DOI 10.1002/art.10766

Effect of caffeine consumption on efficacy of methotrexate in rheumatoid arthritis

One of the leading theories explaining the mechanism of action of methotrexate (MTX) in rheumatoid arthritis (RA) is inhibition of 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) transformylase by MTX polyglutamates, which results in AICAR accumulation and inhibition of adenosine deaminase, leading to an increase in adenosine (1,2). Adenosine modulates cellular functions by interacting with specific receptors on the cell membrane, resulting in antiinflammatory effects (1,2).

Methylxanthines are adenosine receptor antagonists (3). One of the methylxanthines, caffeine, is an ingredient in coffee, tea, cola beverages, cocoa, and chocolate. Because of their interaction with adenosine receptors, methylxanthines may interfere with the effects of MTX. Recently, Montesinos et al reported that caffeine reversed the antiinflammatory effects of MTX in a rat adjuvant arthritis model of RA (4). Because caffeine consumption is very common, we investigated whether caffeine intake affects the efficacy of MTX in patients with RA.

Treatment with MTX, 7.5 mg/week (without folate supplementation), was started in 39 patients with recent-onset RA. All patients met the American College of Rheumatology (formerly, the American Rheumatism Association) classification criteria for RA (5), had normal blood levels of folic acid and vitamin B_{12}, and had been receiving a stable dosage of a nonsteroidal antiinflammatory drug (NSAID) for at least 1 month. Changes in treatment during the 3 months of followup were made according to the clinical response of each patient, at the discretion of the treating rheumatologist. No patient was receiving theophylline.

Five parameters of disease activity (tender joint count, swollen joint count, patient's assessment of joint pain using a visual analog scale of 0–10, duration of morning stiffness, and erythrocyte sedimentation rate) were evaluated before initiation of MTX therapy (visit 0) and at monthly intervals for 3 months. At each visit, 68 joints were evaluated for pain in response to either passive motion or pressure applied directly over a joint, and 66 joints were assessed for swelling (either palpable or visible, excluding bony swelling or nodules). The percentage of improvement in each parameter between visits 0 and 3 was calculated.

Each patient was instructed to report a daily diet diary on 3 different dates. The amount of caffeine was calculated based on its content in different products (6). The mean daily intake of caffeine for each patient was then calculated. The treating physician was blinded to data on caffeine intake until completion of the study. For evaluation purposes, patients were divided into 3 tertiles (groups A, B, and C), according to the amount of daily caffeine intake (Table 1). The Declaration of Helsinki principles were followed throughout the study.

Differences in response to MTX were evaluated by one-way analysis of variance, and further by *t*-test with Bon-

Table 1. Baseline characteristics and response to 3 months of methotrexate treatment in RA patients, according to caffeine consumption*

	Group A	Group B	Group C	*P*
Baseline characteristic				
Caffeine intake, mg/day	88.8 ± 21.9	150.9 ± 18.7	258.5 ± 68.6	<0.001
Age, years	51.1 ± 10.5	51.6 ± 13.0	51.8 ± 9.6	0.986
No. of females/males	9/4	9/4	9/4	1.0
No. of patients who smoked	3	4	5	0.386
Duration of RA, months	5.1 ± 4.0	5.8 ± 4.1	5.2 ± 2.8	0.872
No. of RF-positive patients	9	9	10	0.881
No. of patients receiving prednisone†	6	6	5	0.901
No. of patients receiving HCQ‡	4	5	4	0.891
Tender joint count (68 joints)	23.5 ± 3.9	24.0 ± 6.2	24.5 ± 5.5	0.891
Swollen joint count (66 joints)	6.8 ± 2.0	7.7 ± 3.2	7.1 ± 3.3	0.724
Joint pain score (range 0–10 by VAS)	6.5 ± 0.9	7.0 ± 1.2	6.6 ± 1.0	0.440
Morning stiffness, minutes	85.4 ± 32.0	83.1 ± 30.4	79.6 ± 37.9	0.907
Erythrocyte sedimentation rate, mm/hour	64.3 ± 24.7	70.6 ± 15.6	72.8 ± 16.0	0.511
Percentage improvement from baseline				
Tender joint count	64.3 ± 11.1	58.6 ± 11.0	54.7 ± 10.4	0.086
Swollen joint count	62.8 ± 16.9	57.5 ± 14.0	49.5 ± 12.0	0.074
Joint pain	58.8 ± 17.0	46.3 ± 18.3	41.9 ± 11.5	0.028§
Morning stiffness	58.5 ± 16.0	44.2 ± 13.0	41.2 ± 15.7	0.013§
Erythrocyte sedimentation rate	50.5 ± 9.7	44.1 ± 14.2	40.8 ± 15.4	0.183
Change in medication				
Methotrexate dosage at visit 3, mg/week	11.3 ± 2.2	12.5 ± 3.1	12.9 ± 1.7	0.224
No. of patients who discontinued prednisone	4	1	2	0.212
No. of patients who started prednisone	2	4	5	0.381

* Except where indicated otherwise, values are the mean ± SD. Group A patients had low caffeine intake (<120 mg/day), group B patients had medium intake (120–180 mg/day), and group C patients had high intake (>180 mg/day). RA = rheumatoid arthritis; RF = rheumatoid factor; HCQ = hydroxychloroquine; VAS = visual analog scale.
† 10 mg/day or less for ≥1 month.
‡ 200–400 mg/day for ≥5 months.
§ Group A versus group C only.

ferroni correction. Chi-square analysis of contingency tables was used to compare proportions of variables among the groups.

The baseline clinical and demographic data for the patients are presented in Table 1. There were no significant differences in these variables among the 3 groups. The mean percentage of improvement in disease activity parameters was calculated for each group of patients. Patients in group C (high caffeine intake) experienced significantly less improvement in morning stiffness and joint pain compared with patients in group A (low caffeine intake). There were no significant differences between the responses of group B compared with those of the other 2 groups. Patients in group C experienced less improvement in other parameters as well, but the difference between group C and the 2 other groups did not reach statistical significance.

It is rather difficult to accurately assess daily caffeine intake. A patient may use different strengths of coffee or tea at different times, or may not drink the entire content of a cup, resulting in an overestimation of actual intake. Another problem is individual variability in caffeine clearance and the effect of various factors on the main caffeine-metabolizing enzyme, CYP1A2. With respect to response to treatment, a possibility of confounding does exist, but its impact is probably negligible, because all 3 groups were very similar in terms of patient characteristics (Table 1).

This group of RA patients consumed moderate amounts of caffeine. The mean (±SD) intake of 166 ± 82 mg/day equals two and one-half cups of instant coffee or one and one-fourth cups of brewed coffee and is similar to the average amount (186 mg/day) consumed by residents of Vermont (7). However, in other population studies, larger amounts of caffeine intake were reported, with mean values sometimes exceeding 300 mg/day (8–10). It is possible that intake of larger amounts of caffeine may interfere more significantly with the efficacy of MTX. In the study showing that caffeine reversed the effect of MTX therapy in rat adjuvant arthritis (4), rats were given 10 mg/kg/day of caffeine, an amount that is 3–5 times higher than that consumed by our patients. However, metabolism of caffeine differs in rats and humans, with the half-life being shorter in rodents (3).

Thus far, only one report has addressed the potential antagonistic effect of caffeine on MTX in arthritis patients (11). According to this abstract (presented at the 2001 meeting of the British Society for Rheumatology), 91 patients treated with MTX were interviewed. Twenty-six percent of those who discontinued MTX were regular coffee drinkers, compared with only 2% of patients still receiving MTX. Because treatment failure was the reason for MTX discontinuation in 80% of the patients who discontinued, it was suggested that caffeine interfered with MTX efficacy.

The data presented here suggest that caffeine, in daily amounts >180 mg, interferes with the efficacy of MTX in patients with RA, when compared with patients consuming <120 mg/day. A larger-scale study that includes patients who consume larger daily amounts of caffeine and that measures caffeine plasma levels, together with a caffeine elimination phase, is needed to further evaluate the possible interaction of adenosine receptor antagonists with MTX in RA patients.

Gideon Nesher, MD
Michal Mates, MD
Shoshana Zevin, MD
Shaare-Zedek Medical Center
Jerusalem, Israel

1. Cronstein BN, Eberle MA, Gruber HE, Levin RI. Methotrexate inhibits neutrophil function by stimulating adenosine release from connective tissue cells. Proc Natl Acad Sci U S A 1991;88:2441–5.
2. Cutolo M, Sulli A, Pizzorni C, Seriolo B, Straub RV. Anti-inflammatory mechanisms of methotrexate in rheumatoid arthritis. Ann Rheum Dis 2001;60:729–35.
3. Fredholm BB. Adenosine, adenosine receptors and the actions of caffeine. Pharmacol Toxicol 1995;76:93–101.
4. Montesinos MC, Yap JS, Desai A, Posadas I, McCrary CT, Cronstein BN. Reversal of the antiinflammatory effects of methotrexate by the nonselective adenosine receptor antagonists theophylline and caffeine: evidence that the antiinflammatory effects of methotrexate are mediated via multiple adenosine receptors in rat adjuvant arthritis. Arthritis Rheum 2000;43:656–63.
5. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315–24.
6. Harland BF. Caffeine and nutrition. Nutrition 2000;16:522–6.
7. Hughes JR, Oliveto AH. A systematic survey of caffeine intake in Vermont. Exp Clin Psychopharmacol 1997;5:393–8.
8. Heliovaara M, Aho K, Knekt P, Impivaara O, Reunanen A, Aromaa A. Coffee consumption, rheumatoid factor, and the risk of rheumatoid arthritis. Ann Rheum Dis 2000;59:631–5.
9. Lloyd T, Rollings N, Eggli DF, Kieselhorst K, Chinchilli VM. Dietary caffeine intake and bone status of postmenopausal women. Am J Clin Nutr 1997;65:1826–30.
10. Cook DG, Peacock JL, Feyerabend C, Carey IM, Jarvis MJ, Anderson HR, et al. Relation of caffeine intake and blood caffeine concentrations during pregnancy to fetal growth: prospective population based study. BMJ 1996;313:1358–62.
11. Silke C, Murphy MS, Buckley T, Busteed S, Molloy MG, Phelan M. The effect of caffeine ingestion on the efficacy of methotrexate [abstract]. Rheumatology (Oxford) 2001;40 Suppl:34.