Use of ketorolac in the prevention of suxamethonium myalgia

C. G. Leeson-Payne, J. M. V. Nicoll and G. J. Hobbs

Summary
We have evaluated the effect of ketorolac in the prevention of suxamethonium myalgia. Sixty ASA I patients who presented for extraction of wisdom teeth as day cases were allocated randomly to one of three equal groups. Patients received either 0.9% saline (placebo), atracurium 0.05 mg kg\(^{-1}\) i.v. or ketorolac 10 mg i.v., 3 min before induction of anaesthesia. Follow-up postal questionnaires (97% response rate) at 48 h showed no reduction in the incidence of myalgia after ketorolac pretreatment compared with saline. The use of atracurium reduced the incidence of myalgia by 60% \((P < 0.001)\) and the severity of fasciculations \((P < 0.001)\). There was no difference in the severity of fasciculations between the saline and ketorolac groups. Intubating conditions were comparable in the three groups. (Br. J. Anaesth. 1994; 73: 788–790)

Key words

Myalgia after suxamethonium is common [1]. Many different pretreatments have been used in an attempt to reduce the incidence of myalgia, including non-depolarizing neuromuscular blockers, local anaesthetics, chlorpromazine, benzodiazepines and vitamin E derivates [2–8]. The most effective technique in current use is pretreatment with a small dose of a non-depolarizing neuromuscular blocking agent. However, a meta-analysis of 102 studies [1] demonstrated a reduction in the incidence of suxamethonium myalgia of only 30%. The plethora of pretreatments is evidence of our poor understanding of the pathophysiology of this problem. One study suggested that a similar incidence of myalgia occurred in a group of patients who did not receive suxamethonium [9].

The pathogenesis of suxamethonium myalgia has been the subject of extensive discussion [10]. Suxamethonium-induced fasciculations cause muscle damage, releasing creatine kinase and myoglobin, although the severity of fasciculations is not related to the severity of myalgia [5]. Prostaglandin production and release also contribute to the pain. Prevention of prostaglandin synthesis may therefore reduce the incidence of suxamethonium myalgia.

It has been demonstrated [11, 12] that pretreatment with oral aspirin is as effective as pretreatment with a non-depolarizing blocker. Ketorolac, a non-steroidal anti-inflammatory drug (NSAID), would be expected to be at least as effective as aspirin in the prevention of suxamethonium myalgia and, if so, this would further support the role of prostenoid production in the pathogenesis. In addition, ketorolac is available as an i.v. preparation, ideally suited to preoperative use. Therefore, we investigated the effect of ketorolac pretreatment in the prevention of suxamethonium myalgia.

Patients and methods
Approval for the study was obtained from the Hospital Ethics Committee. Written informed consent was obtained from 60 ASA I patients, aged 18–60 yr, scheduled for extraction of two or more wisdom teeth under general anaesthesia in the day-case unit. No patient was receiving any NSAID before surgery or had any contraindications to the use of NSAID or suxamethonium.

Patients were allocated randomly to receive one of three pretreatments i.v., 3 min before induction of anaesthesia. Patients received either 0.9% saline, atracurium 0.05 mg kg\(^{-1}\) or ketorolac 10 mg. All pretreatments were made up to 1 ml with 0.9% saline by one investigator and flushed with 2 ml of 0.9% saline. The same anaesthetist performed anaesthesia in all patients and was blind to the treatment group. All patients received propofol 2–2.5 mg kg\(^{-1}\) injected over 30 s followed by suxamethonium 1.5 mg kg\(^{-1}\). After nasotracheal intubation, anaesthesia was maintained by spontaneous ventilation of enflurane and 60% nitrous oxide in oxygen. Fentanyl 1 μg kg\(^{-1}\) i.v. was given for intraoperative analgesia. Co-proxamol was given for postoperative analgesia as required.

Immediately after induction the anaesthetist administering the anaesthetic assessed and recorded intubating conditions [13] and muscle fasciculations [14] using the grading systems shown in table 1.

Patients were asked to complete a questionnaire 48 h after surgery and to return it by post in the stamped addressed envelope provided. Four questions were used to record the incidence, severity (mild, moderate, severe or worst pain imaginable),
and pain interfering with daily activities. These data placebo to 30% with treatment can be demonstrated for each patient (table 1).

Power analysis showed that a reduction in the expected incidence of myalgia from 70% with saline to 30% with treatment can be demonstrated for each patient (table 1).

A chi-square test was used to analyse the data. Statistical significance was assumed if $P < 0.05$.

Results

The three treatment groups were comparable in age, weight and sex distribution (table 2). Fifty-eight patients returned their questionnaire (97% response rate). Atracurium was associated with a reduced incidence of myalgia (22%) compared with ketorolac (85%) and saline (85%) ($P < 0.001$) (table 3).

The severity of myalgia after ketorolac was comparable with placebo pretreatment. Intubating conditions in all patients were comparable (table 4). Compared with placebo, atracurium pretreatment reduced the incidence and severity of fasciculations ($P < 0.001$). Ketorolac had no effect in attenuating the fasciculations. The severity of the fasciculations did not correlate with the myalgia or pain score (table 4).

Discussion

We have shown that ketorolac 10 mg i.v., 3 min before induction of anaesthesia did not prevent suxamethonium myalgia. In agreement with other studies, atracurium reduced the incidence of suxamethonium myalgia and the severity of muscle fasciculations. In addition, this study confirmed the absence of a correlation between the severity of fasciculations and the incidence or severity of myalgia. The few patients who experienced myalgia after atracurium pretreatment had severe pain, despite the absence of fasciculations.

It has been postulated that an increase in myoplasmic calcium concentration is important in the initiation of muscle damage [16-18]. As calcium influx occurs with the use of suxamethonium [11], this may be important in the pathogenesis of suxamethonium myalgia. Calcium binds to intracellular calmodulin causing activation of phospholipase $A_2$. This produces membrane phospholipid degeneration releasing lysophospholipids and free fatty acids, including arachidonic acid, the precursor of prostaglandin synthesis. Prostaglandins produce further tissue damage de novo, resulting in more pain and tissue damage. The use of NSAID may interrupt this prostaglandin-mediated destructive cycle and provide a rationale for their use in preventing suxamethonium myalgia [17, 19, 20].

Oral aspirin 1 h before anaesthesia [11, 12] and i.v. lysine acetylsalicylate 3 min before anaesthesia [13] decreased the incidence of suxamethonium myalgia. In another study, i.m. diclofenac 20 min before suxamethonium decreased the incidence of suxamethonium myalgia [21]. Ketorolac acts in a similar way to aspirin but is 350 times more potent. In common with all NSAID it inhibits prostaglandin biosynthesis by action on the cyclo-oxygenase pathway of arachidonic acid metabolism. It was reasonable to assume that ketorolac would have the same effect as aspirin if prostaglandin inhibition is im-

---

**Table 1** Grading systems for assessment of muscle fasciculations, intubating conditions and myalgia

<table>
<thead>
<tr>
<th>Muscle fasciculations [13]</th>
<th>0 = Absent</th>
<th>1 = Slight eyelid and facial fluttering</th>
<th>2 = Large muscle twitching</th>
<th>3 = Major limb movement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intubating conditions [14]</td>
<td>Poor—Difficult passage or/with coughing for more than 10 s</td>
<td>Good—Easy passage with slight cough</td>
<td>Excellent passage without coughing</td>
<td></td>
</tr>
<tr>
<td>Myalgia score [15]</td>
<td>0 = No pain</td>
<td>1 = Pain at one site without functional disability</td>
<td>2 = Pain involving more than one site without functional disability</td>
<td>3 = Pain involving more than one site with functional disability</td>
</tr>
</tbody>
</table>

**Table 2** Patient characteristics (mean (SD or range) or number)

<table>
<thead>
<tr>
<th>Group</th>
<th>Sex (M/F)</th>
<th>Age (yr)</th>
<th>Weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline</td>
<td>12/8</td>
<td>26 (18-55)</td>
<td>69 (13)</td>
</tr>
<tr>
<td>Atracurium</td>
<td>8/12</td>
<td>25 (18-39)</td>
<td>66 (10)</td>
</tr>
<tr>
<td>Ketorolac</td>
<td>8/12</td>
<td>26 (19-41)</td>
<td>65 (10)</td>
</tr>
<tr>
<td>Total</td>
<td>28/32</td>
<td>26 (18-55)</td>
<td>67 (11)</td>
</tr>
</tbody>
</table>

**Table 3** Incidence of myalgia in the three groups. ***$P < 0.001$*** compared with saline and ketoroloc groups

<table>
<thead>
<tr>
<th>Group</th>
<th>No. (%)</th>
<th>Total No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline</td>
<td>17 (85%)</td>
<td>20</td>
</tr>
<tr>
<td>Ketorolac</td>
<td>17 (85%)</td>
<td>20</td>
</tr>
<tr>
<td>Atracurium</td>
<td>4 (22%)</td>
<td>18</td>
</tr>
</tbody>
</table>

**Table 4** Myalgia scores, intubating conditions and fasciculation scores in the three groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Myalgia score</th>
<th>Intubating conditions</th>
<th>Fasciculations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Saline</td>
<td>3</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Ketorolac</td>
<td>3</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Atracurium</td>
<td>14</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>20</td>
<td>4</td>
<td>8</td>
</tr>
</tbody>
</table>

Please note: $P < 0.001$ compared with saline and ketoroloc groups.
portant in the prevention of suxamethonium myalgia. Because of its relatively short duration of analgesic action, a single dose of ketorolac had a limited analgesic effect in the postoperative period. Its primary putative action is inhibition of prostaglandin synthesis at the time of suxamethonium-induced muscle damage. However, as aspirin and salicylate derivatives bind irreversibly and non-competitively to cyclo-oxygenase, their effect in inhibiting prostaglandin synthesis is more prolonged than that afforded by a competitive inhibitor such as ketorolac. Diclofenac, also a competitive cyclo-oxygenase inhibitor, has a longer half-life than ketorolac and so would be expected to have a longer analgesic effect, and so treat suxamethonium myalgia rather than prevent it occurring by a pre-emptive action.

Creatine kinase release has been used as a quantitative measure of tissue damage. Although aspirin has been shown to reduce the incidence of suxamethonium myalgia, it does not prevent release of creatine kinase [5, 12]. Ketorolac 10 mg i.v. provides a conveniently administered alternative to other currently available NSAID. The use of an i.v. preparation is associated commonly with a faster onset of action than that provided by almost any other route. However, the concentration of ketorolac in skeletal muscle may lag behind serum concentrations by several minutes, as a result of its high protein binding (99%) and low volume of distribution (0.17 litre kg⁻¹) [22]. This implies that inhibition of cyclo-oxygenase at the time of suxamethonium-induced muscle damage is delayed also. The use of the i.v. route may therefore confer little advantage. Premedication up to 1 h before surgery by any route in day-case surgery is avoided also. The use of the i.v. route may therefore confer little advantage. Premedication up to 1 h before surgery by any route in day-case surgery is undesirable and commonly impractical. The avoidance of the need for early premedication with an NSAID in the prevention of suxamethonium myalgia was the primary reason for the investigation of ketorolac in this study.

Myalgia and tissue damage appear to be separate components of a complex picture of suxamethonium-induced tissue damage. The production of prostaglandins features in both pathways: in the pathogenesis of tissue damage and as humoral neurotransmitters in afferent pain pathways. We have demonstrated that the pre-emptive use of i.v. ketorolac 3 min before anaesthesia did not prevent suxamethonium myalgia. However, other NSAID which act as non-competitive cyclo-oxygenase inhibitors (aspirin) and long-acting competitive inhibitors (diclofenac) may have a place in the treatment of suxamethonium myalgia.

References