

Acetaminophen's Role in Osteoarthritis Pain Relieved by New Data

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CHICAGO — A new study confirms that acetaminophen is safe and effective for the treatment of pain associated with osteoarthritis of the knee and hip.

The results reinforce the American College of Rheumatology guidelines that recommend acetaminophen as a first-line therapy to relieve osteoarthritis (OA) pain, but contradict other studies that suggest

acetaminophen may not be useful in treating OA pain.

"People were questioning whether acetaminophen had any role, and I think this study clearly shows it does," lead author Roy D. Altman, M.D., reported in a poster presentation at the 2004 World Congress on Osteoarthritis. "People with mild to moderate pain with osteoarthritis often get adequate pain relief from acetaminophen."

These findings are particularly relevant in the post-Vioxx environment, which has

many patients concerned about the safety of some prescription arthritis medications.

ACR guidelines instruct physicians to start treatment with acetaminophen and then move on to nonsteroidal anti-inflammatory drugs and cyclooxygenase-2 (COX-2) inhibitors as the second and third lines of treatment, if pain control is not adequate.

Inadequate pain relief with acetaminophen may result from the adherence to the dosing schedule, said Dr. Altman at the meeting, which was sponsored by the

Osteoarthritis Research Society International. The maximum recommended dosage is 1 g four times per day.

The study randomized 483 patients—who were at least 40 years old with moderate to moderately severe OA pain—to treatment with acetaminophen extended-release (ER) caplets at daily doses of 1,950 mg, 3,900 mg, or placebo. The long-acting formulation reduced the number of daily doses to just two for those taking the higher dose.

"One of the benefits of this dosing is that people will take it twice a day," said Dr. Altman, of the division of rheumatology and arthritis at the University of California, Los Angeles. "Part of the problem is that people haven't been taking acetaminophen in doses that were adequate enough to give them pain relief when they start forgetting to take it."

At 12 weeks, acetaminophen ER 3,900 mg/day was superior to placebo for all

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DR. ALTMAN

three primary efficacy end points: the average change in the Western Ontario and McMaster Universities (WOMAC) osteoarthritis index pain score (mean decrease of 25 mm vs. 19 mm), the WOMAC physical function score (mean decrease of 24 mm vs. 18 mm), and the patient's global assessment of therapy on the 0-4 Likert scale (mean change 2.11 vs. 1.81).

In contrast, acetaminophen ER at 1,950 mg/day was superior to placebo only in the patient's global assessment of therapy (mean change 2.09 vs. 1.81). "I think when you get into 2 grams a day, [the dosage] just isn't adequate, and this [study] shows that," Dr. Altman said.

No serious drug-related adverse events occurred, which was supported by McNeil Consumer & Specialty Pharmaceuticals, the manufacturer of Tylenol.

"There has been an unnecessary battle between NSAIDs and acetaminophen," Dr. Altman said. "Some areas work better than others. My feeling is that combination therapy has to be looked at more carefully."

A second study presented at the meeting found that 4,000 mg/day of acetaminophen was safe for up to 12 months of use.

The double-blind study involved 571 patients with mild to moderately severe OA pain of the hip or knee who were randomized to treatment with 4,000 mg/day of acetaminophen or 750 mg/day of naproxen.

The WOMAC scores in pain, stiffness, and physical function within the 290 patients treated with acetaminophen were comparable to those of patients treated with naproxen, without any clinically important adverse effects, reported lead author Anthony Temple, M.D., vice president of medical affairs at McNeil Consumer & Specialty Pharmaceuticals in Fort Washington, Pa. ■

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BRISLAB PHARMACY, INC.
Brief Summary (See package brochure for full prescribing information).
Tylenol ER (acetaminophen tablets, USP)
Rx only

WARNINGS:

METHEOTREXATE SHOULD BE USED ONLY BY PHYSICIANS WHOSE KNOWLEDGE AND EXPERIENCE INCLUDE THE USE OF ANTI-METHEOTREXATE THERAPY.
BECAUSE OF THE POSSIBILITY OF SERIOUS TOXIC REACTIONS (WHICH CAN BE FATAL), METHEOTREXATE SHOULD BE USED ONLY IN LIFE-THREATENING NEOPLASIA; DISORDERS OR PATIENTS WITH PSORIASIS OR RHEUMATOID ARTHRITIS WHO ARE BEING TREATED WITH METHEOTREXATE WHO ARE NOT ACUALLY RESPONSIVE TO OTHER FORMS OF THERAPY.
CAUTION: METHEOTREXATE IS USED IN THE TREATMENT OF MALIGNANCY, PSORIASIS, AND RHEUMATOID ARTHRITIS.
PATIENTS SHOULD BE CLOSELY MONITORED FOR BONE MARROW, LIVER, AND KIDNEY TOXICITY. (SEE PRECAUTIONS.) PATIENTS SHOULD BE INFORMED BY THEIR PHYSICIAN OF THE RISKS INVOLVED AND BE UNDER PHYSICIAN'S CARE THROUGHOUT THERAPY.
1. Methotrexate has been reported to cause fetal death and/or congenital anomalies. Therefore, it is not recommended for women child-bearing potential unless there is clear medical evidence that the benefits can be expected to outweigh the considered risks. Pregnant women should be advised to avoid becoming pregnant while taking this medication. (SEE CONTRAINDICATIONS.)
2. Methotrexate administration is reduced in patients with impaired renal function, ascites, or dehydration. Such patients require especially careful monitoring to reduce, and require dose reduction in, some cases, discontinuation of methotrexate administration.
3. Methotrexate causes bone marrow depression, leukopenia, and neutropenia. Myelosuppression may be severe and may be accompanied by concurrent changes of leukopenia (usually in high dosage) along with some nonsteroidal anti-inflammatory drugs (NSAIDs). (SEE PRECAUTIONS, Drug Interactions.)
4. Methotrexate causes hepatotoxicity, fibrosis and cirrhosis, but generally only after prolonged use. Acutely, liver enzyme abnormalities are frequently seen. These are often reversible. In long-term treatment, persistent abnormalities in liver function tests may precede development of fibrosis or cirrhosis in the non-alcoholic population. (See PRECAUTIONS, Organ System Toxicity, Hepatic.)
5. Methotrexate-induced lung disease is a potentially dangerous lesion, which may occur shortly after any time course therapy and which has been reported at doses as low as 7.5 mg/week. It is not always fully reversible. Pulmonary symptoms (especially a dry, nonproductive cough) may require extensive investigation for treatment and careful investigation.
6. Rash and ulcerative stomatitis require interruption of therapy. However, hemorrhagic enteritis and death from intestinal perforation may occur.
7. Malignant lymphomas, which may regress following withdrawal of methotrexate, may occur in patients receiving low-dose methotrexate and, thus, may not require cytotoxic therapy. Discontinue methotrexate first and, if the lymphoma does not regress, appropriate treatment should be initiated.
8. In other cytotoxic drugs, methotrexate may induce "Lump Asplenia" syndrome in patients with rapidly growing tumors. Appropriate surgical and pharmacologic measures may prevent or alleviate this complication.
9. Severe, occasionally fatal, skin reactions have been reported following single or multiple doses of methotrexate. Reactions have occurred within days of oral intramuscular, intravenous, or intrathecal administration of methotrexate. Recovery has been associated with discontinuation of therapy. (See PRECAUTIONS, Organ System Toxicity, Skin.)
10. Potential fatal opportunistic infections, especially *Pneumocystis carinii* pneumonia, may occur with methotrexate therapy.
11. Methotrexate given concurrently with radiography may increase the risk of soft tissue necrosis and osteonecrosis.

INDICATIONS AND USAGE:

Neoplastic Diseases:
Tylenol ER (methotrexate tablets) are indicated in the treatment of gestational choriocarcinoma, choriocarcinoma desmoplastic and hybridiform form.
Methotrexate is used alone or in combination with other antineoplastic agents in the treatment of breast cancer, epidermoid cancers of the head and neck, advanced mycosis fungoides, cutaneous T-cell lymphoma, and, occasionally, psoriasis and small cell lung cancer. Methotrexate is also used in combination with other chemotherapeutic agents in the treatment of advanced stage non-small-cell lung carcinoma.
Psoriasis:
Tylenol ER (methotrexate tablets) are indicated in the symptomatic control of severe, recalcitrant, psoriasis vulgaris that is not adequately responsive to other forms of therapy, but only when the diagnosis has been established, as by biopsy and/or after dermatologic consultation. It is important to ensure that a diagnosis is not due to an undiagnosed connective tissue affecting immune response.

Rheumatoid Arthritis: Polyarthralgia Course Juvenile:

Rheumatoid Arthritis:
Tylenol ER (methotrexate tablets) are indicated in the management of selected adults with severe, active, rheumatoid arthritis (AIC criteria) or children with active polyarthralgia-course juvenile rheumatoid arthritis, who have not had sufficient therapeutic response to one or another of the following: low-dose chronic low-dose systemic corticosteroids, nonsteroidal anti-inflammatory agents (NSAIDs), and/or low-dose systemic corticosteroids. However, the possibility of increased toxicity with concurrent use of NSAIDs including salicylates has not been fully explored. (See PRECAUTIONS, Drug Interactions.) Stress may be reduced gradually with patients who respond to methotrexate. Continued use of methotrexate in patients with rheumatoid arthritis may be beneficial, or, if not, may be stopped and may increase the incidence of adverse effects. Rest and physical therapy as indicated should be continued.

CONTRAINDICATIONS:

Methotrexate can cause fetal death or teratogenic effects when administered to a pregnant woman. Methotrexate is contraindicated in pregnant women with psoriasis or rheumatoid arthritis who have existing blood dyscrasias, such as bone marrow hypoplasia, leukopenia, thrombocytopenia or significant anemia. Do not use methotrexate in patients with a known hypersensitivity to methotrexate or its metabolites.
WARNINGS: SEE BOXED WARNINGS.
PRECAUTIONS:
General:
Methotrexate has the potential for serious toxicity. (See Boxed Warnings.) Toxic effects may be related to frequency and severity to dose of frequency of administration but have been seen at all doses. Because they can occur at any time during therapy, it is necessary to follow patients closely. Most adverse reactions are reversible if detected early. When such reactions do occur, the drug should be reduced in dose or discontinued and appropriate corrective measures should be taken. If necessary, this could include the use of folic acid, calcium and/or saline. Intermittent hemodialysis with a high-flux dialyzer. (See OVERDOSAGE.) If methotrexate therapy is reinitiated, it should be carried out with caution with adequate consideration further need for the drug in increased dosage as possible response to therapy. The clinical pharmacology of methotrexate has not been well studied in older individuals. Due to diminished hepatic and renal function as well as decreased albumin in this population, low-dose methotrexate should be considered, and these patients should be closely monitored for early signs of toxicity.
Information for Patients:
Patients should be informed of the early signs and symptoms of toxicity of the need to see their physician promptly if they occur, and the need for close follow-up in patients receiving prolonged laboratory tests to monitor toxicity.
Both the physician and pharmacist should emphasize to the patient that the recommended dose is taken weekly in rheumatoid arthritis and, once established, should not be increased. Only one of the recommended doses should be taken. Precautions should not be written or written on a prescription. Patients should be informed of the potential for serious toxicity in the use of methotrexate. The risk of effects on reproduction should be discussed with both male and female patients taking methotrexate.

LABORATORY TESTS:

Patients receiving methotrexate therapy should be closely monitored so that toxic effects are detected promptly. Baseline assessment should include a complete blood count with differential and platelet counts, hepatic enzymes, renal function tests, and a chest X-ray. During therapy of rheumatoid arthritis and psoriasis, complete blood counts, hepatic enzymes, renal function tests, and chest X-rays should be performed at 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72, 76, 80, 84, 88, 92, 96, 100, 104, 108, 112, 116, 120, 124, 128, 132, 136, 140, 144, 148, 152, 156, 160, 164, 168, 172, 176, 180, 184, 188, 192, 196, 200, 204, 208, 212, 216, 220, 224, 228, 232, 236, 240, 244, 248, 252, 256, 260, 264, 268, 272, 276, 280, 284, 288, 292, 296, 300, 304, 308, 312, 316, 320, 324, 328, 332, 336, 340, 344, 348, 352, 356, 360, 364, 368, 372, 376, 380, 384, 388, 392, 396, 400, 404, 408, 412, 416, 420, 424, 428, 432, 436, 440, 444, 448, 452, 456, 460, 464, 468, 472, 476, 480, 484, 488, 492, 496, 500, 504, 508, 512, 516, 520, 524, 528, 532, 536, 540, 544, 548, 552, 556, 560, 564, 568, 572, 576, 580, 584, 588, 592, 596, 600, 604, 608, 612, 616, 620, 624, 628, 632, 636, 640, 644, 648, 652, 656, 660, 664, 668, 672, 676, 680, 684, 688, 692, 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