

Women Wait Longer for Emergency Angioplasty

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Contributing Writer

Women who presented to Michigan hospitals with acute ST-segment elevation myocardial infarction waited significantly longer than men to undergo emergency angioplasty—and even men waited too long according to Mauro Moscucci, M.D., of the university.

“We have an ideal target for quality im-

provement, something we can easily try to correct,” said Dr. Moscucci, who presented the data at the scientific sessions of the American Heart Association and discussed the findings in a later interview. “If we can improve our treatment times, we can substantially reduce the risk of death.”

Dr. Moscucci and his associates analyzed data collected on 1,551 patients who had primary percutaneous coronary intervention for acute ST-segment elevation during a 20-month period ending in June

2004. Patients had the procedure at 1 of the 16 hospitals participating in the regional Blue Cross Blue Shield of Michigan Cardiovascular Consortium.

The investigators found that only 26% of the 442 women who had an emergency angioplasty—and 34% of the 1,069 men—had the procedure within the 90-minute time frame recommended by the American Heart Association and the American College of Cardiology.

On average, women waited more than

118 minutes before treatment began, compared with 106 minutes for men.

Patients of both sexes whose angioplasty began within 90 minutes of arrival at the hospital had a 50% lower risk of dying in the hospital than those who waited longer, said Dr. Moscucci, director of interventional cardiology at the University of Michigan Cardiovascular Center, Ann Arbor.

“Since there’s been such a focus on angioplasty recently, we wondered whether the recommended door-to-balloon time of 90 minutes was still significant in terms of survival,” he said. “We found that it’s still an important predictor of in-hospital mortality, and that perhaps we’re not doing as well as we should.”

Women in the study were more than twice as likely as men to die in the hospital; their mortality rate was about 7%, compared

with about 3% in men. When the investigators adjusted for the average older age of women and the higher frequency of comorbidities, they still found higher in-hospital mortality rates for women, Dr. Moscucci said.

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The gender-difference findings augment a growing body of research showing that women with heart attacks seek care later, present more often with atypical symptoms and comorbidities such as severe diabetes, and face delays in treatment, he said.

In addition to the greater delays in treatment, the Michigan study showed that it takes longer for women to get to an emergency department in the first place.

Women reported that their symptoms started an average of 105 minutes before they got to the emergency department; the average time for men was 85 minutes.

Dr. Moscucci said that hospital procedures for activating cardiac catheterization labs vary significantly. Labs could be activated faster—which, along with faster diagnosis, would help hasten door-to-balloon times—if more ambulances had the capability to automatically read or transmit ECGs and if more hospitals allowed emergency physicians and not just cardiologists to activate the labs directly, he said.

A recent survey of more than 1,000 women older than 35 years showed that only 47% of women who had head, neck, back, and jaw pain—typical heart attack symptoms—would call their doctor, and just 35% would call 911 or visit an emergency department.

“Women and their families still need a great deal of education. Their symptoms can be very atypical—perhaps only weakness, difficulty breathing, or dizziness,” said Michael J. Bresler, M.D., professor of emergency medicine at Stanford (Calif.) University. Women in whom heart attack is diagnosed “should be rushed to the cath lab or quickly given a lytic drug if immediate catheterization isn’t available,” he said. ■

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 99 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, 0.6%, 1.8%; diarrhea, 1.9%, 5.9%; dyspepsia, 3.8%, 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. **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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MB-B05 4057500/US/11(10/04)



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