Dolasetron prophylaxis reduces nausea and postanaesthesia recovery time after remifentanil infusion during monitored anaesthesia care for extracorporeal shock wave lithotripsy

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Background. Remifentanil is used as an analgesic for different procedures performed during monitored anaesthesia care. Opioid-induced nausea and vomiting can be troublesome.

Methods. This prospective, randomized, double-blind study was performed to evaluate the efficacy of prophylaxis with dolasetron in reducing the frequency of postoperative nausea and duration of discharge time. Forty urological patients, undergoing elective ambulatory extracorporeal shock wave lithotripsy (ESWL) received randomly either dolasetron 12.5 mg i.v. (Group 1) or placebo (Group 2) 10 min before a patient-adapted continuous infusion of remifentanil 0.15–0.4 μg kg⁻¹ min⁻¹ was administered. Frequency and intensity (VAS 0–100 mm) of nausea, retching, and vomiting were assessed by patients and blinded investigators during and after the procedure.

Results. Patient characteristics, baseline values, duration of ESWL, and total dose of remifentanil did not differ between groups. The frequency (Group 1/Group 2: 20/55%; P<0.05) and mean (SD) maximal intensity [15 (9)/45 (14) mm; P<0.05] of nausea during 24 h was significantly reduced after dolasetron and discharge times in Group 1 were less than Group 2 [22 (14)/45 (28) min; P<0.05].

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The ultra-short-acting opioid remifentanil is often used as a sole agent for brief and painful procedures associated with little postoperative pain such as extracorporeal shock wave lithotripsy (ESWL).¹ ² It is also used as a supplemental drug during the performance of eye or peripheral nerve blocks.³–⁶ Remifentanil is beneficial in these settings because of its minimal postanaesthetic sedation effects. However, several studies have shown that remifentanil anaesthesia can be associated with postoperative nausea and vomiting (PONV) which prolongs postanaesthetic recovery in a high number (15–50%) of patients.¹ ² ⁷ ⁸ In addition, patients’ satisfaction with the anaesthetic technique will be reduced when PONV occurs.

Midazolam and propofol have shown to reduce these symptoms when infused in combination with remifentanil.⁹ ¹⁰ Because the emetic effect of remifentanil seems to be dose-dependent,⁵ part of the antiemetic effect of these agents could be explained by the remifentanil dose sparing effect. Also, propofol itself may have antiemetic effects. However, the combination of these drugs with remifentanil increases the rate and severity of respiratory depression. An alternative is the prophylactic use of an antiemetic such as the 5-HT3 antagonist dolasetron, which has good antiemetic efficacy without sedative side-effects.¹⁰ ¹¹ Therefore, in a prospective, randomized and double-blind trial we tested the hypothesis that dolasetron 12.5 mg before remifentanil infusion may reduce the frequency and intensity of nausea and time to ‘home readiness’ after ambulatory ESWL.

Declaration of interest. The work was supported by Aventis Pharma, Germany and included payment of patients insurance and the fee of the local ethics committee.

¹Results of this work have been presented at the German Congress of Anaesthesiology in Munich, May 2000 and at the Annual Meeting of the ASA, in San Francisco, October 2000.

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Methods

After approval of the local ethics committee and written informed consent were obtained, 40 patients (ASA class I-II, aged 20–77 yr) undergoing elective ESWL were included the study. Exclusion criteria were ASA class >III and obstructive pulmonary disease. All patients were asked for risk factors for PONV (Table 1). After arriving in the anaesthetic room and insertion of an i.v. cannula, baseline assessments of ventilatory frequency, heart rate (ECG), non-invasive arterial pressure, pulse oximetry ($S_{aO_2}$), main flow end-tidal carbon dioxide partial pressure ($E_{CO_2}$) via oxygen face mask were performed using a multifunctional monitor system (Eagle, 3000Ô Marquette Hellige, Germany).

According to randomization, patients in Group 1 received in a double-blinded manner dolasetron 12.5 mg i.v. (Anemet®, Aventis, Germany) and Group 2 received the same i.v. volume of placebo (saline) 10 min before the procedure was started. During ESWL, patients received a continuous infusion of remifentanil 0.15 $\mu$g kg$^{-1}$ min$^{-1}$ (Ultiva®, Glaxowellcome, Germany). In the event of pain, the infusion rate was increased in a stepwise fashion (0.05 $\mu$g kg$^{-1}$ min$^{-1}$). No decreases of the infusion rate were made. All patients received oxygen 6 litre min$^{-1}$ insufflation via a face mask.

During remifentanil infusion, respiratory side-effects such as hypoventilation ($E_{CO_2}$ >6 kPa or ventilatory frequency <8 bpm) and oxygen desaturation ($S_{aO_2}$ <90%) were continuously registered. Breathing commands were given if apnea persisted for 20 s or $S_{aO_2}$ decreased more than 5% of baseline values. Frequency and intensity [visual analogue scale (VAS) 0–100 mm] of nausea, retching, and vomiting were assessed by patients and blinded investigators during 60 min. After 24 h, all patients were interviewed by a blinded researcher by telephone. Patients were asked if they experienced PONV using a standardized questionnaire. A rescue dose of droperidol 1.25 mg i.v. was given in case of persistent symptoms (nausea VAS >10 mm for 10 min) in the postanaesthesia care unit (PACU).

On the basis of retrospective data from our institution and the literature in the same patient population, a power analysis was performed by using the proportion of complete responders following the procedure as the primary outcome variable. Complete responders were defined as patients with no emetic episodes, no rescue medication and a maximum VAS of <5 mm (VAS ranging from 0 to 100 mm) within 24 h according to the published data of other study groups.$^{10,15}$ We set 50% as the predicted value for the placebo group. We defined the smallest difference to be clinically significant as 25% ($\alpha=0.05$, $\beta=0.20$). This analysis indicated that a sample size of at least 56 patients per group was necessary. An interim analysis was performed

### Table 1 Patient characteristics, risk factors and technical data, mean (sd or range) or number of patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group 1, Remifentanil + dolasetron ($n=20$)</th>
<th>Group 2, Remifentanil + placebo ($n=20$)</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>45 (20–75)</td>
<td>51 (24–77)</td>
<td>0.11</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>172 (10)</td>
<td>173 (8)</td>
<td>0.78</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>78 (16)</td>
<td>80 (13)</td>
<td>0.78</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>7/13</td>
<td>10/10</td>
<td>0.21</td>
</tr>
<tr>
<td>ASA physical status (I/II)</td>
<td>8/12</td>
<td>6/14</td>
<td>0.51</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of PONV (yes/no)</td>
<td>6/14</td>
<td>8/12</td>
<td>0.48</td>
</tr>
<tr>
<td>Motion sickness (yes/no)</td>
<td>5/15</td>
<td>6/14</td>
<td>0.78</td>
</tr>
<tr>
<td>Non-smoker (yes/no)</td>
<td>14/6</td>
<td>12/8</td>
<td>0.48</td>
</tr>
<tr>
<td>Female patients &lt;50 yr (number)</td>
<td>5</td>
<td>4</td>
<td>0.50</td>
</tr>
<tr>
<td>Duration of remifentanil infusion (min)</td>
<td>33 (11)</td>
<td>34 (15)</td>
<td>0.98</td>
</tr>
<tr>
<td>Mean dose of remifentanil ($\mu$g kg$^{-1}$ min$^{-1}$)</td>
<td>0.19 (0.07)</td>
<td>0.17 (0.04)</td>
<td>0.46</td>
</tr>
<tr>
<td>Duration of ESWL (min)</td>
<td>28 (2)</td>
<td>27 (3)</td>
<td>0.49</td>
</tr>
<tr>
<td>Number of shocks of 18 kV/23 kV</td>
<td>2000 (0)/500 (0)</td>
<td>2000 (0)/500 (0)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Fig 1 Percentage of patients with postoperative nausea (≤5 mm VAS), retching, vomiting, and rescue therapy with droperidol. *$P<0.05$ dolasetron vs placebo.
after every 10 patients. The study was stopped for ethical reasons when the difference of the primary outcome variable reached significance ($P<0.05$). The randomization was done by using a MS Excel macro (Microsoft Corp., USA). We did a blockwise randomization (blocks consisting of 10 patients) to ensure that for interim analysis, which was performed after every 10 patients, the groups did not differ in size. Computerized statistical analysis was performed using SPSS 9.0 (SPSS Inc.) and Instat 2.1 (Graphpad Inc.). Data are given as mean (SD) unless otherwise indicated. Statistical analysis was performed using Student’s $t$-test (patient characteristics), Fischer’s exact test (categorical data) and Mann–Whitney $U$-test (discharge time, VAS values). A value of $P<0.05$ was considered to be statistically significant.

Results

Groups did not differ with respect to patient characteristics, risk factors for PONV and duration or doses of intraoperative remifentanil infusion (Table 1). The intraoperative frequency of respiratory side-effects did not differ between groups. During the first 60 min after the end of the procedure, the frequency of nausea (>5 mm VAS) and retching was less in patients after dolasetron prophylaxis when compared (Fig. 1). The mean maximum intensity of nausea was also reduced in the dolasetron group (Fig. 2). The proportion of complete responders [no emetic episodes within 24 h (≤5 mm VAS)] was significantly higher after dolasetron (80 vs 45%; $P<0.05$). Patients in the dolasetron group reached predefined discharge criteria significantly earlier in comparison with the placebo group [22 (14)/45 (28) min; $P<0.05$]. The requirements for an antiemetic rescue medication tended to be higher in the placebo group but the difference did not reach significance. No patients in our study had postoperative problems with vital parameters, activity level, pain, or bleeding. No difference was seen with respect to patients’ satisfaction with the intraoperative analgesic properties of the anaesthetic regimen or the overall rating for the quality of anaesthesia.

Discussion

The present study demonstrates that dolasetron prophylaxis before single use of remifentanil for ESWL can reduce discharge times and the frequency and intensity of PONV. Studies have demonstrated that the single use of remifentanil is associated with an increased rate of PONV when compared with other anaesthetic regimens.27 Although remifentanil was efficacious intraoperatively, PONV decreased patients’ satisfaction. Also, postanaesthesia recovery time was prolonged. Several studies have demonstrated that dolasetron is an effective and well-tolerated preventive treatment for PONV.11 16–19

Studies have13 20 found that i.v. dolasetron 12.5 mg was the maximally effective dose for preventing PONV so we chose this dose for our present study. In addition this regimen was found to be as effective as i.v. dolasetron 25 mg, i.v. ondansetron 4 mg, or i.v. ondansetron 8 mg in preventing emetic symptoms after otolaryngologic surgery.21 In common with others,13 15 we chose the proportion of complete responders [no emetic episodes in 24 h (<5 mm VAS)] and the maximum nausea (VAS), following the procedure as the primary outcome variable. As expected, antiemetic prophylaxis with dolasetron 12.5 mg did not completely prevent PONV after remifentanil infusion for ESWL in our study, but was able to reduce the incidence and intensity of postoperative nausea and retching significantly with an increased total response in comparison with placebo during the first 24 h. As with other studies of remifentanil for monitored anaesthesia care in patients undergoing ESWL, the frequency of persisting nausea and vomiting was low. Joo and colleagues2 described 27% of patients with nausea but only 3% of them vomited during postoperative period. Nausea and vomiting do not usually occur during remifentanil infusion. Therefore, remifentanil infusion is still a suitable technique. The incidence of PONV
in the placebo group in our present study was comparable with the incidence we found in a previous trial with remifentanil for MAC during ESWL.\(^7\) As in this study, the onset of the symptoms was early (<60 min) and the duration was relatively short in most patients. The severity of the symptoms decreased over time. The majority of studies reported incidences of PONV in the range of 14–42%.\(^1\)\(^2\)\(^8\) The lower doses of remifentanil and the combination with propofol or midazolam can probably explain the lower incidences of PONV in these studies in comparison with our data.

The potential benefit of the ultra-short-acting remifentanil with respect to an earlier discharge from the PACU in comparison to long-acting analgesics and sedatives is limited by its emetic side-effect when given as a sole agent. In our study, PONV symptoms were the main reason preventing earlier discharge. As a consequence, the dolasetron prophylaxis directly improved postoperative recovery and decreased the time to readiness for discharge.

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