Propofol: **NEW** Insights

Physical Chemistry & Pharmacology

Propofol Infusion Syndrome PRIS:

Separating Facts from Fiction

Dr. David Goodale

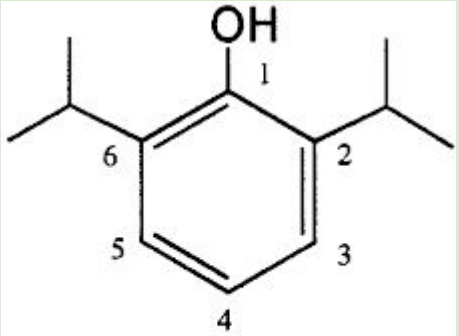
Executive Clinical Director

DBG Pharma LLC

dbgpharma@gmail.com

No Conflicts

Propofol (molecule) Chemistry



2,6-Diisopropylphenol
(propofol)

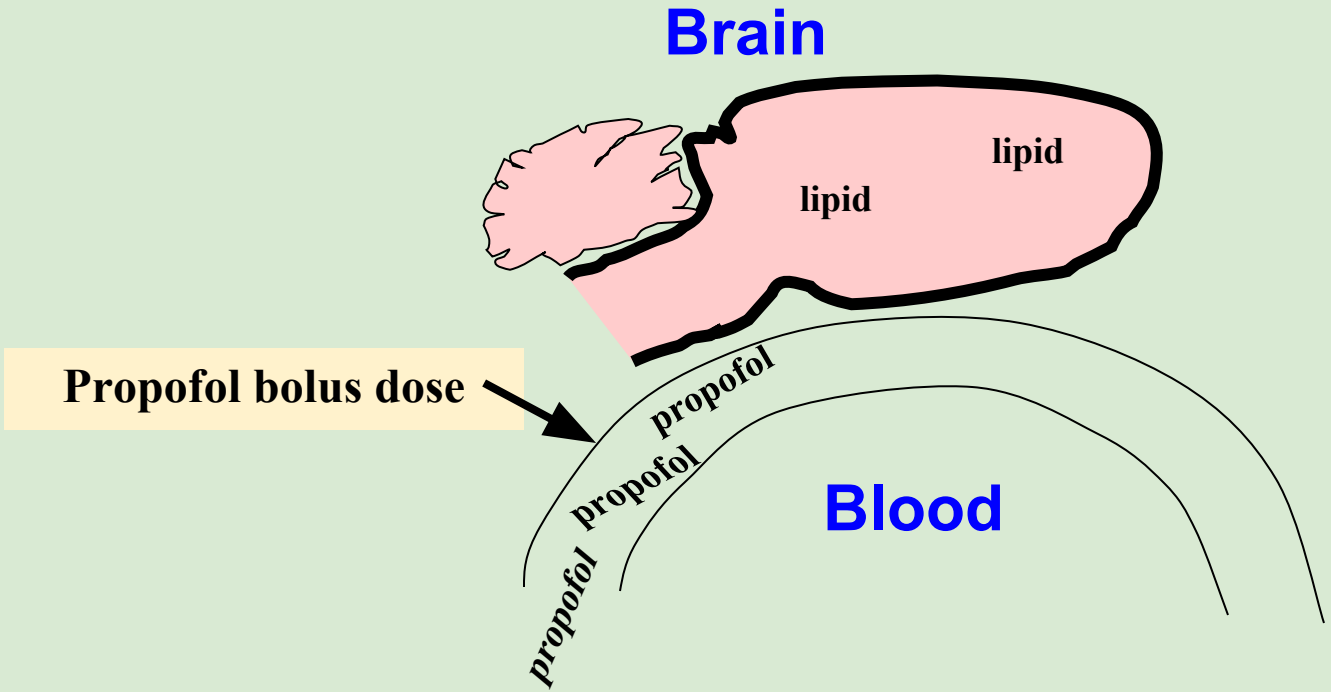
Propofol is a yellow oil liquid, Immiscible in Water

"Insoluble in Water" PubChem Nat'l Library of Medicine
Toxicohttps://toxnet.nlm.nih.gov/cgi-bin/sis/search2/f?./temp/~R1wVSx

Greater potency means greater lipophilicity

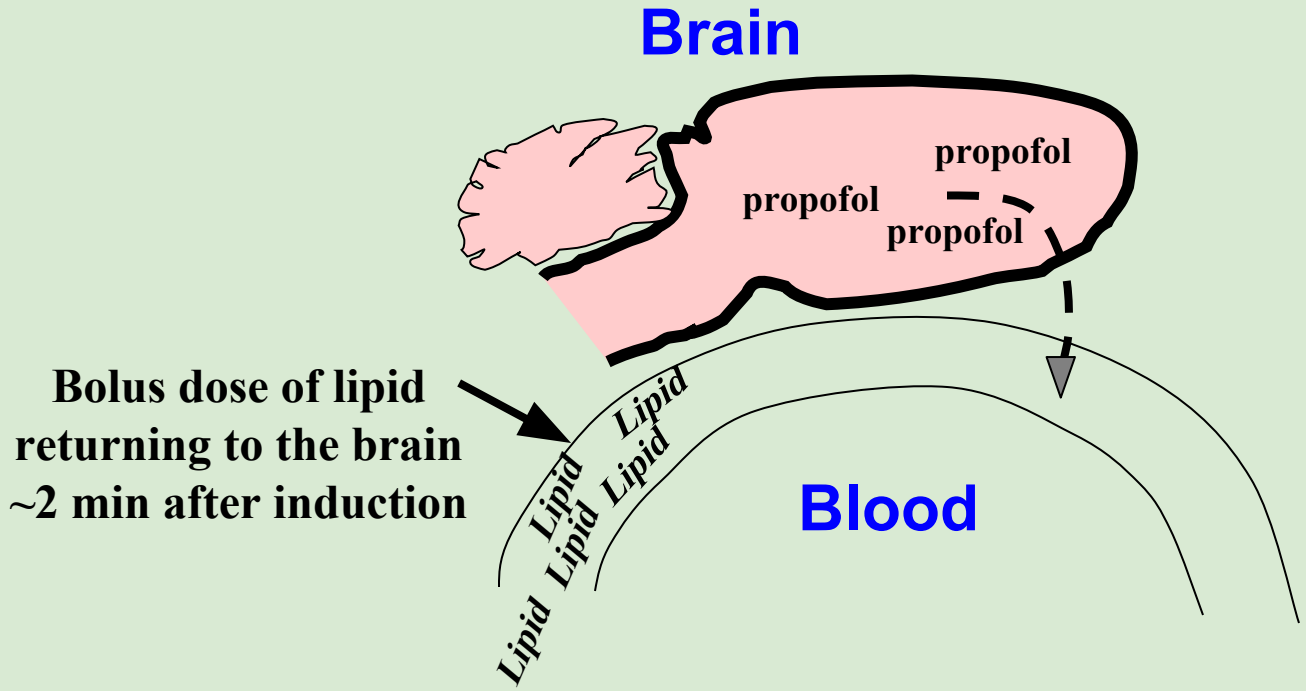
Induction of Anesthesia:

Drug equilibrium between **blood & brain**



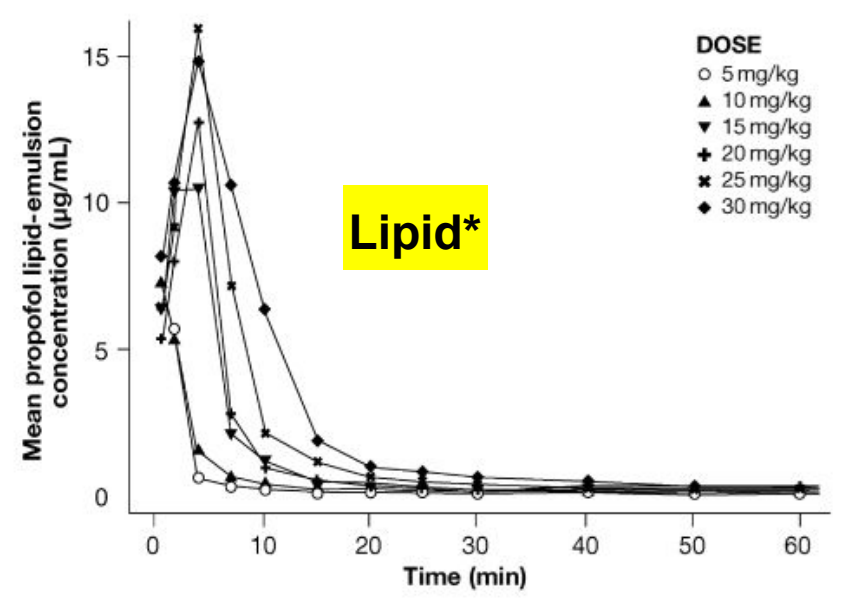
Short Duration of Action:

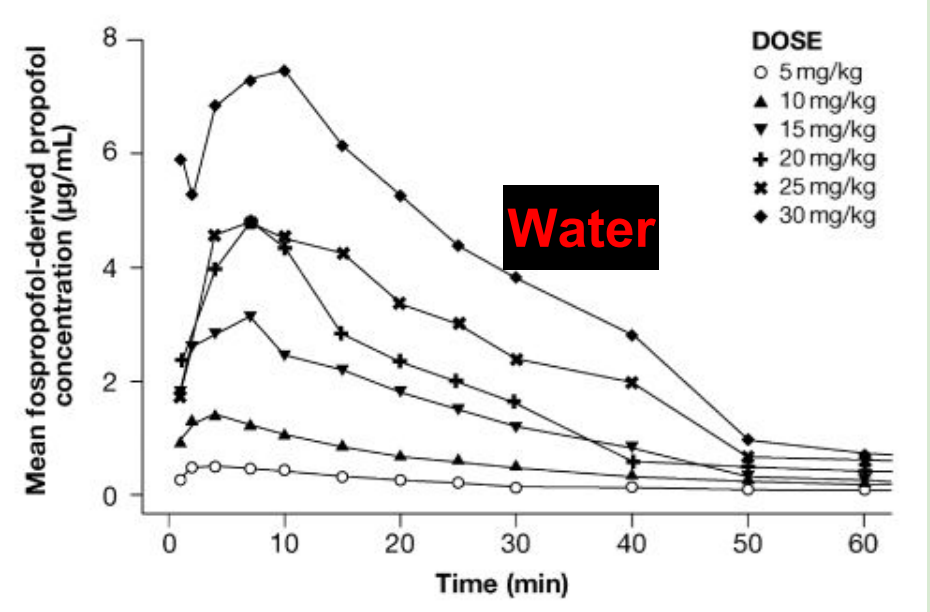
Intralipid pulls propofol out of **brain**



Short-acting: Propofol with Lipid

Longer-acting: propofol with water





* **Human Ref**: figure modified from Rex, D K, Alimentary Pharmacol & Therap 24: 163-171, 2006

Animal Ref: Dutta, S et al: J Pharm Pharmacol 50: 37-42, 1998

Propofol tolerance: Increasing dose requirements with repeated dosages

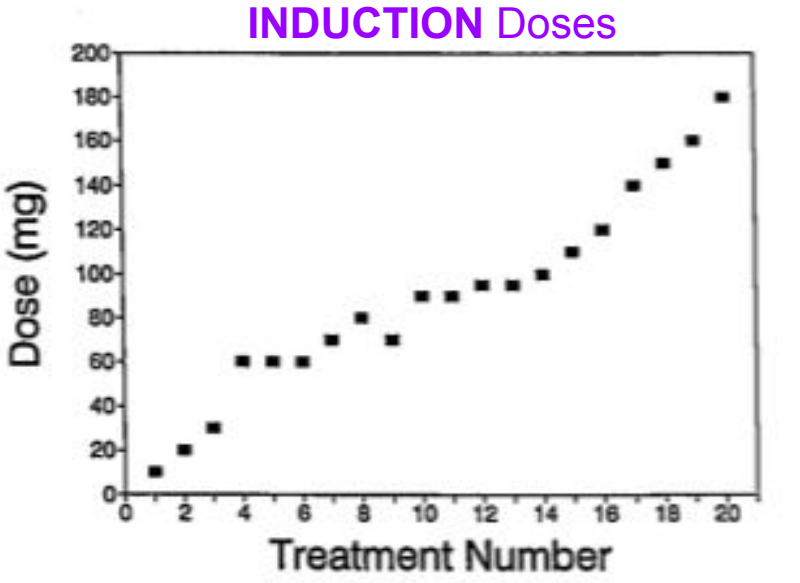


FIG. 1. Induction dose of propofol *versus* treatment number.

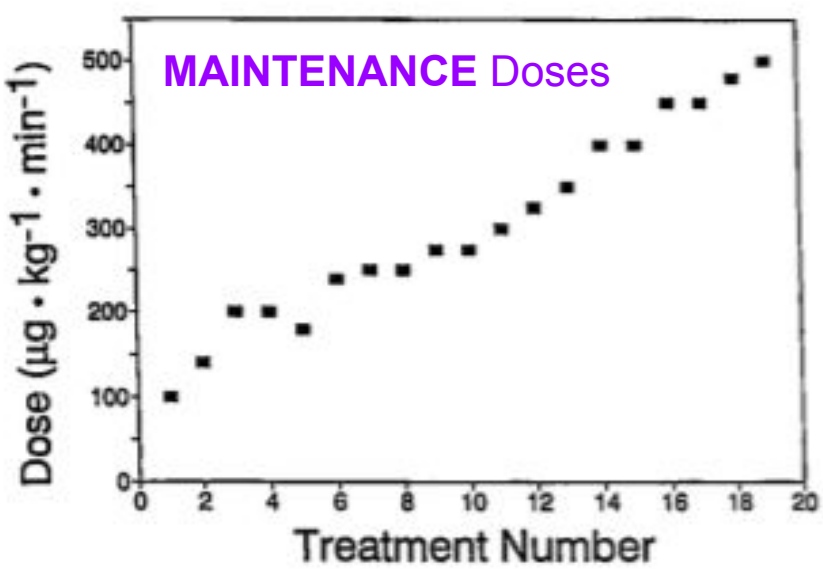


FIG. 2. Maintenance dose of propofol *versus* treatment number.

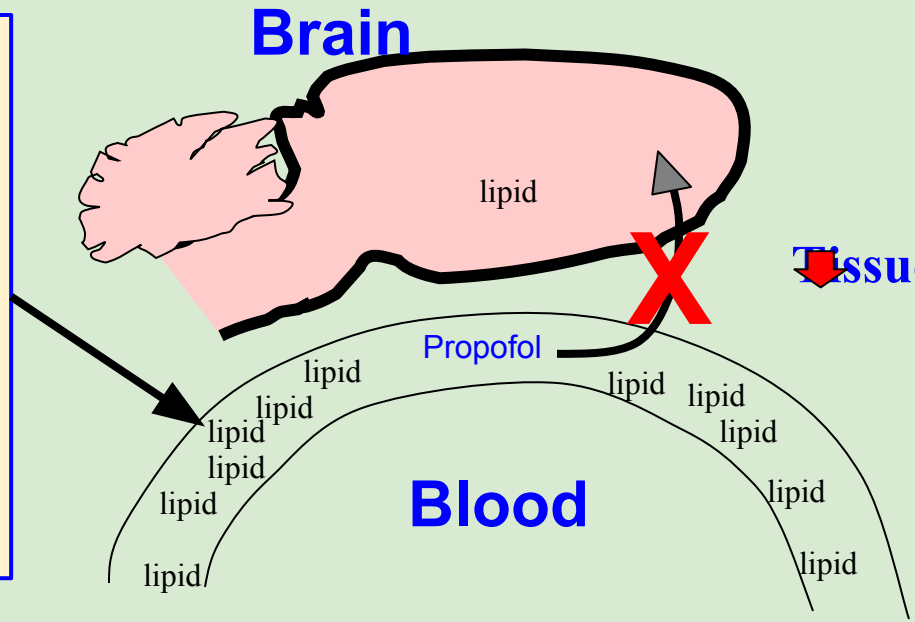
Propofol Tolerances in a pediatric patient, Anesthesiology 77:828-829, 1992 TR Deer and GF Rich

Intralipid *'active'* Vehicle

Lipophilic-Drug Sink in Blood

Hyperlipidemia

- ⬆ Dosage Creep
- ⬇ **Efficacy:** Propofol [1,2]



Tissue Distribution: Blood
Lipids Bind
Propofol

1 Brimacombe, J Resistance to Anesthetic Agents, Anaesthesia and Intensive care 22:236, 1994

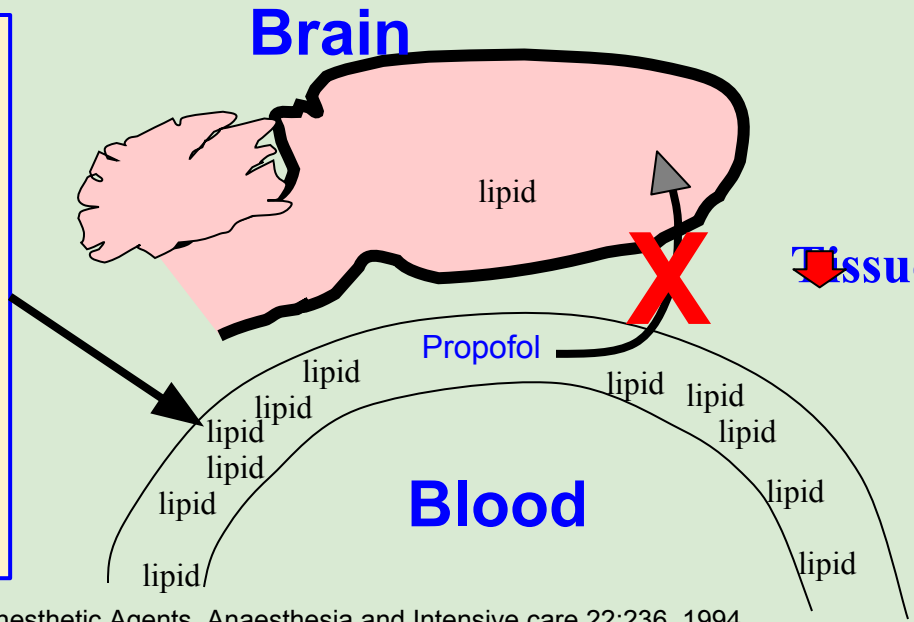
2 Brock-Utne J.G. (2013) Case 62: A Case of Acute Lymphoblastic Leukemia (ALL). In: Near Misses in Pediatric Anesthesia. Springer, NY, NY

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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3 MacLaren, et al. Warfarin Resistance… Pharmacotherapy 17(6): 1331-1337, 1997
4 Cheung, LK et al Warfarin Resistance...Amer J Med Sciences 343(3): 255-258, 2012

Blood Lipids:

Reduced Efficacy of Lipid Soluble Inhaled Anesthetics

Water Soluble

Lipid Soluble

POTENCY & LIPOSOLUBILITY

ANESTHETIC	MAC (%)	λ(oil:gas)
Nitrous oxide	104	1.4
Desflurane	6	19
Sevoflurane	2	51
Enflurane	1.7	98
Isoflurane	1.4	98
Halothane	0.75	224
Methoxuflurane	0.16	960

The potency of an anesthetic increases as its liposolubility increases.

Blood Lipids:

Reduced Efficacy in Piperidine Analgesics

Hydrophilic vs Lipophilic

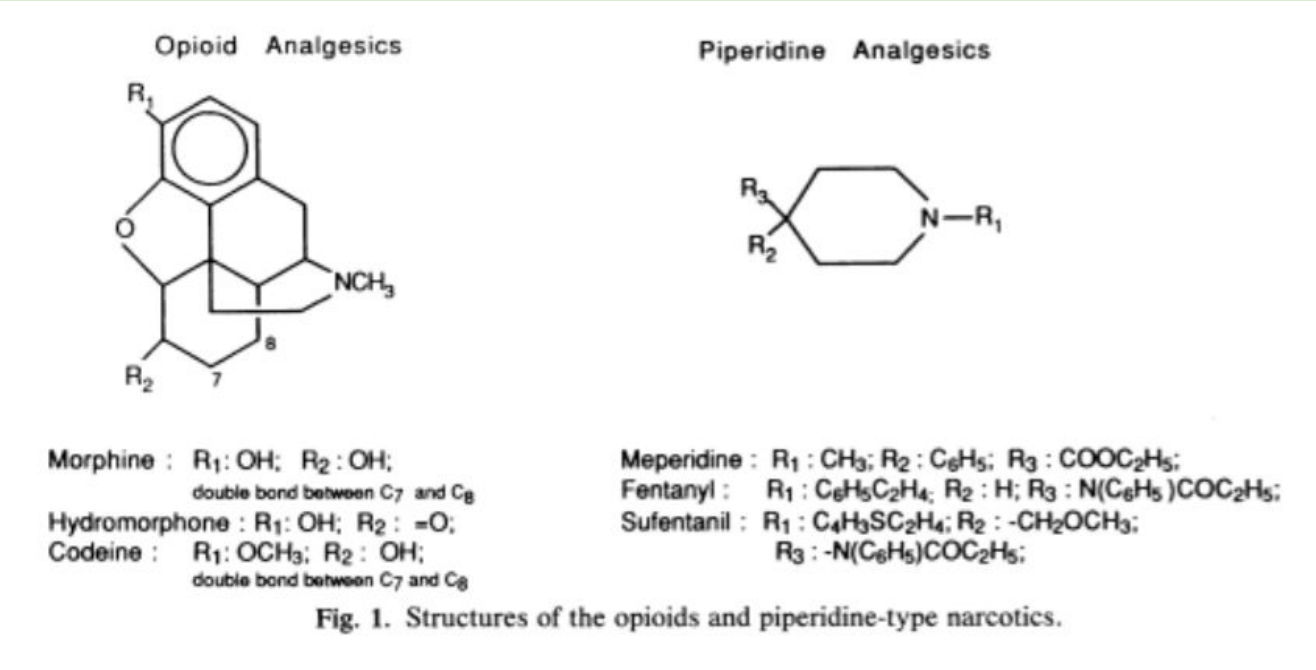
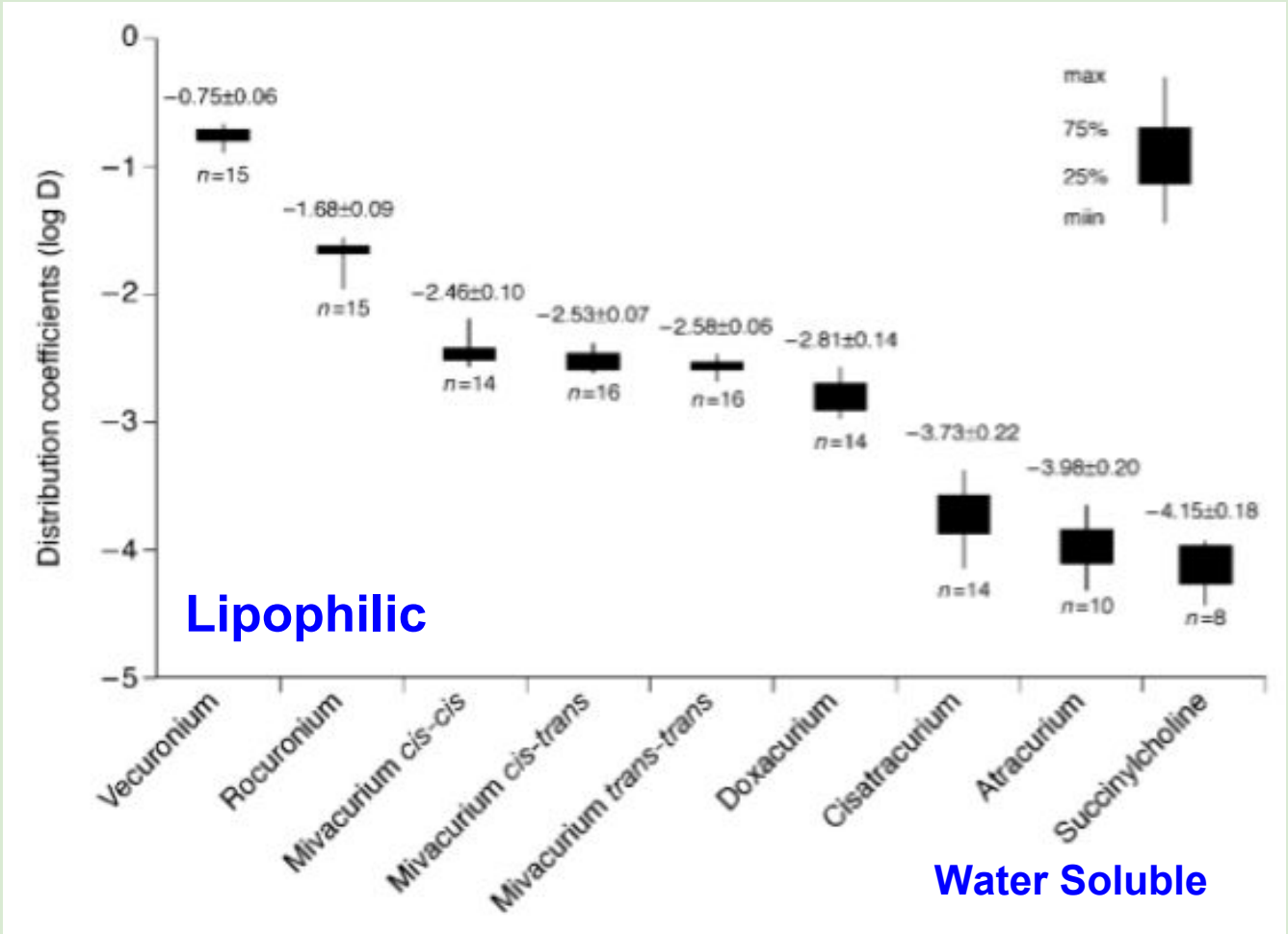


Fig. 1. Structures of the opioids and piperidine-type narcotics.

Roy, SD and Flynn, GL, Pharmaceutical Research 5(9): 580-586, 1988

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
- 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."***
  - BJA 116(1):77-82, 2016. Asserhoj, LL et al
- 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

DavId 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**

Propofol	Sedation	5-30 umol	Blood + Lipid	
Mitochondria				
Branca 1991	Rat liver mitochondria	0-75 umol	Water	No effect on ATP,
Branca 1991	Rat liver mitochondria	0-100	Water	Small Membrane potential
Rogoulet '96	Rat liver mitochondria	25-400	Water	Inhibits Complex 1 & H^+ leak
Schenkman 2000	Guinea pig heart	50, 100, 200	Water/ albumin	No mitochondria studied
Sumi 2018	H neuroblast & Myoblast	25, 50, 100	Water	Inhibits Complex I, II, III
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

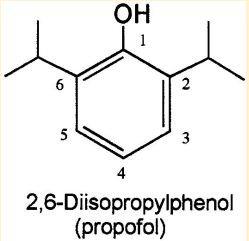
Study Observations:

- 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

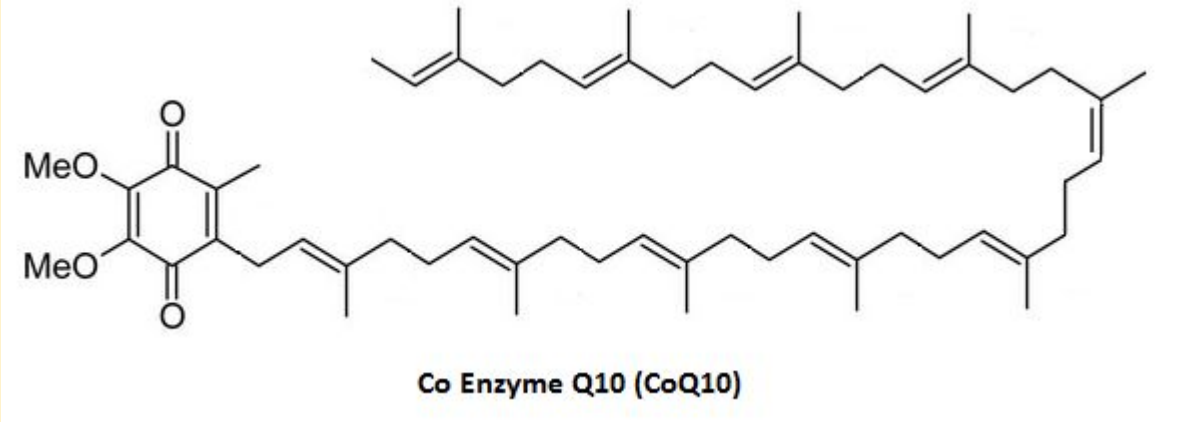
Propofol does not depress cardiac function

Propofol is a great sympatholytic agent: can be a pt benefit or detriment

Propofol has no similarity with CoQ10



2,6-Diisopropylphenol
(propofol)



Co Enzyme Q10 (CoQ10)

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

GLOBAL
MITOCHONDRIAL DISEASE
AWARENESS WEEK

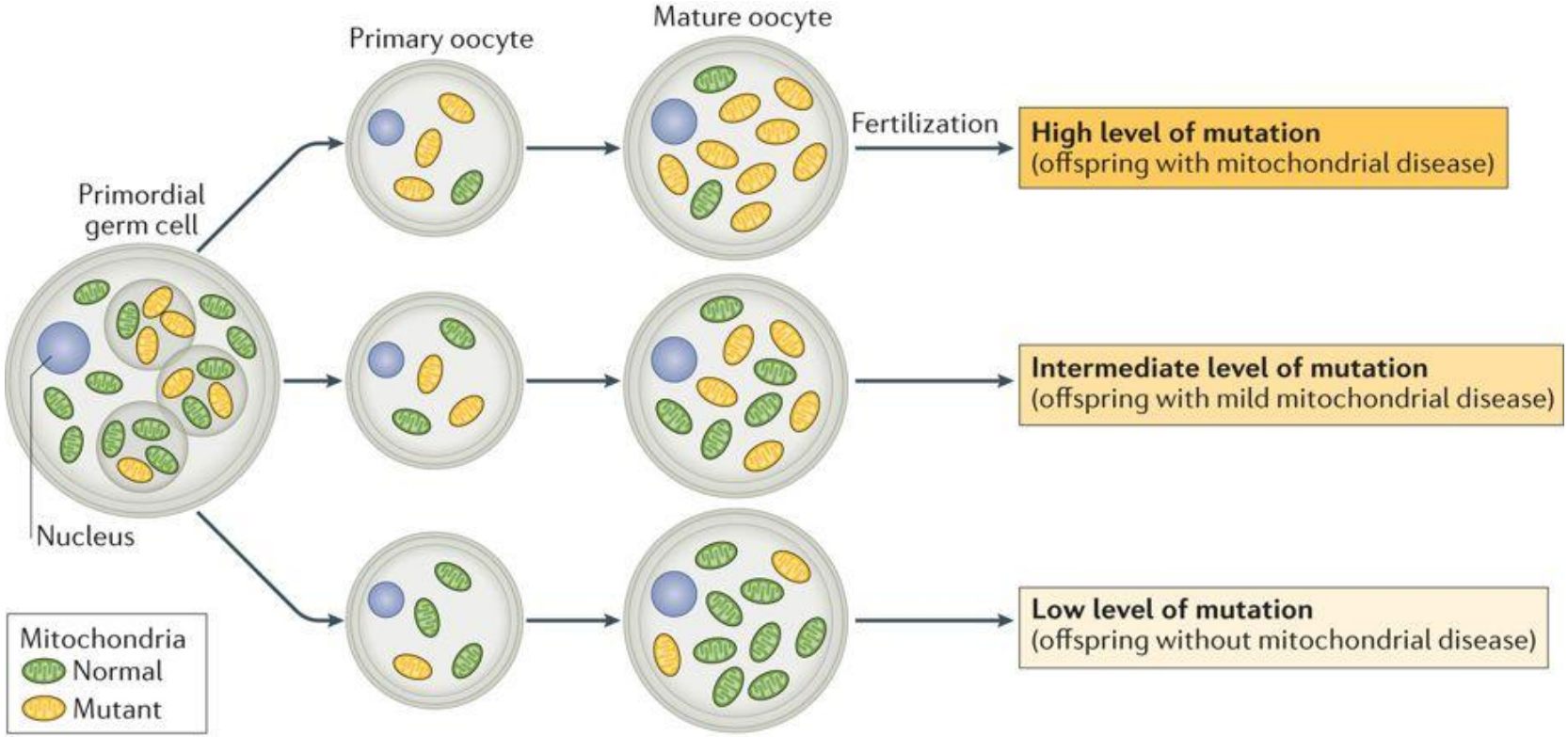
MITO FACT

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



44 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

Ref: Annu Rev Physiol 78:23-44, 2016
Houten, SM et al.

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

Name	Most common alias	Gene	EC number	Phenotype MIM number
Carnitine shuttle				
Carnitine palmitoyltransferase 1A (liver)	CPT1A	*CPT1A*	2.3.1.21	255120
Carnitine palmitoyltransferase 1B (muscle)	CPT1B	*CPT1B*	2.3.1.21	Not reported
Carnitine acylcarnitine translocase	CACT	*SLC25A20*	NA	212138
Carnitine palmitoyltransferase 2	CPT2	*CPT2*	2.3.1.21	600649; 608836; 255110; 614212
Organic cation/carnitine transporter	OCTN2	*SLC22A5*	NA	212140
Fatty acid β-oxidation cycle				
Very long chain acyl-CoA dehydrogenase	VLCAD	*ACADVL*	1.3.8.9	201475
Medium-chain acyl-CoA dehydrogenase	MCAD	*ACADM*	1.3.8.7	201450
Short-chain acyl-CoA dehydrogenase	SCAD	*ACADS*	1.3.8.1	201470
Mitochondrial trifunctional protein, alpha subunit	MTPα	*HADHA*	4.2.1.74; 1.1.1.211	609015; 609016
Mitochondrial trifunctional protein, beta subunit	MTPβ	*HADHB*	2.3.1.16	609015
Short-chain enoyl-CoA hydratase	Crotonase	*ECHS1*	4.2.1.150	616277
Short-chain (*S*)-3-hydroxyacyl-CoA dehydrogenase	SCHAD	*HADH*	1.1.1.35	231530; 609975
Medium-chain 3-ketoacyl-CoA thiolase	MCKAT	*ACAA2*	2.3.1.16	Not reported
Acetoacetyl-CoA thiolase	T2	*ACAT1*	2.3.1.9	203750
Long-chain acyl-CoA dehydrogenase	LCAD	*ACADL*	1.3.8.8	Not reported
Acyl-CoA dehydrogenase 9	ACAD9	*ACAD9*	1.3.8.9	611126
Auxiliary enzymes				
Δ3,Δ2-Enoyl-CoA isomerase 1	DCI	*ECI1*	5.3.3.8	Not reported
Δ3,Δ2-Enoyl-CoA isomerase 2	PECI	*ECI2*	5.3.3.8	Not reported
2,4-Dienoyl-CoA reductase	DECR	*DECR1*	1.3.1.34	Not reported
Δ3,5-Δ2,4-Dienoyl-CoA isomerase	ECH1	*ECH1*	Not assigned	Not reported

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

Fuel Sources

Glucose
Fatty Acids
Amino Acids

ATP

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:

Component	10%
Triglycerides	100 g
Phospholipid	12 g
Glycerol	22.5 g
Water	867 mL
Polyunsaturated Fatty Acids (PUFA)	62 g
Saturated Fat	21 g
P/S Ratio	3.0
Tocopherol	
Total Tocopherol	71 mg (41-111 mg)
Alpha Tocopherol	6 mg (2-19 mg)
Gamma Tocopherol	40 mg (15-72 mg)
Delta Tocopherol	24 mg (11-58 mg)
Vitamin E Activity*	15 mg (22 I.U.)
Vitamin E Activity/ PUFA (Min. Req. =0.4)	0.24
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++	<0.001 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”

J Parenter Enteral Nutr 42(3): 581-586, 2018 Zweers et al

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**

Lactic Acidosis in **80%** of MD patients have elevated lactate without symptoms

Lactic acidemia & Mitochondrial Disease Molecular Genetics & Metabolism 89:3-13, 2006 Robinson, BH

- **Heart, skeletal muscle & kidney use fatty acids as energy fuel**

Cardiomyopathies / Rhythm disturbances in **61%** of LCFAD of MD pts

Rhabdomyolysis / Skeletal Muscle dysfunction in **53%** of LCFAD of MD pts

Liver & Kidney Dysfunction in _ % of LCFAD of MD pts

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 Acetylcarnitine derivatives

Rhabdomyolysis & pulmonary hypertension in a child Intensive Care Med 22(9):997, 1996, van Straaten

Impaired fatty acid oxidation in PRIS Lancet 357:606, 2001 Wolf et al

A Case of Propofol Toxicity: Pediatric Anesthesia 14(6): 505-508, 2004, Withington, DE 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

Inborn OxPhos defect...PRIS Acta Anaesth Scand 56(4):520-525, 2012 Vanlander, et al

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

Low Carbohydrate / Pre-Op Fasting links to PRIS

PRIS in anaesthesia & ICU Curr Opinion in Anaesthesiol 19(4):404-410, 2006 Fudickar et al.

Propofol & lack of dextrose in mitochondrial disease J Child Neurol 29(8):NP40-6, 2014. Mtaweh et al

UNITED MITOCHONDRIAL DISEASE FOUNDATION®

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

Fatty Acid Oxidation Disease ...support group

https://www.fodsupport.org/

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.

Mitochondrial Medicine Society Consensus Statement

19 Pediatric Centers of Excellence

Ref: Genetic Medicine 17(9): 15-16, 2015

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.”

http://www.kintera.org/atf/cf/%7B858ACD34-ECC3-472A-8794-39B92E103561%7D/Metabolic%20Precautions%20and%20ER%20Letter.pdf

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

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

Anesthetic Considerations in Mitochondrial Diseases @UMDF.org by Sirrs, S et al.
http://www.kintera.org/atf/cf/%7B858ACD34-ECC3-472A-8794-39B92E103561%7D/Dr.%20Sirrs.pdf
United Mitochondrial Disease Foundation (UMDF)

Treatment of Catabolism

by

Sumit Parikh, MD
Cleveland Clinic

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 $NaHCO_3$ as a bolus (1 mEq/kg) if acutely acidotic 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

Amer J of Emergency Med 32: 1103-1108, 2014 Cevik et al (Turkey)

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