EFFECTS OF KETOROLAC TROMETAMOL ON RENAL FUNCTION


SUMMARY

We have compared the renal effects of ketorolac trometamol 10 mg administered 4-hourly by intermittent i.m. injection or by continuous i.m. infusion with placebo in a double-blind study in 67 patients who had undergone upper abdominal surgery. Ketorolac was supplemented during the 48-h postoperative study period with bolus doses of morphine delivered by a patient controlled analgesia system. The only significant effect of ketorolac on renal function compared with patients who received placebo was reduced excretion of potassium. The overall changes caused by surgery alone were of much greater magnitude. Bleeding time was increased with ketorolac, but there were no adverse events related to this.

KEY WORDS


Ketorolac trometamol is a new non-opioid analgesic of the non-steroidal anti-inflammatory (NSAID) class. It has been shown to provide a valuable morphine sparing effect when used to supplement opioid analgesia after upper abdominal surgery [1, 2] and, in some studies, to have analgesic activity comparable to that of morphine [3, 4]. Its principal advantage is lack of depression of the cardiovascular and respiratory systems [5]. A major pharmacological activity of NSAID is reduction of prostaglandin synthesis by inhibition of the enzyme cyclooxygenase. In well hydrated individuals with normal renal function, prostaglandins play no apparent role in regulation of renal blood flow or fluid and electrolyte excretion. However, under conditions of reduced renal blood flow, local synthesis of vasodilating prostaglandins has an important role in maintaining renal homeostasis. All NSAID may then cause renal insufficiency by arteriolar vasoconstriction, with subsequent impairment of renal function [6].

As surgery and anaesthesia are associated with activation of renal homeostatic mechanisms, the present study was designed to assess the renal effects of ketorolac administered for 48 h after major surgery.

PATIENTS AND METHODS

We studied 67 patients undergoing elective upper abdominal surgery in a double-blind, placebo-controlled study. The study was approved by the Hospital Ethics Committee and all patients were visited before surgery, the nature of the trial explained, and written informed consent obtained. Exclusion criteria included respiratory insufficiency, hepatic or renal impairment and abuse of alcohol or drugs. A standard anaesthetic was administered to all patients and consisted of premedication with temazepam 20–40 mg, induction with thiopentone 3–6 mg kg⁻¹ and maintenance with nitrous oxide, oxygen and enflurane supplemented with alfentanil.

Patients were allocated randomly and in double-blind fashion to one of three groups to receive: continuous i.m. infusion of ketorolac with intermittent injections of placebo (continuous group); intermittent i.m. injections of ketorolac with continuous infusion of placebo (intermittent group); continuous and intermittent administration of placebo (placebo group).

Patients allocated to the continuous ketorolac group received a continuous i.m. infusion of ketorolac. A loading dose was infused at a rate of 12.5 mg h⁻¹ for 30 min to achieve a steady state concentration rapidly and the dose was then reduced to 2.5 mg h⁻¹ for the duration of the study. They also received intermittent i.m. injections of saline every 4 h. The continuous and intermittent doses were administered into the deltoid muscle through one site via a non-return valve.

Patients in the intermittent ketorolac group received intermittent i.m. injections of ketorolac 10 mg every 4 h and an i.m. infusion of saline at rates to match those in the continuous group.

Patients in the placebo group received intermittent injections and continuous infusions of saline as for the other groups.

At the completion of surgery, each patient was connected to the i.m. delivery system and to a patient controlled analgesia (PCA) apparatus [7] set to

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deliver i.v. bolus doses of morphine 0.02 mg kg\(^{-1}\) with a lockout time between doses of 2 min.

Three 24-h collections of urine were made: one on the day before surgery and one on each of the two study days. Blood samples were taken for assessment of renal function at the preoperative visit and at the end of each 24-h urine collection to coincide with the start or end of the appropriate urine collection. The primary variables measured were urine output, creatinine and urea clearance, urine osmolarity, free water clearance and sodium and potassium output. The following formulae were used to calculate the measures of renal function:

\[
\text{Creatinine clearance (ml min}^{-1}\text{)} = \frac{\text{urine creatinine (mmol litre}^{-1}\text{)}}{\text{serum creatinine (mmol litre}^{-1}\text{)}} \times 1000 \times \text{urine volume (ml min}^{-1}\text{)}
\]

\[
\text{Urea clearance (ml min}^{-1}\text{)} = \frac{\text{urine urea (mmol litre}^{-1}\text{)}}{\text{serum urea (mmol litre}^{-1}\text{)}} \times \text{urine volume (ml min}^{-1}\text{)}
\]

\[
\text{Free water clearance (ml min}^{-1}\text{)} = \frac{\text{urine osmolarity} - \text{plasma osmolarity}}{\text{urine volume (ml min}^{-1}\text{)}}
\]

\[
\text{Sodium output (mmol litre}^{-1}\text{)} = \frac{\text{urine sodium (mmol litre}^{-1}\text{)}}{\text{urine volume (ml min}^{-1}\text{)}}
\]

\[
\text{Potassium output (mmol litre}^{-1}\text{)} = \frac{\text{urine potassium (mmol litre}^{-1}\text{)}}{\text{urine volume (ml min}^{-1}\text{)}}
\]

Bleeding times were measured using a Simplate II device [8] before operation and at 24 h after the start of drug administration. Patient characteristics were analysed using Student's \(t\) test or chi-square test as appropriate. The measures of renal function were analysed using a repeated measures analysis of variance for the difference from baseline data. The factors included were treatment, between-patient error, study day and treatment by day interaction. In the absence of a statistically significant treatment by day interaction, results for the two study days were averaged in the presentation of the results. All three paired comparisons between treatments were carried out by calculating the ratio of the estimated difference between treatments to its standard error (SED) (based on the between patient error) and referring this to the \(t\) distribution. A one-way analysis of variance was performed for bleeding times using differences from baseline, and paired comparisons were made.

**RESULTS**

Sixty-one patients completed the 48 h of the study, and an additional two patients completed 24 h. An additional four patients were withdrawn before 24 h. Withdrawals occurred because of equipment or cannula failure or because of patient request. There were no withdrawals from the study because of adverse events. Patients who received ketorolac were significantly younger than those who received placebo (\(P < 0.05\)) but there were no differences in sex or weight between the groups (table I).

The mean urine output for the first 24 h after operation was less than the baseline output, whereas the mean output for the second 24 h was greater (table II). This was true for all treatments and the analysis of the change from baseline showed that the difference between days 1 and 2 was significant (\(P < 0.01\)). However, the treatment by day interaction was not significantly different (\(P = 0.92\)), so there was no evidence that the difference between days differed from one treatment group to another. The results for the two days have been pooled and the analysis shows that there was no significant difference between any pair of treatment means.

Creatinine clearances decreased from baseline on day 1, followed by an increase from baseline on day 2 (table III). The difference between days was statistically significant (\(P = 0.02\)) but, again, there was no evidence that this difference varied across treatment groups (\(P = 0.55\)). Paired comparison showed no difference between any pair of treatment means.

Urea clearance also decreased from baseline on day 1, followed by an increase from baseline on day 2 (table IV). The difference between days was statistically significant (\(P < 0.01\)), but there was no evidence of an interaction between treatment and study day (\(P = 0.86\)). There were no significant differences between any pair of treatment means.

Urine osmolarity changed little from baseline to day 1 for the ketorolac groups, whereas the placebo
group had a marked increase (table V). In all three groups, values decreased to about 50% of their baseline values on day 2. The difference between days was significant \( (P < 0.01) \), but the treatment by day interaction did not approach significance \( (P = 0.38) \).

Sodium output decreased from baseline to day 1 followed by an increase on day 2 (table VI). The difference between days was significant \( (P < 0.01) \), but there was no difference between treatments \( (P = 0.41) \).

Potassium output decreased from baseline to day 1 for both ketorolac groups, but increased for placebo (table VII). There was little change from day 1 to day 2. The difference between days did not approach significance \( (P = 0.50) \), but there was a significant difference between placebo and intermittent \( (P = 0.02) \) and continuous ketorolac \( (P = 0.04) \). There was no evidence of a difference between the two ketorolac groups \( (P = 0.58) \).

There were no significant differences between the groups in arterial pressure, heart rate, haematological or biochemical analyses, including plasma potassium.
provide useful analgesia, either alone or as a supplement to an opioid, with minimal depressant effects. The analgesic effects of the ketorolac doses used in this study have been reported previously [2] and demonstrated the expected reduction in prostaglandin production by a significant decrease in postoperative morphine requirements.

All NSAID may affect renal function adversely [9, 10], but this appears to be important mainly in patients who have compromised renal blood flow, which is dependent on renal prostaglandins to maintain adequate glomerular perfusion. In several clinical conditions such as congestive cardiac failure, cirrhosis, hypovolaemia and renal insufficiency, the local production of prostaglandins is essential to maintain renal perfusion. Such patients are therefore at increased risk of renal ischaemia after administration of NSAID.

The main aim of this study was to determine the effect of ketorolac on renal function in the immediate postoperative period. The results of the analysis of renal function indicated that there were changes in renal function in all groups, but no significant differences between any of the groups for any of the measures of renal function except for potassium output, which decreased in patients who received ketorolac. Potassium loss is a well recognized response in the postsurgical period and ketorolac appears to prevent this. This effect would seem to be of little practical significance.

A further objective of the study was to identify if any drug effects were different between the first and second days after operation. For all measures of renal function except potassium output, the analyses showed significant differences between the first and second days. However, the treatment by day interactions were not significant, indicating that the differences between the two days were similar for all treatment groups.

The study incorporated a comparison of intermittent and continuous administration of ketorolac. There were no statistically significant differences between the effects of the two dosing techniques on renal function. However, there was a larger increase in urea and creatinine clearances over the study period in the group who received ketorolac continuously, compared with the intermittent group. This may indicate a tendency to faster improvement in renal function after operation when a small steady state plasma concentration was maintained in comparison with the peaks and troughs of an intermittent regimen.

Ketorolac is known to increase bleeding time [11, 12] because of inhibition of platelet aggregation. The mean increase in bleeding time was 35 s in the intermittent group and 55 s in the continuous group, compared with a decrease of 12 s in the placebo group. The greatest increase observed was 250 s in one patient who received continuous ketorolac, but this was still not greater than the normal range for bleeding time. This is similar to the largest increase reported by Power and colleagues [12] of 214 s in one patient.

In conclusion, the analyses of renal function showed consistently that there was a marked concentration. Bleeding times increased from baseline in patients who received ketorolac compared with placebo, but there was no significant difference between intermittent and continuous methods of administration (table VIII).

The most common side effects were nausea or vomiting and urinary retention, but there were no differences between groups.

**DISCUSSION**

Ketorolac has the principal advantage over opioid analgesics of lack of cardiorespiratory effects following administration [5]. Ketorolac may therefore provide useful analgesia, either alone or as a supplement to an opioid, with minimal depressant effects.
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difference between the two postoperative study days and it appears that changes in renal function caused by surgery and the subsequent recovery period were of more clinical importance than any drug induced effect.

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