APSF Vision

New Era in Anesthesia:
Ultra-fast, Safer Therapeutic Anesthesia

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No Conflicts
AZD3043 References

Preclinical Trials

Possible binding sites and interactions of propanidid and AZD3043 within the y-aminobutyric acid type A receptor (GABAAR).
Wang S, Liu Q, Li X, Zhao X, Qiu L, Lin J.

Reduced efficacy of the intravenous anesthetic agent AZD3043 at GABA(A) receptors with β2 (N289M) and β3 (N290M) point-mutations.
Jonsson Fagerlund M, Sjödin J, Dabrowski MA, Krupp J.

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.

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

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.

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.
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

197 Phase 1 & 2 Patients

Human Studies

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 steep; once subjects began to wake
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

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†
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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

Alcohol metabolite: Is it sedating?

Formyl Fluoride: Very Reactive! Hepatotoxic? Tissue Binding?

Figure 3. Proposed biotransformation of sevoflurane. UDPGA, uridine diphosphate glucuronic acid.
## Sevoflurane Exposures with Hepatic Dysfunction & Deaths

### Sevoflurane publications

<table>
<thead>
<tr>
<th>#</th>
<th>Author(s)</th>
<th>Title</th>
<th>Journal</th>
</tr>
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<tbody>
<tr>
<td>3</td>
<td>Spasovska 2013</td>
<td>Acute Fulminant Hepatitis in Renal Transplant</td>
<td>Current Drug Safety 8: 141-144, 2013</td>
</tr>
<tr>
<td>8</td>
<td>Song et al</td>
<td>Acute Hepatic Failure after SEVO in Pediatric Patient</td>
<td>Toxicologic Pathology 35:780-785, 2007</td>
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<tr>
<td>11</td>
<td>Jang &amp; Kim</td>
<td>Severe Hepatotoxicity after sevoflurane anesthesia child...</td>
<td>Ped Anes 15: 1140, 2005</td>
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<tr>
<td>12</td>
<td>Reich et al</td>
<td>Hepatitis after Sevo in Infant with Hyperoxaluria I</td>
<td>Anes &amp; Analg 99:370-372, 2004</td>
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<tr>
<td>14</td>
<td>Bruun et al</td>
<td>Hepatic failure in child after acetaminophen &amp; sevoflurane...</td>
<td>Anes &amp; Analg 92:1446, 2001</td>
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<tr>
<td>15</td>
<td>Ohmori et al</td>
<td>A Case report of postoperative liver dysfunction following sevo...</td>
<td>Jp Jpn Jpn Jpn Anes 42:902, 1993</td>
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<tr>
<td>16</td>
<td>Watanabe et al</td>
<td>Suspected liver dysfunction induced by sevoflurane...</td>
<td>Jp Jpn Jpn Jpn Anes 41:1802, 1992</td>
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<tr>
<td>18</td>
<td>Ogawa et al</td>
<td>Drug induced hepatitis following sevoflurane anesthesia...</td>
<td>Jp Jpn Jpn Jpn Anes 40:1542, 1991</td>
</tr>
</tbody>
</table>
Deuterated Sevoflurane

\[
\begin{align*}
\text{Sevoflurane} & \xrightarrow{P450} \text{Hexafluoroisopropanol} \\
\begin{array}{c}
\text{CF}_3 \\
\text{C} \text{O} \text{CH}_2 \text{F} \\
\text{CF}_3 (-\text{CD}_2 \text{F}) \\
\end{array} & \xrightarrow{\text{P450}} \\
\begin{array}{c}
\text{CF}_3 \\
\text{C} \text{OH} \\
\end{array} & + \ \text{F}^- \\
\end{align*}
\]

**FIG. 1.** Metabolic pathway for sevoflurane.

**TABLE 1**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Nmole Fluoride/Mg Microsomal Protein</th>
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<tbody>
<tr>
<td></td>
<td>Sevoflurane</td>
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<tr>
<td>None</td>
<td>1.36 ± 0.05</td>
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<tr>
<td>Phenobarbital</td>
<td>0.93 ± 0.10</td>
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<tr>
<td>Isoniazid</td>
<td>5.14 ± 0.38b,c</td>
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# APSF Safer Therapeutic Anesthesia Initiative

<table>
<thead>
<tr>
<th></th>
<th>Preclinical</th>
<th>IND-Enabling</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Approved</th>
<th>Phase 4</th>
<th>Commercial Rights</th>
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<tbody>
<tr>
<td>Xenon</td>
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<td>AZD3043</td>
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<td>Astra -Zeneca</td>
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<td>Deuterated Sevoflurane</td>
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<td>Propofol in MCT</td>
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<td>Propofol + Omega 3</td>
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**FDA - APSF Safety Collaboration**

Orphan Drug Status…. Exclusive rights for marketing x years

Expedited Review Status….. for unmet medical need
Table I. Representative list of currently marketed drug containing injectable emulsions

<table>
<thead>
<tr>
<th>Product</th>
<th>Active Ingredient</th>
<th>Market</th>
<th>Composition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diprivan®</td>
<td></td>
<td>Japan</td>
<td>SO: M: F: Lipid: G, disodium oleate: NaOH</td>
</tr>
<tr>
<td>Etomida-Lipuro®</td>
<td></td>
<td>Japan</td>
<td>SO: EL: G, disodium oleate: NaOH, Plan VIA F68, potassium</td>
</tr>
<tr>
<td>Flurbiprofen axetil</td>
<td></td>
<td>Europe, Canada and Australia</td>
<td>SO: EL: G, disodium oleate: NaOH</td>
</tr>
<tr>
<td>Glycerol</td>
<td></td>
<td>Europe, Canada and Australia</td>
<td>SO: M: F: Lipid: G, disodium oleate: NaOH</td>
</tr>
<tr>
<td>Lipo-NSC®</td>
<td></td>
<td>Europe, Canada and Australia</td>
<td>SO: EL: G, disodium oleate: NaOH</td>
</tr>
<tr>
<td>Sestolid®</td>
<td></td>
<td>Europe, Canada and Australia</td>
<td>SO: M: F: Lipid: G, disodium oleate: NaOH</td>
</tr>
</tbody>
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Hippalgaonkar, Majumdar and Kansara