

Calcium Crystals Hold Key Target for OA Tx

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SNOWMASS, COLO. — Calcium crystals are likely to become a major target for future osteoarthritis therapies, Geraldine M. McCarthy, M.D., predicted at a symposium sponsored by the American College of Rheumatology.

Calcium crystals may actually be related to glucosamine's mechanism of action, said Dr. McCarthy, of the division of

rheumatology at Mater Misericordiae Hospital and the Royal College of Surgeons, Dublin, Ireland.

Studies have shown that anywhere from 30% to 70% of patients with osteoarthritis of the knee have calcium crystals in their synovial fluid, Dr. McCarthy said at the meeting.

And yet because the crystals are extremely small, they're difficult to detect, making more precise estimates of their prevalence difficult to obtain.

Dr. McCarthy's interest in arthritis and the role of calcium crystals was spurred by her training at the University of Wisconsin, where Milwaukee shoulder syndrome was identified as the first osteoarthritis entity found to be associated with basic calcium phosphate crystals.

The idea is that these crystals "synergize with other pathogenic mediators of osteoarthritis, thus contributing to the degenerative process," she said.

Calcium pyrophosphate dihydrate crystals

in the synovium are believed to cause pseudogout and pseudo-rheumatoid arthritis.

Basic calcium phosphate crystals, by comparison, are believed to play a role in all osteoarthritis, Dr. McCarthy explained at the meeting.

Research into the role of basic calcium phosphate crystals has been hindered, however, by the size of the crystals. As small as calcium pyrophosphate dihydrate crystals are, basic calcium phosphate crystals are even smaller.

Basic calcium phosphate crystals clump as submicroscopic aggregates ranging in size from 1 µm to 50 µm in diameter.

A radiolabeled bisphosphonate that can detect the crystals has been available at the Medical College of Wisconsin, Milwaukee, but supply is dwindling, and at present no company has stepped up to manufacture more,

The idea is that these crystals 'synergize with other pathogenic mediators of osteoarthritis, thus contributing to the degenerative process.'

Dr. McCarthy said.

Studies have shown that as people age basic calcium phosphate crystals tend to accumulate in the synovial fluid, synovial lining, and hyaline cartilage, and that the presence of these crystals

correlates strongly with radiographic evidence of cartilage degeneration. In vitro experiments have shown that the crystals induce mitogenesis and increase production of prostaglandins and metalloproteinases.

The presence of crystals also is associated with the increased production and activation of cyclooxygenase-1 and -2.

Interestingly, COX-1 is not usually up-regulated by disease processes, so this finding may explain why some osteoarthritis patients do not respond to selective COX-2 inhibitor therapy, Dr. McCarthy suggested.

The crystals appear to be actively generated by articular cartilage matrix vesicles.

"These crystals are not present in other destructive arthropathies," Dr. McCarthy noted. But they are associated with Milwaukee shoulder syndrome, so it's likely that the crystals are also associated with joint destruction, she continued.

Further investigations are needed to identify therapeutic interventions and to determine why some individuals with basic calcium phosphate crystals have symptomatic degeneration while others do not, she said.

Calcium-chelating agents have been tried in the treatment of Milwaukee shoulder syndrome, but their use has caused severe arthritis flares.

In vitro experiments have shown that misoprostol can inhibit crystal formation, and glucosamine appears to directly inhibit the effects of the calcium crystals on mitogenesis and metalloproteinase production. ■

Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenic effect of meloxicam was observed in rats given oral doses up to 0.8 mg/kg/day (approximately 0.4-fold the human dose at 15 mg/day for a 50 kg adult based on body surface area conversion) for 104 weeks or in mice given oral doses up to 8.0 mg/kg/day (approximately 2.2-fold the human dose, as noted above) for 98 weeks.

Meloxicam was not mutagenic in an Ames assay, or clastogenic in a chromosome aberration assay with human lymphocytes and an *in vivo* micronucleus test in mouse bone marrow.

Meloxicam did not impair male and female fertility in rats at oral doses up to 9 and 5 mg/kg/day, respectively (4.9-fold and 2.5-fold the human dose, as noted above). However, an increased incidence of embryolethality at oral doses ≥ 1 mg/kg/day (0.5-fold the human dose, as noted above) was observed in rats when dams were given meloxicam 2 weeks prior to mating and during early embryonic development.

Pregnancy

Teratogenic Effects: Pregnancy Category C.

Meloxicam caused an increased incidence of septal defect of the heart, a rare event, at an oral dose of 60 mg/kg/day (64.5-fold the human dose at 15 mg/day for a 50 kg adult based on body surface area conversion) and embryolethality at oral doses ≥ 5 mg/kg/day (5.4-fold the human dose, as noted above) when rabbits were treated throughout organogenesis. Meloxicam was not teratogenic in rats up to an oral dose of 4 mg/kg/day (approximately 2.2-fold the human dose, as noted above) throughout organogenesis. An increased incidence of stillbirths was observed when rats were given oral doses ≥ 1 mg/kg/day throughout organogenesis. Meloxicam crosses the placental barrier. There are no adequate and well-controlled studies in pregnant women. MOBIC should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects:

Meloxicam caused a reduction in birth index, live births, and neonatal survival at oral doses ≥ 0.125 mg/kg/day (approximately 0.07-fold the human dose at 15 mg/day for a 50 kg adult based on body surface area conversion) when rats were treated during the late gestation and lactation period. No studies have been conducted to evaluate the effect of meloxicam on the closure of the ductus arteriosus in humans; use of meloxicam during the third trimester of pregnancy should be avoided.

Labor and Delivery

Studies in rats with meloxicam, as with other drugs known to inhibit prostaglandin synthesis, showed an increased incidence of stillbirths, decreased length of delivery time, and delayed parturition at oral dosages ≥ 1 mg/kg/day (approximately 0.5-fold the human dose at 15 mg/day for a 50 kg adult based on body surface area conversion), and decreased pup survival at an oral dose of 4 mg/kg/day (approximately 2.1-fold the human dose, as noted above) throughout organogenesis. Similar findings were observed in rats receiving oral dosages ≥ 0.125 mg/kg/day (approximately 0.07-fold the human dose, as noted above) during late gestation and the lactation period.

Nursing Mothers

Studies of meloxicam excretion in human milk have not been conducted; however, meloxicam was excreted in the milk of lactating rats at concentrations higher than those in plasma. Because of the potential for serious adverse reactions in nursing infants from MOBIC, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients under 18 years of age have not been established.

Geriatric Use

Caution should be exercised in treating the elderly (65 years and older).

ADVERSE REACTIONS

The MOBIC phase 2/3 clinical trial database includes 10,122 OA patients and 1012 RA patients treated with MOBIC 7.5 mg/day, 3505 OA patients and 1351 RA patients treated with MOBIC 15 mg/day. MOBIC at these doses was administered to 661 patients for at least 6 months and to 312 patients for at least one year. Approximately 10,500 of these patients were treated in ten placebo and/or active-controlled osteoarthritis trials and 2363 of these patients were treated in ten placebo and/or active-controlled rheumatoid arthritis trials. Gastrointestinal (GI) adverse events were the most frequently reported adverse events in all treatment groups across MOBIC trials.

A 12-week multicenter, double-blind, randomized trial was conducted in patients with osteoarthritis of the knee or hip to compare the efficacy and safety of MOBIC with placebo and with an active control. Two 12-week multicenter, double-blind, randomized trials were conducted in patients with rheumatoid arthritis to compare the efficacy and safety of MOBIC with placebo.

The following adverse events (%) occurred in $\geq 2\%$ of MOBIC 7.5 mg daily (n=154) and 15 mg daily (n=156) patients, respectively, in a 12-week osteoarthritis placebo- and active-controlled trial: abdominal pain, 1.9%, 2.6%; diarrhea, 7.8%, 3.2%; dyspepsia, 4.5%, 4.5%; flatulence, 3.2%, 3.2%; nausea, 3.9%, 3.8%; accident household, 4.5%, 3.2%; edema¹, 1.9%, 4.5%; fall, 2.6%, 0.0%; influenza-like symptoms, 4.5%, 5.8%; dizziness, 2.6%, 3.8%; headache, 7.8%, 8.3%; pharyngitis, 0.6%, 3.2%; upper respiratory tract infection, 3.2%, 1.9%; rash², 2.6%, 0.6%.

The following adverse events (%) occurred with MOBIC 7.5 mg daily in $\geq 2\%$ of patients treated, respectively, in short-term (4-6 weeks) and long-term (6 months) active-controlled osteoarthritis trials: abdominal pain, 2.7%, 4.7%; constipation, 0.8%, 1.8%; diarrhea, 1.9%, 5.9%; dyspepsia, 3.6%, 8.9%; flatulence, 0.5%, 3.0%; nausea, 2.4%, 4.7%; vomiting, 0.6%, 1.8%; edema¹, 0.6%, 2.4%; pain, 0.9%, 3.6%; dizziness, 1.1%, 2.4%; headache, 2.4%, 3.6%; anemia, 0.1%, 4.1%; arthralgia, 0.5%, 5.3%; back pain, 0.5%, 3.0%; insomnia, 0.4%, 3.6%; coughing, 0.2%, 2.4%; upper respiratory tract infection, 0.2%, 8.3%; pruritus, 0.4%, 2.4%; rash², 0.3%, 3.0%; micturition frequency, 0.1%, 2.4%; urinary tract infection, 0.3%, 4.7%.

The following adverse events (%) occurred with MOBIC 15 mg daily in $\geq 2\%$ of patients treated, respectively, in short-term (4-6 weeks) and long-term (6 months) active-controlled osteoarthritis trials: abdominal pain, 2.3%, 2.9%; constipation, 1.2%, 2.6%; diarrhea, 2.7%, 2.6%; dyspepsia, 7.4%, 9.5%; flatulence, 0.4%, 2.6%; nausea, 4.7%, 7.2%; vomiting, 0.8%, 2.6%; edema¹, 2.0%, 1.6%; pain, 2.0%, 5.2%; dizziness, 1.6%, 2.6%; headache, 2.7%, 2.6%; anemia, 0.0%, 2.9%; arthralgia, 0.0%, 1.3%; back pain, 0.4%, 0.7%; insomnia, 0.0%, 1.6%; coughing, 0.8%, 1.0%; upper respiratory tract infection, 0.0%, 7.5%; pruritus, 1.2%, 0.0%; rash², 1.2%, 1.3%; micturition frequency, 0.4%, 1.3%; urinary tract infection, 0.4%, 6.9%.

¹WHO preferred terms edema, edema dependent, edema peripheral and edema legs combined. ²WHO preferred terms rash, rash erythematous and rash maculo-papular combined.

The following adverse events (%) occurred respectively with MOBIC 7.5 and 15 mg daily in $\geq 2\%$ of patients treated in two 12-week rheumatoid arthritis placebo controlled trials: abdominal pain NOS², 2.9%, 2.3%; diarrhea NOS², 4.8%, 3.4%; dyspeptic signs and symptoms¹, 5.8%, 4.0%; nausea², 3.3%, 3.8%; influenza like illness², 2.9%, 2.3%; upper respiratory tract infections-pathogen class unspecified¹, 7.0%, 6.5%; joint related signs and symptoms¹, 1.5%, 2.3%; musculoskeletal and connective tissue signs and symptoms NEC¹, 1.7%, 2.9%; headaches NOS², 6.4%, 5.5%; dizziness (excl vertigo)², 2.3%, 0.4%; rash NOS², 1.0%, 2.1%.

¹MedDRA high level term (preferred terms): dyspeptic signs and symptoms (dyspepsia, dyspepsia aggravated, eructation, gastrointestinal irritation), upper respiratory tract infections-pathogen unspecified (laryngitis NOS, pharyngitis NOS, sinusitis NOS), joint related signs and symptoms (arthralgia, arthralgia aggravated, joint crepitation, joint effusion, joint swelling), and musculoskeletal and connective tissue signs and symptoms NEC (back pain, back pain aggravated, muscle spasms, musculoskeletal pain).

²MedDRA preferred term: diarrhea NOS, abdominal pain NOS, influenza like illness, headaches NOS, dizziness (excl vertigo), and rash NOS.

Higher doses of MOBIC (22.5 mg and greater) have been associated with an increased risk of serious GI events; therefore the daily dose of MOBIC should not exceed 15 mg.

The following is a list of adverse drug reactions occurring in $<2\%$ of patients receiving MOBIC in clinical trials involving approximately 16,200 patients. Adverse reactions reported only in worldwide post-marketing experience or the literature are shown in italics and are considered rare ($<0.1\%$).

Body as a Whole: allergic reaction, *anaphylactoid reactions including shock, face edema, fatigue, fever, hot flushes, malaise, syncope, weight decrease, weight increase* **Cardiovascular:** angina pectoris, cardiac failure, hypertension, hypotension, myocardial infarction, vasculitis. **Central and Peripheral Nervous System:** convulsions, paresthesia, tremor, vertigo.

Gastrointestinal: colitis, dry mouth, duodenal ulcer, eructation, esophagitis, gastric ulcer, gastritis, gastroesophageal reflux, gastrointestinal hemorrhage, hematemesis, hemorrhagic duodenal ulcer, hemorrhagic gastric ulcer, intestinal perforation, melena, pancreatitis, perforated duodenal ulcer, perforated gastric ulcer, stomatitis ulcerative **Heart Rate and Rhythm:** arrhythmia, palpitation, tachycardia **Hematologic:** agranulocytosis, leukopenia, purpura, thrombocytopenia **Liver and Biliary System:** ALT increased, AST increased, bilirubinemia, GGT increased, hepatitis, jaundice, liver failure **Metabolic and Nutritional:** dehydration **Psychiatric Disorders:** abnormal dreaming, anxiety, appetite increased, confusion, depression, nervousness, somnolence **Respiratory:** asthma, bronchospasm, dyspnea **Skin and Appendages:** alopecia, angioedema, bullous eruption, erythema multiforme, photosensitivity reaction, pruritus, *Stevens-Johnson syndrome*, sweating increased, toxic epidermal necrolysis, urticaria **Special Senses:** abnormal vision, conjunctivitis, taste perversion, tinnitus **Urinary System:** albuminuria, BUN increased, creatinine increased, hematuria, *interstitial nephritis*, renal failure.

OVERDOSAGE

There is limited experience with meloxicam overdose. Four cases have taken 6 to 11 times the highest recommended dose; all recovered. Cholestyramine is known to accelerate the clearance of meloxicam.

Symptoms following acute NSAID overdose are usually limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which are generally reversible with supportive care. Gastrointestinal bleeding can occur. Severe poisoning may result in hypertension, acute renal failure, hepatic dysfunction, respiratory depression, coma, convulsions, cardiovascular collapse, and cardiac arrest. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs, and may occur following an overdose.

Patients should be managed with symptomatic and supportive care following an NSAID overdose. In cases of acute overdose, gastric lavage followed by activated charcoal is recommended. Gastric lavage performed more than one hour after overdose has little benefit in the treatment of overdose. Administration of activated charcoal is recommended for patients who present 1-2 hours after overdose. For substantial overdose or severely symptomatic patients, activated charcoal may be administered repeatedly. Accelerated removal of meloxicam by 4 gm oral doses of cholestyramine given three times a day was demonstrated in a clinical trial. Administration of cholestyramine may be useful following an overdose. Forced diuresis, alkalization of urine, hemodialysis, or hemoperfusion may not be useful due to high protein binding.

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