Analgesic Dose–Response Relationship of Ibuprofen 50, 100, 200, and 400 mg after Surgical Removal of Third Molars: A Single-Dose, Randomized, Placebo-Controlled, and Double-Blind Study of 304 Patients

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The purpose of this single-dose, randomized, placebo-controlled, and double-blind study was to evaluate the analgesic dose–response relationship of 50-mg, 100-mg, 200-mg, and 400-mg doses of ibuprofen after third molar surgery. Patients were instructed to take a single dose of either placebo or 50 mg, 100 mg, 200 mg, or 400 mg of ibuprofen when the postoperative pain was moderate to severe. Acetaminophen 500 mg was used as a rescue medication. Pain intensity, pain relief, and any possible adverse events were recorded on self-administered questionnaires hourly for 6 hours after intake of study medication. If rescue medication was taken, the time of intake was registered. A total of 304 patients entered the study, and 258 complied with the protocol. A positive analgesic dose–response relationship of 50-mg, 100-mg, 200-mg, and 400-mg doses of ibuprofen was observed when evaluated by pain intensity difference, sum of pain intensity difference, pain relief, total pain relief, and survival distribution of patients not taking rescue medication. Although significant pain relief was seen after a dose of 50 mg ibuprofen, ibuprofen 400 mg provided maximum pain relief and the longest duration of analgesic effect. Mild transient adverse events were reported by 6.8% of the patients. However, there was no significant difference in frequency between the placebo and 50 mg, 100 mg, 200 mg, and 400 mg ibuprofen dose groups.


Aspirin, acetaminophen, and other related aspirin-like drugs have traditionally been used for pain control after minor surgery. However, nonsteroidal antiinflammatory drugs (NSAIDs), which originally were developed for relief of rheumatoid arthritis pain, are used extensively today for similar indications as traditional aspirin-like drugs due to a similar or superior analgesic effect combined with a low frequency of side effects.1,3–8 Ibuprofen is one of the most used NSAIDs both at low over-the-counter doses or at prescription doses. The analgesic effect of different doses of ibuprofen has previously been evaluated using various acute pain models.1,3–8 However, the dose–response relationship of more than two different doses including a low ibuprofen dose has not been evaluated within the same well-controlled study. It is of clinical interest to evaluate the analgesic dose–response range of ibuprofen in clinically relevant doses using a reliable and valid model of acute pain. The purpose of the present study therefore was to evaluate the anal-
Table I Demographic Data of Patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo</th>
<th>Ibuprofen 50 mg</th>
<th>Ibuprofen 100 mg</th>
<th>Ibuprofen 200 mg</th>
<th>Ibuprofen 400 mg</th>
<th>All groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>56</td>
<td>51</td>
<td>53</td>
<td>49</td>
<td>49</td>
<td>258</td>
</tr>
<tr>
<td>Gender, no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>29 (51.8)</td>
<td>31 (60.8)</td>
<td>26 (49.1)</td>
<td>20 (40.8)</td>
<td>26 (53.1)</td>
<td>132 (51.2)</td>
</tr>
<tr>
<td>Female</td>
<td>27 (48.2)</td>
<td>20 (39.2)</td>
<td>27 (50.9)</td>
<td>29 (59.2)</td>
<td>23 (46.9)</td>
<td>126 (48.8)</td>
</tr>
<tr>
<td>Age, years (mean ± SE)</td>
<td>25.9 ± 0.80</td>
<td>25.1 ± 0.85</td>
<td>25.7 ± 0.91</td>
<td>24.6 ± 0.51</td>
<td>26.6 ± 0.89</td>
<td>25.6 ± 0.36</td>
</tr>
<tr>
<td>Weight, kg (mean ± SE)</td>
<td>67.4 ± 1.51</td>
<td>69.8 ± 1.62</td>
<td>69.6 ± 1.51</td>
<td>67.4 ± 1.51</td>
<td>67.6 ± 1.59</td>
<td>68.3 ± 0.69</td>
</tr>
<tr>
<td>Baseline pain intensity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. (%) of patients with moderate pain</td>
<td>31 (55.4)</td>
<td>32 (62.7)</td>
<td>30 (56.6)</td>
<td>32 (65.3)</td>
<td>24 (49.0)</td>
<td>149 (57.8)</td>
</tr>
<tr>
<td>No. (%) of patients with severe pain</td>
<td>25 (44.6)</td>
<td>19 (37.3)</td>
<td>23 (43.4)</td>
<td>17 (34.7)</td>
<td>25 (51.0)</td>
<td>109 (42.2)</td>
</tr>
<tr>
<td>Mean baseline pain intensity (± SE)</td>
<td>2.45 ± 0.07</td>
<td>2.37 ± 0.07</td>
<td>2.45 ± 0.07</td>
<td>2.35 ± 0.07</td>
<td>2.51 ± 0.07</td>
<td>2.43 ± 0.03</td>
</tr>
</tbody>
</table>

Gesic dose–response relationship of 50-mg, 100-mg, 200-mg, and 400-mg doses of ibuprofen used for treatment of acute postoperative pain after third molar surgery using a single-dose, randomized, placebo-controlled, and double-blind design.

PATIENTS AND METHODS

Patients

Patients referred to the Departments of Oral and Maxillofacial Surgery, Schools of Dentistry, Faculties of Health Sciences at the Universities of Copenhagen and Aarhus, Denmark, for surgical removal of an impacted mandibular third molar were considered for inclusion in the study. All patients included in the study at the two centers were otherwise healthy individuals belonging to class ASA I according to the medical risk categories established by the American Society of Anesthesiologists. Consequently, persons with gastric ulcers, hypersensitivity or previously experienced adverse events to any of the involved study drugs, renal or hepatic diseases, bleeding disorders, or other systemic diseases interfering with the study were excluded. Female patients also were excluded if they were pregnant or lactating. In addition, patients who had taken any analgesics within 12 hours before surgery were excluded. The patients could only participate once in the study.

Inclusion was performed after written informed consent was obtained based on verbal and written information about the study. Gender, age, and weight of the patient were registered if participation in the study was accepted. The patients were free to withdraw from the study at any time for whatever reason. The study was performed according to the Declaration of Helsinki II, with approval of the National Board of Health and the local ethical committees of Copenhagen and Aarhus, Denmark.

The demographic data are presented in Table I. A total of 304 patients were included in the study, and 258 (84.9%) complied with the protocol. Of these, 46 patients were excluded because of no need for analgesics (n = 24), withdrawal not related to adverse events (n = 3), absence of control visit (n = 5), remedication within the first hour after intake of study medication (n = 2), loss of self-administered questionnaire (n = 5), concomitant use of other types of analgesics (n = 3), no indication for surgery (n = 3), and concomitant surgical removal of a maxillary third molar (n = 1). The number of dropouts and additionally extracted maxillary third molars were equally distributed among the five groups. No significant differences were observed in distribution of gender (P = 0.39), age (P = 0.34), weight (P = 0.49), and mean baseline pain intensity (P = 0.48) among the five groups.

Surgery

All patients were treated before noon as outpatients using local analgesia (20 mg/mL + 12.5 µg/mL, usually 2–4 mL, Xylocain adrenaline; Astra, Södertälje, Sweden). No premedication was used. An identical standard surgical procedure was performed to remove one impacted mandibular third molar. A buccal full-thickness mucoperiosteal flap was elevated. If necessary, bone covering the impacted tooth was removed using a drill under profuse sterile saline irrigation. The tooth was sectioned when necessary. After meticulous saline irrigation of the wound to eliminate debris, the flap was repositioned and sutured using 3-0 braided silk sutures (Ethicon; Norderstedt, Germany). If indicated, the maxillary third molar of the same side of the mouth was concomi-
DOSE-RESPONSE RELATIONSHIP OF IBUPROFEN

In this study, patients were instructed to take a single oral dose of ibuprofen (50 mg, 100 mg, 200 mg, or 400 mg of ibuprofen [Nymed Pharma, Roskilde, Denmark]) and maintain an adequate water intake when postoperative pain became moderate to severe. All tablets were identical in number (2), taste, and appearance for all patients. If the pain relief was insufficient 1 hour after intake of study medication, intake of rescue medication was allowed (acetaminophen 500 mg; Nymed Pharma). Use of other types of analgesics or potentially confounding drugs was not allowed.

Analgesic Efficacy Measures

The analgesic evaluation was based on a previously validated and sensitive method for outpatients established by Cooper and Beaver. Briefly, patients were instructed on a five-point verbal rating scale to record baseline pain intensity (0 = no pain, 1 = slight pain, 2 = moderate pain, 3 = severe pain, and 4 = unbearable pain) on specially designed single-page self-administered questionnaires at the time of study medicine intake. In addition, every hour for the 6 hours after intake of study medication patients evaluated their pain intensity using the same scale, and evaluated pain relief on a five-point verbal rating scale (0 = no pain relief, 1 = slight pain relief, 2 = some pain relief, 3 = lot of pain relief, and 4 = complete pain relief).

Any possible adverse events also were recorded hourly for 6 hours. If rescue medication was taken, the time of intake was registered. All patients were provided with written instructions to ensure high compliance. The questionnaires were returned at the time of removal of sutures and control one week after surgery. All questionnaires were reviewed with the patient and corrected for inconsistencies and missing information.

The following analgesic efficacy parameters were evaluated:

Pain intensity difference (PID) was evaluated hourly for 6 hours after intake of study medication. The hourly PID scores were calculated by subtracting the actual pain intensity score from the baseline pain intensity score. For example, if a patient reported severe pain (score 3) at the time of intake of study medication and moderate pain (score 2) after 1 hour, then the pain intensity difference at hour 1 is +1.

Sum of pain intensity difference (SPID) was estimated as the area under the PID versus time curve by adding pain intensity difference scores observed 1, 2, 3, 4, 5, and 6 hours after intake of study medication.

Pain relief (PAR) was evaluated hourly for 6 hours after intake of study medication.

Total pain relief (TOTPAR) was estimated as the area under the PAR versus time curve by adding the pain relief scores observed 1, 2, 3, 4, 5, and 6 hours after intake of study medication.

Time to remedication was defined as the time from intake of study medication until intake of rescue medication became necessary for the patient. Percentage of patients not taking rescue medication was estimated as a survival distribution using the Kaplan-Meier method.

Statistics

Data management and statistical analyses were performed using a PC version of the SAS statistical program (SAS Institute, Cary, NC). Patients taking rescue medication within the first hour after intake of study medication were initially excluded from the study. Demographic data (distribution of gender, age, and weight) were evaluated by Kruskal-Wallis test. Baseline pain intensity at the time of intake of study medication, SPID, and TOTPAR were evaluated by one-way analysis of variance (ANOVA) and Duncan’s multiple range test. Standard adjustment was performed if a patient took rescue medication within the 6-hour evaluation period by using the PID and PAR values registered just before remedication for the rest of the study.

The use of no or other adjustment types did not change the conclusions of this study, as previously observed in a similar study. The percentage of patients not taking rescue medication as a survival distribution was evaluated by the log-rank test. The frequency of adverse events was evaluated by the chi-square test. Level of significance was set at 0.05.

RESULTS

Pain Intensity Difference

Scores for PID and SPID are presented in Figures 1 and 2. A positive dose—response relationship was observed. When evaluated by SPID, all four ibuprofen doses were significantly superior to placebo ($P \leq 0.05$). In addition, the 50-mg dose was significantly
different from the 200-mg and 400-mg doses \((P \leq 0.05)\), but not from the 100-mg dose \((P > 0.05)\). Finally, the 200-mg and 400-mg doses were significantly different from each other as well as from all other doses \((P \leq 0.05)\).

**Pain Relief**

Scores for PAR and TOTPAR are presented in Figures 3 and 4. A positive dose–response relationship was observed. When evaluated by TOTPAR, all four ibuprofen doses were significantly superior to placebo \((P \leq 0.05)\). In addition, the 50-mg dose was significantly different from the 200-mg and 400-mg doses \((P \leq 0.05)\), but not from the 100-mg dose \((P > 0.05)\). Likewise, the 200-mg and 400-mg doses were significantly different from the other doses \((P \leq 0.05)\), but not from each other \((P > 0.05)\).

**Survival Distribution of Patients not Taking Rescue Medication**

The percentage of patients not taking rescue medication is presented in Figure 5 as a survival distribution. A positive dose–response relationship was observed. The 100-mg, 200-mg, and 400-mg doses were significantly superior to placebo \((P \leq 0.01)\). The 50-mg dose was significantly different from the 400-mg dose \((P = 0.0002)\), but not distinguishable from placebo or the 100-mg and 200-mg doses \((P > 0.10)\). In addition, the 100-mg dose was significantly different from the 400-mg dose \((P = 0.002)\), but not from the 200-mg dose \((P = 0.58)\). Finally, the 400-mg dose was significantly superior to all other doses \((P \leq 0.008)\).

**Adverse Events**

All adverse events are presented in Table II. Twenty-three mild transient adverse events were reported by 18 patients \((6.8\%)\), but no serious events were re-
reported. There was no significant difference in frequency of adverse events among the five groups ($P = 0.96$).

**DISCUSSION**

Different pain models have been used for evaluation and comparison of various analgesics. However, most studies evaluating use of analgesics to control mild to moderate pain have used the single-dose mandibular third molar surgery pain model, due to the predictable postoperative local development of inflammation with a maximum pain intensity within the first 12 hours after surgery.\(^5,7,11,14,15\) In addition, patients requiring removal of third molars usually are otherwise healthy individuals who rarely are taking potentially confounding medication. Several of the above-mentioned studies have confirmed that this model generally has a high reproducibility and low placebo response. These aspects are important to recognize in dose-response studies, because they predominantly determine the possibility to separate different doses. Further, the use of an identical standard surgical procedure for removal of third molars generally exhibits low variability of the data. Likewise, only use of local analgesia avoids the influence of premedication and general anesthesia on pain perception.

Although mutual significance between the ibuprofen doses was not always present, evaluation by SPID, TOTPAR, and survival distribution of patients not taking rescue medication demonstrated a positive analgesic dose–response relationship of 50-mg, 100-mg, 200-mg, and 400-mg doses of ibuprofen in this study. Similar results were obtained when other analgesic efficacy parameters were considered (data not reported). In addition, the previously reported
significant pain relief that is achieved after a single 50-mg dose of ibuprofen was confirmed.6

It has been demonstrated previously that pain relief scores are more sensitive than pain intensity scores.10 However, the PID scores seemed more sensitive in separating different ibuprofen doses than did PAR scores in this study. It is unknown whether this apparent disagreement is related to variations in analgesic type or pain model.

The analgesic dose–response relationship of 200-mg and 400-mg doses of ibuprofen has been evaluated previously using various pain models.1,3,4,7,17 However, results from studies involving more than two doses seem questionable. The analgesic effect of 100-mg, 200-mg, and 400-mg doses of ibuprofen has been compared in one study using the third molar surgery pain model.5 In general, no significant differences were observed, but the sensitivity of the study may have been compromised by preoperative use of intravenous meperidine with methohexital or diazepam in the majority of patients. Similarly, in a study evaluating 50-mg, 100-

![Figure 5. Percentage of patients not taking rescue medication in the placebo and 50 mg, 100 mg, 200 mg, and 400 mg ibuprofen dose groups as a survival distribution.](image)

Table II Number of Adverse Events by Treatment Group

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Placebo</th>
<th>Ibuprofen 50 mg</th>
<th>Ibuprofen 100 mg</th>
<th>Ibuprofen 200 mg</th>
<th>Ibuprofen 400 mg</th>
<th>All groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>—</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Vertigo</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>—</td>
<td>4</td>
</tr>
<tr>
<td>Tooth pain</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>1</td>
<td>1</td>
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<td>Headache</td>
<td>1</td>
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<td>Diarrhoea</td>
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<td>—</td>
<td>—</td>
<td>—</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Malaise</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>1</td>
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</tr>
<tr>
<td>Pyrosis</td>
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<td>—</td>
<td>—</td>
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<td>Hot flushes</td>
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<tr>
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<tr>
<td>Tremor</td>
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<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>1</td>
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<tr>
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<td>—</td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td>Tingling skin</td>
<td>1</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>1</td>
</tr>
</tbody>
</table>
mg, and 200-mg doses of ibuprofen in the same pain model an analgesic dose–response relationship was not demonstrated in most instances. However, the use of various preanesthetic and anesthetic agents also may have influenced the sensitivity of this study due to a decreased need for analgesics after surgery. No significant dose–response relationship was identified for 200-mg, 400-mg, and 600-mg doses of ibuprofen in a recently published study also using the third molar surgery pain model, but the use of general anesthesia also may have compromised the sensitivity of this study. However, several studies have demonstrated that the analgesic effect of ibuprofen does not increase with doses above 400 mg, probably due to an analgesic ceiling effect.  

The highest scores for pain intensity difference and pain relief according to Figures 1 and 3 were generally observed within the first 2 to 3 hours after intake of study medication, as in previous studies. These observations also are in accordance with results of a study demonstrating achievement of maximum plasma concentration 1.5 to 2 hours after intake of ibuprofen. However, intake of rescue medication was necessary sooner after intake of the lowest ibuprofen doses, indicating a short and/or low analgesic effect. 

It seems noteworthy that necessity of rescue medication 6 hours after intake of study medication was observed only in 55% and 65% of patients in the 50-mg ibuprofen and placebo groups, respectively. In addition, 8% of the patients were excluded from the study because they did not need analgesics at all. These results are in accordance with those of previous studies. The low percentage of patients requiring rescue medication is probably related to the fact that only one tooth was surgically removed in this and previously published studies.  

Although low doses of ibuprofen seem to provide analgesia after surgical removal of third molars in many patients, the apparently rapid need for remedication and the limited analgesic effect indicate that the use of ibuprofen in low doses cannot be advised for controlling pain after surgical removal of third molars or other types of minor surgery. The 400-mg dose of ibuprofen would be preferable due to its higher and longer duration of analgesic effect. 

Evaluation of analgesics obviously involves more than the mere assessment of analgesic effect. Untoward adverse events are as important a determinant of therapeutic usefulness as the analgesic efficacy. Mild transient adverse events are reported by 6.8% of the patients in this study. No serious events were reported, and withdrawal from the study due to adverse events was not observed. It is unknown whether the observed reactions were drug related or expected sequelae of surgery. However, the frequency of these events was low and no significant difference was observed among the placebo and 50-mg, 100-mg, 200-mg, and 400-mg ibuprofen dose groups. Similar results have previously been reported in single- and multiple-dose studies.  

The most frequently reported adverse events after intake of ibuprofen are related to the gastrointestinal tract, such as peptic ulceration, dyspepsia, abdominal pain, nausea, and vomiting. In addition, skin rashes, headache, dizziness, depression, euphoria, fatigue, and renal impairment have been reported. However, in view of the very high quantities that have been ingested in both therapeutic doses and overdose situations, the risk of severe and fatal reactions is extremely low with short-term use of recommended doses. 

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REFERENCES
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