

Levamisole contamination of cocaine resulting in neutropenia and thrombovasculopathy: a report from the Southern Network on Adverse Reactions (SONAR)

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Background

Levamisole is a pharmaceutical with anthelmintic and immunomodulatory properties that received approval from the Food and Drug Administration in 1991 as part of adjuvant chemotherapy regimens for colorectal cancer. The addition of levamisole to 5-fluorouracil (5-FU) was first evaluated by the North Central Cancer Treatment

Group in a 3-arm clinical trial that found that 5-FU+levamisole for 12 months was superior to either surgery alone or surgery followed by levamisole alone (recurrence rate was reduced by 40% and the death rate by 33% in Dukes' C colon cancer).¹ A subsequent trial intergroup trial randomized patients with Dukes' B2 and C colon cancer to surgery alone or 1 year of adjuvant levamisole or 5FU+levamisole and confirmed the efficacy of 5FU+levamisole with respect to disease free survival and overall survival.² As a result,

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adjuvant chemotherapy became the standard for stage III colon cancer as reported by an National Cancer Institute consensus development panel.³ Subsequently, primarily because of toxicity reasons, leucovorin replaced levamisole in most adjuvant chemotherapy regimens for stage III colorectal cancer.

Clinical toxicity of levamisole was noted as early as 1976 when several cases of leukopenia and agranulocytosis were reported. Recurrence with re-exposure was well described and agranulocytosis spontaneously reversed upon discontinuation of therapy. Vasculitis secondary to levamisole treatment was first reported in 1978, presenting primarily as leukocytoclastic vasculitis, cutaneous necrotizing vasculitis and thrombotic vasculopathy without vasculitis. These findings typically, but not invariably, involve the ear lobes. In the early 1990s, levamisole became unavailable for human use in the United States due to toxicity concerns. Various neurological side effects were described with levamisole therapy, the most concerning complication being multifocal inflammatory leukoencephalopathy. Recently, several persons have developed a novel syndrome characterized by necrotic noses and ears, leg ulcers, agranulocytosis, thrombovasculopathy, and positive antineutrophil cytoplasmic antibodies (ANCA) as a result of the drug cocaine being adulterated with levamisole. We describe the drug below.

Levamisole contamination of cocaine in recent years

Annually, 24 million Americans use cocaine and 500,000 individuals present to emergency departments with cocaine-associated complications.⁴ Cocaine is often adulterated with other substances to increase sale quantities. A newly recognized contaminant is levamisole,² which is used in the treatment of other forms of cancer – breast, bladder, and lung.⁵ Levamisole had previously been used to treat rheumatoid arthritis, nephrotic syndrome, and other immunologic illnesses because of its immunomodulatory properties.^{6,7} In the course of treating immunologic illnesses, idiopathic agranulocytosis developed in 2.5%–13% of treated individuals, resulting in its voluntary withdrawal from sales for human use, although it is still available as an antihelmintic agent for veterinary use.^{8,9}

One report described 5 cocaine users who developed cutaneous thrombovasculopathy, neutropenia, and necrotic noses or ears – later termed cocaine-levamisole-associated neutropenia/thrombovasculopathy (CLANTV).⁷ Cocaine contamination was identified in all 5 patients. Subsequently, 123 additional cases of this novel syndrome have been identified by the Southern Network on Adverse Reactions

(SONAR). Since 2008, the syndrome has been reported with increasing frequency from large cities in the United States and Canada. We review findings for all reported CLANTV cases. Cases were obtained from queries and information obtained from the Drug Enforcement Agency, Poison Control Centers, Medical Toxicology Services, and Departments of Health in the United States and Canada and medical publications (MeSH terms: cocaine, thrombovasculopathy, agranulocytosis). Cases included a diagnosis of neutropenia (absolute neutrophil count < 1,000 cells/mm³), cutaneous thrombovasculopathy, cocaine use, and, for confirmed cases, levamisole documented by laboratory testing.

CLANTV with thrombovasculitis

CLANTV is a new syndrome consisting of cutaneous manifestations, arthralgia, neutropenia, thrombovasculopathy, and positive ANCA. Its manifestations reflect intersecting toxicities of cocaine and levamisole. Cocaine toxicity includes Churg-Strauss syndrome, cocaine-induced midline destructive lesions and cutaneous manifestations.⁸ Levamisole toxicity derives from its thiazole structure as reactive thiol groups act as haptens, triggering immune responses.⁹ Levamisole also causes cutaneous toxicities, including a hypersensitivity vasculitis.⁶ Skin biopsies identify leukocytoclastic vasculitis or thrombotic vasculopathy.⁶ CLANTV should be suspected in patients presenting with neutropenia and nonpalpable purpura on the tip of the nose and ear or on the chest, abdomen, and legs. Supportive measures and abstinence are primary treatments. Management consists of supportive care, cocaine abstinence, wound debridement, and antibiotics. Serologic testing usually normalizes within 2–14 months, independent of corticosteroid administration.⁴ Heightened awareness of this syndrome is warranted.

A major feature of CLANTV stems from cocaine toxicity. Cocaine toxicity includes Churg-Strauss syndrome, cocaine-induced midline destructive lesions and cutaneous manifestations including include Raynaud's syndrome, ANCA-positive cutaneous vasculopathy or vasculitis, palpable purpura, hemorrhagic bullae, skin infarction and digital gangrene (Figure 1).

How we found cases

Using medical records, PubMed searches, queries of clinicians from Departments of Public Health, Poison Control Centers, emergency rooms, hospital pharmacies, and hematology departments, the Southern Network for Adverse Reactions (SONAR) reviewed 124 cases of this syndrome. We specifically identified instances of persons presenting with cocaine use history, severe skin manifestations, neutropenia, and thrombovasculopathy.



FIGURE 1 A major feature of cocaine-levamisole-associated neutropenia/thrombovasculopathy stems from cocaine toxicity. Panels A and B, Nonpalpable purpura on cheeks, retiform purpura on thighs. Panels C and E, Ulcers on thighs and legs, and nonpalpable purpura on left ear. Images courtesy of E. Gilbert and P. Mahindra (A and B) and Irene Dy (C).

Findings included recent cocaine use (100% of cases); and retiform purpura, purpuric rash, hemorrhagic bullae, or skin necrosis (59%); lesions on the ears (35%), upper extremities (33%), torso (22%), or nose (10%); neutropenia (77%), thrombosis (34%), vasculitis (16%), thrombovasculitis (45%) and ANCA (63%). Recovery with supportive care occurred in 95% of cases and relapse following cocaine re-exposure

occurred in 33%. Levamisole contamination of cocaine was identified in 25% and suspected in 75% of affected patients. The Drug Enforcement Agency reports that levamisole contamination of interdicted cocaine increased from 3% in 2003 to 69% in 2009.

CLANTV is a potentially life-threatening syndrome that often responds to supportive management. Relapses

following cocaine re-exposure often occur. Increased cocaine adulteration with levamisole in the 2000s accounts for the recent onset of this syndrome.

Review of reported CLANTV cases

Of 124 reports of CLANTV cases identified by SONAR, the average age of the patients was 44 years (SD, 11 years), and 65% were women. The earliest time to symptom onset was 12 hours following cocaine use. Dermatologic findings included retiform purpura, purpuric rash, hemorrhagic bullae, or skin necrosis (59% of cases), and lesions on the ears (35%), upper extremities (33%), torso (22%), and the nose (10%; Figure 1). Although 25% tested positive for levamisole, findings were similar for cases with positive levamisole toxicology assessments compared with cases with probable CLANTV. Of 79 cases with available absolute neutrophil counts, 72% presented with neutropenia. With respect to vasculitis, 95% of the patients who had serologic tests performed (80 patients) demonstrated ANCA, 31% were positive for proteinase 3 antibodies, 40% were positive for myeloperoxidase antibodies, 32% were positive for IgM cardiolipin antibodies, and 20% were positive for lupus anticoagulant. On pathologic evaluation of biopsy materials, 25% had evidence of thrombosis, 6% had evidence of vasculitis, and 20% had evidence of vasculitis and thrombosis.

Among 63 cases with neutropenia, treatment included supportive care (6 cases; 1 death; 83% recovery; and 50% relapse); granulocyte-colony stimulating factor (15 cases; 100% response; 40% relapse), antibiotics (25 cases; 100% recovery; 28% relapse), and corticosteroids (14 cases; 100% recovery; 28% relapse). Among 30 cases with biopsies identifying thrombosis, treatments included conservative management (5 cases; 100% response rate; 33% relapse) and corticosteroids (13 cases; 100% recovery; 22% relapse); among 9 cases with vasculitis, treatments included conservative treatment (2 patients, both recovered) and corticosteroids (4 cases; 100% response; and 50% relapse). Finally, among 27 cases with thrombosis and vasculitis, treatments included conservative treatment (6 cases; 100% recovery; 50% relapse) and corticosteroids (10 cases; 100% response rates; 40% relapse). Severe skin necrosis treatment included skin allografts (6%), above the knee amputation (1 case), and a nose amputation (1 case). A quarter of the patients experienced re-occurring toxicity, primarily after additional cocaine use.

Conclusion

CLANTV is a novel and recently identified public health problem. It is underreported, as MedWatch reports from Food and Drug Administration databases included only 17 reports of the syndrome. It should be suspected in patients presenting with agranulocytosis and nonpalpable purpura on the tip of the nose and ear or on the chest, abdomen, and legs. A careful history related to recent cocaine use is essential. If uncertainty exists, urine samples should be sent for evaluation of levamisole by gas spectrogram or magnetic resonance spectrogram (some poison control centers have established referral centers). Supportive measures and abstinence are primary treatments. If CLANTV is not recognized, it is often misdiagnosed as necrotizing fasciitis, agranulocytosis of unknown etiology, or other serious illnesses and can result in morbidity and mortality.

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