Study of the prophylactic effect of droperidol, alizapride, propofol and promethazine on spinal morphine-induced pruritus


1Department of Anaesthesiology, Hospital Universitário São Francisco de Paula da UCPEL, Pelotas, RS, Brazil. 2Department of Anaesthesiology, Santa Casa de Misericórdia de Pelotas, Pelotas, RS, Brazil
*Corresponding author: Rua Anchieta, 4043, 96015.420, Pelotas, RS, Brazil. E-mail: marciolhorta@uol.com.br

Background. We have compared the use of alizapride, propofol, droperidol and promethazine for the prevention of spinal morphine-induced pruritus.

Methods. Three hundred ASA I or II women undergoing Caesarean section under spinal anaesthesia, in which morphine 0.2 mg was added to a local anaesthetic, were assigned randomly to receive i.v., in the operating room, just after delivery of the baby, alizapride 100 mg, propofol 20 mg, droperidol 1.25 mg, promethazine 50 mg or saline 2 ml (control group). In the postoperative period, the women were assessed for pruritus (absent, mild, moderate or severe) or other untoward symptoms by blinded observers. We used 95% confidence limits (95% CI) for the cumulative incidence of moderate and severe pruritus to compare the groups, and the NNT and 95% CI to compare droperidol, propofol and alizapride as for their effectiveness in preventing pruritus. For other untoward effects, the \( \chi^2 \)-test was used, results being considered significant when \( P<0.05 \).

Results. The droperidol, propofol and alizapride groups had significantly lower incidences of pruritus compared with the control and promethazine groups, while the incidence of pruritus was similar among the patients assigned to the promethazine and control groups. As for the prevention of moderate and severe pruritus, droperidol had the lowest NNT (3.52; 95% CI: 3.37–3.67), followed by propofol (4.61; 95% CI: 4.45–4.77) and alizapride (5.43; 95% CI: 5.27–5.59). As for untoward effects, droperidol and promethazine increased the incidence of somnolence, which seemed more severe with promethazine. Otherwise, there were no differences between the groups.

Conclusion. Droperidol, propofol and alizapride, in a decreasing order of effectiveness in the doses used in this study, reduced the incidence of pruritus induced by the use of morphine 0.2 mg intrathecally. On the other hand, promethazine 50 mg was shown to be ineffective.

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As pointed out by Waxler and colleagues,7 s.c. applied opioids release histamine, thus inducing pruritus, but when they are used neuraxially, pruritus does not depend on histamine release. Even so, data on antihistamines are contradictory. Most papers report negligible effects,8 and it has been shown that opioids that do not release histamine, such as fentanyl, induce pruritus. Furthermore, naloxone, which releases histamine, counteracts pruritus.9–10 On the other hand, antihistamines, such as promethazine, have been reported to be effective.11

Although naloxone reduces pruritus, it can reduce the required analgesic effect. A range of other drugs that do not directly affect μ receptors and with apparently different pharmacological profiles have been reported to be effective but their relative efficacy is unknown.

Alizapride is a methoxybenzamide (the same class as metoclopramide), and a 50 mg i.v. dose reduces the intensity of spinal morphine-induced pruritus.12 As it is very well tolerated in much higher doses,13–15 we thought it would be important to assess its antipruritic activity using a higher dose (100 mg i.v.). Droperidol (2.5 mg i.v.)16 is active, but concerns about its arrhythmogenicity,17 though contested,18 make the use of smaller doses reassuring. Sub hypnotic doses of propofol are effective for the treatment of pruritus,19 but its prophylactic value has not been tested.

The objective of this paper is to compare, in patients subjected to Caesarean section, alizapride (100 mg i.v.), propofol (20 mg i.v.), droperidol (1.25 mg i.v.) and promethazine (50 mg i.v.) for their prophylactic effect on the pruritus induced by the spinal use of morphine 0.2 mg and for possible important side-effects.

Methods

This study was approved by the Ethics Committees of both hospitals and all the patients gave their signed consent.

In a double-blind randomized clinical trial, 300 ASA I or II patients undergoing Caesarean section were studied independent of the obstetric indication. Besides refusal to participate in this research, the main exclusion criteria for ASA I or II patients were inability to answer questions clearly, inadequate anaesthesia, history of allergy to drugs in use, any cutaneous pathology with pruritus, recent use of opioids or other drugs that could cause respiratory depression, and hyperemesis. When the patients arrived in the operating room, an i.v. infusion of lactated Ringer’s solution was established and metoclopramide 10 mg and fentanyl 50 μg were administered i.v. The total volume of fluids infused during surgery was recorded in three steps: until lumbar puncture, until childbirth, and until the end of surgery. Standard monitoring (non-invasive blood pressure, \(\Delta P_{O_2}\), and ECG) was established.

Spinal anaesthesia was performed using a lateral approach20 with a Quincke needle at the L2–L3 or L3–L4 interspace, using hyperbaric lidocaine 5%, 2 ml (100 mg) or hyperbaric bupivacaine 0.5%, 3 ml (15 mg), to which morphine sulphate 0.2 mg was added. Left uterine displacement was established either by right hip elevation with a wedge, or manually, or by both methods. If hypotension (systolic blood pressure less than 70% of control values or under 90 mm Hg) persisted in spite of left uterine displacement, fractional doses of metaraminol 0.5 or 1 mg were given. Because the main cause of hypotension until childbirth is caval compression, we distinguished between hypotension happening before childbirth (‘initial hypotension’), for which sympathomimetic drugs were used only if improvement in uterine displacement was unsuccessful, and hypotension which happened after childbirth (‘late hypotension’), which was always treated with sympathomimetic drugs. Just after delivery, either methylergonovine 0.2 mg or synthetic oxytocin (the doses varying according to the surgeon’s request—most often 15 u diluted in the i.v. infusion solution) or both, were used as oxytocics.

From a random numbers table, an allocation table was made distributing the 300 patients into five groups of 60. According to this allocation table, the patients were administered i.v., in the operating room, just after delivery of the baby, either alizapride 100 mg (alizapride group), propofol 20 mg (propofol group), droperidol 1.25 mg (droperidol group), promethazine 50 mg (promethazine group), or distilled water 2 ml (control group). Anaesthesia and all drug administrations in the operating room were made by the first two authors. In the postoperative period, patients were assessed by the other members of the group, who were unaware (as well as the patients) of the allocation. They were assessed twice in the first 24 h (about 3 and 6 h after administration of anaesthesia), and at least once a day until discharge from hospital, and besides pruritus, any adverse events observed or reported by patients, even in only one visit, were recorded and considered as positive.

Pruritus was classified as ABSENT, MILD (restricted to one area, such as face or arms, and not troubling the patient; usually reported only after prompting), MODERATE (affecting a larger area, such as face and arms or face and anterior surface of thorax, but not disturbing the patient, and therefore not requiring treatment) or SEVERE (extensive or generalized, often disturbing the patient to the point that treatment was indicated), and was recorded according to the highest severity reported. When proposed and accepted or asked for by the patient, pruritus was treated with i.v. droperidol 1.25 mg. Insufficient postoperative analgesia was treated with i.m. diclofenac 75 mg or i.m. metamizole (dipryone) 500 mg.

As we were interested in comparing individually any group with each other, and as mild pruritus is often denied by the patient,21 we calculated, for each group, the 95% confidence interval (95% CI) for the cumulative incidence of moderate and severe pruritus. For the groups that showed a difference from control, we also calculated the number needed to treat (NNT) and the 95% CIs for that incidence. (See Appendix for the formulas used in these calculations.)
The incidences of other side-effects were compared using the \( \chi^2 \)-test.

Based on previous studies,\(^\text{12} \) we estimated an incidence of 30% of moderate and intense pruritus in the control group. Considering as satisfactory a 66% reduction in this value, we estimated that we would need, for a level of significance of 95% and a power of 80%, 60 patients per group.\(^\text{22} \)

### Results

Table 1 shows the distribution of some baseline characteristics (age, height, weight, BMI and ASA physical status) in the five experimental groups. There was no difference between groups in the volumes of fluid replacement nor in the proportion of patients receiving treatment for hypotension.

Figure 1 shows the incidence and severity of pruritus in the five groups. Table 2 shows the calculation of the 95% CI for the cumulative incidence of moderate and severe pruritus in each group. The droperidol, propofol and alizapride groups had significantly lower incidences of pruritus compared with the control and promethazine groups, while the incidence of pruritus was similar among the patients assigned to the promethazine and control groups. In order to determine if there was any difference in effectiveness, we calculated the NNT and the 95% CI for the prevention of moderate and severe pruritus. This index suggested that droperidol (NNT=3.52; 95% CI: 3.37–3.67) was the most effective, followed by propofol (NNT=4.61; 95% CI: 4.45–4.77) and by alizapride (NNT=5.43; 95% CI: 5.27–5.59), which was the least effective of the three drugs.

In the postoperative period, six patients received droperidol (1.5 mg i.v.) for the treatment of severe pruritus, which had reduced when they were re-assessed 30 min later.

As for other side-effects, the incidence of somnolence in the perioperative period was 8.3% for alizapride, 16.7% for

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**Table 1** Patient characteristics. Values are mean (range) or \( n \); \( N=60 \) for each group

<table>
<thead>
<tr>
<th>Group</th>
<th>Alizapride</th>
<th>Propofol</th>
<th>Droperidol</th>
<th>Promethazine</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>27 (15–41)</td>
<td>27 (14–42)</td>
<td>27 (15–44)</td>
<td>29 (16–46)</td>
<td>28 (15–44)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>160</td>
<td>161</td>
<td>161</td>
<td>162</td>
<td>161</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>74</td>
<td>78</td>
<td>76</td>
<td>76</td>
<td>79</td>
</tr>
<tr>
<td>BMI</td>
<td>29</td>
<td>30</td>
<td>30</td>
<td>29</td>
<td>30</td>
</tr>
<tr>
<td>ASA physical state I/II</td>
<td>46/14</td>
<td>39/21</td>
<td>43/17</td>
<td>41/19</td>
<td>47/13</td>
</tr>
</tbody>
</table>

**Table 2** Cumulative incidence of moderate and severe pruritus and the 95% confidence interval for each group

<table>
<thead>
<tr>
<th>Group</th>
<th>Alizapride (%)</th>
<th>Propofol (%)</th>
<th>Droperidol (%)</th>
<th>Prometazine (%)</th>
<th>Control (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence</td>
<td>23.3</td>
<td>20</td>
<td>13.3</td>
<td>46.7</td>
<td>41.7</td>
</tr>
<tr>
<td>Upper limit</td>
<td>33</td>
<td>30.1</td>
<td>21.9</td>
<td>59.3</td>
<td>54.2</td>
</tr>
<tr>
<td>Lower limit</td>
<td>13.7</td>
<td>9.9</td>
<td>4.7</td>
<td>34.1</td>
<td>29.2</td>
</tr>
</tbody>
</table>

**Fig 1** Incidence and severity of pruritus in the five groups.
Propofol, 25% for droperidol, 31.7% for promethazine, and 6.7% for the control group. In the postoperative period, it was of 8.3% for alizapride, 5% for propofol, 16.7% for droperidol, 23.3% for promethazine, and 0 for the control group. Other side-effects were rare, not serious and there was no difference in their incidences between the groups.

Discussion
There were small differences in baseline characteristics among the groups (Table 1), the most important of them being the higher proportion of ASA II patients in the promethazine and propofol groups. However, as there is no difference in pruritus between ASA I and II patients, we believe our results were not a result of these differences.

The results confirm our previous studies using i.v. alizapride and droperidol to prevent morphine-induced pruritus. Although we cannot make direct comparisons, there seemed to be no advantage in increasing the dose of alizapride to 100 mg compared with 50 mg used previously, and no disadvantage in the reduction of droperidol dose. As droperidol has been shown to have such a good effect on morphine-induced pruritus, we believe it deserves a future dose-finding study. This seems important because effect on morphine-induced pruritus, we believe it deserves.

We used the following statistical formulae:

Calculation of the 95% CIs for the cumulative incidence of moderate and severe pruritus:

\[ P = \frac{1.96 \sqrt{\frac{P(1-P)}{n}}}{n} \]

where \( P \) = cumulative frequency of moderate and severe pruritus, \( n \) = number of cases per group (60 cases in all the groups) and 1.96 is the appropriate value from the standard normal distribution of the 95th percentile.

The addition or subtraction of this value from the cumulative frequency will yield respectively the superior and the inferior limits of the confidence interval.

Confidence interval = \( P \pm 1.96 \sqrt{\frac{P(1-P)}{n}} \).

Calculation of the NNT:

\[ \text{NNT} = \frac{1}{\text{AR}} = \frac{1}{P_c - P} \]

where AR=attributable risk, \( P_c \)=cumulative frequency of moderate and severe pruritus in control group and \( P \)=cumulative frequency of moderate and severe pruritus in treated group.

Calculation of the 95% confidence interval for the NNT:

\[ 95\% \text{ CI for NNT} = \pm 1.96 \left( \frac{P(1-P)}{n} \right) + \frac{P(1-P)}{n} \]

where \( P \)=cumulative frequency of moderate and severe pruritus in the treated group, \( P_t \)=cumulative frequency of moderate and severe pruritus in the control group, \( n \)=number of cases per group (60 cases in all the groups) and 1.96 is the factor for the confidence limit of 95%.

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