Ondansetron Prevents Refractory and Severe Methotrexate-induced Nausea in Rheumatoid Arthritis

Methotrexate (MTX) is one of the most commonly used disease-modifying anti-rheumatic drugs (DMARDs) in rheumatoid arthritis (RA) [1–3]. Nausea is one of the most frequent side-effects, observed in up to 40% of the patients treated with this drug, leading to discontinuation of MTX in 6.8% of the cases [1–3]. Ondansetron is an anti-emetic drug widely used in chemotherapy for patients with malignancy [4]. Many studies have shown that ondansetron is usually more effective and with less side-effects than other anti-emetic drugs [4–7]. Our aim was to evaluate the effects of ondansetron in preventing refractory and severe nausea induced by MTX in RA.

Patients with RA diagnosed according to the ACR criteria who were receiving MTX on single therapy were studied [8]. All patients were also receiving leucovorin (folinic acid) as previously reported [9]. Ondansetron was prescribed if they fulfilled the following inclusion criteria: (a) good response to MTX (reduction in the number of tender and swollen joints); (b) severe nausea by MTX according to a graded scale (none, 0; mild, 1; moderate, 2; severe, 3); (c) refractory nausea for at least 4 weeks despite taking metoclopramide (10 mg/8 h), and switching from oral to i.m. MTX. MTX was given at the minimal dose (7.5–15 mg/week orally in a single dose) to control RA activity. To minimize a possible effect related to MTX, the dosage was maintained unchanged for at least 4 weeks before the onset of ondansetron and during the 24 weeks of follow-up. Leucovorin was given for at least 8 weeks before starting with ondansetron therapy at a standardized dosage: 2.5 mg 24 h after taking MTX [9]. Ondansetron (8 mg orally) was administered weekly 1 h before and 11 h after MTX. All patients were evaluated by the same physician.

Since nausea is a subjective manifestation, its measurement is difficult [10]. We evaluated the intensity and duration of nausea (Table I). During ondansetron therapy, its efficacy and possible side-effects were assessed weekly during the first month of therapy, and then monthly. Possible side-effects related to ondansetron were evaluated according to a specifically designed protocol that included the most important adverse effects previously attributed to ondansetron: headache, constipation, extrapyramidal reactions, flushing and anxiety. Duration of nausea and possible side-effects
TABLE I
Outcome of treatment with ondansetron at baseline (week 0), 1, 4, 8, 16 and 24 weeks in nine patients with rheumatoid arthritis who presented severe and refractory nausea by methotrexate

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Before ondansetron</th>
<th>After ondansetron</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Week 0 (baseline)</td>
<td>Week 1</td>
</tr>
<tr>
<td></td>
<td>Nausea intensity*</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>duration† (h)</td>
<td>2</td>
</tr>
</tbody>
</table>

* Nausea intensity: none, 0; mild, 1; moderate, 2; severe, 3.
† The duration was considered as the number of hours of nausea after MTX was taken.

related to ondansetron were written in a diary daily by the patients. Activity due to RA was examined at baseline and at each visit after ondansetron therapy. Full blood count, ESR, blood chemistry profile and urinalysis were performed monthly. A comparative study of the intensity and duration of nausea at baseline (considered as the symptoms observed a week before onset of ondansetron therapy) with observations at 1, 4, 8, 16 and 24 weeks was performed. A non-parametric analysis of the variance for related samples (Friedman’s test) was applied. Statistical significance was defined at \( P < 0.05 \). There was no financial support from or any relationship with the producer of 16 mg of oral ondansetron. Regarding this, a considerably cheaper alternative to MTX and ondansetron may be to swap the patient over to an alternative DMARD. In conclusion, in RA, ondansetron seems to be useful and safe in preventing refractory and severe nausea induced by MTX. A larger controlled and blinded study is needed to support these promising results.

R. Blanco, M. A. González-Gay, C. García-Porrúa, D. Ibañez, M. J. García-Pais, A. Sánchez-Andrade, M. Vázquez-Caruncho*
Divisions of Rheumatology and *Radiology, Hospital Xeral-Calde, 27004 Lugo, Spain
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Correspondence to: M. A. González-Gay.

Three Infected Injections from the Same Organism

Sir.—Rheumatologists perform injections daily in the normal routine of treatment. These injections carry a tiny risk of infection, quoted as 0.06% for arthrocentesis [1]. This risk can presumably be minimized by reasonable sterile precautions, but practice in this respect varies widely [2]. I wish to report three cases of infection from the same phage type *Staphylococcus* which was present in the operator’s nostrils.

Case 1 was a woman aged 34 yr with a prolapsed lumbar disc with sciatica. She was treated with three sacral epidural injections of 40–60 mg of triaminolone acetonide in 20 ml of 0.25% lignocaine, with 2 months and then 3 weeks between injections. Three weeks after the third injection, she was admitted to hospital with fever and a considerable increase in pain in the back and left leg. ESR was 78 mm, WBC 15.4 × 10⁹/L with 72% neutrophils. Liver function tests were abnormal. A small amount of thick pus was withdrawn by needle puncture of a tender swelling at the left low back. This yielded a heavy growth of *Staphylococcus aureus* sensitive to most antibiotics. Appropriate antibiotics were given and an MRI scan showed a paravertebral muscle abscess with the suspicion of infection within the lumbar epidural space.

At operation by Mr Robert Bradford, neurosurgeon, a large left paravertebral muscle abscess was drained, but fortunately the epidural space was free from infection. The patient made an uneventful recovery.

It seems likely that the second injection caused the infection, after which some deterioration occurred.

Case 2 was a 63-yr-old woman with an ulnar compression neuropathy at the elbow who was given an injection of 25 mg of hydrocortisone acetate to the ulnar groove. Within 4 days, she developed swelling and pain above the injected area, fever, and increased ulnar nerve dysfunction. A diffuse tender swelling proximal to the ulnar groove in the muscles above the elbow was explored with a needle, but no pus was found. ESR and WBC were normal. A week later, ESR was 84 and WBC 12.3 with 84% neutrophils. Flucloxacillin and fucidin were started, and a little blood clot aspirated from the swelling grew *S. aureus* sensitive to those antibiotics. The patient made an uneventful recovery.

Case 3 was a 55-yr-old man with supraspinatus tendinitis who was given an injection of 25 mg of hydrocortisone with 1 ml of 1% lignocaine to the subacromial bursa. A week later, he complained of increased pain in the shoulder, sweating and headache. ESR was 34 mm, WBC normal. A week later, there was still pain and ESR was 29 mm with WBC 12.4 × 10⁹/L with 67% neutrophils. Nothing could be aspirated from the subacromial bursa, but the needle was sent for culture. Flucloxacillin and fucidin were started. Culture from the tip of the needle yielded *S. aureus* sensitive to those antibiotics. The injection

A week later, nasal swabs were taken from the operator (MFG) and from case number 2. MFG yielded *S. aureus* sensitive to erythromycin, flucloxacillin and penicillin. The swab from case 2 was negative. Phage typing was performed on staphylococci grown from all three infections and from the nasal swab of MFG. These were all identical. MFG then undertook a week’s course of standard treatment for staphylococcal carriers. Further nasal swabs taken then and subsequently were negative.

These infections were all undertaken using the moderately rigorous, but not totally aseptic, technique which the author had used for many years. This involved careful hand washing, the use of sterile towels upon which to place prepared syringes, etc., and prior swabbing of the skin with Mediswabs. On microbiological advice, this technique has now been improved by the variable use of disposable sterile gloves, and careful preliminary drying of the injection site. Medical accidents such as infections cannot be eliminated completely, and it is not known whether the incidence of infection is altered by the level of aseptic technique [2]. Skin disinfectants have proven efficacy and are recommended [3], although no difference on microbiological testing of the skin has been shown after using different forms of skin swab [4].

The presence of pathogenic *Staphylococcus* in the nose of an operator performing invasive techniques can have dangerous consequences. Perhaps regular checking of doctors performing such techniques should be performed, but this is not routine practice and it is doubtful whether the yield would make this worthwhile. The three patients reported here were not ill or immunocompromised, but were otherwise healthy people. The risk of introducing infection, and the necessity to consider this diagnosis in the event of untoward reactions to injections, must constantly be borne in mind.

I would like to thank Dr Yasmin Drabu for her...