Xenon – Introduction and Overview

Postgraduate Colloquium, October 25th, 2011

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History

- **1898:** Discovery of xenon *(Ramsay and Travers)*
- **1938:** Hypnotic effects of noble gases *(Behnke and Yarbrough)*
  Xenon = only noble gas with hypnotic properties under normobaric conditions
- **1946:** First xenon anesthesia in an animal model *(Lawrence)*
- **1951:** First xenon anesthesia in man *(Cullen and Gross)*
- **1990:** „Rediscovery“, RCT‘s with xenon *(Lachmann and Erdmann)*
- **2005:** Medicolegal approval in Germany *(ASA I-III)*
- **2007:** Medicolegal approval in Europe *(ASA I-II)*

Sir William Ramsay (1852-1916)  
Morris William Travers (1872-1961)
Pharmacokinetics

Blood-Gas Partition Coefficient

<table>
<thead>
<tr>
<th>Substance</th>
<th>Coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Halothane</td>
<td>2.4</td>
</tr>
<tr>
<td>Enflurane</td>
<td>1.9</td>
</tr>
<tr>
<td>Isoflurane</td>
<td>1.4</td>
</tr>
<tr>
<td>Sevoflurane</td>
<td>0.69</td>
</tr>
<tr>
<td>Nitrous oxide</td>
<td>0.46</td>
</tr>
<tr>
<td>Desflurane</td>
<td>0.42</td>
</tr>
<tr>
<td><strong>Xenon</strong></td>
<td><strong>0.115</strong></td>
</tr>
</tbody>
</table>

Potency

<table>
<thead>
<tr>
<th>Substance</th>
<th>MAC/O₂ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N₂O</td>
<td>101.0 %</td>
</tr>
<tr>
<td><strong>Xenon</strong></td>
<td>63.0 %</td>
</tr>
<tr>
<td>Desflurane</td>
<td>6.0 %</td>
</tr>
<tr>
<td>Sevoflurane</td>
<td>2.0 %</td>
</tr>
<tr>
<td>Enflurane</td>
<td>1.8 %</td>
</tr>
<tr>
<td>Isoflurane</td>
<td>1.2 %</td>
</tr>
<tr>
<td>Halothane</td>
<td>0.8 %</td>
</tr>
</tbody>
</table>

Table 3. MAC-awake Values of Anesthetics Administered Alone

<table>
<thead>
<tr>
<th></th>
<th>Xenon</th>
<th>N₂O</th>
<th>Isoflurane</th>
<th>Sevoflurane</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAC-awake (%)</td>
<td>32.6 ± 6.1</td>
<td>63.3 ± 7.1</td>
<td>0.40 ± 0.07</td>
<td>0.59 ± 0.10</td>
</tr>
<tr>
<td>(95% Confidence interval)</td>
<td>(30.5–34.6)</td>
<td>(59.8–66.9)</td>
<td>(0.37–0.43)</td>
<td>(0.54–0.64)</td>
</tr>
<tr>
<td>MAC-awake/MAC</td>
<td>0.46 ± 0.09</td>
<td>0.61 ± 0.07</td>
<td>0.35 ± 0.06</td>
<td>0.35 ± 0.06</td>
</tr>
<tr>
<td>(95% Confidence interval)</td>
<td>(0.43–0.49)</td>
<td>(0.57–0.64)</td>
<td>(0.32–0.38)</td>
<td>(0.32–0.38)</td>
</tr>
</tbody>
</table>
Pharmacokinetics

Meyer-Overton-Rule

Correlation between anaesthetic potency and hydrophobicity

**Pharmacokinetics**

Dickinson R, Franks NP  
*Bench-to-bedside review: Molecular pharmacology and clinical use of inert gases in anesthesia and neuroprotection.*  
Critical Care 2010, 14:229

### Table 1. Physical properties of the inert gases and nitrogen

<table>
<thead>
<tr>
<th>Physical property</th>
<th>Helium</th>
<th>Neon</th>
<th>Nitrogen</th>
<th>Argon</th>
<th>Krypton</th>
<th>Xenon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atomic number</td>
<td>2</td>
<td>10</td>
<td>7</td>
<td>18</td>
<td>36</td>
<td>54</td>
</tr>
<tr>
<td>Atomic mass (g/mol)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4.0</td>
<td>20.2</td>
<td>14.0</td>
<td>39.9</td>
<td>83.8</td>
<td>131.3</td>
</tr>
<tr>
<td>Density (g/l) (0°C)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.1785</td>
<td>0.900</td>
<td>1.251</td>
<td>1.784</td>
<td>3.736</td>
<td>5.887</td>
</tr>
<tr>
<td>Thermal conductivity (W/m/K) (300 K)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.1499&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.0491</td>
<td>0.0260&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.0178</td>
<td>0.0094</td>
<td>0.0056</td>
</tr>
<tr>
<td>Polarizability α (Å&lt;sup&gt;3&lt;/sup&gt;)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.21</td>
<td>0.39</td>
<td>1.74</td>
<td>1.64</td>
<td>2.48</td>
<td>4.04</td>
</tr>
<tr>
<td>Water/gas partition coefficient at 25°C&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0.0085</td>
<td>0.010</td>
<td>0.015</td>
<td>0.031</td>
<td>0.053</td>
<td>0.095</td>
</tr>
<tr>
<td>Oil/gas partition coefficient at 25°C&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0.016</td>
<td>0.019</td>
<td>0.07</td>
<td>0.14</td>
<td>0.44</td>
<td>1.9</td>
</tr>
<tr>
<td>General anesthetic (atm)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Not anesthetic</td>
<td>Not anesthetic</td>
<td>39</td>
<td>15.2</td>
<td>4.5</td>
<td>0.95 (mouse), 0.6 to 0.7 (human)</td>
</tr>
</tbody>
</table>
Pharmacokinetics: Induction of Anesthesia

Hanne P et al., IntAnesthClinics 2001
Multicenter Randomized Comparison of the Efficacy and Safety of Xenon and Isoflurane in Patients Undergoing Elective Surgery

Rolf Rossaint, M.D.,* Matthias Reyle-Hahn, M.D.,† Jochen Schulte am Esch, M.D.,‡ Jens Scholz, M.D.,§ Philippe Scherpereel, M.D.,∥ Benoit Vallet, M.D.,# Francesco Giunta, M.D.,,** Monica Del Turco, M.D.,†† Wilhelm Erdmann, M.D.,‡‡ Rob Tenbrinck, M.D., Ph.D., §§ Alfons F. Hammerle, M.D.,|| Peter Nagele, M.D.,## for the Xenon Study Group***

- **Subjects:** 224 patients, ASA I-III
- **Centers:** Aachen, Hamburg, Lille, Pisa, Rotterdam, Wien
- **Efficacy:** Recovery Index

\[ \text{RI} = 1 + \text{Aldrete}_{5\text{ min}} / [(2 \times \text{extubation time}) + (1 \times \text{opening eyes time})] \]

- **Safety:** Hemodynamics, Pain, Emergency Medication, ECG, Clinical Chemistry
Efficacy: Emergence/Recovery from Anesthesia

Rossaint R et al.
Multicenter Randomized Comparison of the Efficacy and Safety of Xenon and Isoflurane in Patients Undergoing Elective Surgery.
Anesthesiology 2003; 98:6–13
### Efficacy: Emergence/Recovery from Anesthesia

<table>
<thead>
<tr>
<th>Time</th>
<th>Desflurane</th>
<th>Xenon</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>To open eyes</td>
<td>8.1 (6.3–9.9)</td>
<td>4.8 (3.9–5.7)</td>
<td>0.001</td>
</tr>
<tr>
<td>To react on demand</td>
<td>8.6 (6.7–10.6)</td>
<td>4.9 (3.7–6.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>To extubation</td>
<td>8.9 (6.6–11.2)</td>
<td>4.9 (3.9–5.8)</td>
<td>0.001</td>
</tr>
<tr>
<td>To time and spatial orientation</td>
<td>10.8 (8.7–13.0)</td>
<td>7.4 (6.1–8.8)</td>
<td>0.007</td>
</tr>
</tbody>
</table>

Coburn M. et al.

*Emergence and early cognitive function in the elderly after xenon or desflurane anaesthesia: a double-blinded randomized controlled trial.*

Early cognitive function, recovery and well-being after sevoflurane and xenon anaesthesia in the elderly: a double-blinded randomized controlled trial

**Background**
The postoperative cognitive function is impaired in elderly patients after general anaesthesia. The fast recovery after xenon anaesthesia was hypothesized to be advantageous in this scenario. We compared early postoperative cognitive function after xenon and sevoflurane anaesthesia in this study.

**Methods**
The study was approved by the local ethics committee and written informed consent was obtained from each patient. Patients aged 65-75 years (ASA I-III) scheduled for elective surgery (duration 60-180 min) were enrolled. Investigators performing cognitive testing and patients were blinded towards allocation to either xenon or sevoflurane anaesthesia. Baseline assessment of cognitive function was carried out 12-24 h before the operation. The results were compared to follow-up tests 6-12 and 66-72 h after surgery. Primary outcome parameter was the subtest "Alertness" of the computerized Test of Attentional Performance (TAP). Secondary outcome parameters included further subtests of the TAP, several Paper-Pencil-Tests, emergence times from anaesthesia, modified Aldrete scores and patients' well-being.

**Results**
40 patients were randomized and equally allocated to both groups. No significant differences were found in the TAP or the Paper-Pencil-Tests at 6-12 and 66-72 h after the operation. All emergence times were faster after xenon anaesthesia. The modified Aldrete scores were significantly higher during the first hour in the xenon group. No difference in well-being could be detected between both groups.

**Conclusions**
The results show no difference in the incidence of postoperative cognitive dysfunction (POCD) after xenon or sevoflurane anaesthesia. Emergence from general anaesthesia was faster in the xenon group.
Safety: Hemodynamics

Mean arterial pressure

Xenon 60±5%

Isoflurane 0.5%
+ N₂O 60±5%

P < 0.0001

Heart rate

Isoflurane 0.5%
+ N₂O 60±5%

Xenon 60±5%

P < 0.001

Rossaint R et al.
*Multicenter Randomized Comparison of the Efficacy and Safety of Xenon and Isoflurane in Patients Undergoing Elective Surgery.*
Anesthesiology 2003; 98:6–13
Safety: Hemodynamics

Safety: Hemodynamics

Mean (SD) arterial systolic and diastolic blood pressures

![Graph showing mean arterial blood pressures over time for two regimens: X and P.](image)

Mean (SD) Cardiac Indices

![Graph showing mean cardiac indices over time for two regimens: X and P.](image)

Bedi A. et al.
Use of xenon as a sedative for patients receiving critical care.
Crit Care Med 2003; 31:2470–2477
### Safety: Side Effects: PONV

#### Clinical Investigations

**Multicenter Randomized Comparison of the Efficacy and Safety of Xenon and Isoflurane in Patients Undergoing Elective Surgery**

Rolf Rossaint, M.D.,* Matthias Reyle-Hahn, M.D.,† Jochen Schulte am Esch, M.D.,‡ Jens Schoiz, M.D.,§ Philippe Scherpereel, M.D.,¶ Benoit Vallet, M.D.,# Francesco Giunta, M.D.,** Monica Del Turco, M.D.,†† Wilhelm Erdmann, M.D.,‡‡ Rob Tenbrinck, M.D., Ph.D., §§ Alfons F. Hammerle, M.D.,|| Peter Nagele, M.D.,## for the Xenon Study Group***

<table>
<thead>
<tr>
<th>Side effect (%)</th>
<th>Xenon</th>
<th>Iso/N₂O</th>
</tr>
</thead>
<tbody>
<tr>
<td>PONV</td>
<td>26</td>
<td>22</td>
</tr>
<tr>
<td>Hypertension</td>
<td>16</td>
<td>10</td>
</tr>
<tr>
<td>Hypotension</td>
<td>17</td>
<td>16</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>5</td>
<td>4</td>
</tr>
</tbody>
</table>

Hypertension, hypotension, and bradycardia were defined as a change of > 20% from baseline.
Table 3. Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>Xenon (n = 131)</th>
<th>Isoflurane (n = 128)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PONV</td>
<td>36*</td>
<td>16</td>
</tr>
<tr>
<td>Hypertension</td>
<td>19*</td>
<td>6</td>
</tr>
<tr>
<td>Hypotension</td>
<td>2*</td>
<td>74</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>8*</td>
<td>4</td>
</tr>
<tr>
<td>Shivering</td>
<td>11</td>
<td>12</td>
</tr>
</tbody>
</table>

Data are shown as number of patients with adverse events.

* $P < 0.05$ vs. isoflurane.

Wappler F. et al.
Multicenter Randomized Comparison of Xenon and Isoflurane on Left Ventricular Function in Patients Undergoing Elective Surgery.
Anesthesiology 2007; 106:463–71
# Safety:
## Side Effects: PONV

<table>
<thead>
<tr>
<th></th>
<th>Xenon group (n=71)</th>
<th>Propofol group (n=71)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea in PACU</td>
<td>37 (52.1)</td>
<td>12 (16.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Emetic episodes in PACU</td>
<td>14 (19.7)</td>
<td>5 (7.0)</td>
<td>0.046</td>
</tr>
<tr>
<td>Late-period nausea</td>
<td>19 (26.8)</td>
<td>10 (14.1)</td>
<td>0.095</td>
</tr>
<tr>
<td>Late-period emetic episodes</td>
<td>11 (15.5)</td>
<td>7 (9.9)</td>
<td>0.450</td>
</tr>
<tr>
<td>Nausea from 0 to 24 h after anaesthesia</td>
<td>47 (66.2)</td>
<td>19 (26.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Emetic episodes from 0 to 24 h after anaesthesia</td>
<td>25 (35.2)</td>
<td>12 (16.9)</td>
<td>0.021</td>
</tr>
<tr>
<td>PONV from 0 to 24 h after anaesthesia</td>
<td>47 (66.2)</td>
<td>19 (26.8)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of emetic episodes from 0 to 24 h after anaesthesia</th>
</tr>
</thead>
<tbody>
<tr>
<td>One episode</td>
</tr>
<tr>
<td>Two to five episodes</td>
</tr>
<tr>
<td>More than five episodes</td>
</tr>
<tr>
<td>Cannot tell how often</td>
</tr>
</tbody>
</table>

Coburn M. et al.  
*Incidence of postoperative nausea and emetic episodes after xenon anaesthesia compared with propofol-based anaesthesia*.  
Safety: Airway Resistance

Respiratory Mechanics during Xenon in Pigs

Comparison with Nitrous Oxide

Enrico Calzia, M.D.*, Wolfgang Stahl, M.D.,† Thomas Handschuh, MD, Gebhardt Fröba, M.D.*, Stefan Bäder, Ph.D.,‡ Michael Georgieff, † Peter Radermacher, M.D., Ph.D.¶

Conclusions: Airway pressure and resistance are increased during xenon anesthesia. This response is moderate and not likely to assume major importance for the general use of xenon in anesthesia.

Table 1 Densities (ρ) and Kinematic Viscosity (η) at 0°C, pressure, and water saturated for various gas mixtures as used in this study

<table>
<thead>
<tr>
<th></th>
<th>N₂/O₂ 70/30%</th>
<th>N₂O/O₂ 70/30%</th>
<th>Xenon/O₂ 70/30%</th>
</tr>
</thead>
<tbody>
<tr>
<td>ρ (g litre⁻¹)</td>
<td>1.21</td>
<td>1.67</td>
<td>4.20</td>
</tr>
<tr>
<td>η (10⁻⁵ Pa s⁻¹)</td>
<td>1.81</td>
<td>1.61</td>
<td>2.18</td>
</tr>
</tbody>
</table>

*Corresponding author
**Metabolism**

<table>
<thead>
<tr>
<th>Anesthetic</th>
<th>Metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Halothane</td>
<td>20 %</td>
</tr>
<tr>
<td>Enflurane</td>
<td>5.0 - 7.0 %</td>
</tr>
<tr>
<td>Sevoflurane</td>
<td>2.0 - 5.0%</td>
</tr>
<tr>
<td>Isoflurane</td>
<td>&lt; 1.0 %</td>
</tr>
<tr>
<td>Nitrous oxide</td>
<td>n.a.</td>
</tr>
<tr>
<td>Desflurane</td>
<td>&lt; 0.1 %</td>
</tr>
<tr>
<td>Xenon</td>
<td>0</td>
</tr>
</tbody>
</table>

- No trigger of MH
- No teratogenity
- No toxicity
- Not flammable
Safety

- **N₂O**
  - 230 x potent as a greenhouse gas than CO₂
  - 0.1% of global warming
  - Lifetime in atmosphere: 120 yrs

- **HCFC’s (hydro-chloro-fluoro-carbons)**
  - (Halothane, Isoflurane, Enflurane)
  - Degrading of ozone layer (0.1-1% p.a.)
  - Stop of production in 2030 (Kyoto protocol)

- **FHC’s (fluorinated hydrocarbons)**
  - (Sevoflurane, Desflurane)
  - Less degrading of ozone layer
  - 10x more heat trapping than CO₂

- **Xenon**
  - No air pollution
  - No greenhouse effect
  - but: energy consuming production
Xenon seems to be an (nearly) ideal anesthetic,
**Cost-Effectiveness**

- **Limited Availability**
  - 0.0000087% (87 ppb) of the atmosphere
  - Cannot be synthetized
  - Produced by *fractional distillation of liquified air* (limited capacity)
  - Production of 1L consumes 1.000.000 times more energy than for N₂O
  - High demand also by industry (light technology, plasma screens, aerospace industry)

- **High Costs**
  - Currently 20 € /L
  - Per hour:
    - Isoflurane + opioid: 5 €
    - Propofol + opioid: 10 €
    - Xenon + opioid: 300 €
Cost-Effectiveness

- **Special delivery technique**
- **Closed-circuit anesthesia machines**

Dräger, Physioflex

Taema/ALMS, Felix

EKA, Tangens 2C

- **Future: Scavenging devices? (Medicolegal issue!)**
Xenon

• Many attributes of an ideal anesthetic

• High costs and limited availability

• Routine use is (at present) impossible

• It's use may only be justified in special indications

• These indications are still to be identified
The future of xenon

Introduction and Overview
Xenon and the Heart Contractility

**L-type Ca$$^2+$$ influx ($I_{Ca,L}$)**

- preserved by 1 MAC xenon
- reduced by 1 MAC halothane and isoflurane

Hüneke R. et al.  
*Effects of the Anesthetic Gases Xenon, Halothane, and Isoflurane on Calcium and Potassium Currents in Human Atrial Cardiomyocytes*  
Anesthesiology 2001; 95:999–1006
Xenon and the Heart
Contractility

Contraction force
(single ventricular muscle fibre bundles, guinea pig)

- depressed by isoflurane
- preserved by xenon

Schroth S et al. Xenon Does Not Impair the Responsiveness of Cardiac Muscle Bundles to Positive Inotropic and Chronotropic Stimulation. Anesthesiology 2002; 96:422–7
**Xenon and the Heart Contractility**

### Responsiveness to inotropic stimulation

(single ventricular muscle fibre bundles, guinea pig)

- not affected by xenon

---

**Schroth S et al.**

*Xenon Does Not Impair the Responsiveness of Cardiac Muscle Bundles to Positive Inotropic and Chronotropic Stimulation.*

Anesthesiology 2002; 96:422–7
Xenon and the Heart Contractility

Multicenter Randomized Comparison of Xenon and Isoflurane on Left Ventricular Function in Patients Undergoing Elective Surgery

Frank Wappler, M.D.,* Rolf Rossaint, M.D.,† Jan Baumert, M.D.,‡ Jens Scholz, M.D.,§ Peter H. Tonner, M.D.,§ Hugo van Aken, M.D.,‖ Elmar Berendes, M.D.,‖ Jan Klein, M.D.,# Diederik Gommers, M.D.,** Alfons Hammerle, M.D.,†† Andreas Franke, M.D.,‡‡ Thomas Hofmann, M.D., §§ Jochen Schulte am Esch, M.D.,||| for the Xenon Multicenter Study Research Group##

252 patients, ASA I-II

VCFc =
Rate corrected velocity of fiber shortening

\[
\text{VCFc} = \frac{\text{LVEDC} - \text{LVESC} \cdot \sqrt{\text{RR/40}}}{\text{LVEDC} \cdot \text{LVET/40}}
\]
Xenon and the Heart
Myocardial Blood Flow

Introduction and Overview

Anesthesiology 2011 Jun;114(6):1373-9

Rex S et al.
Xenon and the Diseased Heart Contractility

**Cardiomyopathy**

- Xenon preserves contractility
- Even when administered in addition to isoflurane

Hettrick D et al.  
*Cardiovascular Effects of Xenon in Isoflurane-anesthetized Dogs with Dilated Cardiomyopathy*  
Anesthesiology: Volume 89(5) November 1998 pp 1166-1173
Xenon and the Diseased Heart
Contractility

40 Patients, ASA III-IV, RCRI 3

VCFc
Rate corrected velocity of fiber shortening

Tei-Index

Baumert J.-H. et al.
Xenon or propofol anaesthesia for patients at cardiovascular risk in non-cardiac surgery
Xenon and the **Diseased Heart**

**Cardiac Performance**

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**Graph:**

- **Cardiac Output (l/min)**
  - **Induction**
  - **Sternotomy**
  - **Weaning from CPB**
  - **End of surgery**

- **1 MAC Xenon**
- **1 MAC Sevoflurane**

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**Xenon – Introduction and Overview**
Conclusion: Xenon and the Heart

- Preservation of myocardial contractility
- Preservation of myocardial blood flow
- Protection from reperfusion injury
- Cardioprotection via early and late preconditioning
Xenon and the Heart: Future Research

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

This study is currently recruiting participants. Approved by Air Liquide Santé International, June 2010

First Received: May 4, 2010 Last Updated: June 29, 2010 History of Changes

<table>
<thead>
<tr>
<th>Sponsor</th>
<th>Air Liquide Santé International</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collaborators</td>
<td>BIOMNIS Central laboratory MONITORING FORCE GROUP CROs</td>
</tr>
<tr>
<td>Information provided by</td>
<td>Air Liquide Santé International</td>
</tr>
<tr>
<td>ClinicalTrials.gov Identifier</td>
<td>NCT01120405</td>
</tr>
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</table>

Efficacy and safety of xenon anaesthesia compared to sevoflurane anaesthesia and total intravenous anaesthesia for on-pump coronary artery bypass graft surgery: a randomised, three-arm, single-blind, international study

Protocol identification number: ALMED-09-C3-026 EudraCT number: 2010-020677-17

Final version number 1.0 dated 15 June 2010

Investigational product: Xenon (LENOXe™)
Xenon and the Brain: How does xenon produce anesthesia?

Xenon endofullerenes are self-assembled chains of C60. The observation of these structures raises the hope that refined processing techniques can be developed to produce them in large quantities.

Brian W. Smith* and Marc Monthioux*†,‡

*Laboratory of Materials Science and Engineering, University of Pennsylvania, 3231 Walnut Street, Philadelphia, Pennsylvania 19104-6272, USA e-mail: lizard@fim.upenn.edu

†CEMES, UPR 4601 CNRS, BP 43477, 31045 Toulouse cedex 4, France

II, IV, VI

Xenon

Introduction and Overview

Xenon and the Brain: How does xenon produce anesthesia?

How does xenon produce anesthesia?

Since the discovery that the gas xenon can produce general anesthesia without causing undesirable side effects, we have remained surprisingly ignorant of the molecular mechanisms underlying this clinical activity of an ‘injectable’ gas. Although most general anaesthetics enhance the activity of inhibitory GABA$_A$ (γ-aminobutyric acid, type-A) receptors, we find that the effects of xenon on these receptors are negligible. Instead, xenon potently inhibits the excitatory NMDA (N-methyl-D-aspartate) receptor channels, which may account for many of xenon's attractive pharmacological properties.

We found that xenon had virtually no effect on GABA$_A$ receptors. Currents activated by 3 μM GABA, both in voltage-clamped cultured rat hippocampal neurons and in slice-clamped PA3 cells that stably expressed defined GABA$_A$ subunits, were not significantly affected even by 100% xenon (to function as a human anaesthetic, the half maximal effective concentration ($EC_{50}$) is 71 μM; ref 5). Xenon also had little effect on functional GABA$_A$-releasing synapses in hippocampal cultures with 80% xenon reducing peak inhibitory post synaptic currents by only 8 ± 2%. This result indicates that the presynaptic effects of xenon must also be very modest.

Apart from the GABA$_A$ receptor, the only generally accepted neuronal target of xenon is the NMDA receptor. This subtype of glutamate-activated ionotropic channels is implicated in synaptic mechanisms underlying learning, memory and the perception of pain. The NMDA receptor is also believed to be a target of the intravenous general anaesthetic agent ketamine and possibly nitrous oxide.

We therefore looked at the effects of xenon on NMDA-activated currents in cultured hippocampal neurons. We found that 80% xenon, which will maintain surgical anesthesia, reduced NMDA-activated currents by about 60% (Fig. 1a), with no significant change in the NMDA EC$_{50}$ value or Hill coefficient. This non-competitive inhibition indicates that xenon should strongly inhibit neural transmission, despite the high glutamate concentrations in synaptic clefts.

We then tested this in micropipette cultures of hippocampal neurons that form synapses with themselves (autoapses) 29. A typical glutamatergic postsynaptic current recorded from a hippocampal neuron is shown in Fig. 1b. The control records show a characteristic biphasic time course, with a fast component mediated by non-NMDA receptors and a much slower component mediated by NMDA receptors. This NMDA receptor-mediated component could be readily identified as it was blocked by the highly selective competitive antagonist AP5 (2-amino-5-phosphonopentanoic acid) 30.

Addition of 200 μM AP5 almost completely blocked the slow component, leaving only a fast component, with a single exponential time course very similar to that of the control fast component. The effect of xenon on the glutamatergic postsynaptic current resembled that of AP5 (Fig. 1b). The slow, NMDA-receptor-mediated component was reduced by over 70%, whereas the fast component barely changed. So, not only did xenon inhibit synaptic NMDA receptors, it had little apparent effect on non-NMDA receptors.

If xenon exerts its effects by inhibiting NMDA receptors, then this explains some important features of its pharmacological profile, particularly as NMDA-receptor antagonists can relieve pain and cause amnesia, which are features of xenon anaesthesia. Like nitrous oxide (laughing gas), which may also act, at least partly, on NMDA receptors, xenon can induce a state of hypoxia. Other neuronal targets for xenon may emerge, but its powerful inhibitory effect of the NMDA receptor is likely to be instrumental in the anaesthetic and anesthetic effects of this ‘injectable’ gas.

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Xenon and the Brain: How does xenon produce anesthesia?

Xenon inhibits NMDA receptors by binding at the same site as and inhibiting the coagonist glycine.

Xenon and the Brain: How does xenon produce anesthesia?

Elevated glycine concentrations abolish neuroprotective properties of xenon

Banks P. et al. *Competitive Inhibition at the Glycine Site of the N-Methyl-D-Aspartate Receptor Mediates Xenon Neuroprotection against Hypoxia–Ischemia*. Anesthesiology 2010; 112:614–22
Xenon and the Brain: How does xenon produce anesthesia?

Xenon induces a depression of CMRgIc

- Globally
- Atypically for NMDA-antagonists

Rex S et al.  
Positron Emission Tomography Study of Regional Cerebral Metabolism during General Anesthesia with Xenon in Humans.  
Anesthesiology 2006; 105:1–1
Xenon and the Brain: How does xenon produce anesthesia?

Xenon induces a depression of CMRglc

-and regionally

Rex S et al. 
*Positron Emission Tomography Study of Regional Cerebral Metabolism during General Anesthesia with Xenon in Humans.*
Anesthesiology 2006; 105:1–1
Xenon and the Brain: How does xenon produce anesthesia?

Xenon induces a depression of rCBF

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Rex S et al.  
*Positron emission tomography study of regional cerebral blood flow and flow–metabolism coupling during general anaesthesia with xenon in humans.*  
Br J Anaesth 2008; 100: 667–75
Xenon and the Brain: How does xenon produce anesthesia?

Xenon preserves cerebral flow – metabolism coupling

Rex S et al.
*Positron emission tomography study of regional cerebral blood flow and flow–metabolism coupling during general anaesthesia with xenon in humans.*

Br J Anaesth 2008; 100: 667–75
Xenon and the Brain: How does xenon produce anesthesia?

Two-Pore-Domain $K^+$ Channels Are a Novel Target for the Anesthetic Gases Xenon, Nitrous Oxide, and Cyclopropane

Marco Gruss, Trevor J. Bushell, Damian P. Bright, William R. Lieb, Alistair Mathie, and Nicholas P. Franks

TREK1, TREK 2, TASK1, TASK3, TRESK

Exclusive Target of VA

Xe $\rightarrow$ TREK1

Activation

$K^+$-efflux $\uparrow$

Hyperpolarization

Honoré E

The neuronal background $K_{2P}$ channels: focus on TREK1.

Nature Reviews 2007
Noble Gas Xenon Is a Novel Adenosine Triphosphate-sensitive Potassium Channel Opener

Carsten Bantel, M.D., Ph.D., F.R.C.A., F.F.P.M.R.C.A.,
Xenon and the Brain: How does xenon produce anesthesia?

- Antinociceptive effects?
- Hemodynamic effects?
Xenon and the Brain: Neuroprotection

**Xenon reduces infarct volume after focal ischemia**
Homi et al., Anesthesiology 2003

**Xenon reduces neurological deficit after cardiac arrest**
Fries et al., CCM 2008

**Xenon is neuroprotective against traumatic brain injury**
Coburn et al., CCM 2008

**Xenon improves neurological function after cardiopulmonary bypass**
Ma et al., Anesthesiology 2003

**Xenon reduces infarct volume after peripartal hypoxia/ischemia**
Dingley et al., Stroke 2006

**Xenon reduces neuronal apoptosis**
Ma et al., Ann Neurol 2006
Conclusion: Xenon and the Brain

- Mechanism of action involves glutamatergic signaling
- Neuroprotection in-vivo
- Neuroprotection in subanesthetic doses
- Neuroprotection even after the onset of injury
Xenon and the Liver

- Background anesthesia: *ketamine + flunitrazepam + vecuronium ± increasing xenon concentrations*

- No effect on hepatic arterial blood flow
- Portal venous blood flow: -17%
- Decrease in $\text{DO}_2\text{Liver}$
- Increase in hepatic oxygen extraction
- $\text{PDR}_{\text{ICG}}$ unchanged
- ASAT, ALAT unchanged

Iber et al. *Xenon anesthesia impairs hepatic oxygenation and perfusion in healthy pigs.* MINERVA ANESTESIOL 2008;74:511-9
# Xenon Anesthesia for Liver Transplant Surgery: A Report of Four Cases

*Transplantation Proceedings, 43, 2683–2686 (2011)*

H.J. Wilke, C. Moench, G. Lotz, W. Bechstein, and K. Zacharowski

<table>
<thead>
<tr>
<th></th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
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<tr>
<td><strong>Preoperative data</strong></td>
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<td></td>
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<tr>
<td>Reason for transplantation</td>
<td>Hep. C induced cirrhosis</td>
<td>Re-LTX due to Hep. C recurrence; simultaneous kidney transplant</td>
<td>Alcohol-induced cirrhosis/ HCC; prior resection for HCC</td>
<td>NASH cirrhosis/ HCC</td>
</tr>
<tr>
<td>MELD (lab/special case exception)</td>
<td>32/-</td>
<td>34/-</td>
<td>12/34</td>
<td>9/28</td>
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<tr>
<td><strong>Intraoperative data</strong></td>
<td></td>
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<td>Duration of surgery (min)</td>
<td>300</td>
<td>605</td>
<td>425</td>
<td>310</td>
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<tr>
<td>Liver cold ischemia time (min)</td>
<td>1029</td>
<td>624</td>
<td>825</td>
<td>618</td>
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<tr>
<td>Liver warm ischemia time (min)</td>
<td>36</td>
<td>45</td>
<td>41</td>
<td>37</td>
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<tr>
<td>Ascites drained (L)</td>
<td>11</td>
<td>8</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Complicating factors</td>
<td>Compensated renal insufficiency</td>
<td>Extensive intra-abdominal scarring due to prior LTX; acute renal failure with intraoperative hemodiafiltration</td>
<td>Extensive intra-abdominal scarring due to prior surgery; compensated renal insufficiency</td>
<td>NIDDM type II</td>
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<tr>
<td>Xenon anesthesia</td>
<td>Average inspired xenon concentration (vol %)</td>
<td>66</td>
<td>68</td>
<td>61</td>
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<tr>
<td>Total xenon consumption (L)</td>
<td>27</td>
<td>56</td>
<td>36</td>
<td>28</td>
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<tr>
<td>Cost of xenon (US$)</td>
<td>675</td>
<td>1400</td>
<td>900</td>
<td>700</td>
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</table>
Xenon Preconditioning Protects against Renal Ischemic-Reperfusion Injury via HIF-1α Activation

Daqing Ma,* Ta Lim,* Jing Xu,† Haidy Tang,* Yanjie Wan,† Hailin Zhao,* Mahmuda Hossain,* Patrick H. Maxwell,‡ and Mervyn Maze*
Conclusion: Xenon

- Unique pharmacokinetic/-dynamic properties
- Cardioprotection
- Neuroprotection
- Organ protection

- not a drug to be used in unselected patients

Possible indications:
1. patients at cardiac risk
2. patients in need for neuroprotection
3. patients undergoing organ transplantation
Will Xenon Be a Stranger or a Friend?:
The Cost, Benefit, and Future of Xenon Anesthesia
[EDITORIAL VIEWS]
Goto, Takahisa M.D.*; Nakata, Yoshinori M.D., M.B.A.†; Morita, Shigeho M.D.‡

Xenon: from stranger to guardian
Robert D. Sanders\textsuperscript{a,c} and Mervyn Maze\textsuperscript{a,b,d}

DOI: 10.1093/bja/aeg232

Xenon: no stranger to anaesthesia
R. D. Sanders\textsuperscript{1 3}, N. P. Franks\textsuperscript{1 2*} and M. Maze\textsuperscript{1 2 3*+}
Thank you very much for your attention