BUTTERWORTH HEINEMANN

Ambulatory Surgery, Vol. 3, No. 4, pp. 199–203, 1995

0966-6532/95 $10.00 + 0.00

S0966-6532(96)00005-4

The efficacy of postoperative pain management with ketorolac for day case oral surgery

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The efficacy of the non-steroidal anti-inflammatory analgesic, ketorolac (Toradol), was investigated in 52 day case patients undergoing removal of impacted third molar teeth under intravenous sedation and local analgesia. The study was double-blind, randomized and placebo-controlled. A single 30 mg dose of ketorolac was administered intravenously just prior to induction of sedation with midazolam. Ketorolac was well tolerated and provided good postoperative analgesia. It is suggested that ketorolac is a useful addition to the analgesic armamentarium and appropriately prescribed, provides good pain relief following day case oral surgery.

Key words: Analgesia, postoperative, ketorolac, oral surgery, day case surgery

Introduction

Pain following the surgical removal of third molar teeth may be severe and a common cause of anxiety in patients about to undergo such a procedure[1]. This pain may be reduced by giving a non-steroidal anti-inflammatory drug (NSAID), paracetamol, an opioid or a combination of these. Paracetamol, however, is inadequate for the control of severe pain[2,3], and the respiratory depression caused by the potent opioid analgesics makes them unsuitable for outpatient use and for use in those patients requiring intravenous sedation[4–6]. Although NSAIDs are ideal for dental postoperative pain[7,8], which is largely inflammatory in origin, they have limited use in the control of severe rather than mild or moderate pain[1,9].

The objective of this study was to assess the efficacy and safety of intravenous (iv) ketorolac trometamol (Torodol) in day case patients undergoing surgical removal of an impacted third molar tooth under local anaesthesia and iv sedation. The study was double-blind, randomized and placebo-controlled. Ketorolac is a NSAID described as having potent analgesic and moderate anti-inflammatory activity[10]. It inhibits the cyclo-oxygenase pathway of arachidonic acid metabolism, resulting in the inhibition of prostaglandin biosynthesis, and is considered to be a peripherally acting analgesic. It does not appear to have effects on opiate receptors[11,12].

Accepted: 12 January 1996
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Methods

Fifty-two patients who required removal of an impacted lower third molar, with bone removal and tooth division, and who might also have required extraction of an upper ipsilateral third molar, were entered into the study. Patients were aged 18–65 yr, weighed between 50 and 100 kg and were in general good health. The main exclusion criteria were: pregnancy or lactation; clinically significant co-existing disease or history of gastric or duodenal ulcer; history of drug or alcohol abuse; and recent or concomitant use of medication likely to interfere with the study drug or its assessment. All patients entering the study gave written informed consent prior to its commencement and ethics committee approval of the protocol was obtained.

The study was blinded by means of a placebo solution which was identical to the active medication except for the absence of ketorolac. All packaging was identical with only the patient's number as an identifier. Whether the medication assigned to a given patient number was active or placebo was determined according to a computer-generated randomization code. Patients were assigned their study numbers sequentially as they entered the study. The ketorolac intravenous (iv) solution was supplied as 30 mg ml^{-1} doses in amber ampoules. All treatments were carried out by the same operator and all assessments by a single research nurse.

The patient was placed in the supine position and the ketorolac or placebo administered by slow (30 mg over 15 s) bolus injection via an indwelling cannula in the dorsum of the hand. This was immediately followed by induction of sedation with the 2 mg ml^{-1} preparation of iv midazolam (Hypnovel). The latter was titrated slowly, via the same cannula, to the desired sedation endpoint, but not exceeding 10 mg. Local anaesthesia was induced with prilocaine 4% solution without vasoconstrictor and was therefore shorter acting. The time at which the study medication was administered, the dose of midazolam administered and the times at which surgery started and ended were recorded. At tooth division the intraoperative pain was assessed by the patient according to the verbal rating scale (VRS): none, mild, moderate or severe. At the end of surgery a note was made of whether or not the patient suffered any excessive bleeding or any other adverse event.

Immediately after the completion of surgery, the first postoperative pain assessment was made as a baseline measure. The pain assessments were made by means of a 100 mm visual analogue scale (VAS) and a VRS. The VAS was marked at one end "I have no pain" and at the other, "the worst pain imaginable". The VRS was presented as: none, mild, moderate and severe. Further assessments were made every 15 min until 2 h after baseline and then at 2 h 30 min and finally at 3 h after baseline. Postoperative analgesia, if required, was ibuprofen, 200 mg tablets, the dosage being 400 mg. The time at which any patient requested and took the escape analgesia was recorded.

Shortly before the patient was discharged from hospital, the patient and the investigator made global assessments of the study therapy. Global assessments of the efficacy and tolerability of the medication, and the quality of the sedation, were made by means of the VRS: poor, satisfactory or excellent.

Safety was evaluated by continuous recording by automatic sphygmomanometer and pulse oximeter of blood pressure, pulse rate and arterial oxygen saturation. Any clinically significant deviations in any of these parameters was recorded as an adverse event. Patients were asked for symptomatic complaints using indirect questioning at each assessment. A phase such as "is anything other than the surgery pain bothering you?" was used. All symptoms were recorded as adverse events, whether or not deemed to be causally associated with the study medication. The time of discharge was recorded and the reason for any delay in discharging the patient was noted. At follow-up, 15 days after surgery, the patient was questioned about any adverse events which may have occurred since the end of the study. At this time the patient also made a final global assessment of the study therapy.

Results

All 52 patients who were recruited into the study received the study drug, and all were included in both the efficacy and safety analyses. Twenty-six patients were randomized to receive ketorolac and 26 to receive placebo. Statistical analysis was performed using SAS (production release for Windows). All significance tests were two-tailed and carried out at the 5% level. All summaries of data were by treatment group.

Demographic details are shown in Table 1. The dose of midazolam ranged from 4 to 9 mg in the ketorolac group and from 4 to 10 mg in the placebo group. Mean midazolam doses were 7 mg and 6.8 mg in the ketorolac and placebo groups, respectively. All patients received 4.4 ml of prilocaine for the removal of the lower third molar and 2.2 ml for the extraction of the upper, if this was carried out. The mean duration of surgery was 11.5 min in the ketorolac group and 9.9 min in the placebo group. The overall duration ranged from 8 to 23 min. No excessive bleeding was reported during surgery.

Efficacy

Intraoperative pain severity. Fifteen patients in the ketorolac group (58%) and 16 (62%) in the placebo group reported no intraoperative pain. Of those who did report pain, 10 patients reported it as mild and one as moderate in the ketorolac group and eight reported mild and two moderate pain in the placebo group. In neither treatment group was severe pain reported. The difference between the treatment groups was small and not statistically significant.

Postoperative VAS pain scores. The primary efficacy variable is the area under the curve (AUC) of the postoperative pain assessments measured using a VAS. AUCs are summarized by presenting the median and range for each treatment in Table 2. The study protocol stated that pain assessments need not be continued after a patient had taken postoperative analgesia. However, patients who did take postoperative analgesia carried on with the assessments of pain until 3 h after the baseline assessment with the exception of only a few missing assessments. In order to accommodate these additional data, the AUCs were calculated in two different ways. In the first method, only the missing assessments were substituted using the last observation carried forward (LOCF) method. Assessments made after a patient had taken postoperative analgesia were analysed as if the analgesia had not been taken. In the second method, assessments made after a patient had taken postoperative analgesia were assumed to be missing, and all missing assessments were substituted (using the LOCF

Table 1. Demographic details of study patients

	Ketorolac	Placebo	Overall
No. of patients	26	26	52
Male	7 (27%)	6 (23%)	13 (25%)
Female	19 (73%)	20 (77%)	39 (75%)
Mean age	26.8	26.8	26.8
Mean weight	68.2	63.0	65.6

Table 2. The areas under the VAS curves assessing 3 h of postoperative pain

	Ketorolac	*Placebo*
No. of patients	26	26
Using substitution for missing data only		
Median	1.1	6.1
Range	0.0–37.0	0.3–27.1
Treatment comparison*	$P = 0.005$	
Using substitution for missing data and for data recorded after first use of escape analgesia:		
Median	1.1	9.4
Range	0.0–32.3	0.1–59.0
Treatment comparison*	$P = 0.004$	

* By Wilcoxon rank sum test.

method). Using the substitution for missing data method, the median standardized AUC was 1.1 in the ketorolac group compared with 6.1 in the placebo group. The smaller values indicate less overall pain. The difference between treatment groups tested using the Wilcoxon rank sum test achieved statistical significance ($P = 0.005$). Using substitution for missing data and data recorded after the first use of postoperative analgesia, the median standardized AUCs were 1.1 and 9.4 in the ketorolac and placebo groups, respectively. Again the treatment difference was statistically significant ($P = 0.004$).

Postoperative VRS scores. Maximum VRS pain assessments are summarized in Table 3. Using substitution for missing data only, 46% of patients in the ketorolac group reported some pain and 15% reported moderate or severe pain. In the placebo group 85% of patients reported some pain and 50% reported moderate or severe pain. The treatment difference was statistically significant ($P = 0.004$). Using substitution for missing data and data recorded after the first use of postoperative analgesia, 46% of patients in the ketorolac group reported some pain and 12% reported moderate or severe pain. In the placebo group 77% of patients reported some pain and 46% reported moderate or severe pain. The treatment difference achieved statistical significance ($P = 0.003$).

Time to first postoperative analgesia. The time to first postoperative analgesia is summarized in Table 4 and Figure 1. All patients took ibuprofen only. Twenty-five per cent of ketorolac patients took postoperative analgesia in the 3 h study period, compared with 72% of patients in the placebo group. None of the patients in the ketorolac group had taken postoperative analgesia up to 1 h 45 min from baseline, compared with 10 (40%) in the placebo group. The estimated times at which 50% of patients had taken analgesia using the Kaplan–Meier method were 235 min and 125 min in the ketorolac and patient groups, respectively. The difference between treatments using the generalized Wilcoxon test was statistically significant ($P < 0.001$).

Time to hospital discharge. The mean time to hospital discharge was 185 min and 184.5 min for the ketorolac and placebo groups, respectively.

Table 3. Maximum VRS for 3 h of postoperative pain

	Ketorolac	*Placebo*
No. of patients	26	26
Using substitution for missing data only		
None	14 (54%)	4 (15%)
Mild	8 (31%)	9 (35%)
Moderate	2 (8%)	11 (42%)
Severe	2 (8%)	2 (8%)
Treatment comparison*	$P = 0.004$	
Using substitution for missing data and for data recorded after first use of escape analgesia:		
None	14 (54%)	6 (23%)
Mild	9 (35%)	8 (31%)
Moderate	3 (12%)	11 (42%)
Severe	0	1 (4%)
Treatment comparison*	$P = 0.003$	

* By Wilcoxon rank sum test.

Table 4. Time to first postoperative analgesia

	Ketorolac	*Placebo*
No. of patients	26	26
No. who required postoperative analgesia within 3 h	6 (24%)	18 (69%)
Estimated time* (min) by which:		
25% of patients required analgesia	205	77
50% of patients required analgesia	235	125
75% of patients required analgesia	300	182
Treatment comparison†	$P < 0.001$	

* By Kaplan–Meier
† By generalized Wilcoxon

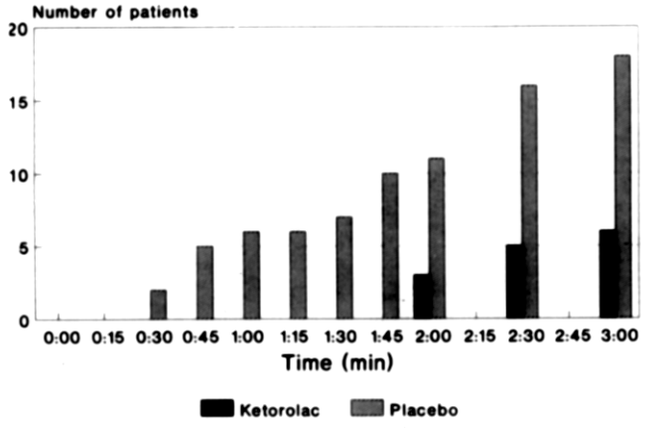

Figure 1. Number of patients who had taken analgesia by each postoperative pain assessment

Global assessment of intraoperative analgesia. In both treatment groups the investigators assessment was 'satisfactory' or 'excellent' for almost all patients, and approximately 90% of the patients' assessments at discharge and follow-up were rated 'excellent'. There was no statistically significant difference between groups.

Global assessment of intraoperative sedation. The assessment by the investigator at discharge, and assessments by the patient at both discharge and follow-up were 'excellent' for almost all patients, and showed no statistically significant difference between treatment groups.

Global assessment of postoperative analgesia. At hospital discharge the investigator rated postoperative analgesia as excellent in 75% of the ketorolac group compared with 46% of the placebo group. The treatment difference was statistically significant ($P = 0.041$). At hospital discharge 80% of patients in the ketorolac group rated postoperative analgesia as excellent compared with 50% in the placebo group. However, at follow-up the treatment difference no longer achieved statistical significance, with 72% of ketorolac patients and 54% of placebo patients giving a rating of excellent.

Safety

Adverse events. A total of 12 ketorolac patients reported 14 adverse events and 13 placebo patients reported a total of 14 adverse events. The most frequently reported adverse event was injection site pain at the time of injection, recorded 11 times in the ketorolac group and 12 times in the placebo group. This pain was not severe enough to prevent completion of injection in any patient, although the slow bolus may have been slowed still further.

There were no clinically significant changes in pulse rate, blood pressure or arterial oxygen saturation in any patient during the study. Syncope was reported by two patients in the placebo group and there was one report of constipation, at follow-up, in the ketorolac group.

Discussion

The two treatment groups were very similar. Approximately 75% of all patients were female, with no co-existing diseases. Surgery details for the two treatment groups were also similar. All patients received an identical dose of prilocaine and the mean dose of midazolam in the two treatment groups was similar (ketorolac 3.5 ml, placebo 3.4 ml). The duration of surgery was slightly longer in the ketorolac group compared to the placebo group (mean 11.5 min compared to 9.9 min) but there was no excessive bleeding in either group or any statistically significant difference in the patients' intraoperative pain.

Efficacy

There were clear treatment differences between the groups regarding postoperative pain assessed by VAS or VRS. The VAS assessments yielded median AUC values of 1.1 in the ketorolac group compared to 9.9 in the placebo group, and this difference was statistically significant ($P = 0.004$). The VRS assessment of postoperative pain also favoured ketorolac. Fewer ketorolac patients than placebo patients reported any pain (46% compared to 85%), and for only 15% of ketorolac patients was the maximum pain severity reported mod-

erate or severe, compared to 50% on placebo. Again this treatment difference was statistically significant ($P = 0.004$).

Twenty-five per cent of ketorolac patients took postoperative analgesia during the study, compared to 72% of placebo patients. Also, the estimated times by which each group had taken a first dose were statistically significantly longer in the ketorolac group ($P = 0.001$).

The global assessments of postoperative analgesia also favoured ketorolac, particularly at discharge, when both the patients' and the investigators' assessments were statistically significantly better for ketorolac than for placebo ($P = 0.027$ and $P = 0.041$, respectively).

Safety

Adverse events reported during the study were similar in the two treatment groups. Injection site pain was the only prominent adverse event. As it was equally common in both treatment groups, it is possible that the injection site pain was caused by some constituent of the vehicle. This adverse event has not been reported in other studies and may have come to light because the small veins on the dorsum of the hand were used for injection in this study.

Conclusion

Administration of a single, preoperative, 30 mg dose of iv ketorolac significantly reduces the postoperative pain experienced by patients undergoing removal of impacted third molar teeth under local anaesthesia and intravenous sedation, as assessed by VAS and VRS. The number of patients requiring postoperative analgesia is reduced and the estimated time when it is first taken is statistically significantly longer in patients who received 30 mg iv ketorolac preoperatively. Intravenous ketorolac was very well tolerated by the study population.

In common with other NSAIDs, ketorolac should not be used in patients with a history of peptic ulceration or gastrointestinal bleeding, a history of haemorrhagic diathesis, a history of asthma or a known sensitivity to NSAIDs or aspirin. Furthermore, it should not be used during pregnancy or lactation, or concomitantly with other NSAIDs or anticoagulants[12,13]. Since this study, the recommended starting dose for parenteral administration has been reduced to 10 mg with subsequent doses of 10–30 mg every 4–6 hr as required[14]. It is suggested that ketorolac is a useful addition to the analgesic armamentarium and appropriately prescribed, provides good pain relief following day case oral surgery.

Acknowledgement

The funding from Syntex Pharmaceuticals Ltd, St Ives Road, Maidenhead, SL6 1RD, UK, that made this study possible is gratefully acknowledged.

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