Serologically Test for Suspected Lyme Borreliosis

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WARSAW — While erythema migrans is the presenting manifestation of Lyme borreliosis in the majority of cases, nonspecific symptoms predominate in many infected children.

Thus, serologic testing should be considered for these children who have a history of tick bite or who have visited a wooded area, Dr. n. med. Ewa Duszczyk said in a poster at an international congress of the World Society for Pediatric Infectious Diseases.

A group of 171 children with suspected Lyme borreliosis who ranged in age from 6 months to 17.5 years underwent serologic testing with an enzyme-linked immunosorbent assay (ELISA). A total of 111 (65%) had a history of tick bite, and 60 (35%) had visited a wooded location.

They were divided into two groups: those with erythema migrans (104 children) and those with nonspecific symptoms such as other skin lesions, lymphadenopathy, fever, and pain and/or edema of joints (67 children).

In the group with erythema migrans, 74 (71%) children were seropositive, 72 with IgM antibodies to *Borrelia burgdorferi,* 17 with IgG antibodies, and 13 with both IgM and IgG antibodies, according to Dr. Duszczyk and her colleagues in the department of children's infectious diseases, Medical University of Warsaw.

In the group with nonspecific symptoms, antibodies were detected in 16 (24%) children. Of these, IgM antibodies were detected in 13 children, IgG in 5, and both IgM and IgG in 2.

All children were treated to symptom resolution. In 35 seropositive children, serologic testing was repeated after 2-20 months; all showed a decline in IgM levels. In three cases followed for 13, 16, and 20 months, respectively, IgM antibodies were still present even though no clinical

symptoms remained. Serology can therefore be used to monitor treatment to some extent, but the persistent presence of antibodies does not necessarily indicate treatment failure, she cautioned.

In another poster session, Prof. dr. hab. Teresa Wozniakowska-Gesicka noted that in a series of 87 children with confirmed Lyme borreliosis, only 57.4% had a history of contact with a tick.

In 42.5% of the infected children, symptoms were nonspecific, whereas, in 28.7%, neuroborreliosis was diagnosed with symptoms that included facial palsy, meningitis, cranial nerve palsy, paresthesias, radiculoneuritis, and mental disturbances. Erythema migrans and acrodermatitis chronica atrophicans were observed in 19.5%, and arthritis in 9.3%, reported Dr. Wozniakowska-Gesicka of the department of pediatrics, Polish Mother's Hospital, Lodz, Poland.

At 7-10 days after treatment began, those with facial palsy began to respond, as did those with meningitis 10-14 days after treatment started.

Acrodermatitis chronica atrophicans is seen primarily in European borreliosis, and is usually associated with infection with *B. afzelii*.

All children received oral amoxicillin or tetracycline, and those with neuroborreliosis were given ceftriaxone intravenously for 3-4 weeks. Complete recovery was seen in 72 (83%) of the children following the first course of therapy.

Improvement was first observed in children with erythema migrans, 5-7 days after treatment began. At 7-10 days those with facial palsy began to respond, as did those with meningitis after 10-14 days.

Recovery following a second course of treatment with amoxicillin or ceftriaxone was seen in four children with fever, in three with headache, in two with nerve palsy, in two with gonitis, and in one with mental disturbances and acrodermatitis chronica atrophicans.

One patient with radiculitis improved after a second course, but muscular atrophy persisted. One child with palsy of cranial nerve VIII experienced irreversible unilateral deafness despite three courses of treatment.

Early diagnosis and directed treatment are needed in this serious diagnostic and therapeutic problem, Dr. Wozniakowska-Gesicka said. ■

aspirin is not generally recommended because of the potential for increased adverse effects.

Concomitant administration of low-dose aspirin with MOBIC may result in an increased rate of GI ulceration or other complications, compared to use of MOBIC alone. MOBIC is not a substitute for aspirin for cardiovascular prophylaxis.

Cholestyramine

Pretreatment for four days with cholestyramine significantly increased the clearance of meloxicam by 50%. This resulted in a decrease in $t_{1/2}$, from 19.2 hours to 12.5 hours, and a 35% reduction in AUC. This suggests the existence of a recirculation pathway for meloxicam in the gastrointestinal tract. The clinical relevance of this interaction has not been established.

Cimetidine

Concomitant administration of 200 mg cimetidine QID did not alter the single-dose pharmacokinetics of 30 mg meloxicam.

Digoxin

Meloxicam 15 mg once daily for 7 days did not alter the plasma concentration profile of digoxin after β-acetyldigoxin administration for 7 days at clinical doses. *In vitro* testing found no protein binding drug interaction between digoxin and meloxicam.

Furosemide

Clinical studies, as well as post-marketing observations, have shown that NSAIDs can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis. Studies with furosemide agents and meloxicam have not demonstrated a reduction in natriuretic effect. Furosemide single and multiple dose pharmacodynamics and pharmacokinetics are not affected by multiple doses of meloxicam. Nevertheless, during concomitant therapy with MOBIC, patients should be observed closely for signs of declining renal failure (see **WARNINGS, Renal Effects**), as well as to assure diuretic efficacy.

Lithium

In a study conducted in healthy subjects, mean pre-dose lithium concentration and AUC were increased by 21% in subjects receiving lithium doses ranging from 804 to 1072 mg BID with meloxicam 15 mg QD as compared to subjects receiving lithium alone. These effects have been attributed to inhibition of renal prostaglandin synthesis by MOBIC. Patients on lithium treatment should be closely monitored for signs of lithium toxicity when MOBIC is introduced, adjusted, or withdrawn.

Methotrexate

NSAIDs have been reported to competitively inhibit methotrexate accumulation in rabbit kidney slices. This may indicate that they could enhance the toxicity of methotrexate. Caution should be used when NSAIDs are administered concomitantly with methotrexate.

A study in 13 rheumatoid arthritis (RA) patients evaluated the effects of multiple doses of meloxicam on the pharmacokinetics of methotrexate taken once weekly. Meloxicam did not have a significant effect on the pharmacokinetics of single doses of methotrexate. *In vitro*, methotrexate did not displace meloxicam from its human serum binding sites.

Warfarin

The effects of warfarin and NSAIDs on GI bleeding are synergistic, such that users of both drugs together have a risk of serious GI bleeding higher than users of either drug alone.

Anticoagulant activity should be monitored, particularly in the first few days after initiating or changing MOBIC therapy in patients receiving warfarin or similar agents, since these patients are at an increased risk of bleeding. The effect of meloxicam on the anticoagulant effect of warfarin was studied in a group of healthy subjects receiving daily doses of warfarin that produced an INR (International Normalized Ratio) between 1.2 and 1.8. In these subjects, meloxicam did not alter warfarin pharmacokinetics and the average anticoagulant effect of warfarin as determined by prothrombin time. However, one subject showed an increase in INR from 1.5 to 2.1. Caution should be used when administering MOBIC with warfarin since patients on warfarin may experience changes in INR and an increased risk of bleeding complications when a new medication is introduced.

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

Because of the known effects of nonsteroidal anti-inflammatory drugs on the fetal cardiovascular system (closure of ductus arteriosus), use during pregnancy (particularly late pregnancy) should be avoided.

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, prolonged delivery, 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.

The effects of MOBIC on labor and delivery in pregnant women are unknown.

Nursing Mothers

It is not known whether this drug is excreted in human milk however, meloxicam was excreted in the milk of lactating rats at concentrations higher than those in plasma. Because many drugs are excreted in human milk and 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

The safety and effectiveness of meloxicam in pediatric JRA patients from 2 to 17 years of age has been evaluated in three clinical trials (see **CLINICAL TRIALS**, **ADVERSE REACTIONS** and **DOSAGE AND ADMINISTRATION** sections).

Geriatric Use

As with any NSAID, caution should be exercised in treating the elderly (65 years and older).

ADVERSE REACTIONS

Adults

Osteoarthritis and Rheumatoid Arthritis

The MOBIC Phase 2/3 clinical trial database includes 10,122 OA patients and 1012 RA patients treated with MOBIC 7.5 mg/day, 3,505 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 ≥ 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%; edema[1], 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%; rash[2], 2.6%, 0.6%.

The following adverse events (%) occurred with MOBIC 7.5 mg daily in ≥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, 3.8%, 8.9%; flatulence, 0.5%, 3.0%; nausea, 2.4%, 4.7%; vomiting, 0.6%, 1.8%; edema[1], 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%; rash[2], 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 ≥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%; edema[1], 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%; rash[2], 1.2%, 1.3%; micturition frequency, 0.4%, 1.3%; urinary tract infection, 0.4%, 6.9%.

[1]WHO preferred terms edema, edema dependent, edema peripheral and edema legs combined.

[2]WHO 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 ≥ 2% of patients treated in two 12-week rheumatoid arthritis placebo controlled trials: abdominal pain NOS[2], 2.9%, 2.3%; diarrhea NOS[2], 4.8%, 3.4%; dyspeptic signs and symptoms[1], 5.8%, 4.0%; nausea[2], 3.3%, 3.8%; influenza like illness[2], 2.9% 2.3%; upper respiratory tract infections-pathogen class unspecified[1], 7.0%, 6.5%; joint related signs and symptoms[1], 1.5%, 2.3%; musculoskeletal and connective tissue signs and symptoms NEC[1], 1.7% 2.9%; headaches NOS[2], 6.4%, 5.5%; dizziness (excl vertigo)[2], 2.3%, 0.4%; rash NOS[2], 1.0%, 2.1%.

[1]MedDRA 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).

[2]MedDRA 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.

Pediatrics

Pauciarticular and Polyarticular Course Juvenile Rheumatoid Arthritis (JRA)

Three hundred and eighty-seven patients with pauciarticular and polyarticular course JRA were exposed to MOBIC with doses ranging from 0.125 to 0.375 mg/kg per day in three clinical trials. These studies consisted of two 12-week multicenter, double-blind, randomized trials (one with a 12-week open-label extension and one with a 40-week extension) and one 1-year open-label PK study. The adverse events observed in these pediatric studies with MOBIC were similar in nature to the adult clinical trial experience, although there were differences in frequency. In particular, the following most common adverse events — abdominal pain, vomiting, diarrhea, headache, and pyrexia — were more common in the pediatric than in the adult trials. Rash was reported in seven (<2%) patients receiving MOBIC. No unexpected adverse events were identified during the course of the trials. The adverse events did not demonstrate an age or gender-specific subgroup effect.

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