The Effect of Ingestion of Ferrous Sulfate on the Absorption of Oral Methotrexate in Patients with Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** To investigate if ingestion of ferrous sulfate, 300 mg twice daily, will reduce the urinary excretion of unmetabolized methotrexate (MTX) in patients with rheumatoid arthritis (RA) who ingest 2 drugs concurrently, and determine if ferrous sulfate interferes with the absorption of oral MTX.

Methods. In this randomized double-blind placebo controlled crossover study, we compared the urinary excretion of unmetabolized MTX in 10 patients with RA who ingested 7.5 mg MTX as their weekly dose and took either ferrous sulfate 300 mg twice daily or placebo.

Results. Ten patients with RA taking 7.5 mg MTX orally once weekly had an average 24 h urine excretion of MTX (while taking 300 mg ferrous sulfate twice daily for one week) of 8.44 µmoles compared to 7.65 µmoles for patients taking placebo. The difference was not statistically significant ($p = 0.50$).

Conclusion. Our results showed no less absorption of MTX for the placebo group compared to the group that took ferrous sulfate. These results do not support the hypothesis that ferrous sulfate interferes with the absorption of oral MTX. (J Rheumatol 2003;30:1948–50)

Key Indexing Terms:
RHEUMATOID ARTHRITIS METHOTREXATE FERROUS COMPOUNDS ABSORPTION

Methotrexate (MTX), an antimetabolite, is the most widely prescribed disease modifying antirheumatic drug (DMARD) for rheumatoid arthritis (RA) in North America[1]. Nonsteroidal antiinflammatory drugs (NSAID) are often concomitantly prescribed in RA, and the combination of "NSAID gastropathy" and NSAID antiplatelet effects[2], along with MTX's effects on the gastrointestinal mucosa[3], may lead to gastrointestinal blood loss and iron deficiency. Hence patients with RA may often use over-the-counter or are prescribed iron supplements.

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Supported by the Research and Development Fund, Faculty of Medicine, Memorial University of Newfoundland.

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Submitted October 4, 2002; revision accepted January 23, 2003.

Iron administration has been shown to be involved in multiple drug interactions among commonly used prescription drugs[4-8]. Indeed, iron has been found to bind and reduce the absorption of penicillamine, another DMARD in the treatment of RA[9]. The chemical structure of MTX would indicate strong binding to iron[10]. In preliminary experiments, mixing MTX with the ferrous form of iron at pH 6.2 resulted in very rapid formation of a colored complex.

Our objective was to determine if ingestion of ferrous sulfate, 300 mg twice daily, reduced the urinary excretion of unmetabolized MTX in patients with RA who ingested the 2 drugs concurrently. It should be recognized that in addition to renal excretion, up to 10–30% of MTX may be excreted via the biliary route[11].

MATERIALS AND METHODS

This was a randomized double-blind placebo controlled crossover study. Ten patients satisfying American Rheumatism Association (ARA) diagnostic criteria for RA[12] were recruited from the outpatient clinic of St. Clare's Mercy Hospital and were already taking MTX. All patients took 7.5 mg orally per week, regardless of their previous dosage. Patients were excluded for significant illnesses other than RA, intolerance to iron supplementation, alcohol or drug abuse, or noncompliance. Patients taking NSAID discontinued them for 12 h prior to and 24 h after the MTX doses were ingested.

During the first week, patients were given an identical-appearing capsule, either ferrous sulfate 300 mg or placebo, and instructed to take the medication for the next 7 days, 12 h apart, at 8:00 am and 8:00 pm. On the sixth day, the patient would take MTX 7.5 mg orally at 8:00 am. At the

same time, the urine collection for MTX would begin and continue for 24 h. During the second week, those who took placebo would take ferrous sulfate 300 mg and vice versa. Laboratory tests were done at the initial visit and at the end of the study, including complete blood count and differential, erythrocyte sedimentation rate, urea, creatinine, AST, ALT, bilirubin, electrolytes, alkaline phosphatase, and urinalysis.

The patients gave informed consent and the study protocol was approved by the Human Investigations Committee of the Faculty of Medicine, Memorial University of Newfoundland.

Analysis. MTX concentrations in the 24 h urine samples were measured by TDx/TrxFLX Methotrexate II Assay[13] by one author (MK). It was assumed that a reduction in absorption of MTX would be reflected by a similar decrease in renal excretion of unmetabolized MTX.

Statistical analysis. MTX concentrations in urine were compared with the placebo and ferrous sulfate using a paired Student t test. This was the primary endpoint of the study. The study required a sample size of 6 to be statistically significant with $p < 0.05$ with a power of 0.9 (beta = 0.9), assuming a 30% reduction in MTX renal excretion.

RESULTS

Ten patients with ARA defined RA included 6 women and 4 men (Table 1). The average age was 58.4 years. The average 24 h urine excretion of MTX for those patients taking ferrous sulfate 300 mg twice daily for one week was 8.44 µmoles compared to 7.65 µmoles for patients taking placebo (Figures 1 and 2). The difference was not statistically significant ($p = 0.50$). There was a statistically insignificant mean increase in MTX excretion of 0.79 µmol (95% confidence interval of –2.3 to 3.88). Thus, the study can rule out a decrease in 24 h MTX excretion of 2.3 µmol/24 h (30%) with 95% certainty.

Table 1. Characteristics of patients with RA, 6 women and 4 men (average values).

Age, yrs	58.4
Weight, kg	71.8
Height, cm	165.5
Hemoglobin, g/l (normal 130-180)	121
ESR, mm/h (normal 0–20)	33
Creatinine, µmol/l (normal 40–130)	90
AST, U/l (normal 22–34)	26
ALT, U/l (normal 6–34)	19

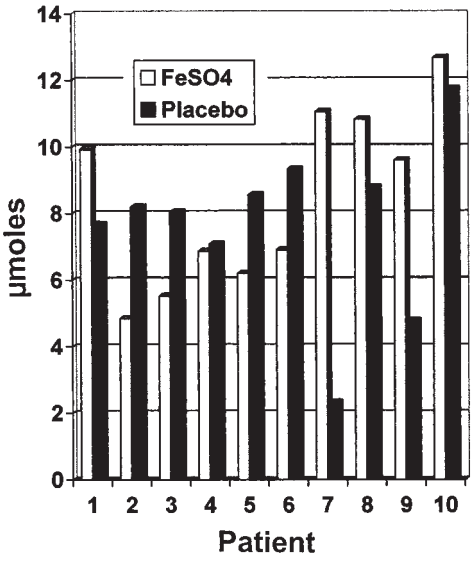

Figure 1. Individual amounts of methotrexate excreted in 10 patients.

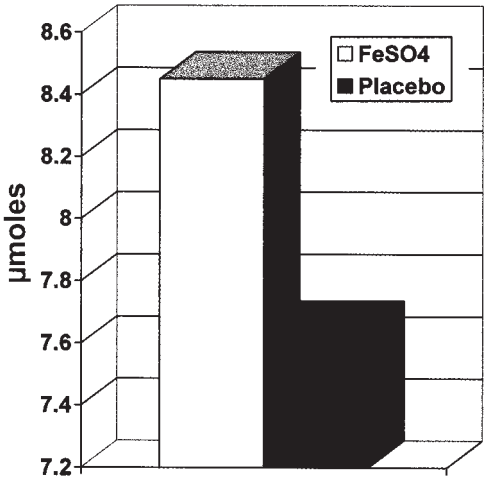

Figure 2. Mean amount of methotrexate excreted.

DISCUSSION

Study results showed similar urinary excretion of MTX when MTX was concurrently ingested with placebo or ferrous sulfate. The study ruled out an effect of iron decreasing MTX excretion by ≥ 30% with 95% certainty. The oral absorption of MTX in the dose range used in this study was close to 80%, although larger doses are less completely absorbed[3,14]. Of the MTX absorbed, 90% of a 10 mg dose in a person weighing 70 kg is excreted, unchanged, in the urine within 48 h and most within 24 h[3]. The 24 h urinary excretion of oral MTX is therefore a reasonable estimate of absorption, recognizing up to 10–30% of MTX may be excreted via the biliary route[11]. Despite theoretical concerns, it is unlikely that iron has a significant interaction in the gastrointestinal tract to reduce absorption of MTX.

To explain the lack of interaction between iron and MTX, studies have suggested that the strength of binding of iron to drug was the most important mechanism[10]. Although the chemical structure of MTX would suggest strong binding to iron[10], active MTX absorption allows binding to the transporter to be greater than that of MTX to iron. Folic acid and MTX have similar functional groups that would bind to iron, but iron does not substantially reduce the absorption of folic acid (pteroylmonoglutamic acid) during coadministration[15]. Higher doses of iron increase the potential for interaction[12]. This study used clinically relevant iron doses, but does not exclude an interaction at higher iron doses. Other factors of importance include the dissolution rate and extent of the iron formulation[13]. Similarly, we cannot exclude an interac-

tion between MTX and more rapidly or extensively dissolving iron preparations. Nevertheless, the lack of discernible effect of iron on MTX excretion in this study makes extensive interaction unlikely with other iron preparations or other clinically relevant iron doses. We do not recommend changes to iron or MTX dosing in patients who require concurrent therapy.

ACKNOWLEDGMENT

We thank Marilyn Power-Shea for secretarial assistance.

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