Methotrexate disposition following concomitant administration of ketoprofen, piroxicam and flurbiprofen in patients with rheumatoid arthritis

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The effects of three non-steroidal anti-inflammatory drugs (NSAIDs) on the pharmacokinetics of methotrexate were studied in 10 patients with rheumatoid arthritis. Ketoprofen (3 mg kg⁻¹ day⁻¹), flurbiprofen (3 mg kg⁻¹ day⁻¹), piroxicam (20 mg day⁻¹) or a non-NSAID control (paracetamol/acetaminophen) were administered to patients for at least 6 days (13 days in the case of piroxicam to establish steady state) in a randomized crossover design prior to receiving a weekly oral dose of methotrexate. In the non-NSAID control portion of the study, MTX oral clearance (CLR) was 11.0 ± 3.9 l h⁻¹, renal clearance (CLR) was 7.9 ± 2.8 l h⁻¹, percent excreted unchanged was 72 ± 19% and fraction unbound (fu) was 0.54 ± 0.11. Values of oral clearance, renal clearance, fraction unbound and percentage excreted unchanged of methotrexate varied no more than 12.2% from non-NSAID control during concomitant administration of ketoprofen, flurbiprofen or piroxicam and were not statistically different from non-NSAID control. In contrast to other NSAIDs such as ibuprofen and salicylates, ketoprofen, flurbiprofen or piroxicam in clinically relevant doses do not appear to affect methotrexate disposition and may be used safely in combination with methotrexate.

Keywords methotrexate non-steroidal anti-inflammatory drugs (NSAIDs) interaction disposition

Introduction

Low-dose methotrexate (MTX) has become increasingly popular as a second-line treatment of patients with rheumatoid arthritis and is frequently administered with other agents, particularly the non-steroidal anti-inflammatory drugs (NSAIDs). Several studies have attempted to determine whether concomitant administration of other NSAIDs alters the disposition of MTX given in low doses to patients with rheumatoid arthritis. Naproxen has been reported to have no effect on either the total [1] or renal clearances of MTX [1–2]. Likewise, Furst et al. [3] reported that neither aspirin nor sulindac significantly affected MTX clearance, although no measurement of renal clearance was made. Others have reported that salicylate decreases the total and renal clearances of MTX and increases its fraction unbound in plasma [2, 4, 5]. In evaluating other NSAIDs, Skeith et al. [6] found no effect of either ibuprofen or flurbiprofen on MTX clearance or half-life. Conversely, Tracy et al. [2] reported a significant impairment of the renal and oral clearances of MTX following coadministration of ibuprofen. The reason for the aforementioned discrepancies with respect to total and oral MTX clearances is unclear but there is agreement with respect to effects on the renal clearance of MTX. These results indicate the need to study the renal clearance of MTX, particularly since active renal secretion is the major route of MTX elimination [7] and is the putative site of potential drug interactions [4, 8]. The studies published to date have revealed no discernible pattern as to which NSAIDs will affect the

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clearance of MTX. However, it seems unlikely that the parent form of the NSAID is the species affecting the renal secretion of MTX since the fraction of the dose of NSAIDs eliminated unchanged by the kidney is very small [9–12]. To explore this issue further, we undertook a four way crossover study comparing the effects of ketoprofen, piroxicam, flurbiprofen and a non-NSAID control (paracetamol/acetaminophen) at steady state on MTX elimination in patients with rheumatoid arthritis. Ketoprofen has a relatively short half-life (1–4 h) and is eliminated primarily by glucuronidation [13]. Flurbiprofen also has a relatively short half-life (3–6 h) but is extensively metabolized to oxidative products which are then glucuronidated [14]. Both ketoprofen and flurbiprofen are chemically related to ibuprofen, which has been reported to alter MTX clearance [2]. Piroxicam has a very long half-life (40 h) relative to the other compounds. It is metabolized by both oxidation and glucuronidation [15].

Methods

Patients and protocol

Ten patients (seven women, three men), aged 34 to 71 (mean 48 years) with rheumatoid arthritis as defined by the American College of Rheumatology criteria [16], were recruited from the Indiana University Rheumatology Outpatient Clinics. They had been taking constant, weekly, oral doses of MTX (range 7.5–17.5 mg) for at least 3 months prior to enrollment in the study, and were not taking any medications known to interfere with the disposition of MTX or the NSAIDs. Six of the patients were taking prednisone (in doses of less than 0.10 mg kg\(^{-1}\) day\(^{-1}\)). None of the patients had a history of intolerance to any of the NSAIDs under study, a history of gastrointestinal bleeding in the past 3 years, or a weekly ethanol intake of greater than 150 g. Serum chemistries were evaluated in all patients prior to entering the study. All procedures were approved by the Indiana University Institutional Review Board and the patients gave written informed consent.

A four-treatment randomized, open-label, crossover study was carried out comparing the effects of ketoprofen [Orudis\textsuperscript{®}, Wyeth, USA] (circa 3 mg kg\(^{-1}\) day\(^{-1}\)) given thrice daily, flurbiprofen [Ansaid\textsuperscript{®}, Upjohn, USA] (circa 3 mg\(^{-1}\) day\(^{-1}\)) given two or three times per day depending on the calculated dose, piroxicam [Feldene\textsuperscript{®}, Pfizer, USA] (20 mg day\(^{-1}\)) or NSAID control [paracetamol/acetaminophen, Tylenol\textsuperscript{®}, McNeil, USA] (two 500 mg tablets as needed) on the disposition of MTX [Rheumatrex\textsuperscript{®}, Lederle, USA]. During the non-NSAID arm of the study patients were allowed to use analgesics (i.e., paracetamol/acetaminophen, propoxyphene, or oxycodone) if needed. Piroxicam was administered for 13 days (to allow attainment of steady state) and in all cases was the last therapy administered. All other treatments were administered randomly on consecutive weeks without interruption for a minimum of 6 days prior to the patient’s usual, weekly MTX dose.

Following overnight fasting, except for clear liquids, studies were conducted the morning on which patients took their usual, weekly, oral dose of MTX. To assure hydration, they were given an initial water load of 10 ml kg\(^{-1}\) orally. One hour prior to receiving their usual MTX dose, patients were given a single, oral dose of flurbiprofen, ketoprofen, piroxicam or non-NSAID. During the flurbiprofen and ketoprofen study arms, additional doses of these drugs were given as scheduled throughout the study day.

Control blood and urine samples were obtained prior to MTX dosing. Following MTX dosing, 7 ml blood samples were obtained at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 h. Urine was collected for 24 h after MTX dosing. Following collection, serum and aliquots of urine were stored at −20° C until assay. Following collection of the 24 h samples, patients were discharged from the hospital and begun on the next therapy.

Analytical methods

Serum and urine concentrations of MTX were measured by fluorescence polarization immunoassay (FPIA) with the Abbott TDx system (Abbott, USA). Control solutions at three concentration ranges (0.06–0.08, 0.36–0.44, and 0.72–0.88 μmol l\(^{-1}\)) were run daily with each assay. The inter- and intra-day coefficients of variation were less than 10% at each of the three control concentrations and the limit of determination of the assay was 0.01 μmol l\(^{-1}\). The manufacturer (Abbott) indicates cross-reactivity with 7-hydroxymethotrexate of less than 1%. Serum protein binding of MTX at 1, 2, 4, and 6 h after dosing was determined by ultrafiltration [2] of serum samples with concentrations ≥ 0.1 μM. Results were averaged within each patient’s study day to give mean fraction unbound values for that treatment.

Data analysis

Values of AUC were estimated using a combination of the linear- and log-trapezoidal methods [17] with extrapolation to infinity after linear regression of the terminal slope of the log plasma drug concentration-time curve.

The oral clearance (CL\(_o\)) of MTX was calculated from Dose/AUC and renal clearance (CL\(_R\)) from urinary recovery at 24 h/AUC.

Statistical analysis was performed using SAS Version 6.03 (SAS Institute, USA). Repeated measures analysis of variance followed by multiple comparison of means (Student-Newman-Keuls test) was used to assess statistical significance at P < 0.05. All data are reported as mean (s.d.).

Results

Ketoprofen, piroxicam and flurbiprofen did not influence the oral or renal clearances of MTX (Figure 1). Furthermore, they did not alter the fraction of MTX unbound in plasma nor the 24 h urinary recovery of MTX (Table 1). Table 2 shows the per-
Although the statistical power of the study was less than 50%, more than one hundred additional patients would be required to increase it to 90%. This, combined with the small magnitude of observed changes, especially when compared with the changes seen with ibuprofen and salicylate coadministration [2], argue against the need for additional studies to be conducted with these particular agents.

Discussion

The lack of effect of the three NSAIDs evaluated in the present study on the renal clearance of MTX contrasts with previous findings with ibuprofen [2] and salicylates [2, 5]. Ibuprofen and flurbiprofen are similar in that both compounds are 2-arylpropionic acids which undergo oxidation and direct glucuronidation and form metabolites which are also glucuronidated [14, 19]. Thus, it is not possible to predict which NSAIDs will interact with low dose MTX \textit{in vivo} on the basis of chemical class or metabolic fate. To date, the interaction of ketoprofen and piroxicam with MTX had not been studied in patients with rheumatoid arthritis despite a retrospective study linking the concurrent administration of ketoprofen and high-dose MTX to fatal toxicity in three of four patients [18]. It seems plausible that a lack of interaction between ketoprofen and low doses of MTX, as used in the present study, may not be directly applicable to administration of high dose MTX. Therefore, continued caution must be exercised when high doses of MTX and ketoprofen (or other NSAIDs) are given together.

To date, a number of NSAIDs, (naproxen, ketoprofen, flurbiprofen, piroxicam and possibly sulindac) have been demonstrated not to affect MTX disposition, unlike ibuprofen and salicylates. Thus, alternatives exist which should allow concomitant dosing of MTX and NSAIDs in patients with rheumatoid arthritis with reasonable confidence that a drug interaction is unlikely. However, since patients studied to date all had normal renal function and, given the significant renal component of MTX elimination, it should be stressed that the safety of such combinations has not been established in the presence of impaired renal function.

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Table 1  Plasma binding and renal excretion of MTX following concomitant NSAID dosing

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Unbound fraction</th>
<th>% excreted unchanged</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0.54 (0.11)</td>
<td>72 (19)</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>0.56 (0.08)</td>
<td>73 (17)</td>
</tr>
<tr>
<td>Flurbiprofen</td>
<td>0.56 (0.06)</td>
<td>63 (15)</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>0.56 (0.07)</td>
<td>71 (15)</td>
</tr>
</tbody>
</table>

Values expressed as mean (s.d.).

centage change (and its 95% confidence interval) of each of the four pharmacokinetic parameters during NSAID treatment when compared with non-NSAID control. Methotrexate was detectable in serum up to 24 h in 20 of the 40 treatment periods and the extrapolated AUC(24,∞) was less than 13% of the total AUC in all but four cases.

Table 2  Percent change in MTX pharmacokinetic parameters with NSAID therapy

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Oral clearance</th>
<th>Renal clearance</th>
<th>% excreted unchanged</th>
<th>Fraction unbound</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketoprofen</td>
<td>-2.4% (-12.1, 8.7)</td>
<td>-2.7% (-19.8, 19.8)</td>
<td>1.7% (-10.9, 19.8)</td>
<td>3.7% (-11.6, 29.4)</td>
</tr>
<tr>
<td>Flurbiprofen</td>
<td>5.9% (-7.4, 27.0)</td>
<td>-8.0% (-20.7, 16.2)</td>
<td>-12.2% (-21.0, 0.0)</td>
<td>3.7% (-12.4, 30.7)</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>-7.0% (-18.0, 13.7)</td>
<td>-10.3% (-30.1, 33.0)</td>
<td>-1.6% (-14.1, 17.6)</td>
<td>3.7% (-9.8, 26.1)</td>
</tr>
</tbody>
</table>

Values are reported as average percent change from non-NSAID control with 95% confidence intervals listed in parentheses. None of the parameters measured during NSAID coadministration was significantly different from non-NSAID control.
References

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