebbar 1997 | CHF Pig myocytes | 6 ug/ml | Water + 0.1% albumin | ↓ Contractile function | |
Propofol does **not** Impair Cardiac Function

Propofol study: **Impaired** Cardiac Output (26 -49%) patients

**Richard Hall** et al., Anesth Analg 77:680-689, **1993**

42 Propofol CHF patients and 18 sufentanil/enflurane CHF patients

Study Observations:

- No evidence of increased myocardial ischemia with propofol
- Propofol reduced Myocardial Lactate versus Control group
- Less Hypotension on Induction than previous study of Cardiac Pts not in congestive failure

Propofol does **not** depress cardiac function

Propofol is a great sympatholytic agent: can be a pt benefit or detriment
Propofol has no similarity with CoQ10

Ref: Possible Pathogenic Mechanism of PRIS involves Coenzyme Q (In Vitro Study)  
Anesthesiology 122:343-352, 2015  Vanlander et al
MITO FACT

Mitochondrial disease is a genetic disorder that robs the body's cells of energy, often causing multiple organ dysfunction.
Mitochondrial Disease

- Simply stated: Mito is an energy shortage within the body!
Mitochondria possess their own DNA
Mitochondrial diseases

- Alpers Disease
- Barth syndrome
- Beta-oxidation Defects
- Carnitine-Acyl-Carnitine Deficiency
- Carnitine Deficiency
- Creatine Deficiency Syndromes
- Co-Enzyme Q10 Deficiency
- Complex I Deficiency
- Complex II Deficiency
- Complex III Deficiency
- Complex IV Deficiency
- Complex V Deficiency
- COX Deficiency
- CPEO
- CPT I Deficiency
- CPT II Deficiency
- Glutaric Aciduria Type II
- KSS
- Lactic Acidosis
- LCAD
- LCHAD
- Leigh Disease or Syndrome
- LHON
- LIC (Lethal Infantile Cardiomyopathy)
- Luft Disease
- MAD
- MCAD
- MELAS
- MERRF
- MIRAS
- Mitochondrial Cytopathy
- Mitochondrial DNA Depletion
- Mitochondrial Encephalopathy
- Mitochondrial Myopathy
- MNGIE
- NARP
- Pearson Syndrome
- Pyruvate Carboxylase Deficiency
- Pyruvate Dehydrogenase Deficiency
- POLG Mutations
- Respiratory Chain
- SCAD
- SCHAD
- VLCAD

www.umdf.org – The United Mitochondrial Disease Foundation
### Mitochondrial Fatty Acid Oxidation Disorders

Houten, SM et al.

#### Table 1  Human mitochondrial fatty acid β-oxidation enzymes and transporters

<table>
<thead>
<tr>
<th>Name</th>
<th>Most common alias</th>
<th>Gene</th>
<th>EC number</th>
<th>Phenotype MIM number</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Carnitine shuttle</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carnitine palmitoyltransferase 1A (liver)</td>
<td>CPT1A</td>
<td>CPT1A</td>
<td>2.3.1.21</td>
<td>255120</td>
</tr>
<tr>
<td>Carnitine palmitoyltransferase 1B (muscle)</td>
<td>CPT1B</td>
<td>CPT1B</td>
<td>2.3.1.21</td>
<td>Not reported</td>
</tr>
<tr>
<td>Carnitine acylcarnitine translocase</td>
<td>CACT</td>
<td>SLC25A20</td>
<td>NA</td>
<td>212138</td>
</tr>
<tr>
<td>Carnitine palmitoyltransferase 2</td>
<td>CPT2</td>
<td>CPT2</td>
<td>2.3.1.21</td>
<td>600649; 608836; 255110; 614212</td>
</tr>
<tr>
<td>Organic cation/carnitine transporter</td>
<td>OCTN2</td>
<td>SLC22A5</td>
<td>NA</td>
<td>212140</td>
</tr>
<tr>
<td><strong>Fatty acid β-oxidation cycle</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Very long chain acyl-CoA dehydrogenase</td>
<td>VLCAD</td>
<td>ACADIVL</td>
<td>1.3.8.9</td>
<td>201475</td>
</tr>
<tr>
<td>Medium-chain acyl-CoA dehydrogenase</td>
<td>MCAD</td>
<td>ACADM</td>
<td>1.3.8.7</td>
<td>201450</td>
</tr>
<tr>
<td>Short-chain acyl-CoA dehydrogenase</td>
<td>SCAD</td>
<td>ACADS</td>
<td>1.3.8.1</td>
<td>201470</td>
</tr>
<tr>
<td>Mitochondrial trifunctional protein, alpha subunit</td>
<td>MTPα</td>
<td>HADHA</td>
<td>4.2.1.74; 1.1.1.211</td>
<td>609015; 609016</td>
</tr>
<tr>
<td>Mitochondrial trifunctional protein, beta subunit</td>
<td>MTPβ</td>
<td>HADHB</td>
<td>2.3.1.16</td>
<td>609015</td>
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<tr>
<td>Short-chain enoyl-CoA hydratase</td>
<td>Crotonease</td>
<td>ECHS1</td>
<td>4.2.1.150</td>
<td>616277</td>
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<tr>
<td>Short-chain (S)-3-hydroxyacyl-CoA dehydrogenase</td>
<td>SCHAD</td>
<td>HADH</td>
<td>1.1.1.35</td>
<td>231530; 609975</td>
</tr>
<tr>
<td>Medium-chain 3-ketoacyl-CoA thiolase</td>
<td>MCKAT</td>
<td>ACAD2</td>
<td>2.3.1.16</td>
<td>Not reported</td>
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<tr>
<td>Acetoacetyl-CoA thiolase</td>
<td>T2</td>
<td>ACAT1</td>
<td>2.3.1.9</td>
<td>203750</td>
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<tr>
<td>Long-chain acyl-CoA dehydrogenase</td>
<td>LCAD</td>
<td>ACADL</td>
<td>1.3.8.8</td>
<td>Not reported</td>
</tr>
<tr>
<td>Acyl-CoA dehydrogenase 9</td>
<td>ACAD9</td>
<td>ACAD9</td>
<td>1.3.8.9</td>
<td>611126</td>
</tr>
<tr>
<td><strong>Auxiliary enzymes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Δ3,Δ2-Enoyl-CoA isomerase 1</td>
<td>DCI</td>
<td>ECH1</td>
<td>5.3.3.8</td>
<td>Not reported</td>
</tr>
<tr>
<td>Δ3,Δ2-Enoyl-CoA isomerase 2</td>
<td>PECI</td>
<td>ECI2</td>
<td>5.3.3.8</td>
<td>Not reported</td>
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<tr>
<td>2,4-Dienoyl-CoA reductase</td>
<td>DECR</td>
<td>DECR1</td>
<td>1.3.1.34</td>
<td>Not reported</td>
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<tr>
<td>Δ3,Δ2,4-Dienoyl-CoA isomerase</td>
<td>ECH1</td>
<td>ECH1</td>
<td>Not assigned</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

Abbreviations: EC number, enzyme commission number; NA, not applicable. The MIM number refers to the numbering in the Online Mendelian Inheritance in Man (OMIM) database.
Anesthesia & ICU

MUST feed all Mitochondrial Disease Patients
DIPRIVAN (propofol) is Complex Anesthetic

Energy Fuel in DIPRIVAN

- 100 mg/ml LC Fatty acids
- 0 Proteins
- 0 Carbohydrates

DIPRIVAN Labeled Ingredients:
- 100 mg Soybean Oil
- 22.5 mg Glycerin
- 12 mg Egg Lecithin
- 10 mg propofol
- .05 mg EDTA

unLabeled Ingredients:

<table>
<thead>
<tr>
<th>Component</th>
<th>100 g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triglycerides</td>
<td>100 g</td>
</tr>
<tr>
<td>Phospholipid</td>
<td>12 g</td>
</tr>
<tr>
<td>Glycerol</td>
<td>22.5 g</td>
</tr>
<tr>
<td>Water</td>
<td>887 mL</td>
</tr>
</tbody>
</table>

Polysaturated Fatty Acids (PUFA)

- Total Tocopherol: 71 mg (41-111 mg)
- Alpha Tocopherol: 6 mg (2-13 mg)
- Gamma Tocopherol: 40 mg (13-72 mg)
- Delta Tocopherol: 24 mg (11-58 mg)
- Vitamin E Activity*: 15 mg (22.1 U.)
- Vitamin E Activity/ PUFA
  - (Min. Req. = 0.4)

Sterols

- Cholesterol: 304 mg (85-409 mg)
- Total Plant Sterols: 370 mg
- Campesterol: 84 mg
- Stigmasterol: 76 mg
- Sitosterol: 210 mg

Electrolytes and Trace Minerals

- Mg++: 0.011 mEq
- Ca++: 0.027 mEq
- Na+: 3.4 mEq
- K+: 0.82 mEq
- Zn++: 0.002 mEq
- Cu++: 4.001 mEq
- Cl-: 3.0 mEq
- Phosphorus (from Phospholipids): 15 mM
- Vitamin K: 150 mcg
Feeding our Mitochondria

Baseline before Hospital:
Patients With Mitochondrial Disease Have an Inadequate Nutritional Intake”

Intralipid Package Insert
10% (fatty acids) should make up no more than 60% of the total caloric input to the patient. Carbohydrate and a source of amino acids should comprise the remaining caloric input.
Clinical Syndrome of PRIS: similar to Subclinical Mitochondrial Disease

- Lactate is a common toxic byproduct with defects in energy production. Lactic Acidosis is present in 80% of MD patients have elevated lactate without symptoms. Lactic acidemia & Mitochondrial Disease Molecular Genetics & Metabolism 89:3-13, 2006 Robinson, BH

Five Scientific Links: PRIS to Mitochondrial Disease

Similar Clinical Defects to Mitochondrial Fatty Acid Defects
Lactic Acidosis, Rhabdomyolysis, Cardiac Myopathies & Arrhythmias, Kidney & Liver dysfunction

PRIS Case Reports no mention: Carbohydrate supplements or Pre-Op Fasting
Analysis of first 50 PRIS adult & pediatric cases found no reporting of pre op fasting or supplemental dextrose fuel administration (D Goodale tables)

Biochemical Links: Elevated Acetylcarnitine derivatives
4 Separate references identified pts with acetylcarnitine elevations

PRIS Genetic Links to Mitochondrial Disease
2 DNA Tests have linked PRIS patients with Mitochondrial genetic defects

PRIS Ultrastructural Link to Mitochondrial Disease
Crit care Med 46:e91-e94, 2018
Refs for: 5 Scientific Links: PRIS to Mitochondrial Disease

Similar Clinical Defects to Mitochondrial Fatty Acid Defects
Lactic Acidosis, Rhabdomyolysis, Cardiac Myopathies & Arrhythmias, Kidney & Liver dysfunction
Biochemistry of fatty acid B-oxidation J Inherit Metab Dis 33:469-477, 2010

Biochemical Links to: Elevated Acetylcar nitine derivatives
Impaired fatty acid oxidation in PRIS Lancet 357:606, 2001 Wolf et al
Propofol Related Infusion Syndrome Crit Care Med 46:e91-e94, 2018 J-P Vollmer et al

PRIS Genetic Links to Mitochondrial Disease
PRIS Heralding a Mitochondrial Disease Neurology 81:770-771, 2013 Savard, et al

PRIS Ultrastructural Link to Mitochondrial Disease Crit care Med 46:e91-e94, 2018

Low Carbohydrate / Pre-Op Fasting links to PRIS
Anesthetic Considerations in Mitochondrial Diseases

Sandra Sirrs, Peter Duncan & Margaret O’Riley

Recommendations

● Avoid Ringer’s Lactate as pts may have pre-existing lactic acidosis
● Try to schedule surgery first thing in the morning to minimize time in NPO
● Minor Surgery: have patient arrive early AM for dextrose infusion
● Major Surgery: start dextrose fluids when pt placed on NPO
● Intraop: monitor temperature, heart rhythm, glucose and electrolytes.
● Post op: careful observation prior to extubation as prolonged effects of NMJs
If hospitalized, it is imperative, according to FOD specialists, that a **10% dextrose IV** (5% is NOT enough) is started immediately following blood chemistry **samplings** waiting hours for the results before putting in the IV can be fatal when an FOD child/adult is in crisis. The **10% dextrose/glucose gives NEEDED FUEL** to the brain and body that normal saline IV cannot provide. Also note that even though the child/adult may appear to be hydrated, it does NOT mean they are not heading toward a crisis ~ they may have fluids onboard, but they **NEED CALORIES to help them prevent and/or get through a metabolic crisis/stress.** Many experts also recommend the **use of carnitine** (Carnitor@ or Levocarnitine - prescribed drugs) and if one cannot keep oral carnitine down due to vomiting, there is an IV carnitine available for emergencies.

https://www.fodsupport.org/
Consensus recommendations for anesthesia

1. Patients with mitochondrial diseases are at an increased risk of anesthesia-related complications.

2. Preoperative preparation of patients with mitochondrial disease is crucial to their perioperative outcome. Patients should minimize preoperative fasting and have glucose added to their perioperative IV fluids, unless they are on a ketogenic diet or have been demonstrated to have adverse reaction to higher glucose intake.

3. Caution must be used with volatile anesthetics because mitochondrial patients may potentially be hypersensitive.

4. Caution must be used with muscle relaxants in those mitochondrial patients with a preexisting myopathy or decreased respiratory drive.

5. Mitochondrial patients may be at a higher risk for propofol infusion syndrome and propofol use should be avoided or limited to short procedures.

6. One should consider slow titration and adjustment of volatile and parenteral anesthetics to minimize hemodynamic changes in mitochondrial patients.

7. Local anesthetics are generally well-tolerated in patients with mitochondrial defects.

8. There is no clear established link between malignant hyperthermia and mitochondrial disease.
Mitochondrial decompensation: catabolism

“When individuals with metabolic disease undergo a normal or abnormal catabolic stress, they begin turning over protein, carbohydrate and fat stores as they should - but due to the inherent chemical disruption create more than normal levels of toxic substances and less than normal levels of the required product.”

<table>
<thead>
<tr>
<th>Stressor</th>
<th>Suggested action</th>
</tr>
</thead>
<tbody>
<tr>
<td>fasting</td>
<td>Perform surgery first thing in the morning if possible; run D10 W when NPO</td>
</tr>
<tr>
<td>hypoglycemia</td>
<td>Intraoperative glucose monitoring</td>
</tr>
<tr>
<td>hyperglycemia</td>
<td>Intraoperative glucose monitoring and use of insulin infusion if glucose &gt;8 mmol/L</td>
</tr>
<tr>
<td>hypotension</td>
<td>Support with fluids; avoid lactate-containing intravenous solutions</td>
</tr>
<tr>
<td>sepsis</td>
<td>Standard management</td>
</tr>
<tr>
<td>hypothermia</td>
<td>Intraoperative temperature monitoring, warm fluids prior to infusion</td>
</tr>
</tbody>
</table>

Table 1. Metabolic stressors that can lead to decompensation in patients with mitochondrial disease

Treatment of catabolism

Once a patient is already in a catabolic state, treatment should begin immediately. This treatment includes:
- Stop the oral intake of a toxic compound, including any applicable medications (usually by making the patient NPO)
- Provide IV fluids with dextrose
- Give IV fluids at a higher than maintenance rate
- Insulin may be needed, not only to prevent hyperglycemia but also to provide the body with a hormonal signal to stop catabolism
- Monitor routine chemistries, glucose, ammonia, ketones and liver function for metabolic derangements
- Correct any metabolic derangements

1) Hypoglycemia - if hypoglycemic, administer 1-2 g/kg of glucose IV STAT; follow with (at least) a 10% glucose solution

2) Metabolic acidosis - administer NaHCO3 as a bolus (1 mEq/kg) if acutely acidic with pH < 7.22 or bicarb level < 14, followed by a continuous infusion.

3) Hyperammonemia - the elevated ammonia reflects a secondary inhibition of the urea cycle. As treatment for the metabolic decompensation proceeds, the ammonia level should diminish. A level > 200 may require treatment.

- Provide medications such as IV levo-carnitine (100 mg/kg/day, divided tid) to facilitate the removal of toxic metabolic species
- Treat any underlying infection and fever
Mitochondrial Disease Websites

United Mitochondrial Disease Foundation:  http://www.umdf.org/

Foundation for Mitochondrial Medicine:  http://mitochondrialdiseases.org/

Fatty Acid Oxidation Disorders (FOD):  https://www.fodsupport.org/

UK International Links for Mitochondrial Dis:  http://mitochondrialdisease.nhs.uk/patient-area/useful-links/
Propofol Truths

Propofol is a **yellowish oil** liquid: immiscible in water

Propofol short duration of action is due to lipid vehicle in the plasma

Propofol infusion rates increases overtime related to elevated blood lipids

Resistance to a Propofol induction is attributable to pre-existing hyperlipidemia

Propofol and morphine* should be not be given in people allergic to red wine.

PRIS is linked to Mitochondrial Disease by 5 separate lines of evidence

* Sulfite preserved propofol and morphine. Sulfite food preservatives induced fatal bronchospasms in a dozen fast food patrons in the mid-1980s. FDA subsequently banned sulfite as fresh food preservatives
Reviews: Lipid Bolus Rescues

Lipid Rescue Inventor: Dr. Guy Weinberg

**Local Anesthetics Poisoning**

Partition Constant & Volume of Distribution as .... Lipid Rescue
Clinical Toxicology (2011) Early Online: 1-9 French D et al

Lipid Emulsion for LA Systemic Toxicity
Anesthesiology Research & Practice 2012: 1-11 Ciechanowicz, S and Patil, V

**Nonlocal Anesthetic Poisoning:**

Intralipid emulsion treatment...antidote in lipophilic drug toxicity


Review of Lipid Emulsion in Nonlocal Anesthetic Poisoning

Pediatr Emer Care 30:427-436, 2014, Kostick, MA and Gorelick, M (Wisconsin)
Propofol is **not** a "Cardiac depressant"

"In rat models, Zhou et al (36, 37) have demonstrated that propofol is a cardiac depressant by antagonism of B-receptors and Calcium channel binding with resulting decrease in myocardial contractility."

Ref 36: Anesth Analg 99:221-226, 2004  *in vitro* water-based study

Ref 37: Anesthesiology 86:670-6, 1997  *in vitro* water + .2% albumin study

Zhou Level 50uM  Recalculated level for oil in water X6,000  =  300,000 uM

Sedation in vivo blood levels 5-30 uM