

BRIEF REPORT

Agranulocytosis from Levamisole-Adulterated Cocaine

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Introduction: Afebrile neutropenia with an absolute neutrophil count (ANC) of zero in a nonimmunocompromised individual is unusual. Outlined is a case of agranulocytosis likely due to levamisole laced cocaine. Given recent publications in the news media and medical journals, this is a pertinent issue for primary care providers.

Case: A 57-year-old female presented with painful bowel movements and difficulty eating. Physical examination revealed two exquisitely tender ulcerated lesions on her lower lip and anus. Laboratory data revealed an ANC of 0 and urine drug screen positive for cocaine. She was prophylaxed with acyclovir, diflucan, and ciprofloxacin, and was started on granulocyte colony stimulating factor for four days. Her ANC normalized, but the cause of her severe neutropenia remained unclear.

Discussion: Levamisole is a veterinary anthelmintic used for treatment of rheumatoid arthritis and colorectal cancer in humans. 88% of regional cocaine samples are testing positive for levamisole, which is thought to potentiate cocaine's effects but can also cause agranulocytosis.

Conclusions: Our patient did not fit the clinical picture for malignancy, viral infection, or bone marrow pathology. Given the high rate of levamisole adulterated cocaine and an otherwise negative work-up, this is the most likely explanation for her agranulocytosis. (J Am Board Fam Med 2012;25:528–530.)

Keywords: Agranulocytosis, Case Reports, Cocaine, Drug Utilization, Hematology, Levamisole

Cocaine abuse remains a prevalent health problem in the United States, but the scope of this issue may be unrecognized by health care providers. According to the National Survey on Drug Use and Health, in 2007, an estimated 2.1 million people in the United States are current users.¹ Crack cocaine addicts numbered 610,000.¹ In 2007, nearly 1.6 million Americans met criteria for dependence or abuse of cocaine in the past 12 months.¹ Going back to 2005, cocaine was involved in nearly one third of emergency department visits for drug abuse.¹ Levamisole, a veterinary anthelmintic agent previously used to treat cancer and rheumatologic conditions, has been identified as an agent used to lace cocaine. Popular because it en-

hances the euphoric effects of cocaine, levamisole is a known cause of agranulocytosis.

Case Presentation

In the autumn of 2009, our patient, a 57-year-old African American woman, was admitted to Contra Costa Regional Medical Center in Martinez, California, with agranulocytosis. She initially complained of extremely painful bowel movements and difficulty eating. She had a remote history of genital herpes, but had no recent outbreaks. She was otherwise healthy, only taking Flexeril (Janssen Pharmaceuticals) and Toradol (Roche Pharmaceuticals) twice daily as needed during the previous week for musculoskeletal rib pain. She denied any sexual intercourse (including genital, anal, or oral contact) in the previous 8 months. Her only current drug use was inhaled crack cocaine the day before admission, with typical weekly use.

At presentation to the emergency department, our patient was afebrile, had stable vital signs, and appeared nontoxic. Her physical examination was only remarkable for 2 exquisitely tender ulcerated lesions on her lower lip and anus. Her white blood cell count was 1900 cells/microliter and her absolute neutrophil count (ANC) was 45/mm³. Her hemoglobin was 13, hematocrit was 38.4, and platelets were 280. Her

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differential was 2.4% neutrophils, lymphocytes 67.1%, monophils 28.6%, eosinophils 1.2%, and basophils 0.7%. Chest radiograph and computed tomography of the head were negative.

She was admitted with neutropenic precautions and treated with acyclovir for presumed disseminated herpes infection. She was given fluconazole and ciprofloxacin for prophylaxis. The following laboratory tests were ordered and results were negative: HIV, hepatitis B surface antigen, antineutrophil antibody, monospot test, blood culture, and urine culture. Herpes simplex viral cultures of the oral and anal lesions were negative. She was started on granulocyte colony-stimulating factor for 4 days, with normalization of her ANC to 2000/mm³. The patient never developed a fever and her hospital course was uncomplicated.

Discussion

Isolated and afebrile neutropenia presenting in a non-toxic fashion is rare. Our patient did not fit the clinical picture for malignancy, viral infection, or rheumatologic disease. Flexeril and Toradol are reported to cause only mild leukopenia. At the time of discharge, the source of her neutropenia was unclear. However, after exploring the Internet and finding recent lay press articles as well as similar case reports of cocaine users, it is plausible this patient's agranulocytosis was caused by levamisole.²⁻⁶

Levamisole is believed to potentiate the euphoric effects of cocaine by raising the level of endogenous opiates, altering the metabolism of norepinephrine, dopamine, and serotonin in the brain. Levamisole metabolizes to aminorex in racehorses, a chemical similar to amphetamines, which may explain its addictive nature.⁷ In several animal studies, aminorex has been showed to potentiate sympathomimetic effects, resulting in synergy when combined with cocaine.⁷ Aminorex and derivatives are restricted by the US Drug Enforcement Agency, but levamisole is commercially available as a veterinary medication and can be used illegally.⁷

Levamisole is cheap, widely available, and its appearance and taste seem to go unnoticed by cocaine users.⁸ However, levamisole can put its users in a potentially catastrophic immunocompromised state. Although the majority of patients who use cocaine test positive for levamisole, only a small proportion (listed in case reports) have experienced severe illness or death. The reason for this is still unknown. Possible hypotheses include the variability that exists in cutting cocaine, a lack of true functional immunosuppression or exposure to serious pathogens, or the rapid recovery of bone marrow infection after exposure to levamisole.

Levamisole was first used in 1966 as an antihelminthic agent.⁹ Currently, it is only used as a veterinary antihelminthic in the United States. It was withdrawn from the US market in 1999 but has been used in the past as an immunomodulator for rheumatoid arthritis and as adjuvant therapy for treatment of colorectal cancer.² In other countries, it has been used to treat AIDS, ulcerative colitis, chronic hepatitis B, nephritic syndrome, malignant melanoma, breast cancer, acute myeloid leukemia, and amyotrophic lateral sclerosis, with inconclusive results.⁷ Agranulocytosis was seen in 2.5% to 13% of those previously taking levamisole when it was approved for clinical treatment purposes.⁴

Beginning as early as 2003, South American cocaine cartels began to add levamisole to shipments destined for the United States.³ In cocaine seized by the US Drug Enforcement Agency from July to September 2008, 30% of samples were contaminated.² In Canada, 11% of samples are laced with this substance. It usually comprises 0.6% to 11.6% of the total product.⁷ When used to lace cocaine, levamisole is estimated to cause reversible agranulocytosis in 20% of cases with recovery after granulocyte colony-stimulating factor and antibiotic therapy, but the long-term effects from levamisole-adulterated cocaine are unknown.²

In April 2008, a New Mexico clinical reference laboratory reported unexplained cases of agranulocytosis confirmed by bone marrow biopsy.⁴ Cocaine use was the common denominator identified in 11 cases of agranulocytosis reported from April 2008 through November 2009. In the midst of this, in November 2008, Canadian reports detailed levamisole-adulterated cocaine. In 2008 in Alberta, Canada, five patients were hospitalized with fever, infection, and agranulocytosis.⁷ In addition, from the time period of April through November 2009, public health officials in Seattle, Oregon, identified 10 cases of agranulocytosis; although only 5 of these patients were tested, 4 of 5 were positive for levamisole.⁴

The patients outlined in the Centers for Disease Control and Prevention report presented with fever as a common presenting symptom (15 of 21 patients).⁴ Other common features were pharyngitis, oral lesions, and swollen gums. A disproportionately high association with human leukocyte antigen B27 also was noted.⁷ In a Canadian study from January 2008 to March 2009, of 42 patients with confirmed or probable neutropenia associated with tainted cocaine, 64% were women, 57% had used crack cocaine, and 43% reported smoking cocaine as the exposure route.⁷

The issue of possible cocaine-related deaths due to levamisole first arose in the lay press in 2009.⁵ In recent months, there have been increasing reports of agranulocytosis linked to cocaine use in the literature. So far, cases of agranulocytosis attributed to levamisole-adulterated cocaine have been reported in the literature found after a PubMed search for Canada (British Columbia and Alberta), Italy, Spain, as well as Colorado, Arizona, New Mexico, and Washington in the United States.⁷ Deaths in Washington, New Mexico, and Canada have been attributed to levamisole-induced agranulocytosis.⁷

In January 2009, the New Mexico Department of Health first detected levamisole using gas chromatography/mass spectrophotometry postmortem in a patient admitted for sepsis and agranulocytosis.⁴ Interestingly, however, it is difficult to detect levamisole because its half-life is believed to be only 5 hours.⁴ Unless toxicology screening is done immediately after use, results may be negative. However, toxicologists at the University of California, San Francisco, speculate that it may be longer given that patients do not typically present immediately after substance use and such a high percentage of samples are positive (based on personal communication and pending publication).⁹ Although our patient's urine was not tested before discharge, it is likely the patient's agranulocytosis was caused by levamisole-tainted cocaine, especially in light of several similar cases at nearby San Francisco General Hospital.⁹

According to the *San Francisco Chronicle* in 2009, 8 cases of illness caused by levamisole were identified in San Francisco.⁶ The University of California, San Francisco, has developed a liquid chromatography-tandem mass spectrometry method to detect levamisole in urine.¹⁰ At San Francisco General Hospital in 2009, of a sample of 191 patients, 88% who tested positive for cocaine were positive for levamisole.¹⁰ Patients most often presented with complaints of fever, swollen glands, painful oral/anal ulcers, and persistent infection. Some developed skin findings, described as "multiple stellate, purpuric macules, and plaques with central necrosis and erythematous borders" in the image description recently published in the *Annals of Emergency Medicine*.¹¹

Patients may be completely asymptomatic, but most presenting to a clinic or emergency department describe flu-like symptoms. Because the clinical presentation is often vague and not overtly concerning, patient complaints may be dismissed by providers without further workup. Clinical suspicion is key to identifying the cause of such a potentially devastating immunocompromised

state in these patients without obvious risk factors for neutropenia. Physicians need to be aware of the prevalence of these cases to direct medical decision making and to provide further education to patients.

Conclusions

Given that a large percentage of cocaine in America is tainted with levamisole, this issue is relevant and topical. Because levamisole can cause agranulocytosis, which is potentially fatal, both provider and patient education about the potential danger is essential.

References

1. National Institute on Drug Abuse. Research report series—cocaine: abuse and addiction. NIH publication no. 09-4166. Washington, DC: U.S. Department of Health and Human Services, National Institutes of Health; 2009.
2. Thompson JS, Herbick JM, Klassen LW, et al. Studies on levamisole-induced agranulocytosis. *Blood* 1980;56:388–96.
3. Zhu NY, LeGatt DF, Turner AR. Agranulocytosis after consumption of cocaine adulterated with levamisole. *Ann Intern Med* 2009;150:287–9.
4. Chang A, Osterloh J, Thomas J. Levamisole: a dangerous new cocaine adulterant. *Clin Pharmacol Ther* 2010;88:408–11.
5. Buchanan JA, Over RJ, Patel NR, et al. A confirmed case of agranulocytosis after use of cocaine contaminated with levamisole. *J Med Toxicol* 2010;6:160–4.
6. Centers for Disease Control and Prevention. Agranulocytosis associated with cocaine use—four states, March 2008–November 2009. *MMWR Morb Mortal Wkly Rep* 2009;58:1381–5.
7. Associated Press. Medicine-laced cocaine kills 2, sickens more than 100. September 1, 2009. Available from: <http://www.foxnews.com/story/0,2933,545127,00.html>. Accessed May 9, 2012.
8. Allday E. Most cocaine diluted with unsafe livestock drug. *San Francisco Chronicle*. December 29, 2009. Available from: <http://www.sfgate.com/cgi-bin/article.cgi?f=/c/a/2009/12/29/MNDS1B6HAS.DTL>. Accessed May 9, 2012.
9. Lynch KL, Dominy SS, Graf J, Kral AH. Detection of levamisole exposure in cocaine users by liquid chromatography tandem mass spectrometry. *J Anal Toxicol* 2011;35:176–8.
10. Szalavitz M. A common cut in cocaine may prove deadly. *Time Magazine*. January 20, 2009. Available from: <http://www.time.com/time/health/article/0,8599,1955112,00.html>. Accessed May 9, 2012.
11. Lung D, Lynch K, et al. Images in emergency medicine. Adult female with rash on lower extremities. Vasculopathic purpura and neutropenia caused by levamisole-contaminated cocaine. *Ann Emerg Med* 2011;57:307, 311.