Incidence of postoperative nausea and emetic episodes after xenon anaesthesia compared with propofol-based anaesthesia

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Background. Xenon has been proved to be safe and efficacious for general anaesthesia in numerous trials. In addition, experimental studies demonstrate that xenon inhibits the 5-hydroxytryptamine type 3 (5-HT3) receptor. As 5-HT3 receptor antagonists are known to decrease postoperative nausea and vomiting (PONV) to an extent comparable with a propofol-based total i.v. technique, we tested the hypothesis that general anaesthesia with xenon would result in a reduced incidence of PONV similar to that observed with propofol-based anaesthesia.

Methods. After obtaining approval from the local ethics committee and written informed consent, 142 patients were randomized to receive xenon anaesthesia or propofol-based total i.v. anaesthesia (TIVA), both supplemented with remifentanil. The incidence of postoperative nausea and emetic episodes was recorded in the post-anaesthesia care unit and on the ward more than 24 h after anaesthesia.

Results. A total of 142 patients were equally distributed between the xenon and TIVA groups. Anaesthesia was maintained with mean (SD) concentrations of either xenon 61 (2)% or propofol 100 (20) μg kg⁻¹ min⁻¹. Incidences of nausea and emetic episodes over the whole 24-h period were 66.2% and 35.2% in the xenon group and 26.8% and 16.9% in the TIVA group (P<0.001 and P<0.021).

Conclusion. Despite knowing the 5-HT3 antagonistic properties of xenon, its use is associated with a higher incidence of nausea and emetic episodes compared with TIVA with propofol.

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Postoperative nausea and vomiting (PONV) remains one of the most undesirable events in the context of general anaesthesia and surgery, with an estimated incidence of 25–30%.1–3 Patients rate PONV as a major cause of discomfort and irritation after surgery, although the condition is usually temporary and self-limiting.4–6 Severe complications, however, include suture dehiscence, oesophageal rupture, and life-threatening aspiration.7

The use of volatile anaesthetics is known to be a principal cause of early PONV.7 Indeed, use of total i.v. anaesthesia (TIVA) reduces PONV to the same extent as the use of a 5-hydroxytryptamine type 3 (5-HT3) antagonist.8

In the recent multicentre trials, xenon has been proved to be a safe anaesthetic agent with remarkable haemodynamic stability.9–11 Official permission for use of xenon as an anaesthetic has now been issued in most European countries. Little, however, is known about the incidence of PONV with xenon anaesthesia.

Of particular interest, xenon has been shown to inhibit 5-HT3 receptors in vitro.12 These receptors are known to be peripherally and centrally located in vivo and are strongly implicated in the vomiting reflex. For this reason,

1Drs M. Coburn and O. Kunitz contributed equally to this study.
2Declaration of interest. Dr M. Coburn and Professor R. Rossaint are paid consultants of Air Liquide Santé International, a company interested in developing clinical applications for medical gases, including xenon.
they are the target of a number of anti-emetics including ondansetron, granisetron, and palonosetron. This study aims to use secondary outcome data from partly published previous studies\textsuperscript{13,14} to determine whether the 5-HT\textsubscript{3} antagonist properties of xenon result in a reduction of PONV similar to that produced by the use of TIVA.

**Methods**

In three studies performed at University Hospital Aachen, 142 total patients (ASA I and II and age 18–60 yr) were consented to receive either xenon or propofol-based anaesthesia. These studies, in which PONV data were also collected, were designed as randomized controlled trials with neuromuscular monitoring data as the primary outcome measure.\textsuperscript{13,14} Each of the published studies included 40 patients. The remaining study, which contains neuromuscular monitoring data are unpublished. Incidences of postoperative nausea and emetic episodes were recorded as secondary outcome measures. Randomization was computer-generated and allocation concealment was ensured by enclosing assignments in sealed, sequentially numbered envelopes. The anaesthetist could not be blinded owing to the different administration methods of the anaesthetics, however, both study personnel (assessing postoperative nausea and emetic episodes in the post anaesthesia care unit and on the ward) and patients were blinded to group assignment (double-blinded observation).

Study inclusion criteria were: age 18–60 yr, ASA classification I and II, and planned duration of anaesthesia of at least 60 min. Exclusion criteria were: body weight greater or less than 20\% of the ideal weight; expected difficult intubation; pre-existing hepatic, renal, or neuromuscular disease; pregnant or nursing women; any known allergic diathesis; and preoperative medications known to interact with non-depolarizing neuromuscular blocking agents.

**Anaesthesia**

Patient monitoring included ECG, pulse oximetry, non-invasive blood pressure, end-tidal carbon dioxide concentration, body temperature, and oxygen and xenon concentrations. Anaesthesia was induced rapidly with propofol 2 mg kg\textsuperscript{-1} and remifentanil 0.5 \(\mu\)g kg\textsuperscript{-1} in both groups. Simultaneously, xenon administration was started in the xenon group via a facemask until an end-tidal concentration was facilitated by a non-depolarizing neuromuscular (Physioflex, Draeger, Lübeck, Germany). Tracheal intubation was performed using a closed-circuit anaesthesia machine (Physioflex, Draeger, Lübeck, Germany). Tracheal intubation was facilitated by a non-depolarizing neuromuscular blocking drug (mivacurium 0.16 mg kg\textsuperscript{-1}, cis-atracurium 0.1 mg kg\textsuperscript{-1}, rocuronium 0.6 mg kg\textsuperscript{-1}, or vecuronium 0.1 mg kg\textsuperscript{-1}).

After tracheal intubation, anaesthesia was maintained either by xenon [60\% in O\textsubscript{2}, reflecting a minimum alveolar concentration (MAC) of 0.9–1.0] or propofol (0.1 mg kg\textsuperscript{-1} min\textsuperscript{-1}). Remifentanil was initiated at 0.2 \(\mu\)g kg\textsuperscript{-1} min\textsuperscript{-1} in both groups and adjusted according to clinical needs. Ventilation was adjusted to maintain an end-tidal carbon dioxide concentration of 4.8–6.0 kPa. Normothermia (35.5–37.0°C) was achieved using forced air-warming blankets. The clinic’s standard treatment of blood loss and fluid replacement strategy was used when necessary. Twenty minutes before the estimated cessation of all surgical procedures, piritramide 0.05 mg kg\textsuperscript{-1} for post-anaesthetic pain management was administered i.v. along with a minimal infusion of metamizole 15 mg kg\textsuperscript{-1}.

Complete recovery of neuromuscular block was reached at the end of the operation in each patient and none of the patients received any pharmacological antagonism. Extubation was performed after ensuring adequate spontaneous breathing. In the event of continued pain [visual analogue scale (VAS >3)] in the post-anaesthesia care unit, piritramide 0.05 mg kg\textsuperscript{-1} was administered as a rescue treatment. All patients were transferred from the operating room to the post-anaesthesia care unit for immediate recovery and subsequently assigned to the ward.

Gender, smoking habits, history of motion sickness or PONV, and Apfel score\textsuperscript{15} were recorded before operation. PONV episodes were divided into an early time period (in the post-anaesthesia care unit) and 24 h after anaesthesia. Nausea was defined as the subjective sensation of an urge to vomit. Nausea was evaluated by the patient in a categorical way (yes or no). An emetic episode was defined as a single or continuing occurrence of vomiting or retching, a failed attempt to vomit (‘dry heaves’). Distinct episodes were defined by an interval of respite of more than 1 min.\textsuperscript{16} Rescue medication was offered if the patient had more than one episode of vomiting or retching, if the patient had nausea lasting longer than 15 min, or if the patient requested it. The anaesthetist could select between tropisetron 2 mg or dimenhydrinate 62 mg as rescue medication. Patients were monitored closely in the post-anaesthesia care unit and in the ward by a study nurse up to 24 h after giving anaesthesia.

Parametric data were tested with one-way ANOVA and presented as means and standard deviations. Categorical data were analysed with the two-tailed Pearson \(\chi^2\) test and are given as numbers and percentages. In addition, we conducted a logistic regression analysis (using forward selection procedure) considering group allocation and all potentially confounding factors (gender, opioid consumption, etc.). Statistical analyses were performed using SPSS software version 15.0 (SPSS Inc., Chicago, IL, USA).

We calculated that for a sample size of 69 in each group, using a two-group large-sample normal approximation test of proportions with a one-sided 0.050, significance level has 80\% power to reject the null hypothesis that the xenon (15\%) and the propofol (20\%) are not equivalent (the difference in proportions, is 0.050 or farther from zero in the same direction) in favour of the
Table 1 Patient characteristics. Weight (in kilograms) and height (in centimetres) are given as mean (SD). Age is given as median (range), gender, smoking habits, history of motion sickness or postoperative nausea and vomiting (PONV), and Apfel score are presented as numbers of patients (n = 71).

<table>
<thead>
<tr>
<th></th>
<th>Xenon group (n = 71)</th>
<th>Propofol group (n = 71)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>71.1 (13.7)</td>
<td>71.6 (12.3)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>172.8 (9.7)</td>
<td>173.1 (8.9)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>37 (18–59)</td>
<td>38 (18–59)</td>
</tr>
<tr>
<td>Female/male</td>
<td>38/33</td>
<td>38/33</td>
</tr>
<tr>
<td>Smoker/non-smoker</td>
<td>28/43</td>
<td>27/44</td>
</tr>
<tr>
<td>History of motion sickness or PONV (yes/no)</td>
<td>33/38</td>
<td>25/46</td>
</tr>
<tr>
<td>Apfel score 1/2/3/4/6</td>
<td>12/34/24/1</td>
<td>17/31/19/4</td>
</tr>
</tbody>
</table>

Table 2 Anaesthesia data. Type of surgery, laparoscopy, use of postoperative opioids, and rescue postoperative nausea and vomiting (PONV) medication are presented as numbers of patients with percentage of group-total in parentheses. Duration of anaesthesia, cumulative piritramide use, and time in the post-anaesthesia care unit (PACU) are presented as mean (SD).

<table>
<thead>
<tr>
<th></th>
<th>Xenon group (n = 71)</th>
<th>Propofol group (n = 71)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trauma/orthopaedic</td>
<td>31 (43.7)</td>
<td>27 (38.0)</td>
</tr>
<tr>
<td>Otolaryngology</td>
<td>4 (5.6)</td>
<td>13 (18.3)</td>
</tr>
<tr>
<td>Urology</td>
<td>4 (5.6)</td>
<td>2 (2.8)</td>
</tr>
<tr>
<td>Gynaecology</td>
<td>23 (32.4)</td>
<td>21 (29.6)</td>
</tr>
<tr>
<td>Plastic surgery</td>
<td>9 (12.7)</td>
<td>8 (11.3)</td>
</tr>
<tr>
<td>Laparoscopy</td>
<td>14 (19.7)</td>
<td>9 (12.7)</td>
</tr>
<tr>
<td>Duration of anaesthesia (min)</td>
<td>133 (77)</td>
<td>123 (56)</td>
</tr>
<tr>
<td>Use of postoperative opioids in PACU</td>
<td>68 (95.8)</td>
<td>58 (81.7)</td>
</tr>
<tr>
<td>Cumulative piritramide dose in PACU</td>
<td>12.9 (6.6)</td>
<td>11.0 (8.2)</td>
</tr>
<tr>
<td>Time in PACU</td>
<td>92 (47) min</td>
<td>87 (51) min</td>
</tr>
<tr>
<td>Rescue PONV medication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dimethyldimethamicine</td>
<td>20 (28.2)</td>
<td>13 (18.3)</td>
</tr>
<tr>
<td>Tropisetron</td>
<td>6 (8.5)</td>
<td>3 (4.2)</td>
</tr>
</tbody>
</table>

Results

In this study, data from a total of 142 patients were included and analysed for incidence of postoperative nausea and emetic episodes. Patient characteristics including weight, height, age, gender distribution, and risk factors for PONV (summarized in the PONV risk score) did not differ between the groups (Table 1).

Anaesthesia was maintained with mean (SD) concentrations of either xenon 61 (2)% or propofol 100 (20) μg kg⁻¹ min⁻¹ and supplemented with remifentanil as needed—in the xenon 0.2 (0.11) μg kg⁻¹ min⁻¹ and in the propofol group 0.2 (0.10) μg kg⁻¹ min⁻¹. Type of surgery, including the use of laparoscopic techniques, duration of anaesthesia, time in the post-anaesthesia care unit, and cumulative piritramide doses per patient did not differ between the groups (Table 2). In the propofol group, significantly fewer patients required postoperative opioids (Table 2).

According to the logistic regression analysis of PONV over the whole 24-h study period, use of xenon was associated with a significantly higher risk [odds ratio (OR) 7.3, P < 0.001] as were the three other factors: female gender (OR 9.0, P < 0.001), non-smoking (OR 2.5, P = 0.031) and the increase of the postoperative opioid piritramide by 1 mg (OR 1.11, P = 0.001).

In the early time period, both nausea and emetic episodes arose in the xenon group significantly more often than in the propofol group. Late nausea and emetic episodes were not significantly different between the two groups, but 24 h after xenon anaesthesia the overall incidence of PONV was higher than with the propofol-based anaesthesia. Interestingly, the incidence of emetic episodes per patient failed to differ between the groups (Table 3).

Discussion

Suzuki and colleagues reported that xenon competitively inhibits human-cloned 5-HT₃ receptors expressed in Xenopus oocytes. 5-HT₃ receptors are diffusely distributed in both the central and peripheral nervous system and are involved in the process of mediating nausea and vomiting. This finding lead to the hypothesis that xenon might decrease the incidence of nausea and vomiting in a manner akin to known 5-HT₃ antagonist anti-emetics. Apfel and colleagues have previously demonstrated in a factorial trial that propofol reduces the risk of PONV by 19% versus the use of volatile anaesthetics. This makes one of the alternative hypothesis that the proportions in the two groups are similar. The post hoc analysis testing for equivalence was performed using nQuery Advisor Version 4.0 (Statistical Solutions, Saugus, MA, USA).
limitations of this study, the use of propofol-based anaesthesia (with its inherent anti-emetic effect \(^7\) \(^8\)) as a control group, obvious. From the clinical perspective, and as a positive control, a volatile anaesthetic would make an interesting comparison; this aspect remains open to further investigations.

We assessed PONV applying the same standardized methodology in the abovementioned studies. These were secondary endpoint measurements.

A further limitation to this study is the fact that nausea was recorded in dichotomous form, allowing only yes or no answers. The use of a continuous measure (such as the VAS) would have provided the advantage of additional data and reduce the possibility of a threshold effect. Further, a 5-HT\(_3\) receptor blocker was used as an anti-emetic in some subjects. This makes a resolution, as a role for xenon block of 5-HT\(_3\) receptors, in late PONV difficult.

The incidence of PONV was reported as a surrogate outcome in two recently published multicentre trials including a total of 483 patients receiving either xenon- or isoflurane-based anaesthesia. In the first study, the occurrence of PONV was 24.1\% in the xenon group and 14.3\% in the isoflurane group.\(^9\) The failure to achieve a significant difference in the first study might be attributable to a type 2 error. In the second trial, the incidence of PONV was significantly higher in the xenon group (27.5\%) compared with the isoflurane group (12.5\%).\(^11\) In both studies, timing of assessment for PONV was not pre-defined. Also, no distinction was made in reporting of nausea, emesis, or both. Further in a study comparing the analgesic potency of MAC-equivalent concentrations of xenon and nitrous oxide in 12 healthy volunteers, both xenon and nitrous oxide evoked nausea and vomiting in a large number of volunteers.\(^18\)

Our data suggest that xenon is associated with a higher incidence of postoperative nausea and emetic episodes when compared with propofol-based anaesthesia. One postulated mechanism involves the unique pharmacodynamic properties of xenon gas.

Induction and recovery from xenon anaesthesia are rapid because of its blood–gas coefficient of 0.115.\(^19\)\(^20\)

Rapid recovery from anaesthesia could result in greater postoperative opioid use, as we observed in our study population (Table 2). Thus, greater postoperative opioid use, a known major predictor for PONV,\(^16\) may be contributing to the observed increase in PONV with xenon anaesthesia rather than the gas itself. However, one would expect an increase in late PONV to occur as well.\(^7\)\(^21\)\(^22\) However, after including the different uses of opioids in a multivariable analysis regarding PONV after 24 h, the difference in the incidence of PONV remained significant between the groups.

Further studies will be needed to determine the exact mechanism, but this study provides evidence that xenon is associated with an increased incidence of PONV when compared with propofol-based anaesthesia.

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**References**


22 Roberts GW, Bekker TB, Carlsen HH, Moffatt CH, Slattery PJ, McClure AF. Postoperative nausea and vomiting are strongly influenced by postoperative opioid use in a dose-related manner. *Anesth Analg* 2005; 101: 1343–8