A New Paracetamol/Paracetamol-Methionine Ester Combination Effects on Postoperative Course

L. A. Skoglund

Institute of Pharmacology and Department of Oral Surgery and Oral Medicine, University of Oslo, Oslo, Norway

Summary. The SUR2647 combination is a sachet formulation containing free paracetamol and its N-acetyl-methionate ester (SUR2647). In a randomized, single-blind, within-patient study the effect of the SUR2647 combination on the postoperative course was investigated in 30 out-patients after bilateral oral surgery. On one occasion they received sachets of SUR2647 combination 2 b.i.d. (equivalent to 2 g paracetamol × 2) on the day of operation, and one sachet b.i.d. (equivalent to 1 g paracetamol × 2) on the following two days. On the other occasion they received placebo caplets. The observed mean reduction in swelling on the third (16%) and seventh (34%) postoperative days after receiving active drug was not significantly different as compared to placebo, nor was there a significant difference between the two treatments with respect to oral temperature, mouth-opening capability or postoperative bleeding. Pain after the SUR2647 combination regime was significantly lower (P<0.01) than placebo until the second postoperative evening. Complaints were registered in both treatment groups, although reports of mild to moderate drowsiness were more common after the SUR2647 combination.

Key words: paracetamol, SUR2647 combination; anti-inflammatory action, swelling, pain, side-effect, oral surgery, wisdom teeth removal

In 1975 Sveen and Gilhuus-Moe reported less swelling in subjects given paracetamol + codeine after oral surgery than in subjects given acetylsalicylic acid (ASA) or placebo [16]. Further studies have demonstrated that paracetamol 1 g q.i.d. can reduce acute postoperative swelling following wisdom tooth surgery [12, 14]. Concomitant administration of paracetamol and methionine to increase the detoxifying capacity of the liver in cases of paracetamol overdosage has been proposed [7]. SUR2647 combination is a mixture of paracetamol-N-acetyl-DL-methionate and free paracetamol.

The present study investigated the effect of the SUR2647 combination in doses equivalent to 2 g paracetamol on postoperative swelling and pain, in comparison with a placebo.

Materials and Methods

Patients

Healthy out-patients requiring prophylactic surgical removal of bilateral, asymptomatic and impacted third molar teeth were asked to volunteer after receiving an explanation of the nature of the study. Verbal informed consent was obtained and 30 patients [18 females and 12 males; mean age 23.8 years, range 18–34 years] completed the trial. Four other patients entered it but had to be excluded as they did not follow the medication procedure. The trial methodology had received prior approval from the Norwegian Research Council for Science and the Humanities, Ethical Committee. The trial was conducted according to the Declaration of Helsinki.

Operations

All patients had both lower molars removed by the same surgeon. The interval between the two operations was >30 days. Surgery was performed by a standardized technique [12] using an identical volume (mean 3.3 ml, range 2.6–3.8 ml) of local anaesthetic (Xylocain-Adrenalin, lidocaine 20 mg/ml + adrenaline 12.5 μg/ml, Astra, Sweden) on both occasions.
Treatments

The patients received SUR 2647 combination, i.e. 1073 mg paracetamol-N-acetyl-DL-methionate (equivalent to 500 mg paracetamol) plus 500 mg free paracetamol per sachet (Sterling-Winthrop, Surrey, UK) as powder on one occasion. On the day of operation a total of 4 sachets was taken, 2 sachets each 3 h and 9 h after surgery. On the following two days a total of 2 sachets was taken daily (1 sachet at 08.00 h and 1 at 16.00 h). On the other occasion they received placebo caplets identical in shape and appearance to Panodil (Sterling-Winthrop) caplets. On the day of operation a total of 4 caplets was taken, 2 caplets each 3 and 9 h after surgery. On the following two days a total of 2 tablets was taken daily (1 caplet at 08.00 and 1 at 16.00 h). Both drugs were taken with half a glass of water. No other drugs or alcohol were permitted for 10 days prior to surgery or during the trial period.

Methodology

The trial was a randomized, single-blind, within-patient comparative study in which the patients acted as their own controls. Acknowledging the single-blind nature of the trial, efforts were made to minimize any errors in the assessments. The patients received their medication in sealed heavy manilla envelopes, packed independently of the surgeon, according to a randomized list. The envelope was to be opened only after leaving the clinic. No information other than instructions concerning drug administration and the assessments were given on the day of operation or until the study was finished. Only measurable observations were recorded by the surgeon during the subsequent assessment visits, and he had no access to the patient’s own assessment sheet during the trial period.

Assessments/Statistical Analyses

Postoperative Swelling. An exact measurement of the postoperative swelling was made with a mechanical device [6]. Mouthopening ability [6] and the local temperature at the site of surgery [12] were also measured.

Bleeding was assessed on a 4 point scale [5]. At the visits on the third and seventh postoperative days, the patients were examined for haematoma/ecchymoses [5]. Wound healing was assessed by the surgeon on the third and seventh days.

Pain was assessed by the patients on visual analogue scales (VAS) that ran from “no pain” (0 mm) to “pain cannot be worse” (100 mm) [15] for a period of 11 h starting immediately after the operation. On the first and second postoperative days pain was assessed at 20.00 h, and at bedtime on the third and fourth postoperative days.

Adverse Effects. On the assessment sheets the patients answered the question “Have you experienced any other effect than pain relief which can be related to the medication?” at bedtime during the 6 evenings of the observation period. The nature of the effect was to be specified.

Global Assessment. On the third postoperative day the patients made an overall assessment of the medication given on a VAS running from “Bad” (0 mm) to “Good” (100 mm).

Statistical Analysis. The data for each variable were assessed for normality. The 2-tailed, paired Student’s t-test [2] was used for the facial swelling, mouth opening ability, oral temperature and global assessment results. The Wilcoxon matched pair signed rank test [2] was used for the pain assessments. Haematomas/ecchymoses and postoperative bleeding were analysed by the χ²-test [2]. A significance level of 5% was used.

Results

Postoperative Swelling

The difference in observed facial swelling after receiving the SUR 2647 combination as compared to placebo on the third (16%) and seventh (34%) postoperative days was not significant (Table 1).

Mouth Opening

On the third postoperative day the average reduction in preoperative mouth-opening ability was 21% after

<table>
<thead>
<tr>
<th>Table 1. Facial swelling (mm) in 30 patients receiving the SUR 2647 combination or placebo following oral surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postoperative day</td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>7</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

N.S. = not significant