Randomized controlled trial of the haemodynamic and recovery effects of xenon or propofol anaesthesia


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Background. There is limited clinical experience with xenon in a large number of patients. We present intra- and postoperative haemodynamic and recovery data comparing xenon and total intravenous anaesthesia with propofol.

Methods. A total of 160 patients aged 18–60 years (ASA I and II) undergoing elective surgery took part in this prospective non-blinded randomized controlled trial. After local ethics committee approval and written informed consent, patients were allocated randomly to either the xenon or the propofol group. Anaesthesia was induced with propofol and remifentanil and was maintained with xenon at 60% (minimal alveolar concentration 0.95) or with propofol 0.1–0.12 mg kg\(^{-1}\) min\(^{-1}\). Remifentanil was titrated to clinical need in both groups.

Results. The two study groups were comparable with respect to age, weight, height, gender and ASA classification. Baseline in heart rate and systolic arterial pressure (SAP) were comparable in both groups. Following induction, SAP initially decreased but returned to baseline values over 15 min in the xenon group and differed significantly from the propofol group. Heart rate decreased significantly only in the xenon group and remained at stable values. Occurrence and duration of hypertension, hypotension and bradycardia showed no significant difference between groups. Patient recovery time in the post-anaesthetic care unit and recovery from anaesthesia was similar in the two groups.

Conclusions. After induction the xenon/opioid regimen maintains systolic blood pressure at baseline levels and a low heart rate. No differences between groups were found in haemodynamic stability during anaesthesia. Recovery from xenon anaesthesia was similar to that observed in the propofol group.


Keywords: anaesthetic gases, xenon; anaesthetics i.v., propofol; pharmacodynamics

Accepted for publication: September 3, 2004

Xenon, which was first used as an anaesthetic in 1951, has become an alternative to the currently used inhaled anaesthetics. Xenon anaesthesia is associated with cardiovascular stability and does not affect myocardial contractility.\(^2\)\(^-\)\(^5\) In vitro and in vivo models have shown neuroprotective effects, as xenon acts via inhibition of the glutamatergic N-methyl-D-aspartate (NMDA) receptor.\(^6\)\(^-\)\(^7\) In a model of transient focal cerebral ischaemia, xenon administration improved both functional and histological outcome.\(^8\) Induction and recovery are rapid because its blood–gas coefficient (0.115) is the lowest of all known anaesthetics\(^9\) and, as it is a noble gas, it has no negative environmental effects. Unfortunately, xenon is an expensive anaesthetic requiring custom-designed closed-circuit anaesthesia machines.\(^10\) However, a few studies of groups of >100 patients have been reported in the last 10 years. The first multicentre study reporting data on the efficacy and safety of xenon–sufentanil compared with isoflurane–nitrous oxide–sufentanil was published in 2003.\(^4\) In this paper we present haemodynamic and recovery data from 160 patients randomly allocated to anaesthesia with xenon–remifentanil or propofol–remifentanil.

Methods

The study was designed as a randomized controlled trial and the study protocol was approved by the local ethics committee. Blinding of the anaesthetist was not possible because of the different administration methods of the anaesthetics (intravenous or inhalation). All patients gave
their informed written consent before participation in this clinical trial.

**Patients**
A total of 160 Caucasian adults were recruited after meeting the following inclusion criteria: age 18–60 yr; ASA I or II; Mallampati classification I or II; elective surgery; planned duration of anaesthesia of at least 60 min. Exclusion criteria included age <18 or >60 yr, ASA III–IV, emergency operation, pregnancy, breast-feeding period, raised intracranial pressure, history of myocardial infarction, alcohol or drug abuse, abnormal hepatic, adrenal or renal function, congestive heart failure, diabetes mellitus, expected difficult intubation, body weight deviating >20% from normal, any known allergy and preoperative medication known to interact with non-depolarizing neuromuscular blocking.

**Protocol**
Premedication was with midazolam 7.5 mg orally 45 min before induction. Monitoring included ECG, pulse oximetry, non-invasive arterial pressure, temperature, end-tidal carbon dioxide, oxygen and xenon concentrations and neuromuscular monitoring (TOF-Watch SX®, Organon Teknika). Non-invasive blood pressure and heart rate measurements were performed every 5 min with an AS/3 monitor (Datex-Ohmeda, Helsinki, Finland). The bispectral index was monitored (BIS Model A-2000®, software version 2.21, Aspect Medical Systems) to provide some information about depth of anaesthesia, although it is not validated for use in xenon anaesthesia. Monitoring was performed to ensure BIS values <50, with suggested tolerance for surgical intervention between 40 and 60, and data were recorded every 5 min.

Anaesthesia was induced in both groups with propofol 2 mg kg\(^{-1}\) i.v. and remifentanil 0.5 µg kg\(^{-1}\) by infusion over 60 s. Xenon administration was started with a face-mask (xenon group) with 60% xenon in oxygen [minimal alveolar concentration (MAC) 0.95, with MAC = 63%]. In the propofol group, propofol was infused continuously and ventilation was performed with oxygen-air mixture. Tracheal intubation was facilitated by the non-depolarizing neuromuscular blocking drugs mivacurium 0.16 mg kg\(^{-1}\), cis-atracurium 0.1 mg kg\(^{-1}\), rocuronium 0.6 mg kg\(^{-1}\) or vecuronium 0.1 mg kg\(^{-1}\). Medical quality xenon was supplied in steel cylinders, each containing 1000 litres (Messer-Griesheim GmbH, Krefeld, Germany). A closed-circuit anaesthesia machine (Physioflex®, Draeger, Lübeck, Germany) with modified software to reduce xenon consumption under minimal flow conditions was used. Inspiratory xenon concentration was determined using the thermoconductivity measuring device incorporated in the Physioflex anaesthesia machine (accuracy, ±3 vol%), which was calibrated automatically at the start.

Maintenance of anaesthesia was achieved using either xenon (60% xenon in oxygen) or propofol (0.1–0.12 mg kg\(^{-1}\) min\(^{-1}\)). If the xenon concentration dropped below 55% during the inhalation period, the Physioflex system was flushed to displace any nitrogen emerging into the closed circuit of the anaesthesia system. Flushing was continued until 60% xenon was reached. Remifentanil was administered via infusion pump at a base rate of 0.15 µg kg\(^{-1}\) min\(^{-1}\) and then titrated to clinical needs based on the patient’s haemodynamic, autonomic and somatic signs. BIS-values were kept <50 in both groups. Haemodynamic signs were defined as a change in systolic arterial pressure (SAP) or heart rate (HR) >20% from baseline in the absence of hypovolaemia. Autonomic signs were defined as sweating, salivation, flushing and somatic signs as movement and swallowing. In response, the remifentanil concentration was increased by increments of 0.05 µg kg\(^{-1}\) min\(^{-1}\) until symptoms resolved. In both groups a single bolus of propofol 0.5 mg kg\(^{-1}\) was administered when haemodynamic, autonomic and somatic signs despite increasing the remifentanil concentration. Antihypertensive, anticholinergic, or inotropic agents could be given during surgery if the heart rate or blood pressure indicated their use despite adequate anaesthesia. Standard treatment of blood loss and fluid replacement were used as necessary.

Ventilation was adjusted to maintain an end-expiratory carbon dioxide partial pressure at 4.8–6.0 kPa. Normothermia (35.5–37.0 °C) was achieved using warming blankets. Anaesthesia was discontinued when all surgical interventions, including the bandaging of the surgical fields, were completed and complete recovery of neuromuscular block was. Adequate spontaneous ventilation, with an end-expiratory carbon dioxide (5.3–6.6 kPa), was maintained and, after the patient had opened eyes on command, the trachea was extubated.

**Statistics**
Demographic data were analysed for homogeneity using the two-tailed Wilcoxon rank-sum test for age, height and body weight of the patient (mean and standard deviation) and the two-tailed Fisher exact test for gender, ASA and Mallampati classifications (frequencies and percentage). BIS monitoring, remifentanil consumption, systolic and diastolic blood pressure, heart rate, Visual Analogue Scale for pain, Aldrete score, duration in the post-anaesthetic care unit, all measurements for additional anaesthesia were analysed with the two-tailed Fisher exact test and shown as frequencies and percentages. Statistical analysis was performed using SAS software version 8.0® (SAS Institute Inc.) and graphs were drawn using Graph Pad Prism 4®.

**Results**
A total of 160 patients (80 assigned to xenon and 80 to propofol) were included in this study. The two groups
were comparable with respect to age, weight, height, sex, ASA and Mallampatti classifications and duration of anaesthesia (Table 1).

At induction of anaesthesia, three patients in the propofol group and two in the xenon group received reduced doses of propofol (1.5 mg kg\(^{-1}\)) and remifentanil (0.4 \(\mu g\) kg\(^{-1}\)) based on their haemodynamic response during induction. Anaesthesia was maintained with xenon 59.6 (± 2.6)% or propofol 0.11 (0.08) mg kg\(^{-1}\) min\(^{-1}\). Total remifentanil consumption was 0.19 (0.09) \(\mu g\) kg\(^{-1}\) min\(^{-1}\) in the xenon group and 0.18 (0.08) \(\mu g\) kg\(^{-1}\) min\(^{-1}\) in the propofol group. During the first 25 min, remifentanil consumption was slightly higher in the propofol group, but this difference was only significant at 5 min. At 25 min, the remifentanil consumption rates intersected and the xenon group had a higher consumption which was significant after 55 min.

Preinduction heart rate was similar but was significantly lower in the xenon group throughout anaesthesia (Fig. 1). The frequency and duration of bradycardia was similar (Table 2). Before induction and during the first 10 min there was no significant difference in SAP or diastolic arterial pressure (DAP) between groups. After 10 min the xenon group had a significantly higher SAP and DAP (Figs 2 and 3). Hypertension occurred in 18 patients in the xenon group and 15 in the propofol group (Table 2), and duration of hypertension was comparable. Hypotension occurred in five of the xenon group compared with six in the propofol group, and the duration showed no significant difference (Table 2).

![Heart rate](image1)

**Fig 1** Heart rate is shown as mean (SD). Induction was at time 0.

![Systolic blood pressure](image2)

**Fig 2** Systolic blood pressure is shown as mean (SD). Induction was at time 0.

### Table 1 Demographic data. Values are shown as mean (SD), except for age which is shown as mean (range). End of anaesthesia is defined as the time point when all surgical interventions were completed. No significant differences between the groups were noted.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Xenon (n=80)</th>
<th>Propofol (n=80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>37.6 (18–60)</td>
<td>38.1 (18–60)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>70.9 (13.3)</td>
<td>71.2 (13.6)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>172.6 (9.3)</td>
<td>172.7 (10.1)</td>
</tr>
<tr>
<td>Sex ratio (female: male)</td>
<td>42:38</td>
<td>42:38</td>
</tr>
<tr>
<td>Physical status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASA I</td>
<td>43</td>
<td>45</td>
</tr>
<tr>
<td>ASA II</td>
<td>37</td>
<td>35</td>
</tr>
<tr>
<td>Duration of anaesthesia (min)</td>
<td>135 (74)</td>
<td>121 (58)</td>
</tr>
</tbody>
</table>

### Table 2 Incidence of adverse events. Xenon/propofol 1, number (percentage) of patients with events; xenon/propofol 2, total number (percentage) of events; xenon/propofol 3, percentage of time with bradycardia (>20% deviation from mean baseline), hypertension (>20% deviation from mean systolic baseline with stable heart rate and no other signs of low depth of anaesthesia such as sweating) and hypotension (>20% deviation from mean systolic baseline) 10 min after induction throughout anaesthesia; values are mean (SD). Additional anaesthesia, propofol 0.5 mg kg\(^{-1}\) as a single bolus.

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Xenon 1</th>
<th>Propofol 1</th>
<th>Xenon 2</th>
<th>Propofol 2</th>
<th>Xenon 3</th>
<th>Propofol 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bradycardia</td>
<td>5 (6.3)</td>
<td>5 (6.3)</td>
<td>5 (6.3)</td>
<td>8 (9.6)</td>
<td>0.6 (2.4)</td>
<td>1.0 (4.9)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>18 (22.5)</td>
<td>15 (18.8)</td>
<td>22 (25.3)</td>
<td>23 (26.7)</td>
<td>2.9 (6.2)</td>
<td>2.8 (6.4)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>5 (6.25)</td>
<td>6 (7.5)</td>
<td>7 (8.5)</td>
<td>10 (11.9)</td>
<td>0.9 (4.0)</td>
<td>1.3 (4.9)</td>
</tr>
<tr>
<td>Cough during intubation</td>
<td>5 (6.3)</td>
<td>5 (6.3)</td>
<td>5 (6.3)</td>
<td>5 (6.3)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Movement during intubation</td>
<td>3 (3.8)</td>
<td>2 (2.5)</td>
<td>3 (3.8)</td>
<td>2 (2.5)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Additional anaesthesia</td>
<td>6 (7.5)</td>
<td>0 (0)</td>
<td>9 (5.5)</td>
<td>0 (0)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Shivering</td>
<td>2 (1.3)</td>
<td>2 (1.3)</td>
<td>2 (1.3)</td>
<td>2 (1.3)</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>
Both groups showed a similar frequency of response to intubation (Table 2). During anaesthesia, the xenon group had significantly lower BIS monitoring levels than the propofol group (Fig. 4). Aldrete scores in both groups immediately after anaesthesia were good (Table 3). Time in the post-anaesthetic care unit was similar: 78.1 (31.5) min for the xenon group and 79.8 (43.6) min for the propofol group.

Discussion

No differences were found in the haemodynamic stability achieved with xenon or propofol anaesthesia. The propofol group had lower SAP and DAP, but the incidences of hypertension, hypotension and bradycardia were similar in the two groups.

It is difficult to assess differences in depth of anaesthesia, especially when comparing inhaled with intravenous anaesthesia, but overall BIS values <50 were comparable (37.7 (8.9) in the xenon group and 42.2 (7.5) in the propofol group). The overall consumption of remifentanil was 0.19 (0.09) µg kg\(^{-1}\) min\(^{-1}\) in the xenon group and 0.18 (0.08) µg kg\(^{-1}\) min\(^{-1}\) in the propofol group. However, the non-blinded nature of this study makes interpretation of opioid requirements and analgesic efficacy difficult. Episodes of hypertension had similar frequencies (per patient, number of events and duration) in both groups. The slightly higher incidence of hypertension in the xenon group compared with the isoflurane–nitrous oxide group in the study by Rossaint and colleagues\(^4\) is explained by the fact that hypertension mainly occurred as a single event in the induction period. For this reason, we measured the occurrence and duration of hypertension, hypotension and bradycardia at time points throughout anaesthesia, starting 10 min after induction. The number of patients with hypotension was similar to that in the study by Rossaint and colleagues. Throughout anaesthesia, the xenon group had a lower heart rate than the propofol group, which may have been due to the higher blood pressure, resulting in a baroreflex-mediated increase in vagal tone. Nevertheless, the incidence of bradycardia was similar in both groups and similar to the results of Rossaint and colleagues\(^4\) who concluded that xenon caused less cardiovascular response than isoflurane–nitrous oxide in a group of healthy patients.

In isolated guinea pig hearts, it has been shown that, unlike other inhaled anaesthetics, xenon does not significantly alter heart rate, atrioventricular conduction time, left ventricular pressure, coronary flow, oxygen extraction, oxygen consumption, cardiac efficiency and flow responses to bradykinin.\(^{13}\) It has also been shown that xenon does not depress L-type calcium currents in human atrial myocytes.\(^{2,3}\) Xenon did not reduce myocardial contractility in dogs with experimentally induced cardiomyopathy.\(^{14}\) In addition, xenon does not impair the reaction of cardiac muscle bundles to positive inotropic stimulation such as isoproterenol or calcium.\(^{5}\)

Recovery from xenon anaesthesia has been shown to be faster than that from isoflurane–nitrous oxide anaesthesia.\(^4\) In our study, the xenon and propofol groups had similar Aldrete scores and recovery times. The recovery from xenon anaesthesia is mainly explained by the low

<table>
<thead>
<tr>
<th>Group</th>
<th>Aldrete(_{10})</th>
<th>Aldrete(_{15})</th>
<th>Aldrete(_{30})</th>
<th>Aldrete(_{45})</th>
<th>Aldrete(_{60})</th>
<th>Aldrete(_{120})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xenon</td>
<td>9.5 (0.7)</td>
<td>9.6 (0.7)</td>
<td>9.7 (0.6)</td>
<td>9.7 (0.6)</td>
<td>9.8 (0.5)</td>
<td>9.9 (0.5)</td>
</tr>
<tr>
<td>Propofol</td>
<td>9.4 (0.9)</td>
<td>9.6 (0.8)</td>
<td>9.7 (0.6)</td>
<td>9.8 (0.4)</td>
<td>9.9 (0.4)</td>
<td>10.0 (0.3)</td>
</tr>
</tbody>
</table>

Table 3 Aldrete scores recorded postoperatively after 5, 15, 30, 45, 60 and 120 min. Values are shown as mean (SD). There was no significant difference between the groups.
blood–gas partition coefficient of 0.115 and is independent of the duration of anaesthesia. Bispectral index monitoring is known to reduce propofol usage and can shorten recovery after propofol anaesthesia. Goto and colleagues studied 11 patients receiving xenon anaesthesia (0.8 MAC) who had a stepwise decrease in xenon concentration (0.1 MAC every 15 min) at the end of anaesthesia. The patients had a median BIS of 40 throughout anaesthesia and at recovery four patients receiving xenon responded to verbal command while BIS was <50. They concluded that low BIS values (<50) did not guarantee adequate hypnosis during xenon anaesthesia. Therefore we measured the BIS as a surrogate parameter. In our study we found that the xenon group had significantly lower BIS values (median 38) throughout the anaesthesia than the propofol group (median 42) with no signs of inadequate anaesthesia. Further studies of the relationship between xenon and BIS monitoring are required.

Following induction of anaesthesia, xenon maintains arterial pressure and a stable low heart rate. No differences were found in haemodynamic stability between xenon and propofol anaesthesia. Speed of recovery from anaesthesia is comparable to that from propofol.

Acknowledgements
This work was supported by Messer Griesheim (donor of xenon) and Organon Teknika (financial support). None of the authors received any corporate support, honoraria etc. from any of the above-mentioned sponsors of this study.

References
1 Cullen SC, Gross EG. The anesthetic properties of xenon in animals and human beings with additional observations on krypton. Science 1951; 113: 580–2
8 Homi HM, Yokoo N, Ma D et al. The neuroprotective effect of xenon administration during transient middle cerebral artery occlusion in mice. Anesthesiology 2003; 99: 876–81
13 Stowe DFM, Rehmert GC, Wai-Meng K, Weigt HU, Georgieff M, Bosnjak ZJ. Xenon does not alter cardiac function or major cation currents in isolated guinea pig hearts or myocytes. Anesthesiology 2000; 92: 516