Adding Clopidogrel May Prevent Vascular Events

BY DIANA MAHONEY

Adding clopidogrel to aspirin therapy significantly reduces the risk of stroke and other major vascular events in patients who have atrial fibrillation and are not candidates for anticoagulation therapy with a vitamin K antagonist, according to Dr. Stuart Connolly of the Population Health Research Institute in Hamilton, Ont.

The rate of major vascular events was 6.8% at a median 3.6 years of follow-up among 3,772 study participants randomized to receive 75 mg per day of the oral antiplatelet agent in addition to aspirin in the multicenter Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events-A (ACTIVE-A). The rate of major vascular events was 7.6% among the 3,782 patients randomized to placebo and aspirin therapy.

The clopidogrel and aspirin regimen was associated "with an acceptable increase in risk of major hemorrhage," Dr. Connolly reported in a press conference at the annual meeting of the American College of Cardiology.

The rate of major hemorrhage, defined as requiring a transfusion of at least two units of blood, increased from 1.3% in the placebo and aspirin group to 2.0% in the clopidogrel and aspirin group. However, this risk is less than the risk of major hemorrhage that has been reported with warfarin therapy, he said.

Additionally, there was a nonsignificant trend toward an increased risk in fatal strokes from 0.2% per year to 0.3% per year with clopidogrel plus aspirin therapy.

Dr. Connolly emphasized that oral anticoagulation therapy with vitamin K antagonists such as warfarin is still the most effective way to reduce major vascular events in high risk patients with atrial fibrillation. However, "40%-50% of the patients who are at high risk for stroke because of atrial fibrillation don't receive anticoagulation therapy because they've been judged to be unsuitable for this treatment."

Dr. Connolly and his colleagues enrolled 7,554 patients who had atrial fibrillation and at least one risk factor for stroke between June 2003 and May 2006. Participants were deemed either to be unsuitable for warfarin therapy because of bleeding risk or did not want to begin warfarin. The mean patient age was 71 years.

Aspirin plus clopidogrel was associated 'with an acceptable increase in risk of major hemorrhage.'

DR. CONNOLLY

The primary study outcome was any major vascular event, including stroke, non–central nervous system systemic embolism, myocardial infarction, or vascular death.

The primary composite outcome was reduced by 11% in the clopidogrel group relative to aspirin only, "a highly statistically significant result," Dr. Connolly noted. "What is of particular importance, however, is that this effect was driven almost entirely by a substantial reduction in strokes of all severities." Strokes were reduced from 3.3% per year to 2.4% per year.

There was a trend of fewer myocardial infarctions, 0.9% per year in the aspirin only group and 0.7% per year in the clopidogrel plus aspirin group, which didn't achieve statistical significance, Dr. Connolly said. However the number of heart attacks in the study was relatively small [90 in the clopidogrel group; 115 in the aspirin plus placebo group], reducing the study's power to detect a significant difference. In studies of several other types of patients, clopidogrel has been shown to reduce heart attacks.

Dr. Connolly reported receiving consulting fees, lecture fees, and grant support from Sanofi-Aventis, Bristol-Myers Squibb, and Boehringer Ingelheim, and grant support from Portola Pharmaceuticals.

This study was published online in the New England Journal of Medicine (doi 10.1056/NEJMoa09013101). ■

moxatag™
(amoxicillin extended-release tablets)
775 mg

The following is a brief summary only; see full Prescribing Information for complete product information.

RX ONLY

INDICATIONS AND USAGE

MOXATAG is a once-daily amoxicillin product indicated for the treatment of tonsillitis and/or pharyngitis secondary to *Streptococcus pyogenes (S. pyogenes)*, more commonly referred to as 'strep throat,' in adults and pediatric patients 12 years or older.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of MOXATAG and other antibacterial drugs, MOXATAG should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria.

DOSAGE AND ADMINISTRATION

The recommended dose of MOXATAG is 775 mg once daily taken within 1 hour of finishing a meal for 10 days. MOXATAG should be taken approximately the same time every day. The full 10-day course of therapy should be completed for effective treatment of tonsillitis and/or pharyngitis secondary to *S. pyogenes*.

Do not chew or crush tablet.

CONTRAINDICATIONS

MOXATAG is contraindicated in patients with known serious hypersensitivity to amoxicillin or to other drugs in the same class or patients who have demonstrated anaphylactic reactions to beta-lactams.

WARNINGS AND PRECAUTIONS

Anaphylaxis and Hypersensitivity Reactions

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients on penicillin therapy. Although anaphylaxis is more frequent following parenteral therapy, it has occurred in patients on oral penicillins. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and/or a history of sensitivity to multiple allergens. There have been reports of individuals with a history of penicillin hypersensitivity who have experienced severe reactions when treated with cephalosporins. Before initiating therapy with MOXATAG, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, or other allergens. If an allergic reaction occurs, MOXATAG should be discontinued and appropriate therapy instituted.

***Clostridium difficile* Associated Diarrhea (CDAD)**

Clostridium difficile Associated Diarrhea (CDAD) has been reported with nearly all antibacterial agents, including amoxicillin, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued.

Superinfections

The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur, amoxicillin should be discontinued and appropriate therapy instituted.

Mononucleosis Rash

A high percentage of patients with mononucleosis who receive ampicillin develop an erythematous skin rash. Thus, ampicillin-class antibiotics should not be administered to patients with mononucleosis.

Development of Drug-Resistant Bacteria

Prescribing amoxicillin in the absence of proven or strongly suspected bacterial infection or treating prophylactically is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

False-Positive Urinary Glucose Tests

High urine concentrations of ampicillin may result in false-positive reactions when testing for the presence of glucose in urine using Clinitest®, Benedict's Solution or Fehling's Solution. Since this effect may also occur with amoxicillin, it is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix®) be used.

ADVERSE REACTIONS

In a controlled Phase 3 trial, 302 adult and pediatric patients (≥12 years) were treated with MOXATAG 775 mg once-daily for 10 days. The most frequently reported adverse reactions (>1%) which were suspected or probably drug-related are vaginal yeast infection (2.0%), diarrhea (1.7%), nausea (1.3%) and headache (1.0%).

DRUG INTERACTIONS

Probenecid

Probenecid decreases the renal tubular secretion of amoxicillin. Concurrent use of MOXATAG and probenecid may result in increased and prolonged blood levels of amoxicillin.

Other Antibiotics

Chloramphenicol, macrolides, sulfonamides, and tetracyclines may interfere with the bacterial effects of penicillin. This has been demonstrated *in vitro*; however, the clinical significance of this interaction is not well documented.

Oral Contraceptives

As with other antibiotics, amoxicillin may affect the gut flora, leading to lower estrogen reabsorption and potentially resulting in reduced efficacy of combined oral estrogen/progesterone contraceptives.

USE IN SPECIFIC POPULATIONS

Pregnancy: Teratogenic Effects. Pregnancy Category B.

Reproduction studies have been performed in mice and rats at doses up to 2000 mg/kg (12.5 and 25 times the human dose in mg/m^2) and have revealed no evidence of impaired fertility or harm to the fetus due to amoxicillin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery

It is not known whether use of amoxicillin in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor, or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary.

Nursing Mothers

Penicillins have been shown to be excreted in human milk. Amoxicillin use by nursing mothers may lead to sensitization of infants. Caution should be exercised when amoxicillin is administered to a nursing woman.

Pediatric Use

The safety and effectiveness of MOXATAG in pediatric patients 12 years of age and older have been established based on results of a clinical trial that included adults and pediatric patients (12 years or older). The safety and effectiveness of MOXATAG in pediatric patients younger than 12 years has not been established.

Geriatric Use

This drug is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Renal Impairment

MOXATAG has not been studied in patients with renal impairment; however, a reduction of amoxicillin dose is generally recommended for patients with severe renal impairment. Therefore, MOXATAG is not recommended for use in patients with severe renal impairment (CrCl <30 mL/min) or patients on hemodialysis.

OVERDOSAGE

In case of overdose, discontinue medication, treat symptomatically, and institute supportive measures as required. If the overdose is very recent and there is no contraindication, an attempt at emesis or other means of removal of drug from the stomach may be performed.

Interstitial nephritis resulting in oliguric renal failure has been reported in a small number of patients after overdosage with amoxicillin.

Crystalluria, in some cases leading to renal failure, has also been reported after amoxicillin overdosage in adult and pediatric patients.

Renal impairment appears to be reversible with cessation of drug administration. High blood levels may occur more readily in patients with impaired renal function because of decreased renal clearance of amoxicillin.

For additional information about overdose treatment, call a poison control center (1-800-222-1222).

HOW SUPPLIED/STORAGE AND HANDLING

MOXATAG tablets for oral administration are provided as blue film-coated, oval-shaped tablets that contain 775 mg of amoxicillin. The tablets are printed with "MB-111" on one side in black edible ink. MOXATAG is packaged in bottles as follows:

Presentation	NDC Code
Bottles of 30	11042-142-03

Storage

Store at 25º C (77º F); excursions permitted to 15–30º C (59–86º F) [See USP Controlled Room Temperature.]

MiddleBrook PHARMACEUTICALS®
Germantown, Maryland 20876 USA

U.S. Patents 6,544,555; 6,669,948; 6,723,341

Issue Date 02/2009
910-0209-0075
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