

APSF Vision

New Era in Anesthesia:

Ultra-fast, Safer Therapeutic Anesthesia

Dr. David B Goodale

Executive Clinical Director

DBG Pharma LLC

dbgpharma@gmail.com

No Conflicts

AZD3043 References

Preclinical Trials

Possible binding sites and interactions of propanidid and AZD3043 within the γ -aminobutyric acid type A receptor (GABAAR).

Wang S, Liu Q, Li X, Zhao X, Qiu L, Lin J.

J Biomol Struct Dyn. 2017 Nov 29:1-12. doi: 10.1080/07391102.2017.1403959

Reduced efficacy of the intravenous anesthetic agent AZD3043 at GABA(A) receptors with β 2 (N289M) and β 3 (N290M) point-mutations.

Jonsson Fagerlund M, Sjödin J, Dabrowski MA, Krupp J.

Eur J Pharmacol. 2012 Nov 5;694(1-3):13-9.

AZD-3043: a novel, metabolically labile sedative-hypnotic agent with rapid and predictable emergence from hypnosis.

Egan TD, Obara S, Jenkins TE, Jaw-Tsai SS, Amagasu S, Cook DR, Steffensen SC, Beattie DT.

Anesthesiology. 2012 Jun;116(6):1267-77.

Phenyl acetate derivatives, fluorine-substituted on the phenyl group, as rapid recovery hypnotic agents with reflex depression.

Zhang H, Xu X, Chen Y, Qiu Y, Liu X, Liu BF, Zhang G.

Eur J Med Chem. 2015 Jan 7;89:524-39.

AZD3043 References

Human Trials

A Recirculatory Model for Pharmacokinetics and the Effects on Bispectral Index After Intravenous Infusion of the Sedative and Anesthetic AZD3043 in Healthy Volunteers.

Björnsson MA, Norberg Å, Kalman S, Simonsson US.
Anesth Analg. 2015 Oct;121(4):904-13.

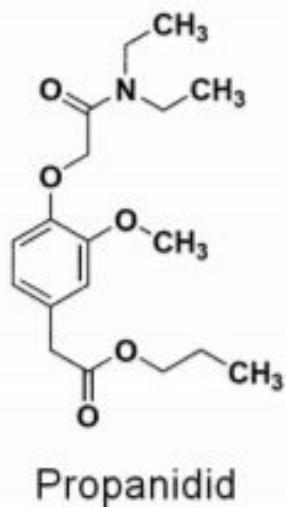
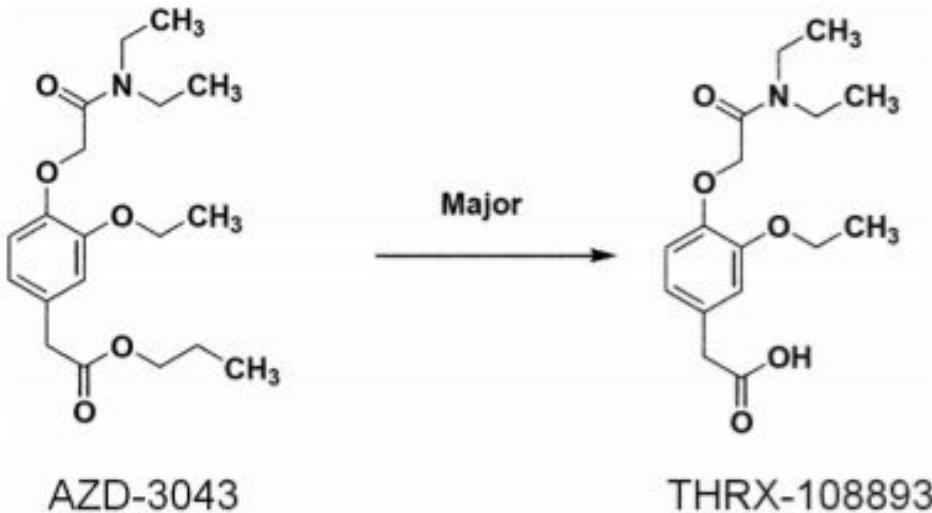
First Human Study of the Investigational Sedative and Anesthetic Drug AZD3043: A Dose-Escalation Trial to Assess the Safety, Pharmacokinetics, and Efficacy of a 30-Minute Infusion in Healthy Male Volunteers.

Kalman S, Koch P, Ahlén K, Kanes SJ, Barassin S, Björnsson MA, Norberg Å.
Anesth Analg. 2015 Oct;121(4):885-93.

A Bolus and Bolus Followed by Infusion Study of AZD3043, an Investigational Intravenous Drug for Sedation and Anesthesia: Safety and Pharmacodynamics in Healthy Male and Female Volunteers.

Norberg Å, Koch P, Kanes SJ, Björnsson MA, Barassin S, Ahlén K, Kalman S.
Anesth Analg. 2015 Oct;121(4):894-903.

AZD 3043 : Propanidid analog



Propanidid: Recovery appears faster

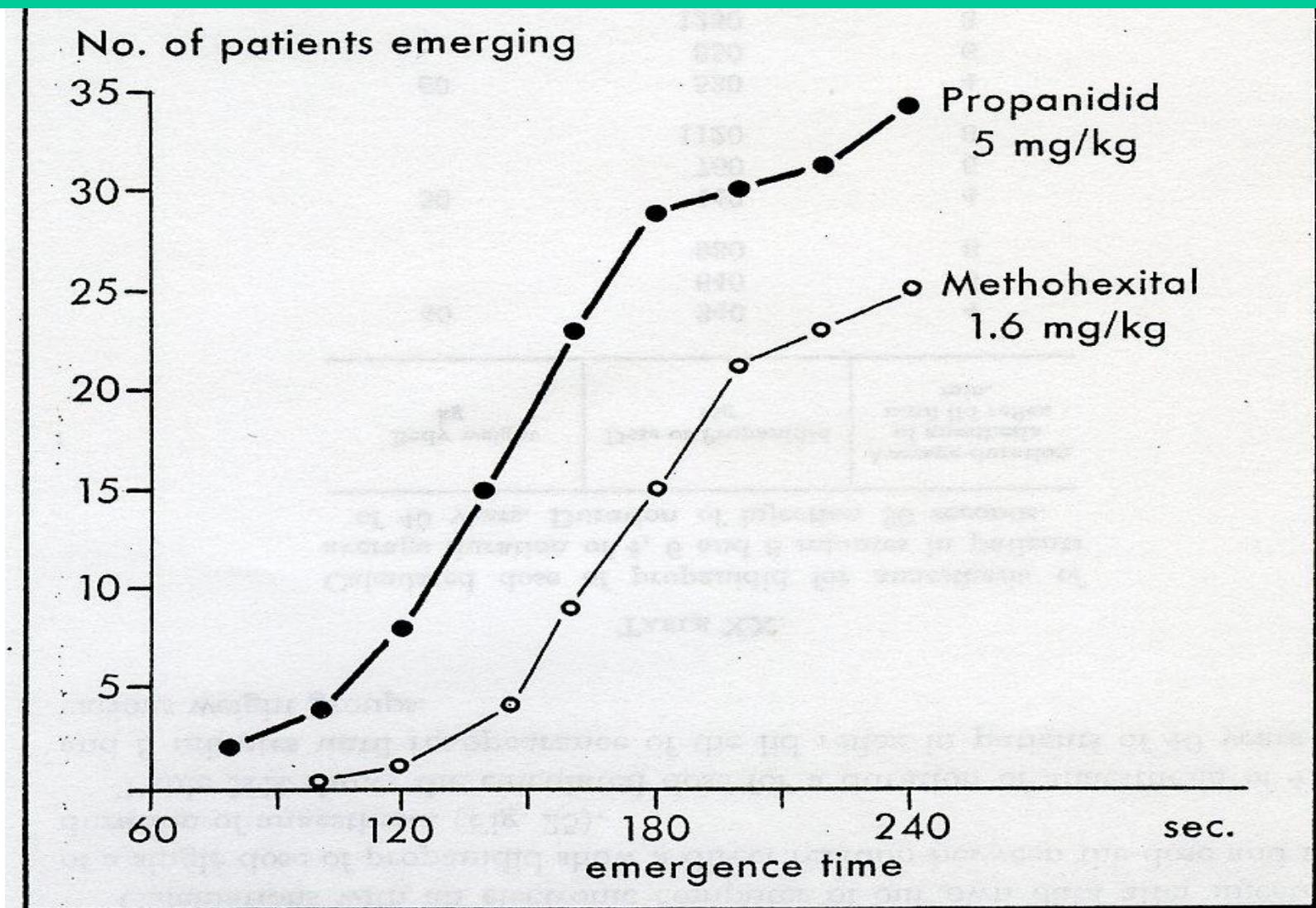
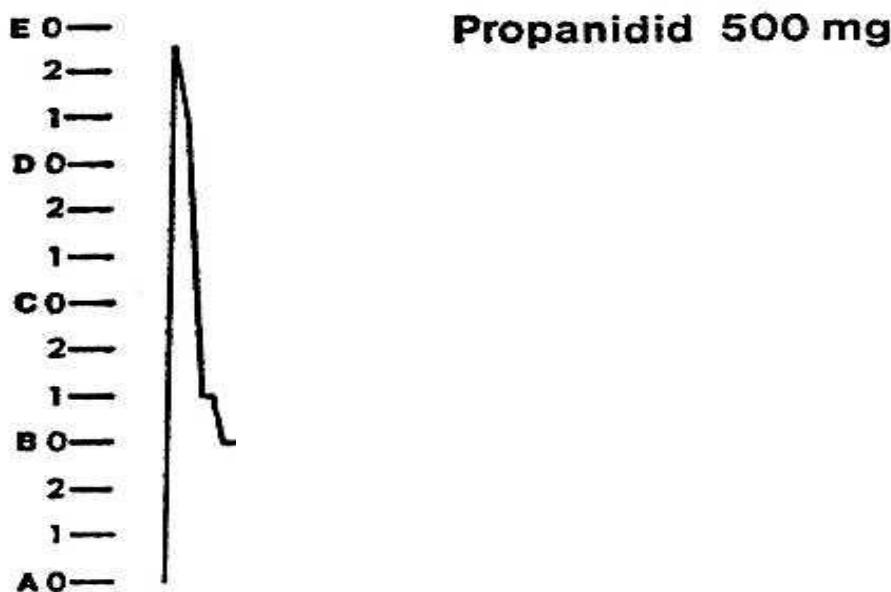
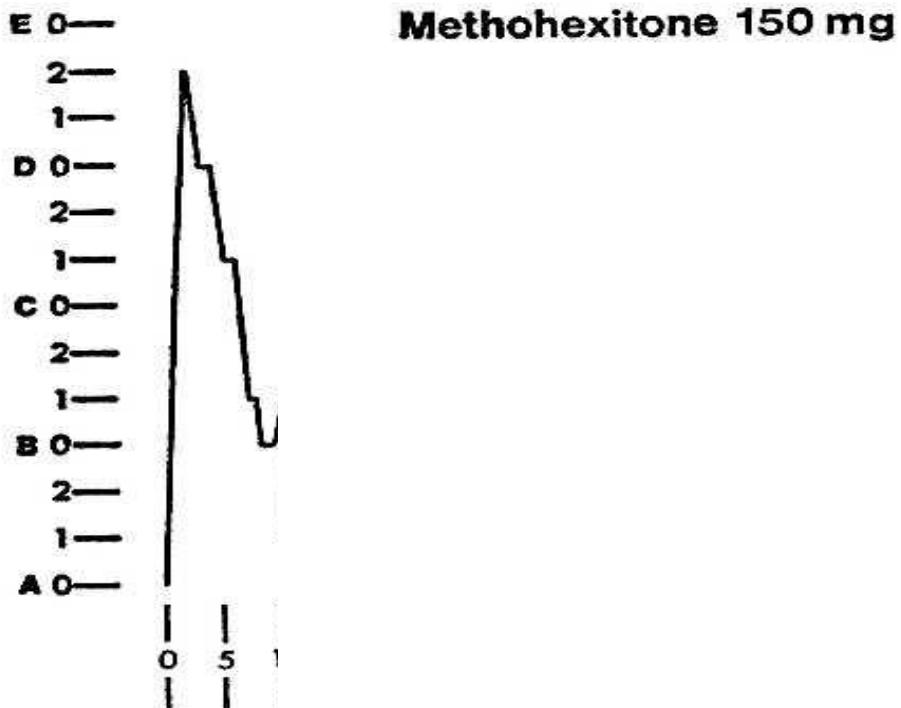


FIG. 24.—Comparison of the number of patients judged emerged from equipotent doses of propanidid and methohexital at the same time intervals.

Fast recovery: Eye opening & Response to command

Ref: 8. The Eugenols by Richard SJ Clarke pp 162-192 In: 'Intravenous Anaesthesia' by Dundee et al pub by Churchill Livingstone, 1974

EEG Loomis Classification for Sleep E = deep sleep.

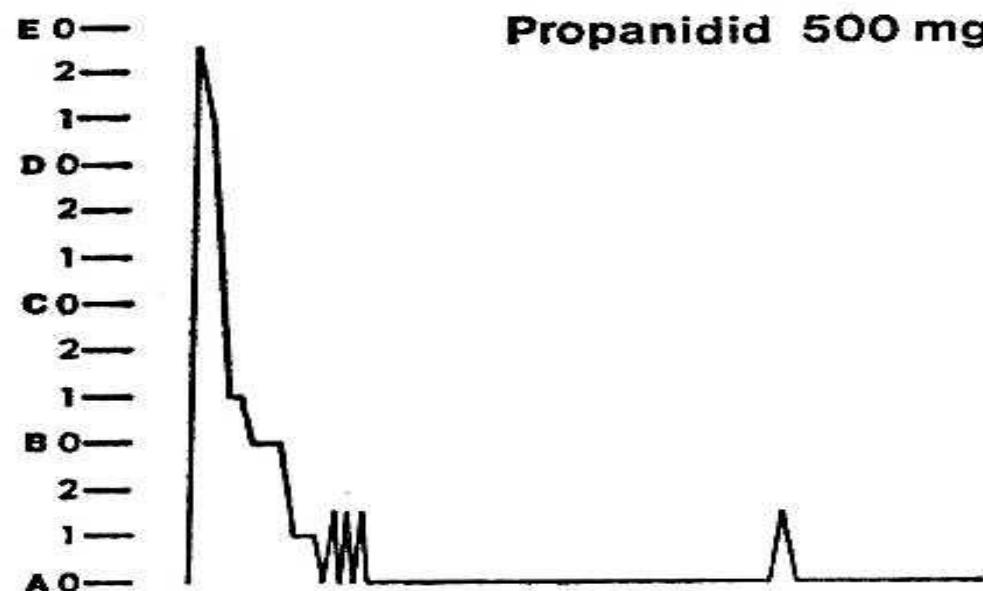
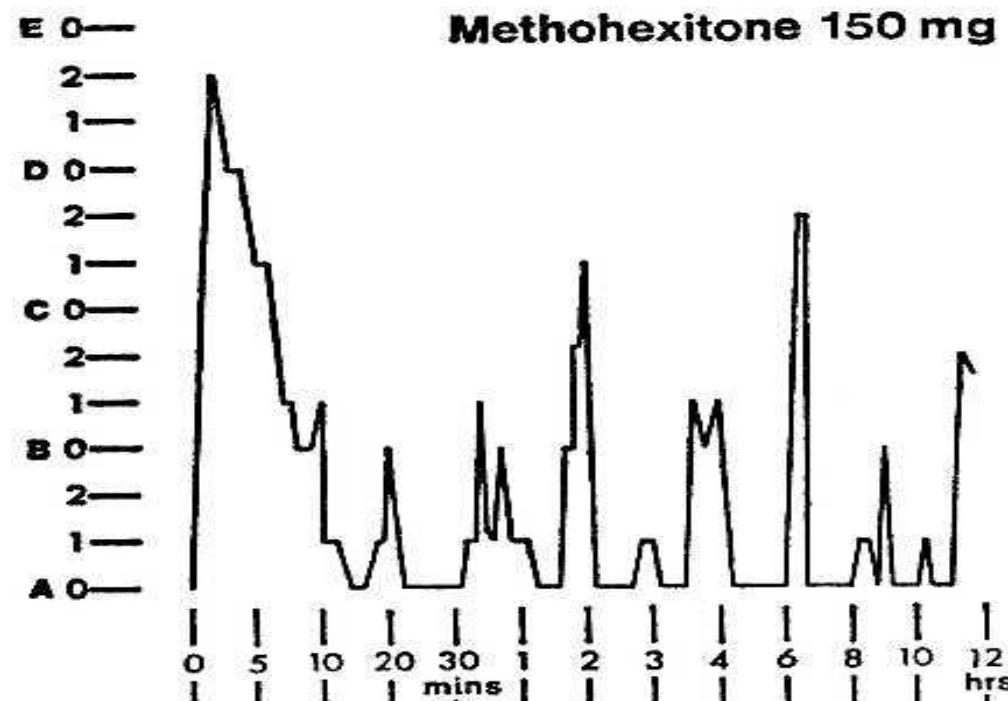


Responsive ?
Yes, but not
totally awake
Sleep spindles

Complete
Recovery:



Value



AZD 3043 : Human Studies

Human Studies

197 Phase 1 & 2 Patients

1. **125 Healthy Volunteers** 18-65 men & women
 - a. Study 1 53 volunteers 30' Infusion 1-81 mg/kg/hr
 - b. Study 2a 40 volunteers 1 min bolus infusion
 - Study 2b 32 volunteers 1min bolus (0.8-4 mg/kg) + 30' infusion (10-40 mg/kg/hr)
Anesth Analg 2015;121:904-13, Bjornsson,Marcus A
2. **72 Healthy Japanese Volunteers** 20-45 men & women
 - a. Study Part A Single Ascending Bolus Dose
 - b. Study Part B Single Bolus followed by Single Infusion Dose

AZD 3043 : Rapid Recovery

All subjects were able to walk 10 m

without support at their first assessment, 30 minutes after end of dosing, except for 1 subject in each of the 2 mg/kg bolus (part A) and 4 mg/kg bolus + 40 mg/kg/h 30-minute infusion (part B) dose groups, who passed this test at the subsequent assessment, 45 minutes after the end of dosing.

The rate of recovery was similar to subjects known to make

Xenon Clinical Trials at Clinical Trials.gov

Xenon-anesthesia on Patients Undergoing Major Liver-resection

A Test of Neural Inertia in Humans With Xenon

Influence of Xenon Anaesthesia on Transpulmonary Pressure and Tidal Volume Distribution

Xenon Against Postoperative Oxygen Impairment

Xenon Combined With Intraoperative Thoracic Epidural Analgesia

Cerebral and Spinal Protection of Xenon Post-conditioning in Patients Undergoing Aortic Dissection Repair

PaNeX: Partial Nephrectomy Under Xenon

Xenon Compared to Sevoflurane and Total Intravenous Anaesthesia for Coronary Artery Bypass Graft Surgery

Hip Fracture Surgery in Elderly Patients

Anesthesia for Obese Patients: Desflurane Versus Xenon

Effect of Xenon and Therapeutic Hypothermia, on the Brain and on Neurological Outcome Following Brain Ischemia in Cardiac Arrest Patients

General Anesthesia With Xenon in Inspiratory Concentrations of 50% and 70% and Total I.V. Anaesthesia.

Cardiovascular Safety of Xenon in General Anaesthesia, in Patient With Cardiovascular Risk in Non Cardiac Surgery

Xenon in Off-pump Coronary Artery Bypass Graft Surgery

Trial of Low-Dose Xenon For The Treatment Of Obsessive-Compulsive Disorder

A Pre- and Post- Coronary Artery Bypass Graft Implantation Disposed Application of Xenon

Depth of Hypnosis and Postoperative Nausea and Vomiting During Xenon Anaesthesia

Hemodynamic Stability During Carotid Endarterectomy.Comparison of LENOXe™ (Xenon 100% v/v) Versus Sevoflurane

Sympathetic Neural Outflow During Xenon Anesthesia in Humans

Xenon World-wide Approval outside USA

Year 2000 Xenon approved for use in Russia for Anesthesia

Year 2005 Xenon approved for use in Germany for Anesthesia

Year 2007 Xenon approved across EU for Anesthesia

Facilities that purify Oxygen & Nitrogen can adapt their machines to also purify Xenon if demand increases

2013 Felix Duo Closed-Circuit Apparatus cut consumption & costs for Xenon Anesthesia

Refs: Xenon: one small step for anaesthesia ... ?

Current Opinion in Anaesthesiology 19:382-384, 2006, Peter H Tonner

Xenon consumption during general surgery:

Medical Gas Research 3:12, 2013 Stoppe, C et al

Xenon Anesthesia Literature *

43 Total Clinical Trials

1,214 Xenon Patients

1,196 Comparator Patients

31 Randomized Controlled Clinical Trial Patients vs Inhalational Agents

841 Xenon Patients

836 Inhalational Patients

12 Randomized Controlled Clinical Trial Patients vs Propofol

373 Xenon Patients

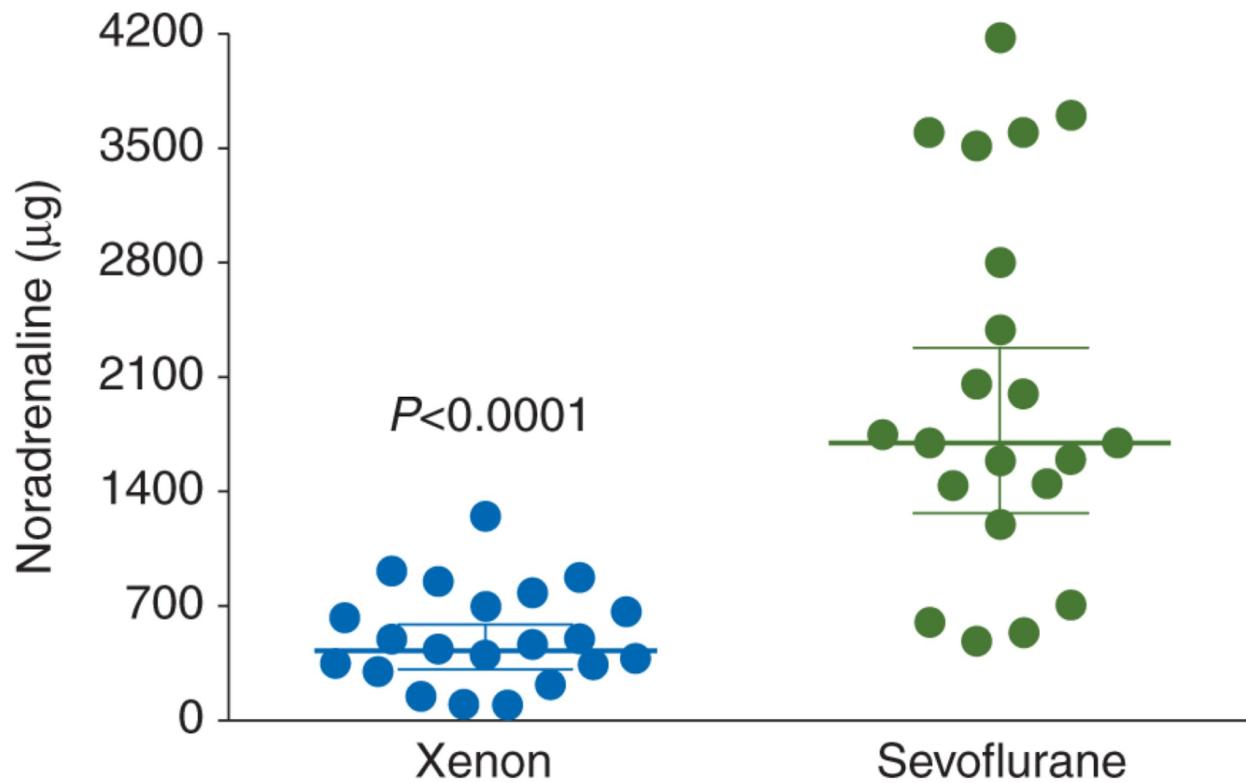
360 Propofol Patient

*Law, L, Lo, E & Gan, TJ: Xenon Anesthesia: A Systematic Review & Meta Analysis... A & A 122(3): 678-697, 2016

Clinical advantages of Xenon Anesthesia

1. **Rapid onset & Offset:** Extremely low blood/gas partition coefficient:
2. **Less cardiovascular depression**
3. **Neuroprotection (& cardiac protection)**
4. **Profound analgesia**

Ref: Brit J Anaesthesia 91(5):709-17, 2003



Xenon anaesthesia for patients undergoing off-pump coronary artery bypass graft surgery: a prospective randomized controlled pilot trial[†]

Br J Anaesth. 2015;115(4):550-559. doi:10.1093/bja/aev303

Br J Anaesth | © The Author 2015. Published by Oxford University Press on behalf of the British Journal of Anaesthesia. All rights reserved. For Permissions, please email: journals.permissions@oup.com

Xenon given FDA fast track status in USA

NEWS

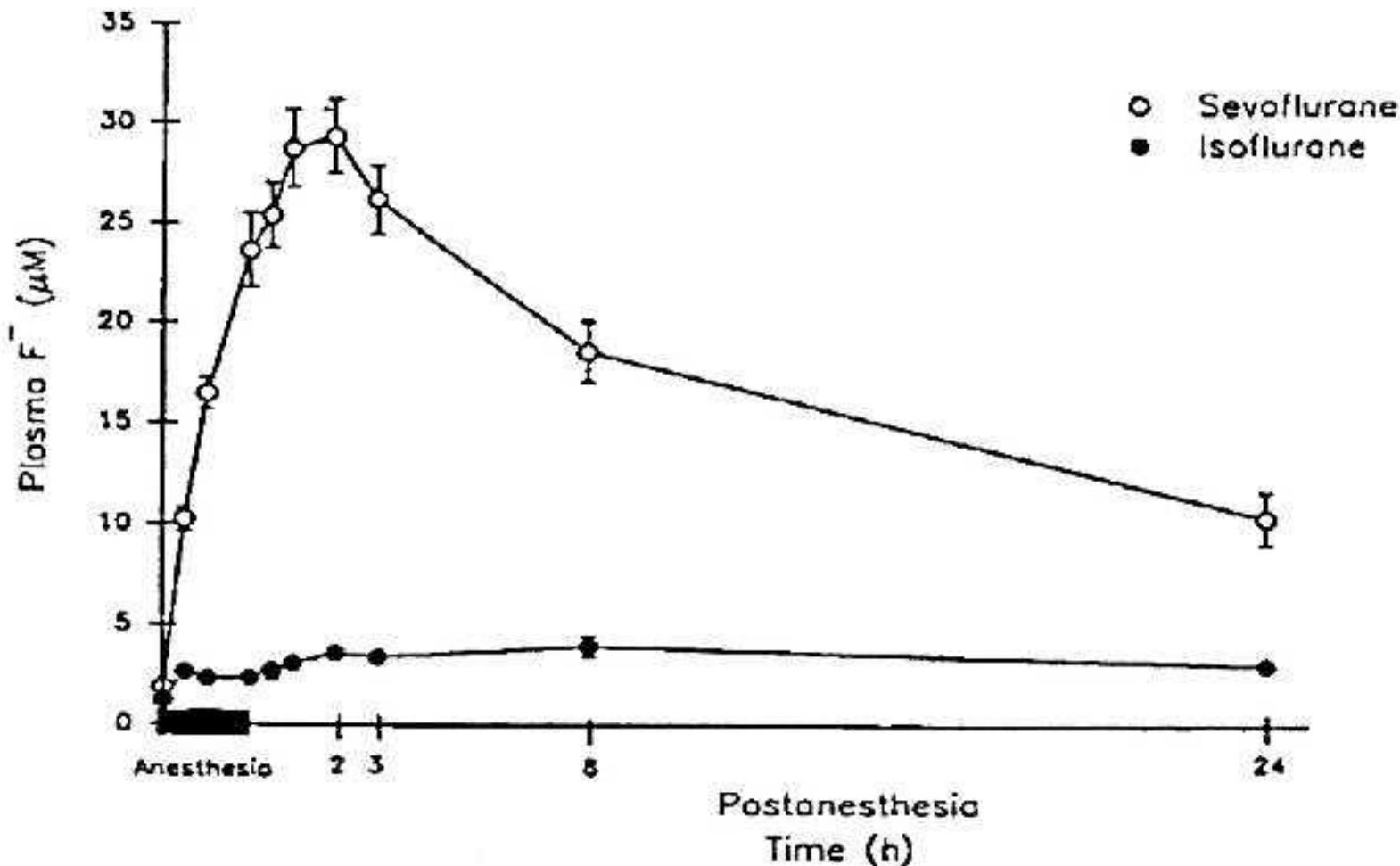
August 2018

MALLINCKRODT AND NPXE ANNOUNCE FDA FAST TRACK DESIGNATION FOR PHASE 3 TRIAL OF INHALED XENON GAS THERAPY

Mallinckrodt plc (NYSE: MNK), a leading global specialty pharmaceutical company, and NPXE Limited (“NeuroproteXeon” or “NPXE”) today announced that the United States Food and Drug Administration (FDA) recently granted Fast Track designation to NPXE’s Phase 3 trial of xenon gas for inhalation in Post Cardiac Arrest Patients. Fast Track designations are provided to drug candidates that “treat a serious condition and fill an unmet medical need.” Xenon gas for inhalation is an investigational drug, the safety and effectiveness of which have not yet been established.. ([Read More](#))

Sevoflurane Metabolism

Plasma Fluoride  @ 24 hours



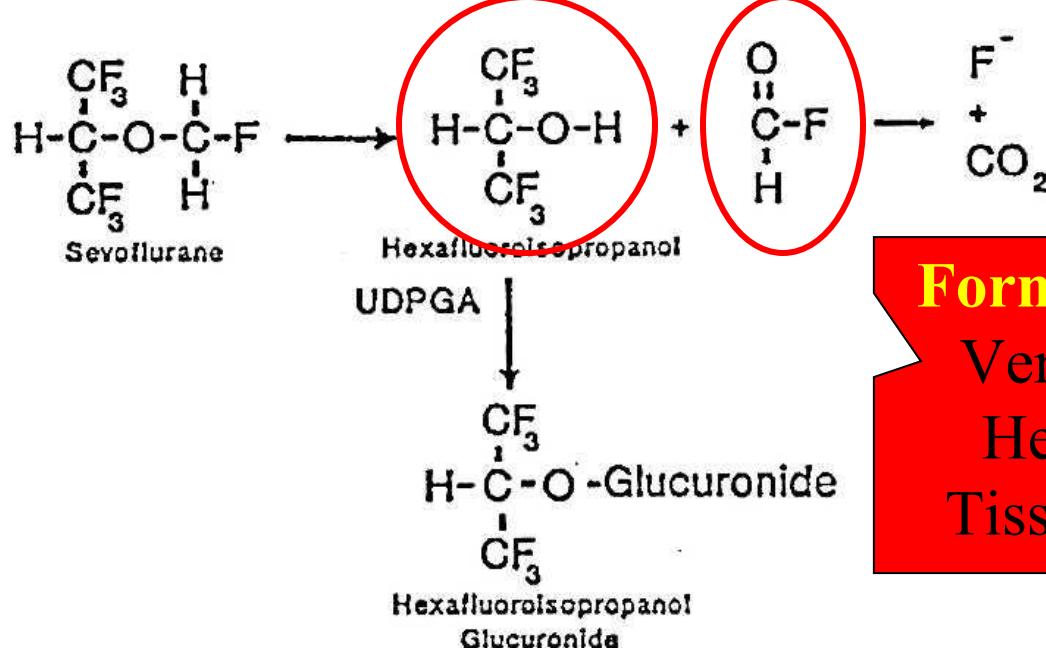
Highlight Sevoflurane Weaknesses

ANESTH ANALG
1992;74:231-5

FRINK ET AL.
INORGANIC FLUORIDE WITH SEVOFLURANE

233

Alcohol metabolite:
Is it sedating ?



Formyl Fluoride:
Very Reactive!
Hepatotoxin?
Tissue Binding?

Figure 3. Proposed biotransformation of sevoflurane. UDPGA, uridine diphosphate glucuronic acid.

Sevoflurane Exposures with Hepatic Dysfunction & Deaths

Sevoflurane publications

1	Bignon et al 2016	A Severe Acute Hepatitis Related to Sevoflurane (in French)	Anesthesie & Reanimation 2:238-242, 2016
2	Shah et al	Hepatotox after Sevo in Pt with Chronic Hepatitis C	Ann Clin Lab Res 3:45, 2015
3	Spasovska 2013	Acute Fulminant Hepatitis in Renal Transplant	Current Drug Safety 8: 141-144, 2013
4	Zizek, D	Subacute Liver Toxicity after multiple Sevoflurane	Eur J Gastroenter Hepatology 22:112-115, 2010
5	Singhal, S	Sevoflurane Hepatotoxicity: Case Report	Amer J Therapeut 17: 219-222, 2010
6	NIH Database	Case 1 Sevo induced Acute Liver Injury	https://livertox.nih.gov/Sevoflurane.htm
7	Alotaibi	Severe Liver Dysfunction in 6 yr old	Saudi Med J 29:1344-1346, 2008
8	Song et al	Acute Hepatic Failure after SEVO in Pediatric Patient	Korean J Anesthesiol 53:781-784, 2007
9	Lehmann et al	Hepatic Failure after Aortic Valve Replacement	Can J Anesth 54:917, 2007
10	Turillazzi et al	Fatal Case of Fulminant Hepatic Necrosis	Toxicologic Pathology 35:780-785, 2007
11	Jang & Kim	Severe Hepatotoxicity after sevoflurane anesthesia child...	Ped Anes 15: 1140, 2005
12	Reich et al	Hepatitis after Sevo in Infant with Hyperoxaluria I	Anes & Analg 99:370-372, 2004
13	Chung et al	Hepatic dysfunction following sevoflurane	Chang Gng Med J 26:357, 2003
14	Bruun et al	Hepatic failure in child after acetaminophen & sevoflurane...	Anes & Analg 92:1446, 2001
15	Ohmori et al	A Case report of postoperative liver dysfunction following sevo...	J Jp Soc Clin Anes 14:68, 1994
16	Watanabe et al	Suspected liver dysfunction induced by sevoflurane...	Jap J Anesthesiol 42:902,1993
17	Shichinohe et al	A case of postoperative hepatic injury after sevoflurane anesthesia	Jap J Anesthesiol 41:1802,1992
18	Ogawa et al	Drug induced hepatitis following sevoflurane anesthesia...	Jap J Anesthesiol 40:1542,1991

Deuterated Sevoflurane

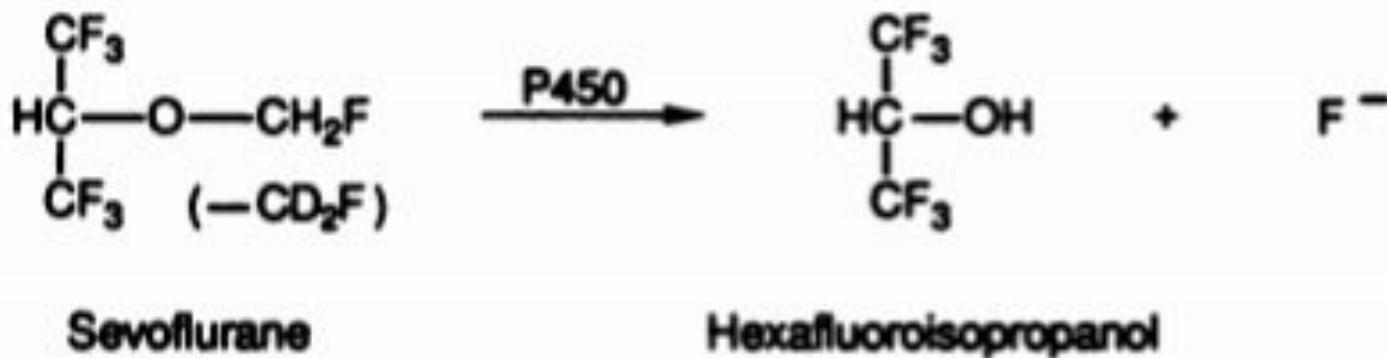


FIG. 1. Metabolic pathway for sevoflurane.

TABLE I

Fluoride release from sevoflurane and deuterated sevoflurane metabolism in hepatic microsomes from untreated, isoniazid-treated, or phenobarbital-treated rats

Treatment	Nmol Fluoride/Mg Microsomal Protein	
	Sevoflurane	Deuterated Sevoflurane
None	1.36 ± 0.05	0.08 ± 0.02* (94)
Phenobarbital	0.93 ± 0.10	0.08 ± 0.04* (91)
Isoniazid	5.14 ± 0.38 ^{b,c}	0.90 ± 0.06 ^{a,c} (82)

APSF *Safer* Therapeutic Anesthesia Initiative

	Preclinical	IND-Enabling	Phase 1	Phase 2	Phase 3	Approved	Phase 4	Commercial Rights
Xenon								
AZD3043								Astra -Zeneca
Deuterated Sevoflurane								
Propofol in MCT								
Propofol + Omega 3								

FDA - APSF Safety Collaboration

Orphan Drug Status.... Exclusive rights for marketing x years
Expedited Review Status..... for unmet medical need

USA behind rest of World in Lipid Emulsions...Why ?

1528

Hippalgaonkar, Majumdar and Kansara

Table I. Representative list of currently marketed drug containing injectable emulsions

Product	Active Ingredient	Market	Composition	Ref
Cleviprex	Clevidipine Butyrate	USA	SO: EP: G	(147, 148)
Diazemuls®	Diazepam	Europe, Canada and Australia	SO: AcM: EP: G: NaOH	(149, 150)
Diazepam-Lipuro®	Diazepam	Europe, Canada and Australia	SO: MCT: EL: G: sodium oleate	(151)
Diprivan®	Propofol	Worldwide	SO: EL: G: disodium edetate: NaOH	(28, 29)
Etomidat-Lipuro®	Etomidate	Germany	SO: MCT: EL: G: sodium oleate	(151)
Fluosol-DA®	Perfluorodecalin, Perflurotripropylamine	Worldwide	EP: pluronic F68: potassium oleate: G	(150)
Liple®	Alprostadil (PEG ₁)	Japan	SO: EP: OA: G	(150)
Limethason®	Dexamethasone Palmitate	Japan, Germany	SO: EL: G	(29, 150)
Lipo-NSAID®	Flurbiprofen axetil	Japan	SO: EL: G	(29, 150)
Stesolid	Diazepam	Europe	SO: AcM: EP: G	(42, 151)
Vitalipid®	Vitamins A, D ₂ , E, K ₁	Europe	SO: EL: G	(29, 150)

SO Soy Oil, AcM Acetylated monoglycerides, G Glycerol, MCT Medium-chain Triglycerides, EP egg phospholipid, EL egg lecithin, OA Oleic acid