PERIOPERATIVE USE OF METHOTREXATE—A SURVEY OF CLINICAL PRACTICE IN THE UK

A. STEUER and A. C. KEAT
Department of Rheumatology, Northwick Park and St Mark's Hospital, Watford Road, Harrow HA1 3UJ

SUMMARY
We have surveyed the use of methotrexate in the perioperative period in patients with rheumatoid arthritis (RA) undergoing surgery. A total of 200 consultant rheumatologists and 200 consultant orthopaedic surgeons in the UK were sent a postal questionnaire. Thirty-five per cent of rheumatologists and 46% of orthopaedic surgeons were concerned that the drug may increase the risk of post-operative complications, although significantly less ‘always’ stopped the drug around the time of surgery. There was great variation in the timing of stopping the drug with most stopping treatment within 2 weeks before surgery and restarting within 2 weeks after surgery. The majority of clinicians surveyed (70%) felt that national guidelines for the perioperative use of methotrexate would be helpful.

KEY WORDS: Rheumatoid arthritis, Methotrexate, Post-operative complications.

METHOTREXATE (MTX) is a folate antagonist that is widely used as a second-line agent in patients with rheumatoid arthritis (RA). It is a potent cellular antimetabolite with effects on several intracellular folate-dependent systems involved in the synthesis of purines, pyrimidines and proteins. The mechanism of action of MTX in RA is incompletely understood; however, an array of effects on immune cells have been documented (reviewed in [1] and [2]). Infectious complications have been reported during the course of treatment, although the majority were not serious [3, 4]. Rarely, severe life-threatening infection may occur [3, 5–7].

Patients with RA are also at increased risk of infection during and after major surgery, in particular joint replacement. There is, therefore, concern that the combination of MTX treatment and major surgery may magnify the infection risk. In addition, there is some evidence that MTX may delay wound healing [8]. Whether either of these concerns is true is unknown. Several small studies have been published [9–14], but there have been no large controlled trials of post-operative complications in this group of patients and no consensus has emerged.

The aim of the current study was to assess the attitude of clinicians to the use of MTX in patients with RA in the perioperative period.

METHODS
A postal questionnaire was sent to 200 randomly selected consultant rheumatologists and 200 consultant orthopaedic surgeons in the UK. The questionnaire dealt specifically with patients with RA undergoing major elective surgery (e.g. joint replacement).

RESULTS
A total of 148/200 (74%) consultant rheumatologists (R) and 104/200 (52%) consultant orthopaedic surgeons (O) responded to the questionnaire.

We asked clinicians for the typical weekly maintenance dose of MTX which they use. Thirty-seven per cent of rheumatologists used a dose of 2.5–7.5 mg weekly, 52% used 10–15 mg. Although not provided as a dose range on the questionnaire, 8% felt 7.5–10 mg to be the most typical maintenance dose. Only 18% of orthopaedic surgeons were familiar with the typical doses in their patients. An estimate of the number of patients seen with RA undergoing major joint replacement per month was requested. Seventy per cent of both rheumatologists and orthopaedic surgeons felt that 1–5 patients/month was typical; 23% of rheumatologists put this figure at 6–10 patients/month. Surprisingly, only 40% of rheumatologists in our survey actually participated actively in the perioperative care. Although a high proportion of clinicians were concerned that MTX may increase post-operative complications (R 35%, O 46%), significantly less ‘always’ advised stopping the drug both pre-operatively (R 20%, O 17%) and post-operatively (R 14%, O 12%). Many advocated ‘sometimes’ stopping the drug perioperatively (pre-operatively: R 26%, O 9%; post-operatively: R 22%, O 6%).

For the rheumatologists who ‘sometimes’ stopped the drug, the decision was based on various factors, including blood count (9%), drug dose (4%), previous post-operative complications (6%) and other factors (7%).

The timing of stopping treatment pre-operatively and restarting after surgery showed great variability, as listed in Table I (which includes those who ‘always’ and who ‘sometimes’ stop the drug).

Some of the clinicians surveyed suggested stopping MTX for any general anaesthetic (R 18%, O 14%). Furthermore, a small percentage advocated cessation of treatment even for a procedure under local anaes-
thetic (R 8%, O 9%). Interestingly, a significant proportion (R 6%, O 9%) felt they would rather delay surgery than operate on a patient who had not stopped MTX. Finally, 70% of rheumatologists and orthopaedic surgeons surveyed felt that national guidelines for the perioperative use of MTX would be helpful.

**DISCUSSION**

The current study highlights the wide variation in clinical practice in the perioperative use of MTX and would appear to reflect the conflicting evidence produced to date [9–14]. Although ~40% of clinicians surveyed were concerned that MTX may predispose to post-operative complications (R 35%, O 46), significantly less ‘always’ stop the drug both pre- and post-operatively, confirming that this issue remains an unresolved concern of many physicians. The manufacturers do not make any specific recommendations as to whether MTX should be discontinued prior to surgery, although the general feeling is that cessation of treatment is unnecessary (Lederle Laboratories, personal communication).

Many rheumatologists surveyed offered practical reasons for their management. Some stopped the drug simply to avoid conflict with their orthopaedic colleagues and to maintain consistent practice for their patients. Others avoided stopping the drug in view of the concern that it may not be re-commenced post-operatively.

An analysis of the timing of stopping the drug perioperatively demonstrated a similarly wide variation in clinical practice. The majority who stopped the drug did so within 2 weeks before surgery and restarted within 2 weeks after surgery. This rationale was presumably to avoid a perioperative flare of RA. However, the limited literature to date has failed to show benefit in stopping the treatment 7 days before surgery [12], although there may be benefit in stopping MTX 4 weeks prior to elective orthopaedic surgery [10]. Nevertheless, very few in our survey felt this to be appropriate practice.

In spite of the variable perioperative use of this drug, the majority of rheumatologists and orthopaedic surgeons felt that national guidelines would be helpful in patients undergoing joint surgery on treatment with MTX if such guidelines were truly evidence based. For this to occur, a large multicentre study would be required, a feat which should not be beyond us given the large and increasing number of patients with RA treated with MTX.

**REFERENCES**


**TABLE I**

Timing of stopping MTX pre-operatively and post-operatively

<table>
<thead>
<tr>
<th></th>
<th>1 week</th>
<th>2 weeks</th>
<th>3 weeks</th>
<th>4 weeks or more</th>
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<td><strong>Pre-operatively</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rheumatologists</td>
<td>20%</td>
<td>15%</td>
<td>6%</td>
<td>&lt;1%</td>
</tr>
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<td>Orthopaedic surgeons</td>
<td>6%</td>
<td>9%</td>
<td>2%</td>
<td>6%</td>
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<tr>
<td><strong>Post-operatively</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rheumatologists</td>
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<td>17%</td>
<td>8%</td>
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<tr>
<td>Orthopaedic surgeons</td>
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