Gynecology OB.GYN. NEWS • July 15, 2005

TMP-SMX Resistance in UTIs 'May Be Leveling Off'

BY ELIZABETH MECHCATIE

Senior Writer

WASHINGTON — The prevalence of urinary tract infections in women resistant to standard treatment has been increasing, but there are indications that the increase has begun to level off, Patricia D. Brown, M.D., said at an update on sexually transmitted infections.

Emerging uropathogenic Escherichia coli antimicrobial resistance—particularly to

the front-line, first-choice treatment of urinary tract infections (UTIs), trimethoprim-sulfamethoxazole (TMP-SMX)—has been documented worldwide. However, much of the data are based on passive surveillance, which can overestimate prevalence, because women with acute, uncomplicated UTIs often do not have cultures performed, so these cases are not reported, said Dr. Brown of Wayne State University, Detroit.

Women who do have a culture have

complicated disease and fail treatment, leading to overestimates of true prevalence, she added. Still, passive surveillance can provide information on trends.

In the United States, active surveillance has been conducted in specific geographic areas, where the true prevalence may not reflect that of other geographic areas, Dr. Brown said at the meeting, sponsored by OB.GYN. NEWS, FAMILY PRACTICE NEWS, and Boston University.

Recent studies indicate that TMP-SMX

References: 1. AMBIEN Prescribing Information, Sanofi-Synthelabo Inc. 2. Roth T, Roehrs T, Vogel G. Zolpidem in the treatment of transient insomnia: a double-blind, randomized comparison with placebo. Sleep. 1995;18:246-251. 3. Office of Applied Studies, Drug Abuse Warning Network (DAWN). Substance Abuse and Mental Health Services Administration, US Department of Health and Human Services. Reports & tables from DAWN emergency department component. Table 2.6.0. Available at: http://dawninfo.samhsa.gov/pubs_94_02/edpubs/2002final/files/PubTablesCh2.xls. Accessed December 9, 2003. 4. Hajak G, Müller WE, Wittchen HU, Pittrow D, Kirch W. Abuse and dependence potential for the non-benzodiazepine hypnotics zolpidem and zopidone: a review of case reports and epidemiological data. Addiction. 2003;98:1371-1378. 5. IMS Health, National Prescription Audit Plus, MAT May 2004. 6. Data on file, Sanofi-Synthelabo Inc.



BRIEF SUMMARY

INDICATIONS AND USAGE

Ambien (zolpidem tartrate) is indicated for the short-term treatment of insomnia.
Ambien has been shown to decrease sleep latency and increase the duration of seep for up to 55 days in controlled clinical studies.
Hypnotics should generally be limited to 7 to 10 days of use, and reevaluation of the patient is recommended if if they are to be taken for more than 2 to 3 weeks.
Ambien should not be prescribed in quantities exceeding a 1-month supply (see Warnions)

CONTRAINDICATIONS

None known.

WARNINGS

Since sleep disturbances may be the presenting manifestation of a physical and/or psychiatric disorder, symptomatic treatment of insomnia should be initiated only after a careful evaluation of the patient. The failure of insomnia to remit after 7 to 10 days of treatment may indicate the presence of a primary psychiatric and/or medical filmess which should be evaluated. Worsening of insomnia or the emergence of new thinking or behavior abnormalities may be the consequence of an unrecognized psychiatric or physical disorder. Such findings have emerged during the course of treatment with seddive/hypnotic drugs, including Ambien. Because some of the important adverse effects of Ambien appear to be dose related (see Precautions and Dosage and Administration), it is important to use the smallest possible effective dose, especially in the delert, A variety of abnormal thinking and behavior changes have been reported to occur in association with the use of sedative/hypnotics. Some of these changes may be characterized by decreased inhibition (eg., aggressiveness and extroversion that seemed out of character), similar to effects produced by alcohol and other CNS depressants. Other reported behavioral changes have included bizarre behavior, agitation, hallucinations, and depersonalization. Amnesia and other neuropsychiatric symptoms may occur unpredictably. In primarily depressed patents, vorsening of depression, including suicidal thinking, has been reported in association with the use of sedative/hypnotics.

I can rarely be determined with certainty whether a particular instance of the abnormal behaviors listed above is drug induced, spontaneous in origin, or a result of an underlying psychiatric or physical disorder. Nonetheless, the emergence of any new behavioral sign or symptom of concern requires careful an immediate evaluation.

ad with withdrawal from other CNS-depressant drugs (see *Drug Abuse and penalence*).

Ambien, like other sedative/hypnotic drugs, has CNS-depressant effects. Due the rapid onset of action, Ambien should only be ingested immediately prior going to bed. Patients should be cautioned against engaging in hazardous cupations requiring complete mental alertness or motor coordination such as erating machinery or driving a motor vehicle after ingesting the drug, includgo the time of the performance of such activities that may occur the y following ingestion of Ambien. Ambien showed additive effects when comeled with alcohol and should not be taken with alcohol. Patients should also be utioned about possible combined effects with other CNS-depressant drugs, sage adjustments may be necessary when Ambien is administered with such ents because of the potentially additive effects.

Laboratory tests: There are no specific laboratory tests recommended.

gypanacy ratogenic effects: Category B. Studies to assess the effects of zolpidem on man reproduction and development have not been conducted. Teratology studies were conducted in rats and rabbits. In rats, adverse maternal and fetal effects occurred at 20 and 100 mg base/kg d included dose-related maternal lethargy and ataxia and a dose-related trend incomplete ossification of fetal skull bones. to incomplete ossification of fetal skull bones.

In rabbits, dose-related maternal sedation and decreased weight ge occurred at all doses tested. At the high dose, 16 mg basekg, there was increase in postimplantation fetal loss and underossification of sternebrae viable fetuses.

This drug should be used during pregnancy only if clearly needed.

Nursing mothers: Studies in lactating mothers indicate that between 0.004 and 0.019% of the total administered dose is excreted into milk, but the effect of zolpi-

have not been established.

Geriatric use: A total of 154 patients in U.S. controlled clinical trials and 897 patients in non-U.S. clinical trials who received zolpidam were ≥60 years of age. For a pool of U.S. patients receiving zolpidam at doese of ≤10 mg or placebo, there were three adverse events occurring at an incidence of at least 3% for zolpidem and for which the zolpidem incidence was at least twice the placebo incidence (i.e., they could be considered drug related).

Adverse Event	Zolpidem	Placebo
Dizziness	3%	0%
Drowsiness	5%	2%
Diarrhea	3%	1%

Typicaniatry 470 01 1,999 patients who received zolpidem at all doses (1 to 50 mg) in similar foreign trials discontinued treatment because of an adverse event. Events most commonly associated with discontinuation from these trials were daytime drowsiness (1.1%), dizziness/vertigo (0.8%), amnesia (0.5%), nausea (0.5%), hadeadche (0.4%), and falls (0.4%).

Data from a clinical study in which selective serotonin reuptake inhibitor (SSRI) treated patients were given zolpidem revealed that four of the seven discontinuations during double-thind treatment with zolpidem (n=95) were associated with impaired concentration, continuing or aggravated depression, and manic reaction; one patient treated with placebo (n=97) was discontinued after an attempted suicide.

events.

Adverse events are further dassified and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are defined as those occurring in greater than 1/100 subjects; infrequent adverse events are those occurring in 1/100 to 1/1,000 patients; rare events are those occurring in less than 1/1,000 patients.

palpitation, sleep disorder, vertigo, vision abnormal, vomiting, Infrequent: abnormal hepatic function, agitation, arthritis, bronchitis, cere-brovascular disorder, coughing, cystifis, decreased cognition, detached, difficul-ty concentrating, dysarthria, dysphagia, dyspnea, edema, emotional lability, eye irritation, eye pain, falling, fever, flatulence, gastroenterrits, hallucination, hyper-glycemia, hypertension, hypoesthesia, illusion, increased SGPT, increased sweating, leg carmps, malaise, menstrual disorder, migraine, pallor, paresthesia, postural hypotension, pruritus, scleritis, sleeping (after daytime dosing), speech disorder, stupor, syncope, tachycardia, taste perversion, thirst, tinnitus, trauma, tremor, urinary incontinence, vaginitis.

ymptomatology, including fatal outcomes, ecommended treatment. General symptomatic and supportive measures nould be used along with immediate gastric lavage where appropriate, travenous fluids should be administered as needed. Flumazenil may be useful. sepiration, pulse, blood pressure, and other appropriate signs should be mon-ored and general supportive measures employed. Sedating drugs should be rithhald following zolpidem overdosage. Zolpidem is not dialyzable. The possibility of multiple drug ingestion should be considered.

sanofi~synthelabo

resistance "may be leveling off" after peaking at about 25%, which is probably because of the reduced use of this treatment, she said. But as the use of TMP-SMX for UTIs has decreased, resistance to other antimicrobial agents has been increasing.

In 890 isolates from women with UTIs in the United States who were a part of the North American Urinary Tract Infection Collaborative Alliance (NAUTICA) study, the prevalence of TMP-SMX resistance was about 23%. Resistance to ampicillin was 38%, and resistance to levofloxacin was nearly 7%.

As the use of TMP-SMX has dropped, the use of fluoroquinolones has increased, Dr. Brown said, noting that rates of resistance to β -lactams such as ampicillin have been high for some time. In the NAUTI-CA study, resistance to nitrofurantoin was only 1.8%, which she said was "remarkable," considering that it has been available for about 50 years. But that rate has probably remained so low because the agent has several mechanisms of action and is indicated only for cystitis, she noted.

There are several clinical implications of these resistance trends: In treatment studies of pyelonephritis, antimicrobial resistance has clearly been shown to increase

The prevalence of TMP-SMX resistance was about 23%; resistance to ampicillin was 38%, and resistance to levofloxacin was nearly 7%. the risks of both clinical and microbiologic failure, she said. She cited a retrospective cohort study of women with acute uncomplicated cystitis, in which the risk of clinical failure was 45.4%, and a prospective study in Israel of empiric

TMP-SMX in an area where the prevalence of resistance was high, in which the risk of clinical failure was 46%.

Identifying risk factors for resistance can help guide antibiotic choice, she said, referring to the difficulty facing clinicians, who usually do not have access to resistance trends and who likely will be given an overestimate of resistance if they call their local microbiology lab.

Results of retrospective case-control studies have identified potential risk factors for infection with a uropathogen resistant to TMP-SMX. Two risk factors found in every such study include recent antibiotic use and recent hospitalization, she said. Recent travel to underdeveloped countries has been identified as an independent risk factor in several studies.

The standard treatment for uncomplicated cystitis is 3 days of double-strength formulations of TMP-SMX twice a day. Avoid empiric treatment with TMP-SMX in patients who have recently been hospitalized or have taken antibiotics in the previous 3 months, she said.

Alternative treatments for those with risk factors for resistance are a 7-day course of nitrofurantoin or a 3-day course of a fluoroquinolone. The major drawback of the Continued on following page

Gynecology

Survey: Prevalence of Fecal Incontinence Is 7%

BY SHERRY BOSCHERT

San Francisco Bureau

RANCHO MIRAGE, CALIF. — The prevalence of fecal incontinence ranged from 3% of women in their 30s and 40s to nearly 15% of women in their 80s and 90s in the first large epidemiologic study of fecal incontinence among women living in a U.S. community.

Overall, more than 7% of the 3,536 women who returned mailed surveys reported fecal incontinence, defined as accidental loss of stool at least monthly. Of those with fecal incontinence, 47% said they used pads for sanitary protection, and 53% said the problem caused them to alter their lifestyle, Jennifer Melville, M.D., and her associates reported in a poster presentation at the annual meeting of the Society of Gynecologic Surgeons.

"Fecal incontinence is very prevalent and causes significant quality-of-life impacts," said Dr. Melville of the University Washington, Seattle, during an oral presentation in which she discussed the findings at the meeting. Physicians can assist women by helping to manage the problem, she added.

The responses made up 64% of 6,000 surveys mailed to women aged 30-90 years

Continued from previous page

former is that a full-week course is necessary. As for the fluoroquinolones, ciprofloxacin is available in generic formulations, so it is less expensive. The Food and Drug Administration has approved gatifloxacin as a single-dose treatment for uncomplicated cystitis. One fluoroquinolone that should not be used for UTI is moxifloxacin, which is indicated for respiratory infections, because treatment results in low levels of the drug in the urinary tract.

A single dose of fosfomycin is another alternative, but this is considered a second-line treatment because the efficacy is not that high and it is expensive. One benefit, however, is that resistance to this agent appears to be low, Dr. Brown said.

Short-course treatment is not appropriate for complicated cystitis, which should be treated with a 7-day course of therapy, she said. Avoid empiric TMP-SMX treatment in patients who have recently been treated with antibiotics or have recently been hospitalized, as you would for uncomplicated cystitis. Culture all patients, and adjust treatment based on susceptibility data, she said.

As many as 25% of women with acute cystitis can develop frequent, recurrent UTIs, which are reinfections, not relapses. (Fewer than 5% of these women have a correctable structural or functional abnormality of the urinary tract.) Management strategies include daily or postcoital prophylaxis and self-start therapy for women concerned about developing a UTI when they are away from home, she added.

Contraceptive methods should be evaluated, Dr. Brown said. She also considers prescribing topical estrogen for postmenopausal women who have recurrent UTIs.

who were enrolled in a nonprofit HMO in Washington state, GroupHealth Cooperative. The surveys asked specifically about fecal incontinence, not anal incontinence, which includes flatus. Of the women with fecal incontinence, 37% said they had daily or weekly episodes of incontinence. They were incontinent of liquid stool in 47% of cases, solid stool in 23% of cases, and both liquid and solid in 30% of cases.

An analysis of the HMO's automated data on the respondents showed that the

women with fecal incontinence were twice as likely to have moderate medical illness and nearly three times as likely to have high-level comorbidity when compared with continent women.

Moreover, women with fecal incontinence were twice as likely to have urinary incontinence and three times as likely to have major depressive disorder as were continent women.

A history of operative vaginal delivery raised the risk for fecal incontinence 58%.

Women with fecal incontinence were more likely to report significant functional impairments, measured in the survey using the World Health Organization Disability Assessment Schedule II. The mean scores on this measure were 24 for women with fecal incontinence and 11 for continent women. The scores for incontinent women are comparable to scores for people with disabling medical conditions like chronic back pain or ankylosing spondylitis, Dr. Melville said.

