Phenytoin Toxicity from Cocaine Adulteration

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The use of phenytoin (PHT) as a cocaine adulterant was reported decades ago; that practice is still current. Ironically PHT has also been used for the treatment of cocaine dependence. A drug smuggler developed PHT toxicity after swallowing several rocks of crack. We investigated the current trends of PHT as a cocaine adulterant and its toxicological implications. We also reviewed the clinical use of PHT in relation to cocaine. The use of PHT as cocaine cut is a current practice. This may affect the clinical manifestations and the management of the cocaine-related visits to the emergency department. West J Emerg Med. 2014;15(2):127–130.

INTRODUCTION
Cocaine is a powerful stimulant of the nervous system and is highly addictive. Non-medical cocaine is commonly diluted (or “cut”) with adulterants or diluents that mimic the drug’s systemic pharmacologic properties, simulate its local anesthetic effect, or resemble the physical appearance of cocaine. Cocaine dealers incorporate these additives to enhance the total volume of their stock and therefore to increase profits. Consequently, the purity of the street cocaine is variable. Various substances, including phenytoin (PHT), have been reported as cocaine adulterants. In the early 1990s, Katz and colleagues reported several patients with PHT toxicity after smoking crack cocaine that was cut with PHT capsules.1 The management of cocaine-related emergencies is well described in the literature. When cocaine is adulterated, clinicians must be vigilant of the unsuspected exposures from the additives; the clinical implications and its complications can be significant. Many past and present cocaine adulterants, such as Levamizole, are otherwise legitimate medications that are used to enhance or alter cocaine’s pharmacological traits. This alteration of cocaine’s pharmacology makes these drugs an interesting class of adulterants.2 Regarding PHT, some have suggested the possibility that it augments cocaine’s effects on the nervous system; others speculate that PHT’s similarities in appearance to cocaine just make it an attractive blender.

CASE REPORT
In Houston, Texas, a 26-year-old male drug smuggler who swallowed several rocks of crack cocaine to conceal evidence while being apprehended by police was taken to our emergency department (ED) for medical clearance. Initially, he was asymptomatic, and his vital signs and physical exam were normal. After 2 hours of observation, he manifested clinical signs of cocaine toxicity including anxiety, pallor, diaphoresis, agitation, tachycardia, and hypertension. His vital signs changed; his blood pressure was 190/110 mmHg, heart rate 120 bpm, respiratory rate 22 breaths per minute, and temperature 99.6 F. His physical exam was otherwise unchanged. He was given intravenous benzodiazepine boluses and was admitted to a medical intensive care unit. Subsequently he developed confusion, truncal ataxia, diplopia, slurred speech, and multidirectional nystagmus; these changes were not explained by his pharmacological management. Additional examinations, including computer tomography of the brain, diagnostic lumbar puncture and extensive blood testing, were negative for any abnormalities. A neurology consult revealed uncertain diagnosis. A PHT level was obtained at the recommendation of the poison control center. The patient’s PHT level was 48 mcg/mL (therapeutic range: 10 to 20 mcg/mL). The patient had no history of seizures or records of prescribed PHT. Supportive care was continued, and eventually the patient was discharged with no further complaints 72 hours after MICU admission. To challenge the uniqueness of the use of PHT as cocaine adulterant a random blood screen of PHT levels was performed in 10 patients presenting with complaints related to cocaine use to an academic ED in New York City (7 were seen for chest pain, 1 for suicidal ideation, 1 for new-onset seizures, and 1 for headache associated with uncontrolled hypertension). One patient with chest pain had a PHT level of 4 mcg/mL.
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The patient presenting with headache had a level of 5 mcg/mL. None of the patients screened had any history of seizure disorders or medical indications for the use of PHT. The patients with positive screening tests were unaware of cocaine adulteration.

DISCUSSION

The history of PHT as a cocaine adulterant is still unclear. The isolation of cocaine by Albert Niemann in 1859 facilitated storage and experimentation by scientists and entrepreneurs. Soon, widespread unrestricted access and increasing reports of fatalities among cocaine consumers became a matter of public health. In response, the United States government passed the Harrison Narcotics Act of 1914 banning nonprescription use of cocaine-containing products. This act resulted in the end of the first American cocaine epidemic. In the 1970s, the introduction of crack ushered in the second epidemic of American cocaine use. Crack then became the preferred presentation of cocaine among young and low-income populations. In 2005, the United States (U.S.) government reported that retail-level prices for cocaine had increased and purity had decreased. Unsurprisingly, many substances have been listed as cocaine adulterants. This list includes local anesthetics (i.e., procaine, lidocaine, and tetracaine), other stimulants (i.e., amphetamine, caffeine, methylphenidate, and strychnine), lysergic acid diethylamide, phencyclidine, heroin, marijuana, and hashish. Similarly, quinine, tale (i.e., magnesium silicate), ascorbic acid, boric acid, chalk, laundry detergent, meat tenderizer, laxatives, plaster of Paris, cornstarch, and lactose are also known cocaine diluents.

Cocaine has been part of U.S. drug-use history for more than a century, whereas PHT was introduced as an effective drug for the treatment of epilepsy only after 1940. The use of PHT as a cocaine adulterant was first documented in the 1990s. Since then, no other reports have been published.

Assessment of Prevalence

In the U.S., information related to collection and analysis of drugs with legitimate medical use is maintained by the U.S. Drug Enforcement Administration, Office of Diversion Control. The National Forensic Laboratory Information System (NFLIS) monitors illicit drug use and trafficking, including the diversion of legally manufactured drugs into illegal markets, by systematically collecting results from drug analyses conducted by state and local forensic laboratories. These laboratories analyze controlled and non-controlled substances secured in law enforcement operations across the country. The NFLIS annual reports include information on specific substances and the characteristics of drug evidence, such as purity, quantity, and drug combinations. Since the inception of the NFLIS in September 1997, an estimated total of 1,660,216 drug reports were submitted to state and local forensic laboratories in the U.S. Regional laboratory analyses of confiscated cocaine showed variability in cocaine purity from 48% (2008) being the lowest and 75% (2006) the highest (mean value 60%). Many of the cocaine-related combinations included excipients used to dilute cocaine. These included non-controlled substances such as procaine, inositol, caffeine, boric acid, benzocaine, and lactose. PHT was not listed as a cocaine adulterant; it is unknown if it was not found or not tested for. The specific locations or the amount of drugs confiscated and analyzed were not specified. Another source for drug information and toxicity statistics is the National Poison Data System (NDPS), formerly performed by the Toxic Exposure Surveillance System (TESS) until 2004, in which no role of PHT as cocaine adulterant was found.

Interaction between PHT and Cocaine

When examining the mechanism of action of cocaine and PHT, it is similarly difficult to elucidate a common link between the 2 drugs that could result in an augmented high. Cocaine blocks the recovery of dopamine at the adrenergic neuronal junction, which leads to increased dopamine receptor activation at the neuronal synapse. In addition to dopamine, cocaine also inhibits norepinephrine and serotonin reuptake, which causes an influx of sodium and an efflux of potassium and results in an action potential at the synapse and subsequent nervous system stimulation. Conversely, PHT can cause central nervous system depression. PHT restricts the repetitive firing of action potentials -- seen with sustained depolarization -- and slows voltage-activated sodium channel recovery in presynaptic neurons. These effects are responsible for its antiepileptic properties. At toxic levels, oral PHT can induce central nervous system manifestations including nystagmus, ataxia, slurred speech, tremor, lethargy, confusion, and disorientation. No cardiac toxicity develops when ingested orally. Conversely, cocaine toxicity includes central and peripheral nervous system manifestations, such as pallor, tremors, tachycardia, hypertension, increased core temperature, anxiety, paranoia, restlessness, hypervigilance, hallucinations, paranoid delusions, and convulsions. As a result of these opposing pharmacological traits, there is no physiological mechanism to explain an augmentation effect of the mechanism of action of cocaine by PHT.

Drug Metabolism

The metabolism of cocaine occurs mainly in the liver but also involves other pathways. More than 10 cocaine metabolites have been discovered; many retain some of the activity of the parent compound, thereby increasing its toxicity. Ecgonine methyl ester, one of the major metabolites, is formed via cholinesterases in the plasma. A reduction in levels or activity of plasma cholinesterase shifts the metabolism of cocaine toward other toxic metabolites. It has been suggested that PHT may act as an inducing agent for plasma cholinesterase and may therefore promote cocaine clearance. The second major metabolite, benzoyl ecgonine, is formed through spontaneous or enzymatic
hydrolysis of cocaine and may be unaffected by the presence of PHT.\textsuperscript{10} Aside from these 2 mechanisms, cocaine is mostly metabolized through the cytochrome P450 enzyme family, more specifically N-demethylation into norcocaine.\textsuperscript{11}

Ironically P450 enzyme induction by PHT does not occur with acute exposure but certainly can be a factor in chronic use of cocaine adulterated with PHT or in patients taking PHT for therapeutic purposes, such as cocaine-induced seizures. Likewise, PHT relies predominantly on the P450 system for metabolism and uses many different subgroups of that system. Whereas PHT is a substrate of 2D6 and an inducer of 3A4 (12,13), cocaine is an inhibitor of 2D6 and a substrate of 3A4. It is possible that cocaine could potentially hinder the metabolism of PHT through the inhibition of 2D6, thus increasing the concentration of PHT, but PHT undergoes numerous transformations through the P450 system, which would minimize this effect. PHT could also potentially induce the metabolism of cocaine through the induction of the 3A4 subgroup. However, in general, no metabolic pathway explains the possibility of cocaine high augmentation by PHT. In fact, through examining these pathways, it appears that PHT may enhance the elimination of cocaine.

**Clinical Use of PHT in cocaine patients**

Metabolic pathways suggest that PHT enhances cocaine breakdown and excretion at an elevated rate. Consequently, it has been tested as a treatment option for cocaine abuse. In one double-blind, placebo-controlled study for the treatment of cocaine abuse, patients treated with PHT had lower rates of cocaine in urine specimens and longer cocaine-free periods. Observations were based on cocaine urinalysis, patients’ self-reported use, overall function, reduced craving intensity, and subject retention.\textsuperscript{14} Conversely, in a pilot study to determine the effects of PHT on cocaine self-administration in a human laboratory model, PHT altered neither the self-administration nor the effects of cocaine.\textsuperscript{15} A systematic review of the use of anticonvulsants, including PHT, to treat cocaine dependence found no significant differences for any of the efficacy measures compared to placebo. In fact, placebo was superior to PHT for fewer side effects.\textsuperscript{16} Interestingly, PHT has been proposed as an alternative for the treatment of cocaine dependence and cocaine-related seizures. However, a limited number of small clinical trials were insufficient evidence to support the clinical use of PHT with this purpose.\textsuperscript{17,18}

**CONCLUSION**

The use of PHT as a cocaine adulterant is still a current practice. Due to the impurity of the street cocaine, clinicians should always consider the presence of adulterants in the differential diagnosis of atypical manifestations of a cocaine-related visit. Awareness of the local trends of cocaine adulteration might facilitate the medical management of these patients, thereby avoiding increased cost and improving resources utilization. On the other hand, we need to acknowledge that a limited number of small clinical trials are insufficient evidence to support the clinical use of PHT for the treatment of cocaine dependence.

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