A Comparison of Zomepirac and Codeine as Analgesic Premedics in Short-stay Surgery


Zomepirac is an orally administered non-narcotic analgesic, which is a prostaglandin synthetase inhibitor. Its analgesic properties appear to be similar to those of morphine.¹ ² Our objective was to assess the efficacy of zomepirac as an orally administered analgesic premedication in short-stay patients, where an effective non-narcotic analgesic might be particularly useful for prophylaxis of postoperative pain. Codeine was chosen for comparison because it is often used for the treatment of postoperative pain.

METHODS

Institutional approval of the protocol was obtained and all patients gave written informed consent. Eighty-eight patients were studied, 40 of whom were scheduled for elective surgical removal of impacted wisdom teeth, and 48 for laparoscopic sterilization. All patients studied were A.S.A. I, aged between 18 and 45 years old (dental patients, 23.2 ± 1.08 years; laparoscopic patients, 31.2 ± 0.75 years), and weighed 45-85 kg (dental, 62.4 ± 1.72 kg; laparoscopic, 62.2 ± 1.20 kg). Patients who were taking medications that could confuse pain assessments were excluded from the study.

Patients were stratified by surgical procedure and randomized to one of two premedication regimens: 100 mg zomepirac or 60 mg codeine administered orally approximately 30 minutes prior to surgery. A double-blind design was assured by the use of drug capsules of identical size and appearance, labeled by number alone. All patients received a standardized general anesthetic; dental patients received thiopental for induction, succinylcholine to facilitate intubation of the trachea, and anesthesia was maintained with enflurane and 70% nitrous oxide with spontaneous respiration; patients undergoing laparoscopy received a similar anesthetic except that ventilation was controlled and muscle relaxation was achieved during maintenance with a succinylcholine infusion. The use of narcotics or local anesthetics was avoided.

All observations were made by one nurse observer. Pain intensity was assessed using a vertical 10-cm visual analogue scale (VAS), and a five-point ordinal scale comprising the following categories: none (0), mild (1), moderate (2), severe (3), and very severe (4), the numerical score being subsequently assigned to facilitate statistical analysis.

Following preoperative practice with the analogue and ordinal scales, pain assessments were made postoperatively at 1.5, 2, 3, 4, 5, and 6 hours following premedication, or until the patient was judged fit for discharge from hospital. Recovery was assessed as the interval from termination of anesthesia until the patient could first recall their date of birth (“recovery time”), and the patients were fit for discharge from the hospital as judged by a modified Faw scoring system (“street fitness time”).

All patients received additional postoperative analgesic drugs on request after assessment by the nurse observer. The time of request was recorded. A standardized regimen was used which comprised 25 mg iv meperidine during the first postoperative hour, and 60

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mg codeine with 600 mg acetaminophen and 30 mg caffeine§ orally thereafter.

All adverse effects volunteered by the patients were noted, and both patient and observer recorded their global impression of analgesic effectiveness at the completion of the study period.

Patient and procedural variables were compared by analysis of variance, and postoperative pain levels and global impressions by analysis of covariance, with chi-square for comparison of frequencies. Remedication times were analysed using a proportional hazards survival model⁶ with patient and procedural variables included as covariates. For the purposes of this study, P ≤ 0.05 was regarded as being statistically significant.

**RESULTS**

Within surgical strata, patients were similar with respect to age, weight, and height for the two premedication groups. The interval between premedication and induction, total anesthesia time, and recovery and “street fitness” times were comparable between premedication groups (table 1).

In the dental group, more of the patients receiving codeine required additional postoperative analgesic drugs than did the patients receiving zomepirac (P < 0.013) (fig. 1). In the laparoscopic group, postoperative medication requirements were similar and showed no significant difference between medication groups (P = 0.71) (fig. 1). At five hours after premedication, the overall incidence of additional medication given in the dental patients was 15 (75%) in the codeine group compared to 6 (30%) in the zomepirac group ($X^2 = 8.1, P < 0.004$). In the laparoscopic patients, 24 (100%) of the zomepirac patients received additional medication at five hours compared to 23 (95%) in the codeine group.

Comparison of mean VAS scores in the dental patients who did not require remedication (table 2) showed consistently higher pain scores in the codeine group compared to the zomepirac group up to 4 hours following premedication (P = 0.05 at 2 h). For all patients in the dental stratum, those premedicated with codeine showed consistently higher VAS scores than did the zomepirac group (P < 0.011) up to five hours after premedication, even though they had received significantly more additional analgesia. In the laparoscopic stratum, mean VAS scores were similar for both premedication groups (P = 0.61). Mean ordinal pain scores reflected similar trends and differences to those found in the VAS scores (P = 0.01 and 0.83, respectively) (table 3).

The overall incidence of side effects in the dental

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§ Tylenol #3, McNeil Laboratories, Fort Washington, Pennsylvania 19034.
CLINICAL REPORTS

TABLE 2. VAS Scores of the Dental Patients not Receiving Additional Medication*

<table>
<thead>
<tr>
<th></th>
<th>1.5</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine</td>
<td>5.0 ± 0.71 (14)</td>
<td>5.5 ± 0.70† (17)</td>
<td>4.5 ± 0.81 (15)</td>
<td>4.7 ± 1.09† (8)</td>
<td>4.0 (1)</td>
<td>4.4 (1)</td>
</tr>
<tr>
<td>Zomepirac</td>
<td>4.2 ± 0.69 (14)</td>
<td>4.4 ± 0.48† (18)</td>
<td>3.7 ± 0.92 (17)</td>
<td>2.5 ± 0.49† (14)</td>
<td>4.4 ± 0.84 (4)</td>
<td>7.7 (1)</td>
</tr>
</tbody>
</table>

* Values are means ± SE, and the number of patients is in parentheses. The discrepancy from original sample size is due to remedication as well as patients not recovered from anesthesia (1.5 h) or discharged from hospital (5 and 6 h).
† Significant difference between groups ($P < 0.05$) by analysis of covariance.

patients was low and was similar for both premedicants (table 4). In the laparoscopic patients, the incidence of side effects was higher. Zomepirac appeared to be associated with a more frequent occurrence of nausea and vomiting than was codeine, but these differences were not statistically significant ($\chi^2 = 2.12$, $P = 0.15$).

For the dental patients, the observer rated eight patients receiving zomepirac as excellent and 12 as good, whereas for the codeine patients, two were rated excellent, 16 good, and two fair (zomepirac vs. codeine, $P = 0.012$). The patients' own global impressions showed no significant differences between the two drugs ($P = 0.63$). In the laparoscopic group, both patient and observer's global impressions were similar for both drugs ($P = 0.31$ and 0.68, respectively).

On the basis of comparing the observer's guess with the actual medication received, there was no evidence for doubting the achievement of blinding ($\chi^2 = 1.16$, $P = 0.28$).

DISCUSSION

Preoperative pain models have been utilized for the comparison of the analgesic properties of drugs.7–9 We designed this study as an improvement on previous methodology reported in analgesic premedicant studies by 1) the inclusion of patients undergoing two specific surgical procedures, both of which usually result in moderate to severe postoperative pain; 2) the use of both VAS and ordinal pain scores; 3) the recording of patient and observer global impressions; 4) the recording of remedication profiles and the use of a standardized postoperative analgesic regimen to facilitate comparison of the other measurements made; and 5) the use of a survival model which allows the duration of analgesia resulting from each drug to be analyzed statistically in a manner similar to the survival data in longitudinal cancer studies.

In this study, the maximum recommended single dose of each dose—60 mg codeine and 100 mg zomepirac—was chosen for study. This design therefore allows only a comparison of the two drugs at these dosage levels, and precludes any inferences regarding the dose-response characteristics or relative potency of codeine and zomepirac.

The relative analgesic effects of codeine and zomepirac differed depending upon the surgical procedure. In the dental patients, zomepirac was more effective than codeine as a prophylaxis against postoperative pain, as judged by remedication time profile, mean pain

TABLE 3. VAS Scores of All Patients by Procedure and Premedication*

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Presedication</th>
<th>1.5</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dental</td>
<td>Codeine</td>
<td>5.0 ± 0.71 (14)</td>
<td>5.4 ± 0.62 (20)</td>
<td>5.1 ± 0.63 (20)</td>
<td>4.4 ± 0.69 (20)</td>
<td>4.4 ± 0.96 (10)</td>
<td>4.6 ± 0.75 (4)</td>
</tr>
<tr>
<td></td>
<td>Zomepirac</td>
<td>4.1 ± 0.69 (14)</td>
<td>4.5 ± 0.45 (20)</td>
<td>3.5 ± 0.47 (20)</td>
<td>2.7 ± 0.85 (20)</td>
<td>3.0 ± 0.67 (8)</td>
<td>4.8 ± 3.0 (2)</td>
</tr>
<tr>
<td>Laparoscopy</td>
<td>Codeine</td>
<td>6.3 ± 0.53 (21)</td>
<td>5.4 ± 0.49 (24)</td>
<td>5.1 ± 0.61 (24)</td>
<td>4.7 ± 0.53 (24)</td>
<td>2.8 ± 0.46 (22)</td>
<td>2.3 ± 0.74 (13)</td>
</tr>
<tr>
<td></td>
<td>Zomepirac</td>
<td>6.1 ± 0.68 (19)</td>
<td>5.9 ± 0.41 (24)</td>
<td>5.1 ± 0.54 (24)</td>
<td>3.6 ± 0.47 (24)</td>
<td>2.4 ± 0.44 (20)</td>
<td>1.8 ± 0.65 (14)</td>
</tr>
</tbody>
</table>

* Values are means ± SE, number of patients in parentheses. The discrepancy from original sample size is due to patients not recovered from anesthesia (1.5 h) and discharged from hospital (5 and 6 h).
TABLE 4. Number of Patients with Elicited Side Effects by Procedure and Premedication

<table>
<thead>
<tr>
<th>Side Effects</th>
<th>Dental</th>
<th>Laparoscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine</td>
<td>Zonepirac</td>
<td>Codeine</td>
</tr>
<tr>
<td>None</td>
<td>17</td>
<td>18</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Hives</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Sweating</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>TOTAL</td>
<td>20</td>
<td>20</td>
</tr>
</tbody>
</table>

levels in non-remedicated patients two hours following premedication, and observer global impression. On the basis of the remedication profile, 100 mg zonepirac appears to be more effective and has a longer duration of action than 60 mg codeine. The incidence of postoperative side effects in these patients was very low. On the basis of these findings, 100 mg zonepirac would appear to be a very satisfactory premedication for use prior to dental anesthesia.

In the patients undergoing laparoscopy, both zonepirac and codeine were similar with respect to remedication profiles, mean postoperative pain levels, and both patient and observer global impressions. However, since the early remedication rate was very high following the use of both premedicants, neither can be regarded as clinically satisfactory for the prophylaxis of postoperative pain.

The explanation of the disparity in the relative analgesic effects of zonepirac and codeine between the two surgical procedures studied is unclear. The findings in the dental stratum are consistent with those of investigators who have compared these two drugs in the postoperative and chronic pain models. Dionne et al. have demonstrated the sensitivity of the preoperative pain model in a similar patient population. In our study, remedication rates, mean pain levels, and observer global impressions were all consistent. Thus, this difference appears to be “real.”

In the laparoscopic patients, no differential analgesic effect between zonepirac and codeine was demonstrated. This may be due to lack of sensitivity in the pain model employed, impaired drug absorption, or ineffectiveness of either drug in preventing the severe pain usually experienced by these patients. In this situation, the inclusion of a placebo group would have allowed an assessment of model sensitivity. The demonstration of a significant separation between placebo and zonepirac or codeine in terms of postoperative pain levels and remedication profile would confirm model sensitivity. Conversely, lack of such a separation would indicate poor model sensitivity which could be due to a large between-patient variation, inadequate sample size, or the beneficial effect of assurance and attention coupled with the personality of the observer. However, the use of placebo medication has ethical implications. Since the analgesic efficacy of zonepirac has been established previously, codeine was chosen as the standard for comparison since it is commonly used for alleviation of postoperative pain, may be administered orally, and has the disadvantage that it is a narcotic. Lasagna suggested that the use of different doses of both the new and standard drugs may substitute for a placebo controlled trial. The demonstration of a dose-response effect, which he notes is not always easy to show, would effectively confirm model sensitivity. In retrospect, the inclusion of either a placebo group or several dosage levels of each drug in the laparoscopic stratum would have been desirable. We believe, however, that lack of model sensitivity is not the explanation, as there were clear differences in the dental stratum. We anticipated a greater sensitivity in the laparoscopic stratum since higher pain levels usually increase model sensitivity. Although drug absorption may have been impaired or delayed due to the use of the Lithotomy position and the intraperitoneal instillation of carbon dioxide, this hypothesis has not been investigated. Neither was there any correlation between patient weight nor total anesthesia time and remedication time. The intense pain, presumably of peritoneal origin, experienced by the laparoscopic patients probably exceeded the analgesic capability of both drugs. However, this hypothesis will need further testing in the future.

In conclusion, 100 mg zonepirac was an effective oral analgesic premedication in dental patients undergoing surgical removal of impacted molar teeth. When compared to 60 mg codeine, it was better in terms of postoperative remedication profile, pain levels, and observer global impression. In patients undergoing laparoscopic sterilization, neither zonepirac nor codeine were effective as orally administered analgesic premedicants.

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Kawasaki Disease—A Disease with Anesthetic Implications

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Kawasaki disease, also known as mucocutaneous lymph node syndrome, is an acute exanthematous disease affecting primarily infants and young children. In 17–30% of the patients, the myocardium, coronary arteries, and/or great vessels are involved significantly resulting in a mortality rate of about 2%. We describe one patient scheduled for cardiac catheterization and discuss the pathophysiology and usual clinical course of patients with Kawasaki disease.

REPORT OF A CASE

An 18-month-old boy was scheduled for elective cardiac catheterization. Nine months previous, he was admitted with a three-week history of vomiting, diarrhea, fever, conjunctivitis, cough, and skin rash. His therapy included antibiotics and aspirin. With this initial admission he was alert but febrile, irritable, and photophbic with conjunctival erythema. His gingiva were hyperemic. Palpable cervical, axillary, and femoral lymph nodes were present. He had a heart rate of 160 beats/min, an arterial blood pressure of 100/40 mmHg, and a grade I/VI systolic ejection murmur with an S2 gallop. The extremities showed a puffy non-pitting edema of the feet with no abnormalities of the joints. The skin showed a diffuse, well-margined, elevated, erythematous eruption which was apparently not pruritic. Anemia and a leukocytosis with a left shift were found on complete blood count.

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Key words: Complications: Kawasaki disease; mucocutaneous lymph node syndrome. Surgery: cardiac. Anesthesia: cardiac.

A chest roentgenogram demonstrated moderate cardiomegaly. Both twelve-lead electrocardiographic and M-mode echocardiographic studies were interpreted as normal. However, a two-dimensional echocardiogram demonstrated dilation of the proximal parts of both left and right coronary arteries. Kawasaki disease was diagnosed and 100 mg · kg⁻¹ · day⁻¹ aspirin administered as treatment during his 15-day hospitalization. During this period the infant was continuously febrile until the last day. Gradual improvement in irritability and appetite was noted. Approximately six weeks following discharge, pulsatile masses in the axillary, brachial, and femoral arteries were first noted.

With this admission, the child was in no distress with no history of exercise limitations. His physical examination was normal except as related to the cardiovascular system. A I/VI systolic ejection murmur was again heard with no gallop or other evidence of failure. The electrocardiogram and chest roentgenograms were within normal limits. Two-dimensional echocardiographic examination again documented dilation of the proximal segments of the coronary arteries. Aneurysms of both axillary arteries, the right brachial artery, and the right femoral artery were palpable.

For cardiac catheterization, the 11.8-kg child was premedicated with 12.5 mg meperidine, 0.12 mg atropine, 3 mg promethazine, and 3 mg chlorpromazine, im. Upon arrival in the cardiac catheterization suite, an intravenous line was established as well as monitoring which included a continuous electrocardiogram, a blood pressure cuff, a Doppler flow probe, and a temperature probe. Immediately prior to the infiltration of the cannulation site with 1% lidocaine, 1 mg/kg ketamine and 1 mg/kg thiopental were administered iv. The course of cardiac catheterization was uneventful and no further medications were required. Vascular pressures and oxygen saturation values obtained during the catheterization were within normal limits. Cinangiograms confirmed the presence of a right coronary artery aneurysm measuring approximately 1 by 2.5 cm. Blood flow through this aneurysm was very sluggish. Smaller aneurysms of the left main and left anterior descending arteries were also found.

The post-catheterization course was uneventful and the child was discharged the following day on 40 mg · kg⁻¹ · day⁻¹ aspirin and 2 mg · kg⁻¹ · day⁻¹ diprydamole. The possibility of myocardial revascularization was entertained, but in view of the child’s size and current clinical status, deferred for further consideration for several years.

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