

Criteria Aid in UTI Prescribing Over the Phone

BY KATE JOHNSON

MONTREAL — Uncomplicated urinary tract infections can be diagnosed and treated by a medical assistant over the telephone with no increased risk to the patient and at a substantial cost savings, according to the findings of a randomized, controlled trial.

Patients had similar outcomes and levels of satisfaction regardless of whether

they were randomly assigned to be treated in house or over the telephone, according to the findings that were presented at a poster at the annual meeting of the North American Primary Care Research Group.

“There was no statistically significant difference between the groups,” said co-investigator Dr. Chandrika Iyer from St. John Hospital and Medical Center in Detroit.

The literature shows that women have a 50% likelihood of having a urinary tract infection (UTI) if they present with at least one of the following symptoms: dysuria, urgency, frequency, or abdominal pain, Dr. Iyer said in an interview.

With the specific combination of dysuria and frequency, and in the absence of vaginal discharge or itching, there is a 90% likelihood of UTI (JAMA 2002; 287:2701-10). “Physical examination and

lab testing don’t add much more,” she continued.

To test this observation, the study was conducted at two primary care centers: the Masonic Medical Center, in St. Clair Shores, Mich., a private practice; and the Family Medical Center in Detroit, a family medicine residency clinic.

A total of 122 women, aged 18-65 years, who called the clinic with symptoms of uncomplicated UTI, were invited to participate and screened for inclusion. Exclusion criteria were pregnancy, diabetes, kidney disease, UTI in the past month, bladder catheterization in the past 6 months, chemotherapy, vaginal discharge, flank pain, fever, chills, vomiting, or nausea. A total of 36 patients were excluded and 5 declined to participate, leaving 81 patients (mean age 39 years) to be randomized to either office or telephone treatment.

Participants in the telephone treatment arm were managed by a medical assistant who called or faxed a prescription to the patients’ pharmacy. Treatment included 3 days of trimethoprim and sulfamethoxazole (Bactrim DS), one tablet twice daily, or, in the case of sulfa allergy, ciprofloxacin 500 mg twice daily. Questionable cases were reviewed with the patient’s assigned physician or the principal investigator.

Patients randomized to office treatment had a regular visit with a primary care physician, where urine analyses and cultures were performed and treatment was prescribed.

In the case of persistent symptoms, women in both groups were instructed to call the clinic and be seen by their physician.

All women were called 1 week after treatment for a survey about their symptoms and satisfaction with treatment.

Ten patients did not follow up after treatment, and one patient was later diagnosed with vaginitis. Of the remaining participants, there were no statistically significant differences between groups in the rate of symptom resolution (80% with the telephone treatment versus 70% with office treatment), or complete satisfaction (86% with telephone treatment versus 79% with office treatment). Eighty percent of the telephone treatment group and 85% of the office treatment group said they would like the same treatment next time.

A cost comparison of both strategies revealed a saving of between \$49 and \$133 per patient in the telephone treatment group, Dr. Iyer said. This was calculated based on an office visit code of 99212 or 99213, at a cost of \$34 or \$68, respectively (excluding patient copayment). The average patient copayment ranges from \$10 to \$20. In addition, urine analysis costs up to \$5 and urine cultures cost up to \$40.

With an estimated 8.5 million women seeking care for bladder infections each year, at a cost of about \$2.5 million, telephone treatment is an appealing alternative to office-based management, Dr. Iyer said.

The incidence of adverse events was not dose-related and did not correlate with gender, age, or race of patients.

The incidence of cough occurring with telmisartan in 6 placebo-controlled trials was identical to that noted for placebo-treated patients (1.6%).

In addition to those listed above, adverse events that occurred in >0.3% of 3500 patients treated with telmisartan monotherapy in controlled or open trials are listed below. It cannot be determined whether these events were causally related to telmisartan tablets: **Autonomic Nervous System:** impotence, increased sweating, flushing; **Body as a Whole:** allergy, fever, leg pain, malaise; **Cardiovascular:** palpitation, dependent edema, angina pectoris, tachycardia, leg edema, abnormal ECG; **CNS:** insomnia, somnolence, migraine, vertigo, paresthesia, involuntary muscle contractions, hypoesthesia; **Gastrointestinal:** flatulence, constipation, gastritis, vomiting, dry mouth, hemorrhoids, gastroenteritis, enteritis, gastroesophageal reflux, toothache, non-specific gastrointestinal disorders; **Metabolic:** gout, hypercholesterolemia, diabetes mellitus; **Musculoskeletal:** arthritis, arthralgia, leg cramps; **Psychiatric:** anxiety, depression, nervousness; **Resistance Mechanism:** infection, fungal infection, abscess, otitis media; **Respiratory:** asthma, bronchitis, rhinitis, dyspnea, epistaxis; **Skin:** dermatitis, rash, eczema, pruritus; **Urinary:** micturition frequency, cystitis; **Vascular:** cerebrovascular disorder; and **Special Senses:** abnormal vision, conjunctivitis, tinnitus, earache.

During initial clinical studies, a single case of angioedema was reported (among a total of 3781 patients treated).

Clinical Laboratory Findings

In placebo-controlled clinical trials, clinically relevant changes in standard laboratory test parameters were rarely associated with administration of telmisartan tablets.

Hemoglobin: A greater than 2 g/dL decrease in hemoglobin was observed in 0.8% telmisartan patients compared with 0.3% placebo patients. No patients discontinued therapy due to anemia.

Creatinine: A 0.5 mg/dL rise or greater in creatinine was observed in 0.4% telmisartan patients compared with 0.3% placebo patients. One telmisartan-treated patient discontinued therapy due to increases in creatinine and blood urea nitrogen.

Liver Enzymes: Occasional elevations of liver chemistries occurred in patients treated with telmisartan; all marked elevations occurred at a higher frequency with placebo. No telmisartan-treated patients discontinued therapy due to abnormal hepatic function.

Cardiovascular Risk Reduction Trials

In clinical studies with patients at high risk of developing major cardiovascular events, cases of sepsis, including some with fatal outcomes, have been reported.

Amlodipine

Amlodipine has been evaluated for safety in more than 11,000 patients in U.S. and foreign clinical trials. Most adverse reactions reported during therapy with amlodipine were of mild or moderate severity. In controlled clinical trials directly comparing amlodipine (n=1730) in doses up to 10 mg to placebo (n=1250), discontinuation of amlodipine due to adverse reactions was required in only about 1.5% of amlodipine-treated patients and was not significantly different from that seen in placebo-treated patients (about 1%). The most common side effects were headache and edema. The incidence (%) of side effects which occurred in a dose-related manner are presented in Table 3.

Table 3: Incidence (%) of Side Effects with Amlodipine at Doses of 2.5 mg, 5.0 mg, and 10.0 mg or Placebo

Adverse Event	Amlodipine 2.5 mg n=275	Amlodipine 5.0 mg n=296	Amlodipine 10.0 mg n=268	Placebo n=520
Edema	1.8	3.0	10.8	0.6
Dizziness	1.1	3.4	3.4	1.5
Flushing	0.7	1.4	2.6	0.0
Palpitations	0.7	1.4	4.5	0.6

Other adverse experiences which were not clearly dose related but which were reported with an incidence greater than 1% in placebo-controlled clinical trials are presented in Table 4.

Table 4: Incidence (%) of Adverse Experiences Not Clearly Dose Related but Reported at an Incidence of >1% in Placebo-controlled Clinical Trials

Adverse Event	Amlodipine (n=1730)	Placebo (n=1250)
Headache	7.3	07.8
Fatigue	4.5	2.8
Nausea	2.9	1.9
Abdominal pain	1.6	0.3
Somnolence	1.4	0.6

The following events occurred in <1% but >0.1% of patients in controlled clinical trials or under conditions of open trials or marketing experience where a causal relationship is uncertain; they are listed to alert the physician to a possible relationship:

Cardiovascular: arrhythmia (including ventricular tachycardia and atrial fibrillation), bradycardia, chest pain, hypotension, peripheral ischemia, syncope, tachycardia, postural dizziness, postural hypotension, vasculitis; **Central and Peripheral Nervous System:** hypoesthesia, neuropathy peripheral, paresthesia, tremor, vertigo; **Gastrointestinal:** anorexia, constipation, dyspepsia, dysphagia, diarrhea, flatulence, pancreatitis, vomiting, gingival hyperplasia; **General:** allergic reaction, asthenia, back pain, hot flushes, malaise, pain, rigors, weight gain, weight decrease; **Musculoskeletal System:** arthralgia, arthrosis, muscle cramps, myalgia; **Psychiatric:** sexual dysfunction (male** and female), insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization; **Respiratory System:** dyspnea, epistaxis; **Skin and Appendages:** angioedema, erythema multiforme, pruritus, rash, rash erythematous, rash maculopapular; **Special Senses:** abnormal vision, conjunctivitis, diplopia, eye pain, tinnitus; **Urinary System:** micturition frequency, micturition disorder, nocturia; **Autonomic Nervous System:** dry mouth, sweating increased; **Metabolic and Nutritional:** hyperglycemia, thirst; **Hemopoietic:** leukopenia, purpura, thrombocytopenia.

**These events occurred in less than 1% in placebo-controlled trials, but the incidence of these side effects was between 1% and 2% in all multiple dose studies.

The following events occurred in <0.1% of patients: cardiac failure, pulse irregularity, extrasystoles, skin discoloration, urticaria, skin dryness, alopecia, dermatitis, muscle weakness, twitching, ataxia, hypertension, migraine, cold and clammy skin, apathy, agitation, amnesia, gastritis, increased appetite, loose stools, coughing, rhinitis, dysuria, polyuria, parosmia, taste perversion, abnormal visual accommodation, and xerophthalmia.

Other reactions occurred sporadically and cannot be distinguished from medications or concurrent disease states such as myocardial infarction and angina.

Amlodipine has not been associated with clinically significant changes in routine laboratory tests. No clinically relevant changes were noted in serum potassium, serum glucose, total triglycerides, total cholesterol, HDL cholesterol, uric acid, blood urea nitrogen, or creatinine.

Amlodipine has been used safely in patients with chronic obstructive pulmonary disease, well-compensated congestive heart failure, coronary artery disease, peripheral vascular disease, diabetes mellitus, and abnormal lipid profiles.

Adverse reactions reported for amlodipine for indications other than hypertension may be found in the prescribing information for Norvasc®.

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of telmisartan or amlodipine. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate reliably their frequency or establish a causal relationship to drug exposure. Decisions to include these reactions in labeling are typically based on one or more of the following factors: (1) seriousness of the reaction, (2) frequency of reporting, or (3) strength of causal connection to telmisartan or amlodipine.

Telmisartan

The most frequently spontaneously reported events include: headache, dizziness, asthenia, coughing, nausea, fatigue, weakness, edema, face edema, lower limb edema, angioneurotic edema, urticaria, hypersensitivity, sweating increased, erythema, chest pain, atrial fibrillation, congestive heart failure, myocardial infarction, blood pressure increased, hypertension aggravated, hypotension (including postural hypotension), hyperkalemia, syncope, dyspepsia, diarrhea, pain, urinary tract infection, erectile dysfunction, back pain, abdominal pain, muscle cramps (including leg cramps), myalgia, bradycardia, eosinophilia, thrombocytopenia, uric acid increased, abnormal hepatic function/liver disorder, renal impairment including acute renal failure, anemia, and increased CPK, anaphylactic reaction, and tendon pain (including tendonitis, tenosynovitis).

Rare cases of rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers, including telmisartan.

Amlodipine

Gynecomastia has been reported infrequently and a causal relationship is uncertain. Jaundice and hepatic enzyme elevations (mostly consistent with cholestasis or hepatitis), in some cases severe enough to require hospitalization, have been reported in association with use of amlodipine.

USE IN SPECIFIC POPULATIONS

Pregnancy: Teratogenic Effects, Pregnancy Categories C (first trimester) and D (second and third trimesters). See Warnings and Precautions. **Nursing Mothers: Telmisartan:** It is not known whether telmisartan is excreted in human milk, but telmisartan was shown to be present in the milk of lactating rats. Because of the potential for adverse effects on the nursing infant, decide whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother. **Amlodipine:** It is not known whether amlodipine is excreted in human milk. In the absence of this information, it is recommended to discontinue nursing while amlodipine is administered. **Pediatric Use:** Safety and effectiveness of TWYNSTA in pediatric patients have not been established. **Geriatric Use: TWYNSTA Tablets:** Of the total number of 3282 hypertensive patients receiving a telmisartan/amlodipine combination in clinical studies, 605 (18%) patients were 65 years of age or older and of these, 88 (3%) patients were 75 years and older. No overall differences in efficacy or safety of TWYNSTA tablets were observed in this patient population. **Telmisartan:** Of the total number of patients receiving telmisartan in clinical studies, 551 (18.6%) were 65 to 74 years of age and 130 (4.4%) were 75 years and older. No overall differences in effectiveness and safety were observed in these patients compared to younger patients and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. **Amlodipine:** Clinical studies of amlodipine besylate tablets did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy. Elderly patients have decreased clearance of amlodipine with a resulting increase of AUC of approximately 40-60%, and a lower initial dose may be required. Since patients age 75 and older have decreased clearance of amlodipine, start amlodipine or add amlodipine 2.5 mg to telmisartan. The lowest dose of TWYNSTA is 40/5 mg; therefore, initial therapy with TWYNSTA tablets is not recommended in patients 75 years of age and older. **Hepatic Insufficiency:** Monitor carefully and up-titrate slowly in patients with biliary obstructive disorders or hepatic insufficiency. Since patients with hepatic impairment have decreased clearance of amlodipine, start amlodipine or add amlodipine 2.5 mg to telmisartan. The lowest dose of TWYNSTA is 40/5 mg; therefore, initial therapy with TWYNSTA tablets is not recommended in hepatically impaired patients. **Race:** The magnitude of blood pressure lowering in black patients approached that observed in non-black patients but the number of black patients was limited (237 of 1461 patients).

OVERDOSAGE

Telmisartan

Limited data are available with regard to overdosage in humans. The most likely manifestations of overdosage with telmisartan tablets would be hypotension, dizziness, and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted. Telmisartan is not removed by hemodialysis.

Amlodipine

Single oral doses of amlodipine maleate equivalent to 40 mg/kg and 100 mg/kg amlodipine in mice and rats, respectively, caused deaths. Single oral doses equivalent to 4 or more mg/kg amlodipine in dogs (11 or more times the maximum recommended human dose on a mg/m² basis) caused a marked peripheral vasodilation and hypotension.

Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension. In humans, experience with intentional overdosage of amlodipine is limited. Reports of intentional overdosage include a patient who ingested 250 mg and was asymptomatic and was not hospitalized; another (120 mg) who was hospitalized and underwent gastric lavage and remained normotensive; the third (105 mg) was hospitalized and had hypotension (90/50 mmHg) which normalized following plasma expansion. A case of accidental drug overdosage has been documented in a 19-month-old male who ingested 30 mg amlodipine (about 2 mg/kg). During the emergency room presentation, vital signs were stable with no evidence of hypotension, but a heart rate of 180 bpm. Ipecac was administered 3.5 hours after ingestion and on subsequent observation (overnight) no sequelae was noted.

If massive overdose should occur, active cardiac and respiratory monitoring should be instituted. Frequent blood pressure measurements are essential. Should hypotension occur, cardiovascular support including elevation of the extremities and the judicious administration of fluids should be initiated. If hypotension remains unresponsive to these conservative measures, administration of vasopressors (such as phenylephrine) should be considered with attention to circulating volume and urine output. Intravenous calcium gluconate may help to reverse the effects of calcium entry blockade. As amlodipine is highly protein bound, hemodialysis is not likely to be of benefit.

Rx only



Copyright © 2009, Boehringer Ingelheim International GmbH

ALL RIGHTS RESERVED

Rev: October 2009

MC-BS (10-09)

TW67787