Analgesic Efficacy of Low-Dose Diclofenac Versus Paracetamol and Placebo in Postoperative Dental Pain

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Aims: *To compare the efficacy and safety of diclofenac-K (12.5 mg) vs paracetamol (500 mg) and placebo given in a flexible dosage regimen to treat pain resulting from extraction of impacted third molar teeth.* ***Methods:*** *This was a 2-day, double-blind, double-dummy, randomized, parallel-group, placebo-controlled study of diclofenac-K (12.5 mg) tablets vs paracetamol (500 mg) tablets and placebo in patients with moderate or severe pain within 8 hours of extraction of impacted third molars.* ***Results:*** *After the first 2-tablet dose, patients took on average 2.5 additional tablets of diclofenac-K or 2.4 tablets of paracetamol, almost all as 1-tablet doses. Most placebo patients discontinued by taking rescue medication (ibuprofen 200 mg) on the first day. Pain relief after the initial dose of diclofenac-K (2 × 12.5 mg) was superior to placebo ($P < .01$ for all efficacy outcomes) and comparable to paracetamol (2 × 500 mg). About 30% of patients in each active treatment group took rescue medication during the study, compared to 78% on placebo. About 70% in each active treatment group considered the overall pain relief to be "some," "a lot," or "complete" compared to only 15% on placebo. The incidence of adverse events in each active treatment group was low and comparable between the treatments.* ***Conclusion:*** *An initial double-dose of diclofenac-K (2 × 12.5 mg) or paracetamol (2 × 500 mg) adequately relieved the most intense postoperative pain, and the flexible multiple dose regimen (1 or 2 tablets) maintained adequate pain relief thereafter. Most patients needed only 1-tablet doses following the initial 2-tablet dose.*

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Key words: diclofenac, paracetamol, dental pain, flexible dosage regimen, analgesia

The pain resulting from the surgical removal of 1 or more impacted third molars is a validated pain model. The pain in this model is both predictable and consistent, beginning 1 to 3 hours after surgery and ranging in intensity from moderate to severe.[1] The efficacy of a single dose of paracetamol (1,000 mg) in relieving this pain has been demonstrated in numerous studies in which paracetamol served as the active control.[2–4] These studies were generally conducted to demonstrate the efficacy of nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, flurbiprofen, ketoprofen, and naproxen. Several of these have been demonstrated effective in both a low dose available over-the-counter (OTC) and at a higher dose available by prescription.[3,4] More recent studies have also considered the efficacy of the newer cyclo-oxygenase-2 (COX-2)-selective NSAIDs, rofecoxib and celecoxib, which are available only by prescription.[5,6]

Diclofenac is a NSAID that has also been demonstrated to be effective in relieving postsurgical dental pain in a single 50-mg dose, which is available by prescription.[7] Formulations tested at the 50-mg dose include the sugar-coated immediate-release form (diclofenac-K; Cataflam or Voltaren Rapid [50 mg]), the enteric-coated form (diclofenac-Na; Voltaren or Voltarol), and a drinkable formulation of diclofenac dispersible. Recently a new, immediate-release formulation of diclofenac-K containing 12.5 mg has been developed to provide satisfactory efficacy with improved safety at a lower dose that would be suitable for OTC use. A flexible dosing regimen is proposed starting with an initial dose of 2 tablets (2 × 12.5 mg) followed by 1 or 2 tablets, 4 to 6 hours as needed, to a maximum of 75 mg daily for up to 5 days.

The comparative dental pain studies published to date have all been single-dose studies, with levels of analgesia typically assessed over 8 hours post-dose for prescription doses of NSAIDs and 6 hours for OTC doses of NSAIDs. The published studies of rofecoxib extended to 24 hours but were single-dose studies nonetheless.[5,6] To test not only efficacy of the proposed initial 25 mg dose of diclofenac, but also the overall efficacy of the flexible dosing regimen, efficacy assessments were extended over 2 days, covering the normal course of 2 days of pain that follow extraction of an impacted third molar.[8] The purpose of this study was to demonstrate the efficacy of both the single initial dose and the flexible multiple-dosing regimen of low-dose diclofenac (12.5-mg tablets) in comparison to a standard OTC flexible dosing regimen of paracetamol (500 mg) tablets and to placebo.

Materials and Methods

Patients

A total of 245 patients experiencing moderate to severe pain within 8 hours after extraction of 1 or 2 impacted third molars were recruited from German dental practices. The study was performed in accordance with the current version of the Declaration of Helsinki and the national requirements for the conduct of clinical trials in Germany. Local Ethics Committees approved the protocol and the study was conducted according to the International Conference on Harmonization – Good Clinical Practice (ICH–GCP) standard. All patients provided written informed consent before enrollment. Patients were excluded for known hypersensitivity or allergy to NSAIDs and related products; for severe or uncontrolled renal, hepatic, hematologic, endocrine, pulmonary, cardiac, neurologic, or cerebral disease; and for active peptic ulcer disease or a history of significant gastrointestinal disease or any gastrointestinal bleeding during the past year. Patients were also excluded if they were taking heparin or coumarin-type anticoagulants, anti-depressants, tranquilizers, muscle relaxants, sedatives or hypnotics, steroids, lithium, anti-inflammatory agents or analgesics (other than the study medication following surgery), or if they made chronic use of NSAIDs or used analgesics, tranquilizers, or muscle relaxants during the week before enrollment. Pregnant or breast-feeding women, individuals with a known drug dependency or history of current drug or alcohol abuse, and patients who had participated in an investigational drug trial in the past 30 days were also excluded.

Study Design and Assessments

This was a double-blind, double-dummy, placebo-controlled, parallel-group, randomized trial. Patients were randomly allocated to 1 of 3 treatment groups. Tablets of the 2 active drugs differed in shape and size. To preserve blinding, a double-dummy design was therefore used with placebo tablets to match each of the 2 active treatment tablets.

Ibuprofen (200 mg) was the rescue medication that could be used from 1 hour after the first dose of study medication if patients were still experiencing moderate or severe pain. Patients who took rescue medication were withdrawn from the trial.

The 48-hour treatment period started with an initial dose of 2 tablets (2 × 12.5 mg of diclofenac-K or 2 × 500 mg of paracetamol or placebo) followed by 1 or 2 tablets of each type, as needed, every 4 to 6 hours, up to a maximum daily dose of 6 tablets of each type (75 mg for diclofenac-K or 3 g for paracetamol). Placebo tablets were incorporated into each dose of study medication for all patients as appropriate to the double-blind, double-dummy design of the study.

Procedures for anesthesia and extraction were standardized. Extraction of 1 or 2 impacted third molar teeth was carried out under local anesthesia. Local anesthesia was achieved by injecting a maximum dose of 2 mL/tooth of articaine (Ultracain) or mepivacaine and a maximal dose of 0.5 mL vasoconstrictor to minimize bleeding. Patients who were due to have only 1 tooth extracted were recruited only if the tooth was in the mandible. Patients who were due to have 2 teeth extracted were recruited only if the 2 extractions were on the

same side—1 from the maxilla and 1 from the mandible.

Efficacy assessments were as follows: *(1)* pain intensity, scored on a 4-point categorical scale at baseline, and then at 30 minutes, 1, 2, 3, 4, 5, and 6 hours after dosing; *(2)* pain relief, scored on a 5-point categorical scale at 30 minutes, 1, 2, 3, 4, 5, and 6 hours after dosing; *(3)* an initial dose global assessment, scored on a 5-point categorical scale at 6 hours after the dose or at the time of rescuing or remedication if earlier; *(4)* a global assessment scored on a 5-point categorical scale at the end of days 1 and 2; *(5)* an overall global relief score, assessed on a 5-point categorical scale at the end of the study; *(6)* time to either rescue medication or repeat dosing with study medication within 6 hours of the initial dose; *(7)* time to rescue medication over the whole study period. Adverse events and concomitant medications were recorded throughout the study.

Statistical Methods

The primary efficacy outcome for the initial dose was the pain relief score at 1 hour. A sample size of 70 per group was selected to provide at least 80% power to detect a difference of 0.5 in this outcome between active and placebo patients through the use of a Student unpaired *t* test. A common standard deviation of 1- and 2-sided testing at $\alpha = 0.05$ was assumed. The primary multiple-dose efficacy outcome was the end of the study global evaluation. This sample size also provided at least 80% power to detect a difference of 0.7 in this outcome between active and placebo after multiple doses, using the Student unpaired *t* test and assuming a common standard deviation of 1.2. The expected differences and standard deviations were based on results from earlier single-dose, dental pain studies of diclofenac-K (12.5 mg).

Rules were prespecified in the protocol for imputation of missing assessments due to use of rescue medication or for other reasons. Other rules were prespecified in the protocol to ignore pain intensity or pain relief assessments made more than 15 minutes after rescue medication or global efficacy assessments made on days when no medication was used.

Of the efficacy outcomes after the initial dose, pain relief scores by time point were analyzed with analysis of variance (ANOVA), including main effects of treatment and center and the treatment-by-center interaction. Differences from baseline in pain intensity (PIDs) were analyzed similarly, with the main effect of baseline severity and the interaction of baseline severity and treatment included in the ANOVA. For this purpose, baseline severity was treated as a categorical effect. TOTPAR-3 (area under the pain-relief-vs-time curve over hours 0 to 3) and SPID-3 (area under the PID-vs-time curve over hours 0 to 3) were computed and analyzed with the same ANOVA models as the pain relief and PID scores, respectively.

To facilitate comparisons of efficacy in this study with results of other recent and future studies, TOTPAR-6 was computed (in parallel fashion to TOTPAR-3) and the percent of subjects achieving 50% of the maximum possible TOTPAR-6 value (50% maxTOTPAR-6) was calculated for each treatment group. Differences between treatment groups in number of subjects achieving 50% maxTOTPAR-6 were tested with the Cochran-Mantel-Haenszel (CMH) test stratified by center. These percents were then used to compute the number needed to treat (NNT) with respect to achieving 50% of maximum pain relief over hours 0 to 6.[9] Two-sided 95% confidence intervals (CIs) on NNT were generated from the normal approximation to the binomial distribution.

Time to rescue medication or redosing with study medication within the first 6 hours was analyzed with the log-rank test stratified by center. Subjects were censored if they did not take rescue medication or redose with study medication within the first 6 hours. The first dose global efficacy assessment was analyzed with the CMH test of mean ridits stratified by center.[10]

Of the multiple-dose efficacy outcomes, the end of the study global evaluation was assessed at the end of the 2-day treatment period or at the time of rescue medication. It was analyzed with the CMH test of mean ridits stratified by center. Time to rescue medication over the entire treatment period was analyzed with the log-rank test stratified by center. Subjects who did not take rescue medication were censored as of the time they completed the end of the study global assessment. The day 1 and day 2 global evaluations did not provide any additional insights into efficacy beyond the results of the other outcomes and those outcomes are therefore not discussed further.

We present the results for the intent-to-treat (ITT) population, which included all randomized patients who used trial medication and provided efficacy data. Per protocol efficacy analyses were also conducted and these mirrored the ITT population results. The safety population comprised all patients taking at least 1 dose of trial medication and included all randomized patients.

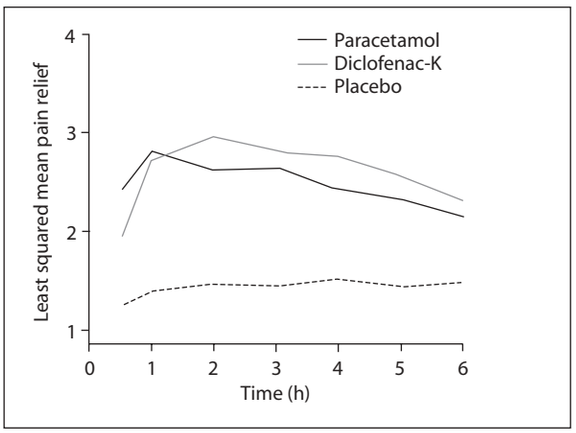

Fig 1 Mean profile of pain relief with time after initial dose (ITT population): Pain relief scale, 1= no relief, 2 = a little relief, 3 = some relief, 4 = a lot of relief, 5 = complete relief. Analysis of variance (ANOVA) model includes main effects of center and treatment and treatment-by-center interaction.

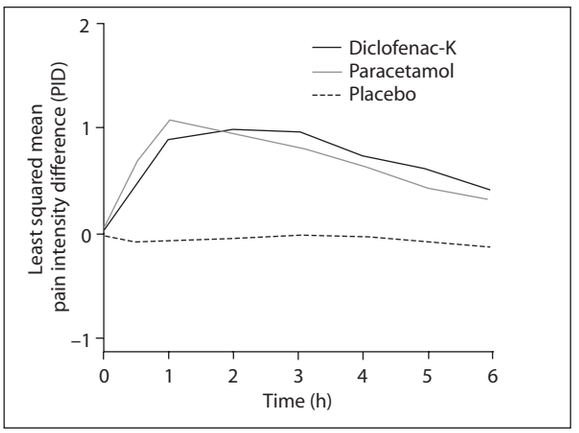

Fig 2 Mean profile of pain intensity differences with time after initial dose (ITT population).

Results

Study Population

A total of 245 patients, 83, 78, and 84 in the diclofenac-K, paracetamol, and placebo groups, respectively, were randomized in 7 German centers. All were included in the ITT efficacy and safety populations. The 3 groups were similar demographically and in severity of baseline pain. Approximately 40% of patients were male. All were Caucasian and the average age was 26. Baseline pain intensity was reported as moderate by 65% to 76% of patients in each group. One patient per group took the first dose with less than moderate baseline pain intensity, but these were not excluded from the ITT efficacy population. Withdrawal rates were comparable for the 2 active treatment groups, ie, 34.9% in the diclofenac-K and 29.5% in the paracetamol group compared to 79.8% in the placebo group. All withdrawals were due to unsatisfactory therapeutic effect (ie, use of rescue medication), except for 1 placebo patient withdrawn by the investigator after dosing because of a protocol violation (dosing 14 hours after surgery).

Study Drug Usage

Usage patterns of diclofenac-K and paracetamol were very similar. All patients used study medication on the first day. The average diclofenac-K or paracetamol user took 3.1 and 3.2 tablets, respectively, on the first day in similar, corresponding patterns of usage. Thus, after the initial 2-tablet dose, 90% of patients took at most 2 additional tablets, generally in 1-tablet doses. The average placebo patient used only 2.5 placebo tablets on the first day. This lower usage was primarily due to increased early termination in this group.

On the second day, 51% of diclofenac-K patients used study medication, averaging 2.4 tablets per person. About 95% of these tablets were taken as 1-tablet doses. In the paracetamol group, 38.5% of patients used study medication, averaging 2.8 tablets per person. About 83% of these tablets were taken as 1-tablet doses. Few placebo patients used study medication on day 2 and very few study patients used study medication on day 3.

Over the 2-day study period, the average diclofenac-K patient took 4.5 tablets. After the initial 2-tablet dose, 94% of the additional 2.5 tablets were taken as 1-tablet doses. The average paracetamol patient used 4.4 tablets. After the initial 2-tablet dose, 88% of the additional 2.4 tablets were taken as 1-tablet doses.

Analgesic Efficacy of First Dose

Comparisons to Placebo. The first dose of 25 mg (2 × 12.5 mg) diclofenac-K provided effective analgesia by a variety of measures. The profile of analgesia in terms of pain relief is shown in Fig 1 and as PIDs in Fig 2. Differences from placebo

Table 1 Selected First Dose Efficacy Outcomes (Intent-to-Treat Population)

	Diclofenac-K	Placebo	Paracetamol
n	83	84	78
Average pain relief score at 1 hour—mean (SD)*	2.71† (1.29)	1.43 (0.70)	2.96† (1.07)
TOTPAR-3—mean (SD)	7.78† (3.13)	4.18 (1.79)	7.95† (2.65)
SPID-3—mean (SD)	2.34† (2.36)	–0.27 (1.67)	2.25† (1.73)
End of first dose global assessment of pain relief—n (%)			
1 = poor	21 (25.3)	64 (76.2)	14 (17.9)
2 = fair	16 (19.3)	12 (14.3)	20 (25.6)
3 = good	21 (25.3)	7 (8.3)	27 (34.6)
4 = very good	24 (28.9)	1 (1.2)	15 (19.2)
5 = excellent	1 (1.2)	0	2 (2.6)
Mean SD	2.61† (1.19)	1.35 (0.69)	2.63† (1.07)
No. (%) achieving 50% maxTOTPAR-6‡	42/72 (58.3)†	7/73 (9.6)	45/69 (65.2)†
NNT (95% CI)§	2.1 (1.6–2.9)	—	1.8 (1.2–2.4)

*1= no relief, 2 = a little relief, 3 = some relief, 4 = a lot of relief, 5 = complete relief.
†Significantly different from placebo, $P < .001$.
‡TOTPAR-6 is ≥ 50% of its theoretical maximum value.
§Number needed to treat based on achieving 50% maxTOTPAR-6.
SD = standard deviation, CI = confidence interval.

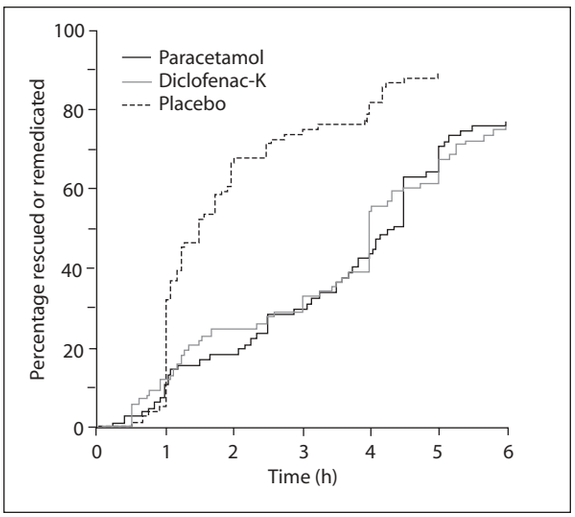

Fig 3 Time to rescue or re-dosing with trial medication within 6 hours after the initial dose (ITT population).

were statistically significant at all time points in both Figs 1 and 2 ($P < .01$). This demonstrates that onset of analgesia was within 30 minutes and lasted for 6 hours. This efficacy is summarized in Table 1 over the first 3 hours as TOTPAR-3 and SPID-3. The global assessment of pain relief after the initial dose similarly shows that over half the diclofenac-K patients considered their first dose pain relief to be either "good," "very good," or "excellent," compared to over 90% in the placebo group who considered it either "fair" or "poor." The percent of diclofenac-K patients achieving 50% maxTOTPAR-6 was far greater than in the placebo group ($P < .01$). Figure 3 also shows dramatic differences between diclofenac-K and placebo in the time to rescue medication or redosing with study medication after the first dose. Whereas half the diclofenac-K patients waited 4.3 hours before needing additional medication, half of placebo patients required further medication within 1.5 hours ($P < .001$).

The first 1,000-mg dose of paracetamol provided a similar profile of analgesia to that provided by diclofenac-K. The onset of effect was within 30 minutes and it lasted for 6 hours. The superiority of the first dose of paracetamol (2 × 500 mg) over placebo was generally comparable in extent to the superiority of the first dose of diclofenac-K (2 × 12.5 mg) over placebo.

Diclofenac Potassium (2 × 12.5 mg) vs Paracetamol (2 × 500 mg). Differences between diclofenac-K and paracetamol in pain relief or PID at any time point were generally modest. At 30 minutes, pain relief in the paracetamol group was significantly greater than in the diclofenac-K group ($P < .01$). However, at 2 hours and beyond, differences favored diclofenac-K, although these differences did not achieve statistical significance. Figure 3 shows that there was little difference between the treatments in the times at which patients felt the need for additional analgesia. The end of first dose global assessments show nearly identical mean scores. This suggests that neither the lower level of analgesia in the diclofenac-K group at 30 minutes after the initial dose nor the somewhat higher level of analgesia in the diclofenac-K group at 2 hours and beyond had an impact on how the patients perceived the overall efficacy of the first doses of the products.

Table 1 shows also comparable percentages of diclofenac-K and paracetamol patients achieving 50% maxTOTPAR-6. Correspondingly, NNT values of the 2 treatment groups were similar: 2.1 (1.6 to 2.9) for diclofenac-K and 1.8 (1.4 to 2.4) for paracetamol.

Table 2 Selected Flexible Dosing Regimen Efficacy Outcomes (Intent-to-Treat Population)

	Diclofenac-K	Placebo	Paracetamol
n	83	84	78
Cumulative % of patients who took rescue medication within*			
6 hours	26.6	73.9	25.7
12 hours	31.8	78.0	30.0
24 hours	35.8	78.0	30.0
End of study	35.8†	78.0	30.0†
End of study global assessment of pain relief—n (%)			
1 = None	16 (19.3)	59 (71.1)	16 (20.5)
2 = A little	10 (12.0)	11 (13.3)	6 (7.7)
3 = Some	18 (21.7)	7 (8.4)	27 (34.6)
4 = A lot	33 (39.8)	6 (7.2)	24 (30.8)
5 = Complete	6 (7.2)	0	5 (6.4)
Mean (SD)	3.04† (1.26)	1.52 (0.93)	2.95† (1.22)

*Based on life-table methods.
†Significantly different from placebo, $P < .001$.
SD = standard deviation.

Analgesic Efficacy of the Flexible Multiple-Dose Regimen

The flexible multiple-dose regimen refers to the recommended dosing regimen for both diclofenac-K and paracetamol, ie, an initial dose of 2 tablets (25 mg) followed by 1 or 2 tablets every 4 to 6 hours, as needed, up to a maximum of 6 tablets per day.

Comparisons to Placebo. The efficacy of the flexible multiple-dose regimen is summarized in Table 2. Only about one quarter of diclofenac-K patients required rescue medication during the first 6 hours after the first dose, and only an additional 10% used rescue medication at any time thereafter. In contrast, almost 75% of placebo patients took rescue medication within the first 6 hours ($P < .001$). The end of the study global assessment of pain relief showed that two thirds of diclofenac-K patients considered the amount of relief provided over the course of the study to be "some," "a lot," or "complete," compared to the placebo group in which 84% of patients considered the amount of relief over the course of the study to be "a little" or "none." The superiority of paracetamol over placebo over the entire period of use was comparable in extent to the superiority of diclofenac-K over placebo.

Diclofenac Potassium vs Paracetamol. Table 2 shows that differences in efficacy between diclofenac-K and paracetamol over the entire course of the study were minimal and of no consequence. About 25% of patients in each group took rescue medication within 6 hours of the first dose and there was little additional use of rescue medication beyond 6 hours in either group. The mean score on the global assessment of overall relief of pain was nearly identical for the 2 active treatment groups—3.04 for diclofenac-K and 2.95 for paracetamol. However, about 47% of patients in the diclofenac-K group considered their relief to be "a lot" and "complete" when compared to only 37.2% in the paracetamol group.

Safety and Tolerability

The percentages of patients reporting adverse events were comparable in the diclofenac-K (7.2%) and paracetamol (5.1%) treatment groups and slightly higher than for the placebo group (2.4%). Four diclofenac-K group patients (4.8%) complained of gastrointestinal adverse events (nausea, stomachache, dysphagia, and diarrhea). One of these patients took ibuprofen 45 minutes after the first dose and therefore, the associated diarrhea and nausea could have been caused by the addition of rescue medication to the treatment regimen. Two paracetamol-treated patients complained of gastrointestinal adverse events (nausea). Two placebo-treated patients complained of gastrointestinal adverse events: 1 case of nausea and 1 case of stomachache. There were no serious adverse events, no deaths, and no patients were discontinued prematurely due to an adverse event.

Discussion

This study demonstrates that a single dose of diclofenac-K (25 mg) and the flexible daily dosing regimen (2 × 12.5 mg initially followed by 1 or 2 tablets as needed, not to exceed 6 tablets/day) effectively relieves moderate to severe pain after surgery of impacted third molars. Pain relief was comparable to the effect of a single dose of paracetamol (1,000 mg) and to the corresponding flexible daily dosing regimen of paracetamol tablets. Paracetamol is a well-established analgesic, used both in the clinic and as self-medication for dental pain.[11] The significant superiority of paracetamol over placebo confirms the sensitivity of the assay and parallels the results of numerous single-dose studies employing the same 1,000-mg dose of paracetamol.[3]

A recent initiative in the pain literature is the computation of NNT values to allow a more calibrated comparison of efficacy of analgesics across studies. It is interesting to consider the NNT results reported in Table 1 in the context of what

has been reported for diclofenac-K and paracetamol elsewhere. Such a comparison is facilitated by the categorical scale used in this study to measure pain relief, which matches the scale typically used in studies of analgesia in the dental pain model, and from which NNT is generally computed.

A recent review, which summarized results from 7 dental pain studies that included a single dose of paracetamol (1,000 mg), reported a NNT of 4.0 (95% CI = 3.2 to 5.2).[2] This is considerably larger than the value of 1.8 (95% CI = 1.4 to 2.4) reported in our study. There is no overlap between the respective 95% confidence intervals. Thus, paracetamol (1,000 mg) was much more effective in our study than has typically been reported.

Another recent review summarized results from 5 dental pain trials and 1 trial of pain following gynecological surgery in which diclofenac was used.[7] For a single 50-mg dose the reported NNT was 2.3 (95% CI = 2.1 to 2.7) and for a single 25-mg dose the reported NNT was 2.6 (95% CI = 1.9 to 4.5). This is reasonably consistent with the NNT for diclofenac (25 mg) reported in our study: 2.1 (95% CI = 1.6 to 2.9). This review also reported an NNT of 2.7 (95% CI = 2.5 to 3.0) for a single dose of ibuprofen (400 mg) based on 25 dental pain studies, 5 studies of postpartum pain, and 4 studies of postoperative pain. This is somewhat higher than the NNT of 2.1 (95% CI = 1.6 to 2.9) reported for diclofenac (25 mg) in our study. The overlap in the corresponding 95% confidence intervals suggests that one could expect comparable efficacy in either analgesic at these doses.

This study also investigated how the patients would use a flexible daily dosing regimen over the 2-day period as a function of the change in the intensity of their pain over time. The low rate of medication use on the second day of the study (40% to 50% of active-treated subjects) and the low number of tablets used by these patients on day 2 suggests that 2 days is a sufficient duration for a multiple-dose dental pain study. This is in agreement with previous findings that the intensity of pain after third molar extraction follows a variable time course, peaking 6 to 8 hours after surgery, then fading in intensity over approximately 2 days.[12–14]

The initial 2-tablet loading dose was adequate for the most intense pain starting immediately after surgery and reaching its maximum in 6 to 8 hours. After the initial 2-tablet dose, about 90% of subsequent doses were 1-tablet doses of diclofenac-K (12.5 mg) or paracetamol (500 mg), which were adequate for the subsequent milder pain. The average in either active treatment group of 4.5 tablets over the entire 2-day treatment period represents 37.5% of the maximal allowable dosage of 6 tablets per day (12 tablets over 2 days). Although patients used only a fraction of the study medication available to them through the flexible daily dosing regimen, this was sufficient to manage the pain adequately over the entire 2-day period in most patients as indicated by the responses to the end of the study global assessment of pain relief (Table 2).

The incidence of adverse events, predominantly gastrointestinal, was low and comparable for the 3 treatment groups, and no serious adverse events were reported. These tolerability results, although not unexpected in such a short-term study, confirm that the benefit:risk ratio of administering low-dose NSAIDs after dental surgery is extremely favorable. Although chronic use of NSAIDs is associated with gastric erosion and the risk of gastric bleeding, especially in those with pre-existing peptic ulceration,[15,16] the risk is considerably less for acute usage, such as that described in this study.

We therefore conclude that flexible dosage regimen treatment with diclofenac-K (12.5 mg) provides comparable pain relief to that produced by paracetamol (500 mg) after the surgical extraction of impacted third molars. This flexible dosage regimen allows patients to adapt their treatment to the pain intensity and mirrors the normal pattern of use for nonprescription analgesics.

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