Letters to the Editor

Send letters to Kenny Lin, MD, Associate Medical Editor for *AFP* Online, e-mail: afplet@aafp.org, or 11400 Tomahawk Creek Pkwy., Leawood, KS 66211-2680.

Please include your complete address, e-mail address, telephone number, and fax number. Letters should be fewer than 500 words and limited to six references and one table or figure.

Letters submitted for publication in *AFP* must not be submitted to any other publication. Possible conflicts of interest must be disclosed at time of submission. Submission of a letter will be construed as granting the American Academy of Family Physicians permission to publish the letter in any of its publications in any form. The editors may edit letters to meet style and space requirements.

Do Vaginal Estrogens Increase Endometrial Proliferation Risk?

Original Article: Counseling Patients About Hormone Therapy and Alternatives for Menopausal Symptoms

Issue Date: October 1, 2010

Available at: http://www.aafp.org/afp/2010/1001/p801.html

TO THE EDITOR: I am concerned about a discrepancy in this article on the risk of endometrial proliferation with use of vaginal estrogens. In the Vulvovaginal Symptoms section, it says: "Physicians should reassure patients that vaginal estrogen does not cause endometrial proliferation and that adding a progestogen for endometrial protection is not necessary." However, the next paragraph states: "Vaginal administration of estradiol may cause an increase in serum estradiol levels in some patients, but data are lacking about the long-term risks of breast cancer, [venous thromboembolism], or endometrial proliferation for patients who use low-dose vaginal estrogen therapy."

I would like clarification about whether data on the risks of endometrial proliferation with vaginal estrogen use are unclear or not.

SONI ANDREINI POULSEN, MD
Arnold, Calif.
E-mail: andreiSL@ah.org

Author disclosure: No relevant financial affiliations to disclose.

IN REPLY: Dr. Andreini asks about the risk of endometrial proliferation with use of vaginal (topical) estrogen therapy for vulvovaginal symptoms. Patients using recommended doses of intravaginal estrogen to treat vulvovaginal atrophy have a very low risk of endometrial proliferation or hyperplasia. Numerous studies have compared the effectiveness and safety of various local estrogen formulations, including effects on the endometrium. However, it can be hard to evaluate these studies. Some use endometrial biopsy results, a robust indicator of proliferation or hyperplasia, whereas others use arguably less definitive indicators, such as bleeding after progestogen challenge testing or endometrial thickness measured by transvaginal sonography.

Data are available that used endometrial biopsy to assess the safety of local estrogen therapy. A Cochrane review of 19 trials found a nonsignificant 2 percent incidence of simple hyperplasia (vaginal ring versus cream) and a 4 percent incidence of hyperplasia (one simple, one complex) when conjugated equine estrogen cream (Premarin) was compared with an estradiol tablet.[1] Recent year-long studies of vaginal conjugated estrogen cream (423 patients) and low-dose estradiol vaginal tablets (292 patients) revealed no cases of endometrial hyperplasia or cancer as determined by endometrial biopsy.[2,3] These reassuring data have led several organizations to state that patients using only local estrogen do not need cotherapy with progestogens for endometrial protection.[4,5] However, as stated in our review, it is unknown if endometrial proliferation, hyperplasia, or malignancy can occur after long-term treatment (many years) with local estrogen.

Patients considering local estrogen therapy should be told that short-term data are reassuring that endometrial proliferation, hyperplasia, or malignancy appears to be rare (and nonexistent in several newer studies), but we recommend that they return for evaluation if unexpected vaginal bleeding occurs. We thank Dr. Andreini for the interest in our review.

D. ASHLEY HILL, MD
Orlando, Fla.
E-mail: D.Ashley.Hill.MD@FLHOSP.ORG

SUSAN R. HILL, MD
Orlando, Fla.

Author disclosure: No relevant financial affiliations to disclose.

REFERENCES

1. Suckling J, et al. Local oestrogen for vaginal atrophy in postmenopausal women. *Cochrane Database Syst Rev.* 2006;(4):CD001500.
2. Bachmann G, et al. Efficacy and safety of low-dose regimens of conjugated estrogens cream administered vaginally. *Menopause.* 2009;16(4):719-727.

3. Ulrich LS, et al.; VAG-1748 trial investigators. Endometrial safety of ultra-low-dose Vagifem 10 microg in postmenopausal women with vaginal atrophy. *Climacteric.* 2010;13(3):228-237.
4. Estrogen and progestogen use in postmenopausal women: 2010 position statement of The North American Menopause Society. *Menopause.* 2010;17(2):242-255.
5. Reid RL, et al.; Society of Obstetricians and Gynaecologists of Canada. Menopause and osteoporosis update 2009. *J Obstet Gynaecol Can.* 2009;31:(suppl 1):S1-S48.

Case Report: Agranulocytosis Attributed to Levamisole-Tainted Cocaine

TO THE EDITOR: A 24-year-old man presented to the emergency department with a fever, sore throat, and a lingering productive cough for the past month. He also had experienced myalgias and shortness of breath, and noticed he had sores in his mouth and throat for two days. He denied any recent travel or exposure to anyone with tuberculosis.

Physical examination revealed a temperature of 102.5°F (39.2°C) and an apparent left-sided peritonsillar abscess that was confirmed on head computed tomography *(see accompanying figure)*. The patient was leukopenic (white blood cell count of 2,100 cells per mm^3 [2.1×10^9 per L]) with an absolute neutrophil count of zero. His urine drug screening was positive for cocaine, opiates, and cannabinoids. The cause of the neutropenia was determined to be levamisole, a common contaminant in cocaine. The patient eventually admitted to heavy crack cocaine use. The abscess was drained and he was discharged on intravenous antibiotics in stable condition five days later.

Approximately 2 million Americans use cocaine each month.[1] Cocaine contaminated with levamisole has been reported in North America and Europe since 2004.[2] As of July 2009, levamisole contaminated at least 70 percent of the cocaine that came into the United States and was seized by the U.S. Drug Enforcement Administration.[3]

Levamisole is a veterinary antihelminthic previously used as an immunomodulator in rheumatoid arthritis, and as adjuvant therapy in the treatment of colorectal cancer. It is no longer available in North America for human use; it is still available in the United States and South America for veterinary administration.[4] Up to 20 percent of users develop agranulocytosis.[5] This adverse effect appears to be caused by an autoimmune response, but the exact mechanism is unknown.[4-6] Once patients become neutropenic, they are at risk of opportunistic infections. The likelihood of finding levamisole in blood or urine decreases markedly after 48 hours of use because of its short half-life of approximately five hours.[3] The effect of levamisole on cocaine is unknown, but it has been speculated that it may increase the drug's psychoactive effects.[1,4-6]

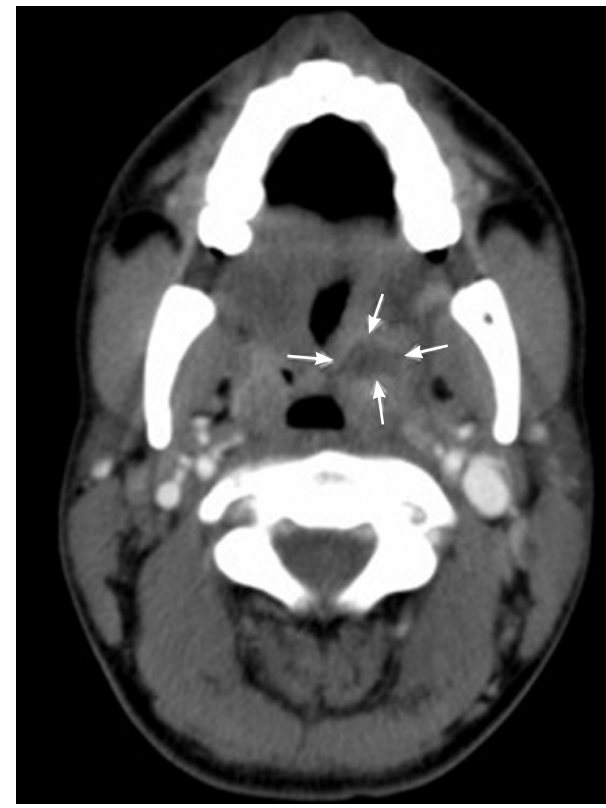

Figure. Computed tomography scan showing left palatine tonsile necrotic lesion *(arrows),* most likely an abscess.

We recommend that patients who use cocaine and develop signs of infection have a complete blood count to evaluate for neutropenia. In addition, levamisole-tainted cocaine use should be considered in the differential diagnosis of patients with unexplained agranulocytosis.

DUNCAN CHAPMAN, MD
Denver, Colo.
E-mail: duncan.chapman@ucdenver.edu

MORTEZA KHODAEE, MD, MPH
Denver, Colo.
E-mail: Morteza.Khodaee@ucdenver.edu

Author disclosure: No relevant financial affiliations to disclose.

REFERENCES

1. Buchanan JA, et al. A confirmed case of agranulocytosis after use of cocaine contaminated with levamisole. *J Med Toxicol.* 2010;6(2):160-164.
2. Knowles L, et al. Levamisole tainted cocaine causing severe neutropenia in Alberta and British Columbia. *Harm Reduct J.* 2009;6:30.
3. Centers for Disease Control and Prevention. Agranulocytosis associated with cocaine use—four States, March 2008-November 2009. *MMWR Morb Mortal Wkly Rep.* 2009;58(49):1381-1385.
4. Czuchlewski DR, et al. Clinicopathologic features of agranulocytosis in the setting of levamisole-tainted cocaine. *Am J Clin Pathol.* 2010; 133(3):466-472.
5. Zhu NY, et al. Agranulocytosis after consumption of cocaine adulterated with levamisole. *Ann Intern Med.* 2009;150(4):287-289.
6. Chang A, et al. Levamisole: a dangerous new cocaine adulterant. *Clin Pharmacol Ther.* 2010;88(3):408-411. ■