CASE REPORT

Palpable Purpura Complicated by Streptococcal Toxic Shock Syndrome Resulting in Limb Necrosis and Amputation: A Case of Levamisole and Cocaine Coingestion

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Palpable purpura resulting from cocaine and levamisole coingestion has been reported with increasing frequency over the last several years as distribution of this drug combination becomes more universal. Toxicity from ingestion of this dangerous combination is difficult to diagnose due to the multitude of possible clinical presentations, variety of possible adulterants, and elusive nature of levamisole given its short half-life and limited availability of detection methods. Levamisole is a chemotherapeutic and immunomodulatory agent currently marketed as a veterinary anthelmintic. We describe the case of a 48-year-old woman admitted to our intensive care unit with a diagnosis of streptococcal toxic shock syndrome (STSS), confirmed from fluid taken from an elbow lesion that grew *Streptococcus pyogenes*. She was noted to have bullae of the elbow and diffuse purpura with necrotic centers covering a large portion of her body (trunk, legs, arms, back, toes, fingers, and tip of nose). On further evaluation, she was found to have ingested levamisole-tainted cocaine. The patient's complications related to either cocaine and levamisole coingestion or STSS included thrombocytopenia, acute renal failure, and limb necrosis. Thrombocytopenia gradually improved upon treatment with prednisone, and acute renal failure improved with intravenous fluid resuscitation; however, she subsequently required several appendage amputations due to severe gangrene. Clinicians must have high suspicion for ingestion of this drug combination and request prompt testing of urine samples for levamisole if a patient who admits to illicit drug use presents with purpuric or necrotic skin lesions.

Key Words: levamisole, purpura, cocaine, adverse drug reaction, gangrene, necrosis.

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Illicit recreational drug use poses diagnostic and management challenges to clinicians who encounter patients in the acute care setting. One of the most commonly used illicit substances in the United States is cocaine, which is most commonly taken by direct powder inhalation (snorting), although it may also be ingested through smoking and by injection. Several adverse effects of cocaine are well documented in the literature, including neuropsychiatric complications,[1] myocardial infarction,[2] large-vessel thrombosis,[3] and small-vessel vasculitis[4, 5]; most of which are related to the sympathomimetic activities of the drug. However,

clinicians who regularly treat patients who use cocaine are well aware that ingestion of cocaine alone is the exception rather than the rule.

Many drug dealers engage in the practice of "cutting" cocaine with other chemical compounds. Reasons for cutting include enhancement of desired effect, attenuation of adverse effects, or dilution of the illicit substance in order to increase profits.[6] In the past, popular cutting agents included those with minimal pharmacologic activity, such as lactose, mannitol, niacinamide, talc, flour, and boric acid, mostly because they match the appearance of cocaine and serve as an inexpensive diluent.[6, 7] Recent years have brought a shift toward cutting agents that have considerably more pharmacologic activity such as benzocaine, lidocaine, procaine, acetaminophen, quinine, atropine, caffeine, hydroxyzine, diltiazem, methylphenidate, amitriptyline, aspirin, and pseudoephedrine.[6, 7] Many of these agents serve to augment the sympathomimetic effects of cocaine. Local anesthetic compounds are often chosen because they enhance the local anesthetic effects of cocaine, which causes the user to suspect the product is of higher quality.[7]

Levamisole is a synthetic imidazothiazole derivative that was approved by the United States Food and Drug Administration for use as adjuvant therapy with 5-fluorouracil in the management of colorectal cancer. It was voluntarily withdrawn from the U.S. market for human use because of agranulocytosis, but it is widely available in North and South America as an anthelmintic drug commonly used in veterinary medicine. In 2005, the U.S. Drug Enforcement Agency (DEA) reported that bricks of cocaine were seized that contained levamisole as an adulterant.[6] In 2009, the U.S. Substance Abuse and Mental Health Services Administration (SAMHSA) announced that over 70 percent of illicit cocaine analyzed by the DEA was positive for levamisole and that in Seattle, Washington, about 80 percent of individuals who tested positive for cocaine also tested positive for levamisole.[8]

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Diagnosing ingestion of cocaine tainted with levamisole can be particularly challenging given that few case reports exist to describe the clinical presentation of patients who are definitely known to have ingested this combination. We describe the case of a patient admitted to a medical intensive care unit (ICU) for an initial diagnosis of streptococcal toxic shock syndrome (STSS) who was subsequently found to have ingested cocaine tainted with levamisole, resulting in widespread tissue necrosis requiring amputation of multiple appendages. Our patient's case is distinct from previously reported cocaine and levamisole mixed adverse drug events because it was complicated by the presence of STSS, acute renal failure, thrombocytopenia, symptomatic anemia, and diffuse purpura ultimately resulting in widespread gangrene.

Case Report

A 48-year-old woman came to an acute care facility for treatment of a right elbow wound she sustained after a fall. She admitted to recent cocaine use. Her elbow was sutured, and she was discharged home. Forty-eight hours later, she presented to a community hospital with new complaints of nausea, vomiting, and continued right elbow pain. A lesion on her right elbow was diagnosed as an abscess and was drained, and she was treated with intravenous vancomycin and piperacillin-tazobactam. Shortly thereafter, she began to show signs of sepsis and was transferred to our hospital as a direct admission to the ICU.

We received documentation from the community hospital that fluid collected from the patient's elbow lesion had grown *Streptococcus pyogenes* (group A *Streptococcus*). Upon admission to our hospital, laboratory results revealed acute renal failure (serum creatinine concentration 5.0 mg/dl [baseline ~1.0 mg/dl]), thrombocytopenia (platelet count 34 x 10^9/L), and lactic acidosis (serum lactate level 3.3 mmol/L). She was noted to have bullae of the right elbow and diffuse purpura with necrotic centers covering a large portion of her body, including her trunk, legs, arms, back, toes, fingers, and tip of nose. The patient had no significant medical history and was not known to be taking any prescription or over-the-counter drugs or supplements. She admitted to frequently snorting cocaine and stated her last exposure was a few days earlier. She denied ever injecting cocaine or other illicit substances. Her urine toxicology

panel on admission was positive for opiates and cocaine.

Vancomycin and clindamycin were started for treatment of STSS from group A *Streptococcus*. The patient's antimicrobial therapy was later changed to ceftriaxone in addition to clindamycin based on group A *Streptococcus* susceptibilities. A dermatology consultation was ordered to investigate the etiology of her diffuse purpura and skin necrosis. Skin biopsy specimens were obtained from several sites, which later revealed purpura with dermal vessel fibrin thrombi formation. Intravenous immune globulin 48 g was given on days 0, 1, and 3 for the treatment of STSS. The consulting dermatologist subsequently requested the assistance of a clinical toxicologist to review the case and to request a urine sample to test for the presence of levamisole.

The patient required mechanical ventilation for 7 days due to septic shock, lactic acidosis, and acute renal failure. At no point during the patient's hospital admission did she require hemodialysis. A two-dimensional echocardiogram was obtained to investigate suspected congestive heart failure and showed a normal ejection fraction with no evidence of endocarditis. During her hospitalization, 12 units of platelets were transfused because of worsening thrombocytopenia (platelet nadir of 13 x 10^9/L). She also developed severe anemia during her hospitalization requiring blood transfusions (hemoglobin nadir of 6.9 g/dl). The patient's haptoglobin level was within the normal range on admission, and a site of active bleeding was never discovered. Her acute renal failure improved with intravenous fluid resuscitation over approximately 5 days. Her thrombocytopenia gradually improved in response to treatment with prednisone. Definitive diagnoses for her acute renal failure and thrombocytopenia were never identified.

Ten days after her admission to our ICU, the urine sample collected on admission tested positive for levamisole at a concentration of 0.81 μg/ml. A sample collected about 55 hours after her ICU admission was negative for levamisole. Shortly after extubation, she was transferred to a general practice ward, where she subsequently required amputation of four fingers on each hand and four toes on her left foot, as well as a right below-the-knee amputation, due to severe gangrene. The patient developed transient neutropenia (absolute neutrophil count < 1.5 x 10^9 L) during hospital days 25 and 39, complicated by vancomycin-resistant *Enterococcus faecium* and *Candida* species found on bone cultures after amputation. The patient was discharged to a long-term rehabilitation facility on day 40 of her hospitalization.

Discussion

Much of clinicians' previous experience with levamisole comes from its use as a chemotherapeutic and immunomodulatory agent. Although initially approved for the treatment of colorectal cancer, levamisole has been used in breast cancer and in autoimmune conditions such as rheumatoid arthritis and nephritic syndrome. The immunomodulatory mechanism of levamisole is unclear but may include stimulation of antibody production, enhancement of T-cell immune responses, increased chemotaxis, as well as enhancing neutrophil activity.[9]

Shortly after SAMHSA's 2009 announcement that over 70% of illicit cocaine analyzed by the DEA was positive for levamisole, and that in Seattle, Washington, about 80% of individuals who tested positive for cocaine also tested positive for levamisole,[8] similar reports followed. The European Monitoring Centre for Drugs and Drug Addiction reported that levamisole was present in more than 50% of cocaine samples tested in the Netherlands and United Kingdom.[10] Of 970 urine drug screens done at San Francisco General Hospital clinical laboratory in October 2009, 87% were positive for levamisole.[11] Levamisole-tainted cocaine has also been identified in shipments from Australia, Colombia, France, Belgium, Guyana, Italy, Jamaica, Spain, and Switzerland.[7] Levamisole reportedly was detected in approximately 11% of cocaine samples seized in Alberta, Canada, in an 8-month span in 2008.[12] In 2008, the Wayne County Medical Examiner's Office in Detroit, Michigan, reported that levamisole was found in roughly 37% of postmortem cases in which cocaine and/or its metabolites were detected, demonstrating the presence of levamisole in the geographic area in which our case arose.[13] Levamisole has also been detected in less than 3% of heroin samples seized by the DEA, albeit in trace amounts compared with the 10% weight by weight present in DEA-seized cocaine samples.[14]

The point at which levamisole is added to cocaine (i.e., by the manufacturer, dealer, or user) is somewhat unclear. A recent case report of a man who traveled from Guatemala and was discovered to have four bags of levamisole-

tainted cocaine in his colon on presentation to a hospital suggests that levamisole is added at the point of manufacture.[15] Also, there is currently no clear answer as to why cocaine is adulterated with levamisole. The primary rationale is thought to be that levamisole augments the desirable effects of cocaine for the user. Levamisole may have acetylcholinesterase inhibitory activity and may also inhibit monoamine oxidase and catechol-*O*-methyltransferase, thus augmenting the sympathomimetic effects of cocaine.[7,13] Levamisole, or one of its metabolites, may exert sympathomimetic effects either by postganglionic nicotinic receptor agonism or directly through enhancement of catecholamine release. The anthelmintic activity of levamisole results from nicotinic receptor agonism, leading to spastic muscle paralysis in nematodes.[6,13] This mechanism of action is thought to be species specific due to the unique nicotinic receptor structure of the nematode compared with mammals and is supported by the absence of nicotinic adverse effects when the drug is used as a chemotherapeutic agent.[6]

Aminorex, a schedule I amphetamine-like compound with significant abuse potential, has been identified as a metabolite of levamisole in humans. Aminorex was present in urine samples at 3 and 6 hours after oral administration of levamisole 47 mg in four female subjects and 58 mg in four male subjects.[16] Animal studies have suggested that levamisole increases dopamine levels in the same euphoric centers of the brain as does cocaine in rats and also increases central nervous system concentrations of endogenous opiates.[17] Studies conducted in the 1970s demonstrated elevated mood and increased sympathomimetic activity in dogs receiving levamisole.[13]

A major complicating factor in diagnosing ingestion of cocaine tainted with levamisole is attributing symptoms to cocaine itself, or any one of the multitude of possible adulterants that have been found in seized cocaine samples. Although cocaine metabolites can be detected in the urine for approximately 3 days after ingestion, the half-life of levamisole is very short (~5.6 hrs), making prompt serum and urine sampling of utmost importance.[18] This is reflected in our patient by the fact that a second urine sample tested for levamisole came back negative 55 hours after the first sample. Only 2–5% of levamisole is present in the urine as the parent drug and is not detected by routine immunoassay toxicology screening tests.[18, 19]

As a chemotherapeutic and immunomodulatory agent, adverse effects from levamisole ingestion include thrombocytopenia,[20] microvascular thrombosis resulting in formation of palpable purpura, vasculitis, and ulcers of the mouth and skin.[21] The purpura that results seem to have a predilection for involving the ear lobes.[22] Cases of purpura from levamisole-tainted cocaine have reported involvement of the lower extremities, thighs, buttocks, trunk, upper extremities, ear lobes, and tip of nose.[23] The lesions have been described as tender, erythematous, stellate plaques with necrotic centers.[23] Differences in clinical presentation between previously reported cases of cocaine-levamisole coingestions and our case are described in Table 1.

One group of authors recently described two patients who developed cocaine-related purpura, mainly affecting the legs.[22] In the first case, a 39-year-old woman presented with an 8-week history of extensive purpura affecting her legs and trunk. The patient openly admitted to regular use of crack cocaine, but denied recent intravenous drug use. Purpura involved approximately 15% of the patient's body surface area. During her 4-month hospitalization, she discontinued the use of cocaine and observed improvement in her lesions; however, because of deep skin necrosis, surgical debridement and skin grafts were necessary. Months after discharge, the patient again presented with similar lesions after admitting to using cocaine.

In the second case, a 49-year-old woman presented with extensive lower limb purpura of 3 weeks' duration.[22] She admitted to using crack cocaine as well as a remote history of intravenous drug use. The patient was advised to avoid further exposure to cocaine, but later that year

Table 1. Differences in Clinical Presentation Between Our Patient and Patients from Previous Reports of Cocaine-Levamisole Coingestion

Our Patient's Presentation	Typical Clinical Presentation[22-26]
Purpura sparing the ear lobes	Purpura with a predilection for the ear lobes
Irreversible necrotic damage requiring amputation	Lesion resolution without permanent sequelae
Presence of group A streptococcal toxic shock syndrome	Absence of infection at presentation
Acute renal failure	Absence of acute renal insult
Thrombocytopenia	Lack of thrombocytopenia
Symptomatic anemia	Lack of anemia or erythrocytic involvement

presented with a similar cutaneous eruption after a cocaine binge.

Both patients described above had urine samples that tested positive for levamisole.[22] The first patient was noted to have a transiently positive lupus anticoagulant, whereas both were positive for antinuclear antibodies. Similar cutaneous lesions to those described in these two cases have been reported in children receiving levamisole for nephrotic syndrome.[9]

Cocaine, in the absence of known adulteration with levamisole, has been documented to cause purpura and pseudovasculitis, reportedly distinguished from a true autoimmune vasculitis by the presence of antineutrophil cytoplasmic antibodies reacting with human neutrophil elastase.[27] Pseudovasculitis is described as clinical and local findings suggestive of a systemic vasculitis but lacking histopathologic evidence of vasculitis.[22] The mechanism behind levamisole-induced cutaneous purpura has not been elucidated, but hypotheses include immune complex deposition in the skin as well as formation of lupus anticoagulant, which may result in localized tissue thrombosis and necrosis.[9] Levamisole is known to be associated with a positive lupus anticoagulant, which may place patients exposed to levamisole at increased risk for thrombosis.[19, 28] Levamisole has also been associated with the generation of antinuclear antibodies as well as antineutrophil cytoplasmic antibodies.[27]

Our patient's biopsy results suggested dermal vessel thrombus formation, consistent with previously reported cases of levamisole-induced purpura.[8, 21, 23, 24] Similar histologic findings are found in several autoimmune vasculitides such as leukocytoclastic vasculitis and antiphospholipid syndrome.[29] In the case of autoimmune vasculitis, influx of immune cells such as lymphocytes, eosinophils, or neutrophils are typically noted at biopsy.[29] Immune cells were not noted to be present in our patient's biopsy sample.

Sepsis could also be a possible cause of our patient's purpuric lesions; however, no positive blood cultures were identified throughout her hospitalization. Gram-positive endocarditis and sepsis have been documented to result in petechial, purpuric, or ecchymotic lesions;[30, 31] however, our patient's echocardiogram was not suggestive of endocarditis. At biopsy, septic vasculitis typically shows neutrophil- and bacteria-containing thrombi with extravascular neutrophilia,[24] neither of which was noted in our patient's biopsy specimen. Symmetric peripheral gangrene is associated with disseminated intravascular coagulation and has been reported with both gram-positive and gram-negative sepsis, and results in necrosis of the fingers, toes, nose tip, and ears.[31] Neither inflammatory cells nor bacteria are usually present at biopsy in great numbers. Generalized petechiae that coalesce to form purpura have been reported from group A *Streptococcus* sepsis.[31] Receipt of vasopressors for the treatment of septic shock is also associated with tissue necrosis; however, our patient never received vasopressor agents. It is possible that STSS contributed to our patient's purpuric lesions and that causative microbes were never isolated at biopsy because she received previous antimicrobials before biopsy samples were taken.

Cases of skin necrosis involving cocaine itself have been documented previously in the literature. In one case report, a 30-year-old woman developed full-thickness skin necrosis after injections of cocaine and heroin.[32] Before onset of necrosis, the patient had developed an abscess at the site of injection of the illicit drugs. Cultures grew *S. pyogenes*. The authors hypothesized that *S. pyogenes* may produce proteases that degrade skin, and in the presence of localized thrombosis and hypoperfusion secondary to cocaine, the two factors may have a synergistic effect in causing skin necrosis.[32] At the time of that case report, levamisole was not known to be a common cocaine adulterant. In contrast to our patient, that case[32] did not describe the clinical syndrome of STSS, as defined by the Working Group on Severe Streptococcal Infections, characterized by the presence of shock and multiorgan failure early in the course of streptococcal infection.[33] Our patient never developed necrosis at the site where group A *Streptococcus* was isolated.

Cocaine, in the absence of any known adulterants, has been documented to cause various connective tissue diseases,[34] Raynaud's phenomenon,[34] acute renal failure,[35] bullous skin disease,[36] necrotizing angiitis,[37] necrotizing fasciitis,[38] and thrombocytopenia.[39] A 38-year-old woman presented with hemolytic anemia, acute renal failure, and thrombocytopenia that was most likely related to inhalation of crack cocaine by the patient for 7 consecutive days before admission.[35] Renal biopsy suggested glomerulosclerosis as well as partial collapse and thrombosis of several glomeruli that was thought to be secondary to cocaine-induced ischemic injury. The authors who reported that case suggest that cocaine may cause thrombosis through enhance-

ment of platelet responsiveness to arachidonic acid, impairing endothelial vasodilation, increasing endothelial vasoconstriction, and by inducing platelet and endothelial damage. Although a renal biopsy was not performed in our patient, it is plausible to think that her acute renal failure, anemia, and thrombocytopenia may have been related to cocaine itself; however, the possibility of levamisole and septic shock contributing to the pathogenesis of these conditions is also likely.

Much of the literature regarding levamisole-tainted cocaine describes neutropenia and/or agranulocytosis in patients exposed to the combination. Reversible agranulocytosis occurs in up to 20% of patients who use levamisole as a chemotherapeutic agent; however, information regarding the incidence of agranulocytosis with use of levamisole-contaminated cocaine is unavailable.[19]

Some patients may have a genetic predisposition for severe hematologic adverse effects from levamisole based on *HLA-B27* + genotype.[40] One group of authors described 20 cases of idiopathic agranulocytosis, 14 of which had documented cocaine use.[40] Three of the five patients tested were positive for both *HLA-B27* + genotype and antineutrophil cytoplasmic antibodies. Another group of authors describe 42 cases (16 confirmed, 26 probable) of severe neutropenia associated with exposure to cocaine and levamisole in the provinces of Alberta and British Columbia, Canada, between January 1, 2008, and March 31, 2009.[12] Of the patients who identified the type of cocaine ingested, 93% used crack cocaine, 7% used cocaine powder, and overall, 72% administered cocaine by smoking it. Patients who developed neutropenia after exposure to levamisole-tainted cocaine admitted to using cocaine within 2 days of presentation to a physician and presented with a variety of infections including invasive group A *Streptococcus* infections, septic shock, pneumonia, and cellulitis.[12] One patient tested positive for antineutrophil antibodies, and four of five patients tested positive for antineutrophil cytoplasmic antibodies. Two patients who used crack pipes tested positive for levamisole as well as one for cocaine. It was thought that the number of confirmed exposures would have been greater had clinicians known to test patients' urine within 48 hours of levamisole exposure, given its short half-life.[12] Cocaine has not been documented to cause agranulocytosis or neutropenia in the absence of adulteration.[14]

Conclusion

The number of reports describing the use and adverse events related to levamisole-tainted cocaine has grown significantly in recent years. Ingestion of this dangerous combination is difficult to diagnose given the multitude of possible clinical presentations, the wide variety of possible adulterants, and the elusive nature of levamisole given its short half-life and limited availability of detection methods. Clinicians must have high clinical suspicion for ingestion of this combination and request levamisole testing of urine samples promptly if a patient admits to illicit drug use and presents with purpuric or necrotic skin lesions. Only a few reports have been published regarding the clinical presentation and management of patients with toxicity from levamisole and cocaine.

This case report is distinctive given the patient's presentation with thrombocytopenia, acute renal failure, diffuse purpura that spared the ear lobes and led to widespread gangrene, severe anemia, as well as a clinical syndrome of shock and multiorgan failure, consistent with the definition of STSS as proposed by the Working Group on Severe Streptococcal Infections. To our knowledge, this is the first report of a case of severe gangrene induced by the combination of cocaine and levamisole that required amputation of multiple appendages. Clinicians must be aware of the prevalence and potentially dangerous outcomes associated with the combination of cocaine and levamisole.

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