ToxTalks:

A Bulletin for Healthcare Professionals Who Manage Poisoned Patients

In Partnership with the UVA Division of Medical Toxicology – Department of Emergency Medicine

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Levamisole: Implications of the common cocaine adulterant on patient care

What is Levamisole?

Levamisole was initially introduced in the 1960s as a veterinary antiparasitic agent to treat helminth infections. The drug was later used as an anthelminthic agent in humans. In the 1970s, levamisole was found to have immunomodulatory properties, both stimulating and suppressing the immune responses, which led to its use in the treatment of colorectal cancer and rheumatoid arthritis. In the 1990s, levamisole was FDA approved as an adjuvant therapy for the treatment of colorectal cancer. In 2000, levamisole was found to be associated with adverse effects including agranulocytosis, opportunistic infections, and vasculitis. It was withdrawn from the U.S. market. It remains approved for human use in other countries and for veterinary use in the U.S., and therefore remains easily accessible and is inexpensive. Levamisole was first detected in the illicit drug supply in the early 2000s, most notably cocaine, and remains a common adulterant, detected in nearly 80% of seized cocaine samples.

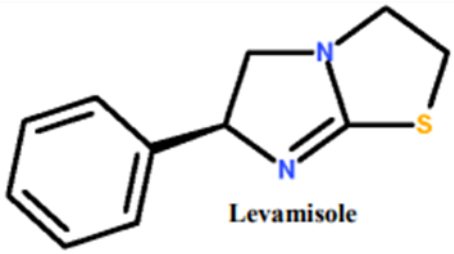

Image from Center for Forensic Science Research and Education public health notice

Pharmacology

Levamisole's anthelminthic activity comes from its action on nicotinic acetylcholine receptors. It acts as a nicotinic receptor agonist in helminthic muscle and nerve cells causing diffuse muscle contraction and spastic paralysis. This renders the parasite immobile, allowing it to pass through the human GI tract. The discovery of levamisole's immunomodulatory activity on human T-cells is what broadened its use to colorectal cancer and rheumatoid arthritis. The full mechanism is still unclear, but levamisole may have some activity on cholinergic receptors of T-lymphocytes, promoting their activity and antibody formation. This mechanism may be the cause of the autoimmune adverse effects of vasculitis and agranulocytosis.

Why is it added to the drug supply?

There are multiple theories to why levamisole is added to the cocaine supply. One theory is that it has a similar color and texture to cocaine and is available at a low cost, which makes adding it to cocaine an easy way to bulk

and increase profit while limiting its detection. Another theory is that it may have a synergistic effect with cocaine, increasing the release of dopamine and norepinephrine and prolonging cocaine-like euphoria.

Clinical Effects

Agranulocytosis is an uncommon clinical effect of levamisole but can be severe and life-threatening when present, and is the reason the drug was pulled from the US market for humans. Agranulocytosis and neutropenia from levamisole adulterated cocaine have been reported to cause life threatening infections in cocaine users. This is generally considered to be reversible upon discontinuation of exposure. Cutaneous effects can also occur, generally resembling an immune-mediated vasculitis, characterized by purpura, especially in the face and ears, as well as peripheral ulcerations and necrotic lesions. Rare cases of multifocal inflammatory leukoencephalopathy have also been associated with levamisole.

Management

When caring for a patient with a history of cocaine use with vague, nonspecific symptoms including fatigue, malaise, fever, and possibly skin changes, effects of levamisole from cocaine adulteration should be considered. Though testing for levamisole itself is not readily available in most hospitals, patients can be screened for neutropenia and agranulocytosis with a complete blood count. Patients should also be treated for opportunistic infections when needed. In regard to management of vasculitis and skin changes, appropriate wound management and treatment of overlying infection are important and surgical debridement or amputation have been required in severe cases. There is little evidence available for other treatment for levamisole-associated vasculitis, but some cases have been treated successfully with steroids in addition to drug discontinuation. Leukoencephalopathy associated with levamisole has been described as reversible with drug discontinuation but does not have a specific treatment otherwise.

Summary

Levamisole is an antiparasitic agent with immunomodulatory effects in humans. It remains a commonly used adulterant in the illicit drug supply, especially cocaine. Clinical effects of levamisole can include life-threatening opportunistic infections secondary to agranulocytosis, immunogenic vasculitis, and reversible multifocal leukoencephalopathy. It is important that clinicians are aware of levamisole as an adulterant, especially of cocaine, and that it may be responsible for symptoms alluded to above.

Case reports containing helpful clinical images of levamisole-induced vasculitis:

Abdul-Karim R, Ryan C, Rangel C, Emmett M. Levamisole-induced vasculitis. Proc (Bayl Univ Med Cent). 2013 Apr;26(2):163-5. doi: 10.1080/08998280.2013.11928946. PMID: 23543977; PMCID: PMC3603736.

Mya Abousy, Scott Sylvester, David Milek, C. Scott Hultman, Julie Caffrey. Surgical management and outcomes of levamisole-induced vasculitis in a burn center: A case series. JAAD Case Reports. Volume 13, 2021, Pages 36-42, ISSN 2352-5126.