Intra-articular injection of ketorolac in the rat knee joint: effect on articular cartilage and synovium

M. G. IRWIN, K. M. C. CHEUNG, J. M. NICHOLLS, N. THOMPSON

Summary

We have investigated the effects of intra-articular (i.a.) administration of ketorolac in the rat knee joint. Thirty Sprague—Dawley rats were given 0.25 ml of a standard preparation of ketorolac trometamol (10 mg ml⁻¹) by injection into the right knee joint and 0.25 ml of 0.9% physiological saline solution by injection into the left knee as a control. Ten rats were killed at 24 h, 10 at 48 h and 10 at 5 days after injection. The joints were prepared and sectioned for histological examination. There was significantly more inflammation in those knees that had received i.a. ketorolac at all times of examination, with the most severe changes occurring 5 days after injection. A further group of 10 rats were given 0.25 ml of 10% w/v ethanol in physiological saline (similar to the vehicle for parenteral ketorolac) injected into the knee joint, with a 0.9% saline control injected in the other knee. These rats were then killed at 5 days (as this was the time interval after which we found the maximum inflammatory response in the earlier phase of our study). The joints were prepared and examined histologically. We feel that the absence of inflammatory changes in these joints make it unlikely that ethanol was responsible for the inflammation produced by ketorolac injection. (Br. J. Anaeth. 1998; 80: 837–839)

Keywords: analgesics non-opioid ketorolac; analgesia intra-articular; rat

Intra-articular injection of local anaesthetic drugs or opioids or both is commonly used to manage pain after arthroscopic knee surgery, although opioids have been inconsistent in their efficacy. Ketorolac, a powerful analgesic agent of the non-steroidal, anti-inflammatory class (NSAID), inhibits the cyclo-oxygenase enzyme system and hence prostaglandin synthesis. It has been shown to be an effective non-opioid analgesic for this type of surgery when given systemically, reducing pain and joint swelling.¹ There are, however, several well documented side effects associated with the use of NSAIDs, particularly at higher dosages. This has prompted the manufacturer of ketorolac, Syntex Pharmaceuticals, in conjunction with the Committee on Safety of Medicines,² to recommend a lower dose regimen for the drug that may not be quite as efficacious.³ It is interesting to speculate that ketorolac may be at least as effective if administered directly to the site of tissue trauma, producing higher local tissue concentrations and less risk of systemic upset.⁴⁵ Although it is approved for i.v., i.m. and oral use, no toxicological data exist regarding i.a. administration. Using the knee joint of rats, we investigated ketorolac’s effects on synovium and articular cartilage after direct injection.

Methods and results

Approval for the study was obtained from the University of Hong Kong Committee on the Use of Live Animals in Teaching and Research. Thirty mature Sprague—Dawley rats each weighing 250–300 g were anaesthetized using 35 mg kg⁻¹ of intraperitoneal phenobarbital. Under aseptic conditions, 0.25 ml of a standard preparation of ketorolac trometamol (10 mg ml⁻¹), which also contains ethanol (10% w/v), sodium chloride and water, was injected into the right knee joint and 0.25 ml of physiological 0.9% saline into the left. The animals were then allowed to awaken and were returned to their cages.

The rats were killed by a lethal injection of phenobarbital, 10 at 24 h, 10 at 48 h and 10 at 5 days after drug administration. The knee joints were detached and examined for gross signs of haematoma. They were labelled (left/right and time of death), then placed in 10% neutral buffered formalin for 2 weeks. The joints were then decalcified in 14% EDTA for another 3 weeks, when they were embedded in paraffin and processed for sectioning. Sectioning was carried out at 5 μm intervals and the resulting slide preparations stained with haematoxylin and eosin. The same pathologist (JN) examined all the slides and was blinded to the injectate used in each joint.

Inflammatory changes in the joints were classified as follows:
1 = No inflammation;
2 = Minimal inflammation (mild congestion and oedema);
3 = Mild inflammation (congestion and oedema, small number of neutrophils);
4 = Moderate inflammation (congestion and oedema, abundant neutrophils);
5 = Severe inflammation (congestion and oedema, high number of neutrophils)

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Table 1  Incidence and severity of knee joint inflammation (5 =
most severe). P value is the probability of between-group
differences being attributable to change

<table>
<thead>
<tr>
<th>Time after injection</th>
<th>Control group Inflammation</th>
<th>Ketorolac group Inflammation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 2 3 4 5</td>
<td>1 2 3 4 5</td>
</tr>
<tr>
<td>24 h (P=0.034)</td>
<td>7 3 0 0 0</td>
<td>2 6 2 0 0</td>
</tr>
<tr>
<td>48 h (P=0.458)</td>
<td>7 3 0 0 0</td>
<td>1 4 3 2 0</td>
</tr>
<tr>
<td>5 days (P=0.0029)</td>
<td>6 0 4 0 0</td>
<td>0 0 1 0 9</td>
</tr>
</tbody>
</table>

4 = Moderate inflammation (neutrophils and macrophages, synoviocyte hyperplasia);
5 = Severe inflammation (neutrophils and macrophages, synoviocyte hyperplasia, fibrin exudation).

The Mann–Whitney U test was used to calculate the probability of the differences between the experimental and control groups at 24 h, 48 h and 5 days being attributable to chance. P < 0.05 was taken as significant.

The incidence of haematoma over the joint capsule was examined histologically as before. All these joints
had received i.a. ketorolac at all times of examination, with the most severe changes occurring 5 days after injection (fig. 1).

In the light of these results, we decided to investigate the possible role of the drug vehicle in producing these inflammatory changes. We studied a further group of 10 rats, and injected 0.25 ml of a solution of 10% w/v of ethanol in physiological saline (similar to the vehicle for parenteral ketorolac) into one knee joint of each animal. An equal volume of plain 0.9% saline solution was injected into the opposite knee as a control. These rats were killed at 5 days after injection (fig. 1).

Discussion

Although the mode of action and chemical type of different NSAIDs varies significantly, ketorolac is the only parenteral preparation that has a product license for i.v. administration. It also appears to cause less pain on injection. This would suggest that it is less irritant to tissue than other parenterally administered NSAIDs, although in vitro studies investigating cartilage metabolism and proteoglycan synthesis have shown that different NSAIDs have different effects, and it has been suggested that ketorolac is not the most suitable agent for i.a. use. Ketorolac is not licensed by the United States Food and Drug Administration for i.a. use and the manufacturer was unable to provide any animal toxicological data regarding such administration. However, there has been interest in i.a. use of ketorolac in humans. In another investigation these workers showed that 60 mg of i.a. ketorolac in 30 ml saline with 30 ml of 0.25% bupivacaine instilled into the knee joint after arthroscopy, and found that visual analogue pain scores were lower in the immediate postoperative period with bupivacaine but did not differ significantly between the groups over the following 5 days. In another study, Reuben and Connelly concluded that 60 mg of i.a. ketorolac improved comfort in the early postoperative period in patients undergoing knee arthroscopy, especially when combined with i.a. bupivacaine, and provided better analgesia compared with i.a. bupivacaine alone. In another investigation these workers showed that i.a. ketorolac produces comparable analgesia to that achieved with i.a. morphine, with no benefit when given in combination.

Although these results are interesting, and suggest a potential new application for NSAIDs, there are concerns about exposing patients to the use of a drug in an area where there is little evidence to suggest that it is safe in the short or long term. It is important to consider the ethical, legal and financial consequences of a patient developing a complication of i.a. ketorolac in this context.

We have shown in this animal study that a relatively high local dose of a standard preparation of ketorolac causes severe synovial inflammation that is not seen in control joints injected with saline. This would appear to be a local effect, because the rats' opposite knee joints were used as the controls. It is interesting also that the maximal inflammatory response was
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seen at 5 days after injection. As most arthroscopic surgery is performed as a day-stay procedure, this is beyond the observation period in the human studies where out-of-hospital data have been collected by questionnaire or telephone follow-up without joint examination or biopsy.

The control solution for injection did not contain ethanol, which is present in 10% weight by volume (w/v) in the parenteral ketorolac preparation used, as we wished to assess the direct effects of the preparation rather than just ketorolac itself. We have been unable to find any scientific literature on the effects of direct application of ethanol to synovial tissue, so we investigated its effects in the second phase of our study. We feel that the lack of changes in joints injected with ethanol makes it unlikely that ethanol is responsible for the inflammation found earlier.

Joint changes in rats may not, of course, be directly comparable to those found in humans. It is not possible to make a direct comparison without investigating humans. However, the Sprague–Dawley rat has often been used as a convenient animal model for toxicology studies. We can only surmise that, if such significant synovitis is produced in rats, it may well occur in other animals. There is a need for caution when contemplating i.a. administration of ketorolac in humans.

A longer study may have shown a natural regression of the degree of inflammation. However, we consider that the degree of inflammation found at 5 days is relevant to the clinical situation, and that our findings are important because they question both the suitability of this route of administration for the currently available parenteral ketorolac preparation, and the ethics of performing such studies on human subjects without appropriate toxicological data.

Although the systemic and in vitro effects of NSAIDs have been extensively studied, we feel that our results indicate that more attention should be paid to the toxicology of i.a. ketorolac administration before its widespread clinical use.

References