Management of opioid-induced pruritus: a role for 5-HT$_3$ antagonists?

K. Kyriakides*, S. K. Hussain and G. J. Hobbs

University Department of Anaesthesia, Queen’s Medical Centre, University Boulevard, Nottingham NG7 2UH, UK

*To whom correspondence should be addressed

We have evaluated the efficacy of ondansetron in the prevention of opioid-induced pruritus in a prospective, randomized, double-blind, placebo-controlled study. Using a ‘human model’ of opioid-induced pruritus, 80 ASA I–II patients about to undergo routine surgery were given either ondansetron 4 mg i.v. or 0.9% saline i.v. (40 in each group), 30 min before alfentanil 10 mg kg$^{-1}$ i.v. During the following 5 min, patients were observed for signs of perinasal scratching and at 5 min were asked about symptoms of pruritus. The study was then terminated and anaesthesia was induced. There was a significant reduction in the incidence of scratching in patients receiving ondansetron compared with placebo (42.5% vs 70%, respectively, $P<0.013$). The incidence of itching in the ondansetron group was less than that in the placebo group but this was not statistically significant (30% vs 42.5%, respectively, $P=0.245$). We conclude that the 5-HT$_3$ antagonist ondansetron may have a role in the management of opioid-induced pruritus.

Br J Anaesth 1999; 82: 439–41

Keywords: complications, pruritus; pharmacology, ondansetron

Accepted for publication: October 19, 1998

Pruritus or itch is a subjective, unpleasant and irritating sensation arising from the superficial layers of skin that provokes an urge to scratch. It is a common side effect of opioid administration and is usually localized to facial areas innervated by the trigeminal nerve. A central enkephalinergic mechanism has been proposed to explain this localization. Animal studies suggest the presence of an itch centre in the lower medulla with the trigeminal nucleus involved in the itch reflex. The incidence of opioid-induced pruritus varies widely depending on the opioid used and its mode of administration. The highest incidence (up to 80%) is associated with intrathecal morphine. Although often mild, symptoms may cause the patient considerable distress and even necessitate termination of opioid analgesia.

The current management strategies for opioid-induced pruritus are unsatisfactory. Histamine release, once thought to underlie the phenomenon, is not causative as opioids that do not release histamine also produce pruritus. In addition, antihistamines (H$_1$ antagonists) have low efficacy and an unfavourable side effect profile. Naloxone reversibility of opioid-induced pruritus supports the existence of an opioid receptor-mediated central mechanism. However, the use of naloxone may reverse the analgesic effect of opioids.

Opioid and serotonergic systems interact closely in the central nervous system, and the role of serotonin (5-HT) in pain transmission and nausea and vomiting is well established. A possible interaction between the opioid and serotonergic systems has also been suggested in the pathogenesis of pruritus in cholestatic jaundice. Recent evidence suggests that endogenous opioid compounds may be important mediators of pruritus in this condition. Moreover, ondansetron, a specific 5-HT$_3$ receptor antagonist with a favourable side effect profile, has been shown to have a potent anti-pruritic effect in patients with cholestasis. Our clinical experience suggests that ondansetron may have efficacy in treating pruritus after intrathecal administration of morphine. Therefore, in order to further establish the efficacy of 5-HT$_3$ antagonists in the management of opioid-induced pruritus, we performed this study to evaluate the efficacy of ondansetron in the prevention of opioid-induced pruritus.

Methods and results

After obtaining approval from the Local Ethics Committee and written informed consent, we studied 80 patients in a prospective, randomized, double-blind, placebo-controlled study. Patients were aged 16–70 yr, ASA I–II, unpremedicated and undergoing any type of surgery where the use of alfentanil formed part of the anaesthetic technique. Exclusion criteria included co-existence of any pruritogenic medical condition (dermatological or systemic), concurrent
patients were given alfentanil 10 mg kg$^{-1}$ i.v. given over 1 min. with 0.9% saline given over 1 min, or 0.9% saline equal groups to receive either ondansetron 4 mg diluted to 10 ml with 0.9% saline given over 1 min, or 0.9% saline 10 ml i.v. given over 1 min.

Thirty minutes after administration of the study drug, patients were given alfentanil 10 mg kg$^{-1}$ i.v. over 15 s. During the following 5 min, patients were observed for signs of perinasal scratching (defined as purposeful limb movement resulting in scratching of the perinasal area). Five minutes after administration of alfentanil, patients were asked about the presence of itching and then, if appropriate, its location and intensity (using a standard 100-mm visual analogue scale (VAS)). The study was then terminated. The primary outcome measure was the incidence of perinasal itching. Secondary outcome measures were the incidence and intensity of perinasal itching.

Data were analysed using the chi-square, Student’s $t$ and Mann–Whitney $U$ tests, where appropriate. $P<0.05$ was considered statistically significant. Assuming a 50% incidence of facial scratching in the placebo group (from previous audit data) and a 50% reduction in the incidence of scratching to be clinically significant, a sample size of 80 patients conferred a power of at least 0.9 at $\alpha=0.05$.

Data from all 80 patients were collected and analysed. Patient characteristics and incidence of scratching and itching for both groups are shown in Table 1.

Weight and sex were comparable between the two groups. The mean age of patients receiving saline was less than that of those receiving ondansetron, but this difference was not statistically significant ($P=0.059$). There was a 39% reduction in the incidence of scratching in patients receiving ondansetron compared with those receiving saline ($P=0.013$). There was a 29% reduction in the incidence of itching in patients receiving ondansetron compared with those receiving saline but this was not statistically significant ($P=0.245$). The intensity of itching in both groups was mild and comparable (median VAS 1.3 (range 0.5–2.6) and 1.4 (0.4–3.5) for ondansetron and saline, respectively).

### Table 1 Patient characteristics and outcome data (mean (sd or range) or number (%)). *$P<0.05$ compared with saline

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Ondansetron ($n=40$)</th>
<th>Saline ($n=40$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>42 (16–79)</td>
<td>35 (16–71)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>71 (13)</td>
<td>69 (16)</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>12/28</td>
<td>10/30</td>
</tr>
<tr>
<td>Scratching</td>
<td>17 (42.5)*</td>
<td>28 (70)</td>
</tr>
<tr>
<td>Itching</td>
<td>12 (30)</td>
<td>17 (42.5)</td>
</tr>
</tbody>
</table>

administration of any medications likely to influence the incidence or severity of pruritus (for example antihistamines) and contraindications to the use of alfentanil and ondansetron, or both.

On arrival in the anaesthetic room, all patients had an i.v. cannula placed on the dorsum of the hand after local anaesthesia. Routine patient monitoring was instituted with pulse oximetry, ECG and non-invasive arterial pressure. Patients were then allocated randomly using a sealed, sequentially numbered, envelope technique to one of two equal groups to receive either ondansetron 4 mg diluted to 10 ml with 0.9% saline given over 1 min, or 0.9% saline 10 ml i.v. given over 1 min.

The results of our randomized, double-blind, placebo-controlled study suggest that the 5-HT$_3$ antagonist ondansetron may have a role in the management of opioid-induced pruritus. Therefore, this class of drugs may have a clinical role in the management of this common and potentially distressing problem.

We used a ‘human model’ of opioid-induced pruritus in which alfentanil 10 µg kg$^{-1}$ i.v. was likely to elicit pruritus, manifesting as perinasal scratching, itching or both. Unlike itching, an intrinsically subjective outcome, scratching is objective and more reliably evaluated. Therefore, the primary outcome measure chosen for our study was the presence or absence of scratching. We acknowledge that this model has not been validated; however, all practising anaesthetists recognize the association between i.v. opioid administration and facial scratching during the perioperative period. Further, an ‘animal model’ of opioid-induced pruritus has been described in the monkey (Macaca fascicularis) in which microinjections of morphine into the medullary dorsal horn induces facial scratching abolished by naloxone.7 Acknowledging that the short study period of 5 min made it difficult to evaluate the efficacy of ondansetron in the prevention of opioid-induced pruritus, using the above mentioned human model, we have shown that pretreatment with ondansetron 4 mg i.v. caused a significant reduction in the incidence of perinasal scratching compared with placebo.

The incidence and severity of itching were secondary outcome measures. Although pretreatment with ondansetron caused a reduction in the incidence of itching consistent with the drug having a prophylactic effect, this was not statistically significant. Failure to do so might have been caused by several factors. First, we cannot exclude a type II error as the sample size was calculated using the likely incidence of scratching. Post hoc power analysis on the actual results obtained in our study showed that our study had insufficient power to detect a significant difference in the incidence of itching between the two groups. A sample size in excess of 100 patients per group would be required to give a power of 0.8. Second, the efficacy of ondansetron is likely to be dose-related. Had we used a higher dose of ondansetron, for example 8 or 16 mg, greater efficacy may have been demonstrated. There is evidence of dose-related efficacy in the treatment of opioid-induced nausea and vomiting.8 Third, itching is a subjective sensation and as such a very difficult outcome measure to quantify. Indeed, although several of our patients did not complain of facial itching per se, and therefore were recorded as having ‘no itch’, on closer questioning some admitted to experiencing a range of other facial sensations which might have been opioid-induced.

Although not statistically significant, there was a difference in mean age between the two groups. However, this difference is unlikely to have been a confounding factor in our results. The possibility also exists that ondansetron has
an additional, yet unknown, behavioural or motor effect which may explain our results, but we believe this is unlikely.

The results of this preliminary study suggest that the 5-HT3 antagonist ondansetron may have a role in the management of opioid-induced pruritus. However, further work to confirm our results and evaluate possible dose-related efficacy is required.

References