Use of ketorolac in the prevention of suxamethonium myalgia

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

<table>
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<tr>
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<tr>
<td>0 = Absent</td>
<td>Poor—Difficult passage or/with coughing for more than 10 s</td>
<td>0 = No pain</td>
</tr>
<tr>
<td>1 = Slight eyelid and facial fluttering</td>
<td>Good—Easy passage with slight cough</td>
<td>1 = Pain at one site without functional disability</td>
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<tr>
<td>2 = Large muscle twitching</td>
<td>Excellent passage without coughing</td>
<td>2 = Pain involving more than one site without functional disability</td>
</tr>
<tr>
<td>3 = Major limb movement</td>
<td></td>
<td>3 = Pain involving more than one site with functional disability</td>
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site of any pain unrelated to the operation site (neck/shoulders, arms, chest, abdomen, back or legs) and pain interfering with daily activities. These data were used to calculate a combined myalgia score [15] for each patient (table 1).

A chi-square test was used to analyse the data. Statistical significance was assumed if \( P < 0.05 \). Power analysis showed that a reduction in the expected incidence of myalgia from 70% with placebo to 30% with treatment can be demonstrated for each patient (table 1).

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-
important 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 prosta-
glandin 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 de-
layed 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 avoid-
ance of the need for early premedication with an
NSAID in the prevention of suxamethonium my-
algia 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 prosta-
glandins features in both pathways: in the patho-
genesis of tissue damage and as humoral neuro-
transmitters 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 in-
hibitors (aspirin) and long-acting competitive inhib-
itors (diclofenac) may have a place in the treat-
ment of suxamethonium myalgia.

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