Levamisole: A High Performance Cutting Agent

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ABSTRACT

Levamisole is an imidazothiazole chemical most frequently used as an antihelminthic agent in cattle. Over the last decade, levamisole has been increasingly encountered as an additive in both powder and crack cocaine. A white powder with a "fish scale" appearance, the chemical is physically similar to powder cocaine. *In vivo*, levamisole is metabolized to aminorex, a compound with amphetamine-like psychostimulatory properties and a long half-life; *a priori*, this property allows levamisole to potentiate and prolong the stimulatory effects of cocaine while bulking up the drug to increase profit for the dealer. As use of cocaine cut with levamisole becomes more prevalent, complications directly attributable to the chemical are increasingly being recognized. *Acad Forensic Pathol. 2017 7(3): 469-476*

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INTRODUCTION

Amphetamine and cocaine are abused for stimulatory effects achieved through the alteration of monoamine concentration and duration at the synapse. Amphetamine increases monoamine release, whereas cocaine targets monoamine reuptake, including the serotonin reuptake transporter (SERT), norepinephrine transporter (NET), and dopamine transporter (DAT). Ultimately, both cocaine and amphetamines prolong the actions of serotonin, norepinephrine, and dopamine at the synaptic cleft until they are eventually broken down by monoamine oxidase (MAO) and catechol-o-methyl transferase (COMT) (1). When introduced into the body, cocaine is quickly metabolized by hepatic and plasma cholinesterases; it has a half-life of only 30 to 60 minutes (2). Its metabolites are water-soluble and excreted by the kidneys (2).

Since monoamine metabolism plays an important role in the dopamine reward system, it's not surprising that polymorphisms in the *COMT* gene have been associated not only with cocaine dependence, but also with a number of substance abuse disorders (3). In using cocaine and other drugs affecting dopamine release and reuptake, individuals with a low-activity *COMT* allele may have even further reduction in the rate of dopamine metabolism at the synapse and are subsequently suspected to experience a prolonged effect of dopamine in the brain, increasing the duration and intensity of the high and ultimately driving future reward-seeking behavior and cocaine dependence (3).

Because illicit drugs are unregulated, they are frequently diluted, or "cut," with a wide variety of other materials prior to sale/resale in order to bulk up the product and increase profit (1, 4). Cutting can occur at any stage of the chain of distribution, but a study analyzing cocaine seized by the Brazilian Federal Police found that drugs intended for international trafficking had already been significantly adulterated prior to leaving Brazil (5).

Many diluting agents (e.g., sugars and starches) are easily purchased, pharmacologically inactive, and carry minimal risk of adverse effects much beyond minor nasal irritation (6). However, a variety of pharmacologically active chemicals are used as cutting agents because of their physical or chemical resemblance to cocaine, their low cost, or their added physiological effects; these substances are correctly referred to as adulterants, as opposed to diluents, which have no physiologic effect (4, 6). For example, caffeine is a common additive to cocaine and heroin because it is cheap and widely available (4). Further, adding caffeine to heroin allows the heroin to vaporize at a lower temperature when smoked, thus mildly increasing its efficacy. On the other hand, as a stimulant, caffeine makes a mild contribution to the intrinsic effects of cocaine (4). Heroin has a bitter taste, so it is sometimes cut with the bitter-tasting antifungal griseofulvin to give the impression that the heroin is a purer sample. Paracetamol/acetaminophen may also be used to adulterate heroin due to its similar bitter taste, with its analgesic effects and similar melting point to heroin being additional benefits (4).

An ideal cutting agent physically resembles the drug it is used to adulterate; accordingly, chemicals used to cut powder cocaine hydrocholoride are typically white powders. The most commonly encountered white powder additives include, in addition to sugars and starches, lidocaine, levamisole, and diltiazem. A purchaser sampling cocaine before a possible buy notes the numbing effect of the drug on the gums, since cocaine has an anesthetic effect on mucous membranes; a benefit of cutting cocaine with lidocaine is that the latter is a more powerful anesthetic than cocaine, potentiating the impression that the cocaine is of higher quality (4). The literature yields no clear explanation for the fairly common use of diltiazem as a cutting agent; while it arguably confers some cardioprotective effect through its vasodilatory properties, it is a relatively expensive chemical; drug runners are hardly known for their largess. Other common additives to cocaine include hydroxyzine (a first-generation antihistamine), levamisole, and phenacetin (an analgesic) (4, 7, 8).

DISCUSSION

Levamisole as a Cocaine Adulterant

As of July 2009, the Drug Enforcement Agency (DEA) reported that levamisole was a component of 69% of seized cocaine coming into the United States (9), and more recent reports estimate that the proportion of cocaine laced with levamisole may now be higher than 80% (10, 11).

First produced in 1966 (12), the imidazothiazole derivative levamisole (8) is an anthelminthic agent that acts as a ganglion stimulant in mammals and as a depolarizing muscular blocker in nematodes. By stimulating acetylcholine receptors (AChR), levamisole results in calcium influx and causes sustained muscle contraction (13). Aminorex, a levamisole metabolite and amphetamine-like substance, was marketed as an anorectic (appetite suppressant) in the mid-1960s in Austria, Switzerland, and Germany. It was subsequently found to cause pulmonary vasoconstriction and after a number of fatalities due to pulmonary hypertension, the drug was subsequently withdrawn in 1972 (1, 8, 14). In humans, levamisole was used clinically as an anthelminthic and as an immunomodulatory agent for inflammatory conditions (such as pediatric nephritic syndrome and rheumatoid arthritis) (15) and colorectal cancer (brand name: Ergamisol) (16). In 2000, it was withdrawn from the US market due to side effects and is currently marketed only for veterinary purposes (1, 8), although detection of its metabolites—including aminorex, rexamino, and 4-phenyl-2-imidazolidinone (II)—in some recent official blood and urine samples from racehorses has highlighted the potential use of levamisole to dope racehorses (17).

Initially regarded as a curious contaminant, levamisole in cocaine gradually began to develop a higher profile. In April 2008, New Mexico experienced a mysterious cluster of cases of agranulocytosis (9). Further investigation revealed cocaine as the common exposure in 11 cases between April 2008 and November 2009 (9). Around the same time, in November 2008, public health officials in British Columbia and Alberta, Canada, reported detection of an additional drug, levamisole, from cocaine samples and paraphernalia of cocaine users with agranulocytosis (9). An additional ten cases of agranulocytosis were identified in cocaine abusers between April and November 2009, in Seattle, Washington, and of the 21 New Mexico agranulocytosis cases, levamisole was detected in four of five specimens taken from patients (9). Shortly thereafter, a series of six cases was identified in which levamisole-contaminated cocaine exposure was associated with the development of purpura, vasculitis, and neutropenia; all six patients presented with purpura and necrotic skin lesions on various parts of the body, with bilateral ear necrosis occurring in five of the six patients, skin biopsy results revealed intravascular thrombi in four patients, small vessel vasculitis in two patients, leukocytoclastic vasculitis in two patients, and neutropenia in three patients (18).

On its own, cocaine can precipitate life-threatening cardiac events, even at fairly low doses and in the absence of apparent underlying cardiovascular system (CVS) disease (2, 19); however, patients with cocaine-associated myocardial infarction (MI) have been observed to be of older age and have a medical history significant for coronary artery disease (CAD) and chest pain (although less frequently) (20). As a sympathomimetic, cocaine induces vasoconstriction, raises blood pressure, and has positive chronotropic and inotropic effects on the heart (15, 19, 21). With chronic use, it accelerates atherosclerosis, increases platelet aggregation, and prompts plaque rupture and thrombus formation (21). It is believed that increased myocardial oxygen demand in response to cocaine intoxication produces ischemia, particularly via generalized vasoconstriction of the coronary arteries, thereby raising the risk of MI, and, subsequently, arrhythmias such as ventricular tachycardia, ventricular fibrillation, or *torsades de pointes* (19, 20, 22). Development of arrhythmias is also associated with cocaine's effects on ion channels. Sodium channel blockade by cocaine is associated with wide QRS complex tachycardia, which is similar to the tachycardia associated with the sodium channel blocking effects of tricyclic antidepressants (TCAs) (20). Potassium channel blockade, on the other hand, may result in a widened QT with absent or insignificant prolongation of QRS, and atyp-

ical T waves may also be seen. In severe cases, potassium channel blockade can lead to monomorphic or polymorphic ventricular tachycardia (i.e., *torsades de pointes*). Arrhythmia may also result from catecholamine excess, presenting in milder cases with psychomotor agitation and benign sinus tachycardia manageable with supportive care, or in more severe cases with reentrant supraventricular tachycardia or atrial fibrillation (20). Other associated CVS complications include myocarditis, endocarditis, hypertensive crisis, cardiomyopathy, and aortic dissection or rupture (2). Seizures are another common complication (19), as well as toxic leukoencephalopathy (23). Toxic effects of cocaine emerge at concentrations of 0.25-0.5 mg/L in blood, but lethal outcomes occur may be seen at very low concentrations. The final common mechanistic pathway in sudden death associated with cocaine use is typically an arrhythmia (24). Most frequently, autopsy in cocaine-related sudden death reveals no gross structural cardiac abnormality.

Levamisole is 100- to 300-times less potent than cocaine in blocking norepinephrine (NE) and dopamine (DA) reuptake, and it has low affinity for the serotonin transporter (1). The drug is available in tablet, solution, or powder form (25). It has a half-life of three to eight hours and is subject to first-pass metabolism, and some of its metabolites (p-hydroxylevamisole) undergo conjugation with glucuronic acid as well (25, 26). As such, its clearance depends on normal hepatic and renal function (26). Despite its short serum half-life, levamisole has a high volume of distribution (26).

In vivo, levamisole is metabolized to aminorex, which is bioactive (1). A study of levamisole metabolism demonstrated the presence of unchanged levamisole and several metabolites including aminorex in the urine: 100 mg of levamisole were administered orally to a human subject, and of that only 0.5% was found to be excreted unchanged. The highest urinary concentration of levamisole (>1000 ng/mL) was noted three hours after intake, the concentration remained high (>1000 ng/mL) for up to 20 hours, and levamisole remained detectable in the urine for 39 hours. Aminorex reached its peak concentration in the urine within seven hours of levamisole administration and could be detected for up to 54 hours after levamisole was ingested (27).

The potency of aminorex has been found to be comparable to cocaine, and aminorex may be responsible for levamisole's psychostimulant effects due to its amphetamine-like properties (1). Levamisole, which is highly lipophilic, readily crosses the blood brain barrier (BBB) and has a longer half-life than cocaine (1). As such, at high doses it may reach higher concentrations in the brain than cocaine and potentiate the action of cocaine by providing additional neurotransmitter releasing action on NET, DAT, and SERT (1). Levamisole also prolongs the actions of cocaine by decreasing its metabolism by cholinesterase, which processes cocaine to its inactive metabolites and it has been suggested that levamisole may change ganglionic nicotinic receptors and increase the number of D1 dopamine receptors in the brain as well (8, 15). Levamisole may also enhance monoamine transmission via inhibition of the monoamine-metabolizing enzymes MAO or COMT (12). Furthermore, due to its longer half-life (as previously noted, aminorex is detectable in human urine up to 54 hours after levamisole administration), levamisole may continue to affect neurotransmitter reuptake, providing amphetamine-like stimulant effects even after cocaine is no longer present and its direct effects have worn off (1). In addition to these psychoactive characteristics, addition of levamisole to cocaine increases profits as a diluent (7, 8, 10). These features make levamisole (and aminorex) an attractive choice as a cocaine additive (1).

In a study of 104 samples of "cocaine" voluntarily provided by drug users participating in a drug-check program, 66 contained varying amounts of levamisole, with some samples containing as little as 1% and others containing up to 20 times more levamisole than cocaine (1). As much higher doses of levamisole are required to affect monoamine reuptake in a way similar to cocaine, users of drugs containing a high levamisole-to-cocaine ratio are likely to consume significant amounts in order to achieve the desired effects, putting them at higher risks of severe side effects of the adulterants (1).

Levamisole use can present with a number of adverse effects, include nausea and vomiting, headache, fa-

tigue, fever, diarrhea, myalgia, dizziness, confusion, and rash (25). Serious complications include agranulocytosis, leukopenia, thrombocytopenia, vasculopathy and vasculitis, dermal necrosis, leukoencephalopathy, psychosis, pulmonary hypertension and hemorrhage, glomerulonephritis, emboli, arthritis, CAD, and collapse (1, 8, 25, 28). Some of these complications—including agranulocytosis, skin rash, dermal necrosis, vasculopathy and vasculitis, and glomerulonephritis—appear to be associated with levamisole's propensity to provoke hypersensitivity reactions in people with certain genetic predispositions (12, 15). For instance, Le Garff et al. described the eruption of skin lesions in a female patient after cocaine/levamisole exposure, presenting as necrotic purpura of the nose, cheeks, and extremities (12). Such reactions have been reported previously, with reoccurrence of symptoms after re-exposure (12). Reviews on immunologic associations note positive anti-neutrophil cytoplasmic antibodies (ANCA), including p-ANCA (frequently associated with such conditions as microscopic polyangitis), and, less commonly, c-ANCA (anti-PR3, frequently associated with Wegener granulomatosis), as well as type III cryoglobulinemia (12). In terms of p-ANCA, the antigens targeted by the immune response include human neutrophil elastase (HNE), myeloperoxidase (MPO), lactoferrin, and cathepsin G (12, 28).

More than half of those who develop agranulocytosis have ANCA, and a recent case-control study demonstrated a significant association between cocaine associated agranulocytosis and HLA-B27 (frequently associated with the seronegative spondyloarthropathies, including ankylosing spondylitis and reactive arthritis) (16, 29). Anti-HNE has been observed in many cases, although whether it is diagnostic for levamisole-induced agranulocytosis and cutaneous vasculitis has not yet been determined (12). Levamisole-associated vasculitis appears to be related to circulation and deposition of immune complexes (16).

The side effect of pulmonary hypertension sometimes observed in association with exposure to levamisole is consistent with aminorex's effect on SERT and is theorized to be due to dysregulation of peripheral serotonin transporters and serotonin efflux (1).

Fatalities Associated With Levamisole-Tainted Cocaine

Toxicological detection of cocaine with levamisole has been reported in association with a number of case fatalities, typically attributed to pathology of the heart, brain, or lungs.

Indorato et al. reported on two fatalities. The first, a 38-year-old male, had engaged in an intravenous cocaine binge with a friend. Shortly thereafter, he was transported to the emergency department (ED) via ambulance with complaints of chest pain and nausea, and died on arrival. Autopsy revealed a heart weighing 454 g and histological analyses revealed minor atherosclerotic CAD, pulmonary edema with low protein content, and focal segmental glomerulosclerosis (FSGS). In the second case, a 31-year-old male who had snorted cocaine was found deceased in a car. Autopsy findings were unrevealing: histological examination of sections of the 304 g heart revealed localized fibrosis and minor atherosclerotic CAD. Cocaine and levamisole were detected in heart blood in both patients. In both patients, levamisole concentrations were highest in the blood, lungs, and liver (30).

Brajkovic et al. described the death of a "body packer," a person attempting to smuggle drugs secreted within the body cavities. A 26-year-old man was delivered to the hospital with no vital signs, and efforts at resuscitation were unsuccessful. Autopsy revealed 66 packets of cocaine in his digestive tract, one of which had ruptured, leading to severe intoxication. Investigation revealed hyperemia of the majority of the patient's internal organs and edema of the lungs and brain. High concentrations of cocaine, its metabolites, and levamisole were detected in postmortem blood and tissues (24).

In these cases, the relative contributory roles of cocaine and levamisole cannot be discerned; the circumstances and the blood concentrations of cocaine encountered in many of these cases would be considered sufficient in and of themselves to cause death. Indeed, it is likely that most forensic pathologists practicing in the United States today have assigned such deaths

simply to acute cocaine intoxication, without considering levamisole toxicity as a contributory factor. While sequelae of long-term levamisole exposure have been documented, little is known regarding the acute effects of exposure to high concentrations of the drug and the potential mechanism of death in associated fatalities, but it is possible that levamisole enhances the toxic effects of cocaine on the CVS just as it potentiates cocaine's psychostimulant effects, ultimately leading to sudden death in these patients (30).

Michaud et al. reported on a 25-year-old man, a known cocaine addict with a recent history of a Q-wave MI (one year prior), who died suddenly after complaining of retrosternal pain. Electrocardiogram (ECG) revealed ventricular fibrillation. Examination of the heart, weighing 330 g, revealed two fibrous scars consistent with healed infarctions in the left ventricular myocardium. Pleural effusions and pulmonary edema were also present. Histological analysis revealed eosinophil infiltration of the adventitia and intima of the left anterior descending (LAD) artery. Levamisole was detected in the urine and pericardial fluid (15). Although vasculitis and eosinophilic myocarditis have been reported as a complication of cocaine use, eosinophilic inflammation of the coronary arteries has not. Eosinophil infiltration of the coronary arteries has, however, been associated with coronary dissection and Kounis syndrome (hypersensitivity coronary syndrome), which includes vasospastic allergic angina, and allergic MI and stent thrombosis with eosinophil and mast cell infiltration of the occluding thrombus. As a toxic substance known to induce hypersensitivity reactions, the presence of eosinophils may be related to levamisole exposure via allergic or immune-mediated mechanisms (15).

Hantson et al. described an unusual case in which a previously healthy 22-year-old man with a history of cannabis and cocaine abuse was admitted to the hospital with headache, ataxia, and right-sided paresthesias. Magnetic resonance imaging (MRI) revealed multiple sclerosis (MS)-like leukoencephalopathy throughout the supra- and infratentorial white matter and within the corpus callosum, mimicking Susac syndrome (23). Susac syndrome, an autoimmune microangiopathy of the brain, retina, and cochlea characterized by encephalopathy, occlusions of branches of the retinal artery, and hearing loss, presents with midline lesions of the corpus callosum. Although a specific offending antigen has yet to be identified in Susac syndrome, anti-endothelial cell antibodies have been detected in a subset of patients, and examination of the cerebrospinal fluid (CSF) typically reveals elevated protein and mild lymphocytic pleiocytosis, which may reflect dysfunction of the blood brain barrier (BBB). In this particular patient, the lesions in the corpus callosum advanced to become necrotic and cystic. Despite interventions, the patient remained minimally conscious and died after three months from septic complications (23). Although the exact etiology in this patient is unclear, multifocal inflammatory leukoencephalopathy has been reported in association with levamisole monotherapy, and levamisole was detected in this patient via hair testing (23, 31). In patients with levamisole-induced leukoencephalopathy, T2 MRI reveals hyperintense foci, which may be enhanced with gadolinium or accompanied by edema. Brain biopsy reveals active demyelination with loss of myelin and lymphocytic infiltration of the perivascular space (31).

Karch et al. described a case in which a 51-year-old male was transported to a local hospital due to severe dyspnea, but arrived in cardiac arrest and could not be resuscitated. He had a history of cocaine and heroin abuse, as well as a history of asthma, and had undergone nine months of methadone replacement therapy. Consistent with this history, inhalers (salbutamol, salmeterol, fluticasone) were found in his possession, as well as 8 mg of white powder. Morphine, 6-monoacetylmorphine, cocaine, benzoylecgonine, methadone, and EDPP were detected in multiple biological samples, and levamisole and aminorex were detected in the urine and hair. Analysis of the white powder revealed it to be 75.2% cocaine and 6.9% levamisole. Microscopic examination of lung tissue revealed findings consistent with idiopathic pulmonary hypertension (IPH), including fibromuscular dysplasia and intimal hypertrophy obliterating the lumen of almost half of the small pulmonary arteries. Focal regions of over-inflation were also present, along with anthracosis (consistent with smoking crack cocaine) (32).

In a more recent publication, Karch et al. described two cocaine/levamisole-associated case fatalities with prominent features of pulmonary vasculitis. The first, a 51-year-old man with an extensive history of cocaine abuse, was taken to the hospital due to bizarre behavior, but died suddenly. Autopsy revealed the presence of severe pulmonary edema and a significantly enlarged heart. While microscopic examination of the heart revealed changes consistent with long-term abuse of stimulants, histological examination of the lungs revealed pulmonary edema and lymphocytic infiltration of small pulmonary vessels, along with perivascular fibrosis and transforming fibroblasts. The second case described a 35-year-old male—again with a long history of cocaine abuse—who reportedly collapsed at a party approximately 30 minutes after snorting cocaine and died shortly thereafter. Autopsy revealed a heart of normal size and shape, although hypertrophy of the left ventricular wall was noted. The only other findings were severe edema of the lungs and brain. Histologic examination of the heart revealed regions of myocardial necrosis with hypercontracted myocytes, while examination of the lungs revealed edema, intimal thickening and lymphocytic infiltration of arteriolar walls, and perivascular infiltrates. The vascular lymphocytic infiltrate was mixed in both cases, containing B cells and T cells; when compared to a control group of 11 cocaine-associated deaths where levamisole was not present, the authors noted that no pulmonary vasculitis was detected in any of these cases. This suggests that the pulmonary lymphocytic vasculitis demonstrated in the two presented cases may be a complication of levamisole use (or its metabolite) (14).

CONCLUSION

In many ways, levamisole may be the ideal cutting agent for manufacturers and distributers. Easy to obtain, inexpensive, physically similar in its presentation, and with the inherent ability to potentiate and prolong the effects of the primary agent, it seems the perfect choice for maximizing profit while leaving consumers none the wiser…except in those cases with deadly consequences.

The cause of death in patients with cocaine and levamisole intoxication may be due to any number of mechanisms, ultimately severely impacting the heart, lungs, and brain. Given its prominence as a cocaine additive, its presence in a majority of cocaine specimens evaluated in numerous centers around the world, its known side effect profile and role in autoimmune reactions, and potential role in facilitating or exacerbating pathological processes leading to sudden death, toxicological screening for levamisole is an appropriate element in the analysis of suspected cocaine-related fatalities.

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