

Unexpected Complications With TOT Reported

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MONTREAL — Although the complication rate remains low with the use of transobturator tape to treat stress urinary incontinence, unexpected complications are beginning to emerge as this treatment becomes more widely used, according to Sarah Hamilton Boyles, M.D., an instructor and fellow in obstetrics and gynecology at Oregon Health and Science

University's Center for Women's Health in Portland.

"There are documented cases of complications that the companies had said could not occur, and it's important that we are all aware of these complications," Dr. Hamilton Boyles said in an interview.

In a study she presented at the annual meeting of the International Continence Society, Dr. Hamilton Boyles searched the Manufacturer and User Facility Device Experience (MAUDE) database to identi-

fy all complications reported with the use of three transobturator tape (TOT) techniques available in the United States. These included ObTape (manufactured by Mentor, Minneapolis), Monarc (American Medical Systems, Minnetonka, Minn.), and the TVT Obturator System (Gynecare, Somerville, N.J.).

MAUDE, maintained by the Food and Drug Administration, collects voluntary physician reports and mandatory reports from manufacturers, distributors, and

user facilities. A review of published literature revealed that documented complications with TOT are low, and include bladder, urethra, and vaginal perforation; vaginal and urethral erosion; thigh pain; infection; urinary retention; and bleeding of 200-300 cc, she said. In addition, many of these problems were associated with a different TOT (UraTape), which is no longer on the market.

However, her search of MAUDE revealed some other unexpected complications. "Unique complications that are only easily discovered when searching a large surgical database such as MAUDE were found in the categories of infection, neuropathy, and bleeding," she reported.

The study revealed 173 reports of complications in 140 patients from January 2004 to January 2005. Among the complications were 25 cases of infection, 4 cases of neuropathy, and 5 cases of bleeding. A total of 18 of the infection cases were associated with erosion, including one vaginal abscess just below the mucosa and 2 ischioanal fossa abscesses occurring remote from placement at about 2 months post procedure—both of which required surgical drainage.

There were two other abscesses not associated with erosion. Both of these occurred by the adductor muscle and also required surgical drainage. And five other infections were not specified.

Among the neuropathy cases, two involved gait difficulty, one of these with a confirmed obturator injury. In addition, there was a case of peripheral numbness, and one other case which was not specified.

Among the bleeding cases, the procedure was aborted in one case after an estimated blood loss of 600 cc during urethral dissection.

Another case involved an estimated blood loss of 650 cc during the pass of the right trocar. In addition, there was one injury to the iliac vessel that required embolization, another case involving a hemoglobin drop to 4 g/dL during the procedure, and another case of an unspecified hematoma, Dr. Hamilton Boyles said.

She cautioned that a comparison of complications according to technique is impossible since the MAUDE database records only reported complications and did not record what percentage they represent of the total number of procedures performed.

However, among the 25 infection cases and 105 erosion cases reported to the database, 22 and 99, respectively, occurred with the ObTape. In addition, all three of the urethral injuries, three of the four cases of neuropathy, and eight of the nine reports of pain occurred with the TVT Obturator System.

"Even though the overall rate of complications is low, because so many of these procedures are done, it is societally important to know about them," she said.

A recent survey of members of the International Urogynecology Association revealed that although tension-free vaginal tape is the most popular treatment for stress urinary incontinence, 13% of respondents preferred TOT, she said (Eur Urol. 2005;47:648-52).

ZOVIRAX® (acyclovir) Ointment 5% Begins to Comfort on Contact to Heal Herpes Fast

Symptoms With Primary First Episode of Genital Herpes¹

Duration vs Placebo*

Itching	4.4 days shorter (P<0.01)
Pain	1.8 days shorter (P<0.05)
Lesion duration	4.6 days shorter (P<0.05)
Viral shedding from lesions	3.3 days shorter (P<0.001)

*Duration of itching: ZOVIRAX® Ointment (3.6 days) vs placebo (8.0 days) at primary first episode of genital herpes.

Duration of pain: ZOVIRAX® Ointment (5.2 days) vs placebo (7.0 days) at primary first episode of genital herpes.

Duration of lesion: ZOVIRAX® Ointment (11.2 days) vs placebo (15.8 days) at primary first episode of genital herpes.

Duration of viral shedding: ZOVIRAX® Ointment (2.3 days) vs placebo (5.6 days) at primary first episode of genital herpes.

Reference: 1. Corey L, Benedetti JK, Critchlow CW, et al. Double-blind controlled trial of topical acyclovir in genital herpes simplex virus infections. *Am J Med.* 1982;73:326-334.

ZOVIRAX® (acyclovir) Ointment 5%

INDICATIONS AND USAGE

ZOVIRAX (acyclovir) Ointment 5% is indicated in the management of initial genital herpes and in limited non-life-threatening mucocutaneous Herpes simplex virus infections in immunocompromised patients.

CONTRAINDICATIONS

ZOVIRAX Ointment 5% is contraindicated in patients who develop hypersensitivity to the components of the formulation.

WARNINGS

ZOVIRAX Ointment 5% is intended for cutaneous use only and should not be used in the eye.

PRECAUTIONS

General: The recommended dosage, frequency of applications, and length of treatment should not be exceeded (see DOSAGE AND ADMINISTRATION). There are no data to support the use of ZOVIRAX Ointment 5% to prevent transmission of infection to other persons or prevent recurrent infections when applied in the absence of signs and symptoms. ZOVIRAX Ointment 5% should not be used for the prevention of recurrent HSV infections. Although clinically significant viral resistance associated with the use of ZOVIRAX Ointment 5% has not been observed, this possibility exists.

Drug Interactions: Clinical experience has identified no interactions resulting from topical or systemic administration of other drugs concomitantly with ZOVIRAX Ointment 5%.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Systemic exposure following topical administration of acyclovir is minimal. Dermal carcinogenicity studies were not conducted. Results from the studies of carcinogenesis, mutagenesis, and fertility are not included in the full prescribing information for ZOVIRAX Ointment 5% due to the minimal exposures of acyclovir that result from dermal application. Information on these studies is available in the full prescribing information for ZOVIRAX Capsules, Tablets, and Suspension and ZOVIRAX for Injection.

Pregnancy: Teratogenic Effects: Pregnancy Category B. Acyclovir was not teratogenic in the mouse, rabbit, or rat at exposures greatly in excess of human exposure. There are no adequate and well-controlled studies of systemic acyclovir in pregnant women. A prospective epidemiologic registry of acyclovir use during pregnancy was established in 1984 and completed in April 1999. There

were 749 pregnancies followed in women exposed to systemic acyclovir during the first trimester of pregnancy resulting in 756 outcomes. The occurrence rate of birth defects approximates that found in the general population. However, the small size of the registry is insufficient to evaluate the risk for less common defects or to permit reliable or definitive conclusions regarding the safety of acyclovir in pregnant women and their developing fetuses. Systemic acyclovir should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether topically applied acyclovir is excreted in breast milk. Systemic exposure following topical administration is minimal. After oral administration of ZOVIRAX, acyclovir concentrations have been documented in breast milk in 2 women and ranged from 0.6 to 4.1 times the corresponding plasma levels. These concentrations would potentially expose the nursing infant to a dose of acyclovir up to 0.3 mg/kg per day. Nursing mothers who have active herpetic lesions near or on the breast should avoid nursing.

Geriatric Use: Clinical studies of ZOVIRAX Ointment 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. Systemic absorption of acyclovir after topical administration is minimal (see CLINICAL PHARMACOLOGY).

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

In the controlled clinical trials, mild pain (including transient burning and stinging) was reported by about 30% of patients in both the active and placebo arms; treatment was discontinued in 2 of these patients. Local pruritus occurred in 4% of these patients. In all studies, there was no significant difference between the drug and placebo group in the rate or type of reported adverse reactions nor were there any differences in abnormal clinical laboratory findings.

Observed During Clinical Practice: Based on clinical practice experience in patients treated with ZOVIRAX Ointment in the US, spontaneously reported adverse events are uncommon. Data are insufficient to support an estimate to their incidence or to establish causation. These events may also occur as part of the underlying disease process. Voluntary reports of adverse events that have been received since market introduction include:

General: Edema and/or pain at the application site.

Skin: Pruritus, rash.

OVERDOSAGE

Overdosage by topical application of ZOVIRAX Ointment 5% is unlikely because of limited transcutaneous absorption (see CLINICAL PHARMACOLOGY).

DOSAGE AND ADMINISTRATION

Apply sufficient quantity to adequately cover all lesions every 3 hours, 6 times per day for 7 days. The dose size per application will vary depending upon the total lesion area but should approximate a one-half inch ribbon of ointment per 4 square inches of surface area. A finger cot or rubber glove should be used when applying ZOVIRAX to prevent autoinoculation of other body sites and transmission of infection to other persons. **Therapy should be initiated as early as possible following onset of signs and symptoms.**

HOW SUPPLIED

Each gram of ZOVIRAX Ointment 5% contains 50 mg acyclovir in a polyethylene glycol base. It is supplied as follows:
15-g tubes (NDC 64455-993-94)
3-g tubes (NDC 64455-993-41)
Store at 15° to 25°C (59° to 77°F) in a dry place.

Manufactured by
GlaxoSmithKline
Research Triangle Park, NC 27709
for

BIOVAIL
Pharmaceuticals, Inc.
Bridgewater, NJ 08807

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