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The efficacy of ketoprofen and paracetamol (acetaminophen) in postoperative pain after third molar surgery

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1 A placebo-controlled, double-blind, randomized trial was carried out to evaluate the efficacy of single doses of racemic ketoprofen 12.5 and 25 mg and paracetamol 500 and 1000 mg in patients with post-operative pain after third molar surgery over a 6 h investigation period.
2 Outcome variables included overall pain scores (AUC(0,360 min), maximum pain relief, pain relief at 1 h after dosage and the number of patients taking escape analgesics.
3 Overall pain scores (AUC(0,360 min) were significantly lower for all active treatments when compared to placebo ($P<0.01$).
4 Both ketoprofen treatments and patients treated with paracetamol 1000 mg reported significantly greater pain relief ($P<0.01$) and a later time to taking escape analgesics ($P<0.01$) than patients medicated with placebo.
5 At 1 h after dosage, pain scores were significantly less ($P<0.01$) after both doses of ketoprofen when compared with placebo.
6 Single doses of ketoprofen 12.5 and 25 mg, together with paracetamol 1000 mg are effective analgesics for treating post-operative pain after third molar surgery. These treatments provide up to 4 h of pain relief after this surgical procedure.

Keywords ketoprofen paracetamol third molar surgery postoperative pain

Introduction

Ketoprofen is a propionic acid derivative which possesses analgesic, anti-inflammatory and antipyretic properties. The drug is widely used in the management of musculo-skeletal disorders and evidence from clinical trials suggests that ketoprofen is as effective as other non-steroidal anti-inflammatory drugs in reducing the pain and discomfort associated with these disorders. [1, 2]. A few studies have evaluated the efficacy of ketoprofen in post-operative pain after third molar surgery. [3–5]. These single dose studies have demonstrated that ketoprofen at dosages of 25, 50 and 100 mg is more efficacious than either placebo or codeine phosphate 90 mg [3] or aspirin 650 mg [4]. A further study has shown that a single dose of ketoprofen 25 mg and ibuprofen 400 mg provide similar dose-effect curves in patients with post-operative pain after third molar surgery [5].

Evidence for a dose-response for ketoprofen in post-operative dental pain is inconclusive, with one study demonstrating a clear dose-response [6] whilst the other failed to substantiate this finding [3]. There is no evidence that dosage of ketoprofen below 25 mg is efficacious after third molar surgery. Thus, the aims of the present study were to evaluate the efficacy of two doses of racemic ketoprofen (12.5 and 25 mg) in patients with post-operative pain after removal of their impacted third molars, and to compare pain relief obtained with the two doses of ketoprofen with that obtained after paracetamol 500 and 1000 mg.

Method

A single dose, placebo-controlled, double-blind study of parallel design was carried out on 206 patients who had undergone third molar surgery. Informed written consent was obtained from each patient prior to their entry

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into the study (i.e. before surgery), which had received prior ethical approval from the Joint University/Health Authority Ethics Committee. Patients enrolled into the study were fit and healthy and complied with the criteria of the American Society of Anaesthesiologist Category 1 (A.S.A.1). They had undergone removal of their impacted third molars under general anaesthesia. Any patient who had taken analgesics in the previous 12 h was excluded from the trial. The anaesthetic regimen was standardised for each patient. All patients were premedicated with oral diazepam 2 h before surgery and received atropine sulphate 0.6 mg intramuscularly 30–60 min prior to the operation. Anaesthesia was induced with intravenous propofol (2–2.5 mg kg^{-1} body weight), and muscle relaxation achieved with intravenous suxamethonium chloride (1–1.5 mg kg^{-1} body weight). Maintenance of anaesthesia was achieved with nitrous oxide 30%, oxygen and enflurane. Peri-operative analgesia was provided by a single bolus dose of fentanyl (1 μg kg^{-1} body weight).

Impacted third molars were removed following a standard technique. Bone removal was carried out with a drill under saline spray. The operating time (from first incision to completion of last suture) was recorded for each patient.

On completion of the surgical procedure, time was allowed for the patients to fully recover from the effects of the anaesthetic. They then returned to the ward where they were monitored by the study nurse and their pain assessed on 10 cm visual analogue scales (VAS) at 10 min intervals. The boundaries of the scale were marked 'no pain' and 'unbearable pain'. When their pain reached a level in excess of 30 mm on the VAS, they were entered into the study, and randomly allocated to one of the following treatment groups:

(a) placebo
(b) ketoprofen 12.5 mg
(c) ketoprofen 25 mg
(d) paracetamol 500 mg
(e) paracetamol 1000 mg

If patients did not reach this level of pain within 1 h, they did not participate in the study.

The ketoprofen dosages were identical in appearance and standard paracetamol tablets were used. Matched placebos were prepared for both medications. To ensure double-blind conditions, the double-dummy technique was used. Thus, each patient received both preparations which were swallowed with sips of water.

Pain was recorded on consecutive VAS at 0, 15, 30, 45, 60, 90, 120, 180, 240, 300 and 360 min after dosage. In the event of poor pain control, patients were allowed access to alternative analgesia (Co-codamol tablets). Patients requiring escape analgesia in the first hour were exited from the study and replaced. For those patients taking escape analgesic after 60 min, their previous VAS recording was extrapolated over the remaining time points [7].

On completion of the investigation period, patients were asked to make a global assessment of their medication on a 5-point scale. The categories were: 1 = very good, 2 = good, 3 = satisfactory, 4 = poor, 5 = very poor.

Throughout the investigation, the study nurse was responsible for monitoring the patient and recording any adverse events.

Analysis

The following information was available for each patient in the five treatment groups.

(a) Serial visual analogue scales recorded over a time period of 6 h were compiled into a graph of pain (mm) *vs* time (h). The area under the graph was measured using the trapezoidal method and recorded as AUC(0,360 min). Such a measure gives an overall assessment of each patient's pain experience throughout the investigation period [8].
(b) Maximum pain relief (in mm) was obtained by subtracting the minimum pain score achieved throughout the investigation period from the baseline (time 0) score. This measure is not affected by escape as all patients achieved their minimum pain before an escape analgesic was taken.
(c) Speed of onset of relief was assessed by determining the % pain relief at 1 h. This time point was chosen since it was not affected by patients taking escape analgesics.
(d) The number of patients taking escape analgesic and the time these were taken were recorded for each treatment group.
(e) Overall assessment of medication on the 5-point categorical scale.

A one-way analysis of variance was used to assess differences between treatment groups for the AUC(0,360 min) scores, maximum pain relief and pain relief at 1 h. Differences between treatment groups were further determined using adjusted *t*-tests based upon the pooled s.d. from the ANOVA. This analysis is described as 'unadjusted' in the results. A second analysis taking into account the variables sex, age, weight, operating time, baseline pain scores and whether or not an escape was taken, was performed via analysis of covariance. Of the three outcome measures, only AUC(0,360 min) required escape instruction to be used as a covariate.

The number of patients taking escape analgesic for each treatment group was compared using chi-squared statistic. The analysis of time to taking escape analgesic is essentially a survival analysis problem where the probability of survival is plotted against time for each group. In this study, 'survival' is defined as 'not taking the escape medication'. The survival curves for each treatment were compared using the Kaplan-Meier list. Differences in patient's global assessment between treatment groups were assessed using the chi-squared statistic. A P-value of <0.05 was considered statistically significant.

Results

Of the 206 patients enrolled into the study, six were excluded due to inadequate pain control in the first

Table 1 Demographic details of patients who participated in study (where appropriate, results are expressed as means and s.d.

Variable	*Placebo*	*Ketoprofen 12.5 mg*	*Ketoprofen 25 mg*	*Paracetamol 500 mg*	*Paracetamol 1000 mg*
Number of patient	41	42	41	41	41
Exclusions	2	2	0	1	1
Sex ratio M : F	15 : 24	13 : 27	12 : 29	12 : 28	12 : 28
Mean age (years) (s.d)	24.6	24.4	25.7	23.8	27.7
	(5.1)	(5.0)	(5.9)	(4.0)	(8.5)
Mean weight (kg) (s.d)	67.8	69.6	63.4	68.2	65.8
	(12.2)	(14.5)	(9.2)	(16.9)	(9.8)
Mean operating time (min) (s.d)	24.2	25.1	23.5	24.4	23.6
	(10.4)	(13.5)	(11.6)	(12.5)	(11.3)
Mean baseline pain scores (mm) (s.d.)	56.5	53.7	55.9	54.9	54.2
	(14.9)	(13.5)	(15.5)	(13.7)	(15.9)

hour. The distribution of these exclusion for each treatment group are shown in Table 1. Randomization ensured that there were approximately 40 patients per treatment group. Each group also contained a similar proportion of males:females. Demographic details of the patients, together with the operating time and baseline pain scores are shown in Table 1. Analysis of variance showed that there was no significant difference ($P > 0.05$) between the five treatment groups for any of these parameters.

All patients entered the study within 2 h of the completion of surgery. Mean pain scores for each time point throughout the 6 h investigation period for the various treatment groups are depicted graphically in Figure 1. Pain scores after both doses of ketoprofen and paracetamol are shown with respect to placebo treatments. The mean AUC(0,360 min) (both unadjusted and unadjusted with respect to differences in baseline pain scores) are shown in Table 2. All active treatments resulted in significantly less pain ($P < 0.01$) than placebo. For the adjusted means the same pattern emerges, however for these results, patients treated with ketoprofen 25 mg reported significantly less pain ($P = 0.037$) than those treated with paracetamol 500 mg.

Maximum pain relief (in mm) is reported in Table 2. Both ketoprofen treatments and paracetamol 1000 mg provided significantly greater pain relief ($P < 0.01$) when compared with placebo. For this parameter, slightly greater pain relief ($P = 0.01$) was observed after ketoprofen 25 mg than after paracetamol 500 mg.

Pain relief at 1 h (which is not affected by patients taking 'escape' analgesics) is also reported in Table 2.

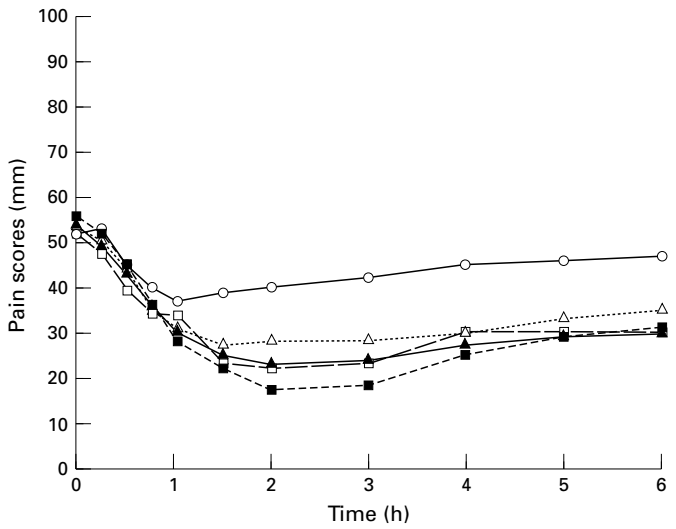

Figure 1 Mean pain score (in mm) throughout 6 h investigation period for placebo (○), paracetamol 500mg (△), paracetamol 1000mg (▲), ketoprofen 12.5mg (□) and ketoprofen 25mg (■).

Table 2 Various efficacy outcome variables—results are expressed as mean values

Variable	*Placebo*	*Ketoprofen 12.5 mg*	*Ketoprofen 25 mg*	*Paracetamol 500 mg*	*Paracetamol 1000 mg*	*Pooled s.d.*	*Standard error of differences*
AUC(0,360 min) (mm h^{-1})							
Unadjusted	263.3	176.3†	164.8†	194.8†	177†	104.5	23.4
Adjusted	243.3	192.8†	162.5†‡	199.6†‡	177.6†	78.8	17.5
%pain relief at 1 h							
Unadjusted	35.3	49.6*	50.9*	43.7	43.7	30.4	—
Adjusted	35.2	48.3*	52.8*	42.8	44.3	29.9	—
Maximum pain relief (mm)							
Unadjusted	27.4	38.4*	42.3*	33.9	38.3*	19	4.2
Adjusted	26.3	38.3†	43†‡	33.5‡	39†	16.5	3.7

*significant difference from placebo ($P < 0.05$) † significant difference from placebo ($P < 0.01$) ‡ significant difference between treatment groups ($P < 0.05$).

Only the two ketoprofen treatments were providing significant pain relief at this time point ($P < 0.05$).

The number of patients taking 'escape' analgesic and the time to taking such medication is shown in Table 3. The proportion of patients needing additional analgesia throughout the 6 h investigation period is similar for each treatment group. However, in the placebo group, patients required escape at an earlier time ($P < 0.01$) than in the other four active treatment groups. A further significant difference in the time to take escape analgesia was seen between patients treated with ketoprofen 25 mg and those treated with paracetamol 500 mg ($P = 0.04$).

The overall assessment results are shown in Table 4. For analysis the scoring was divided into three categories: very good and good (i.e. scores 1 and 2) and satisfactory (score 3), poor and very poor (i.e. scores 4 and 5). Both ketoprofen treatments and paracetamol resulted in a significantly better overall assessment when compared with placebo ($P < 0.05$). Between the active treatment groups, both ketoprofen treatments provided a significantly higher overall assessment score ($P < 0.04$) when compared with treatment after paracetamol 500 mg.

None of the patients in the present study experienced or reported any adverse effects related to their medication.

Discussion

Evidence from various clinical trials suggests that ketoprofen is an effective analgesic. The therapeutic effect was usually achieved at doses ranging from 100 to 300 mg day^{-1} [1]. The findings from this single dose study suggest that ketoprofen at a dosage as low as 12.5 mg still provides significant analgesia in an acute pain model. Furthermore, the pain responses in patients taking the low dose ketoprofen were similar to the other active treatment groups.

Using identical methodology, we have obtained similar findings with single doses (200, 400 and 600 mg) and different preparations of ibuprofen. Thus, the efficacy of low doses of ketoprofen in post-operative dental pain is comparable with that achieved after ibuprofen [14, 18].

Both ketoprofen treatments provided significantly better pain relief with respect to placebo, at 1 h after dosage, whereas the difference in pain scores between placebo and both paracetamol treatments was not significant at this time point. This would suggest that ketoprofen is providing a more rapid reduction in pain when compared with paracetamol. Such differences may be related to the anti-inflammatory properties of both drugs and the nature of acute post-operative dental pain or to differences in the pharmacokinetics between the two analgeics. Ketoprofen is a potent inhibitor of eicosanoids, blocking both cyclo-oxygenase and lipoxygenase pathways [2]. Further anti-inflammatory actions of the drug may be related to its anti-bradykinin action [1], a stabilizing effect on lysosomal membranes [9] and an inhibitory effect on PMN chemotaxis [10]. By comparison, paracetamol has weak anti-inflammatory properties [11, 12]. After third molar surgery the post-operative sequelae of pain and swelling are driven by the local inflammatory response [13]. A drug which has an established anti-inflammatory action is likely to be of more value in the early post-operative phase, than one which has weak properties.

Many of the patients in the present study required to take escape analgesics. Based upon the median time to taking such medication, it can be seen that both ketoprofen treatments and paracetamol 1000 mg provided sufficient pain control for up to 4 h after dosage. This is similar to the duration of analgesia obtained after ibuprofen [14, 18]. Such findings may be related to the nature of acute pain after removal of impacted third molars, or a true reflection of the drug's efficacy. Pain intensity in this model usually reaches its maximum in the first 12 h after surgery and declines rapidly thereafter [15, 16]. Since non-steroidal anti-inflammatory drugs are most widely used and efficacious

Table 3 Number of patients requiring 'escape' analgesia and median time to dosage

	Placebo	*Ketoprofen 12.5 mg*	*Ketoprofen 25 mg*	*Paracetamol 500 mg*	*Paracetamol 1000 mg*
Numbers of patients taking 'escape' analgesics	38/39	30/40	31/41	32/40	33/40
%	97.4	75	75.6	80.9	82.5
Median time to dosage (min)	110	240*	245*†	165*†	243*
95% confidence intervals (min)	95–120	200–245	220–275	130–210	180–270

*significant difference from placebo ($P < 0.01$) † significant difference between treatment groups ($P = 0.04$).

Table 4 Patients' overall assessment of their medication

Score	*Placebo*	*Ketoprofen 12.5 mg*	*Ketoprofen 25 mg*	*Paracetamol 500 mg*	*Paracetamol 1000 mg*	*Total*
1 or 2	8	28	28	15	23	102
3	12	5	9	13	9	48
4, 5	19	7	4	12	8	50
Total	39	40	41	40	40	200

in the treatment of post-operative dental pain [17], it is important that patients are re-medicated every 4 h to ensure effective pain control in the first 12 h.

We can conclude from the study that ketoprofen 12.5 mg, 25 mg and paracetamol 1000 mg are effective and safe analgesics for controlling post-operative pain after third molar surgery. These three treatments provide significant pain relief for up to 4 h after dosing. The two ketoprofen treatments offer a slight advantage over paracetamol by providing an earlier onset of pain relief.

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