

High On The Designer Drug Naphyrone: A Case Report Of “Bath Salt” Toxicity

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Abstract

The use of designer drugs, especially non-regulated bath salts, has become increasingly popular and increasingly dangerous. Problems with designer drugs are numerous on a number of legal, societal, and clinical levels. The effects that may be observed include peripheral nervous system effects on the heart and peripheral vasculature as well as central nervous system effects and psychotic effects. This article presents a case exemplar and reviews the diagnosis and clinical management of acute stimulant toxicity from the use of naphyrone, an unregulated bath salt.

INTRODUCTION

Designer drugs such as “bath salts” are pharmaceuticals produced to skirt existing drug-control laws. Existing patents, publications, and research data from reputable sources are often exploited by enterprising chemists to engineer new, unregulated substances that mimic the effects of illegal drugs. A variety of stimulant substances, including naphyrone, are produced by foreign research chemical companies or in clandestine laboratories. The products are promoted as “legal highs” and widely available for purchase on the Internet.¹

Designer drugs are often created when a structural or functional group is added to or removed from a chemical with demonstrated pharmacological activity.² Synthetic cathinones are increasingly reported to regulatory agencies as new psychoactive substances. These designer compounds are derivatives of the parent compound cathinone which is structurally related to amphetamine. One of these compounds is mephedrone, also known as 4-methylmethcathinone or 4-methylephedrone. Mephedrone is a synthetic stimulant drug of the cathinone class. Similar to amphetamines, cathinones act primarily on catecholamine transporters.² Mephedrone is suspected to also act in this way. Mephedrone has been banned in a number of countries but its successor naphyrone, known to users as NRG-1 or Rave, has become available.³

Non-regulated bath salts have become increasingly popular and increasingly dangerous. These drugs are not to be confused with Epsom salts or perfumed salts commonly used to enhance the bathing experience. Bath salts are sold

in convenience stores, smoke shops, and on the Internet. By marketing designer drugs as bath salts and labeling them “not for human consumption,” organizations that produce these substances have been able to skirt existing drug laws. Poison centers throughout the United States have reported growing numbers of calls about these synthetic stimulants.⁴ An increasing number of states are banning the bath salts, but currently no federal laws prohibit their sale. For bath salts to be labeled as illegal, a law must label them as a Schedule 1 substance, defined as: a drug with no medical value but high potential for abuse.³

Primary users of bath salts are teenagers and young adults. An increase has occurred in use designer drugs, including bath salts, associated with the “rave” phenomenon. Young adults ingest the drugs and dance all night in clubs and crowded venues.⁵ Bath salts may be smoked, snorted, swallowed, or injected. These designer drugs are known by many names such as Ivory Wave, Bliss, White Lightning, Hurricane Charlie, Vanilla Sky, Charge, and White Knight.⁶ Problems of designer with drugs are numerous on a number of legal, societal, and clinical levels. Designer drugs are an international problem with reports from Australia, China, Sweden, and the United Kingdom. Internet advertising and sales have contributed to the growth of these substances. Consumption or sales are difficult to measure, but popularity of bath salts has grown rapidly in a short time period. Between March and June 2009, the number on Internet vendors of the drug went from less than 10 to dozens, with new sites opening every week.⁶

Regulation of specific drugs to reduce or prevent abuse is

complicated, time-consuming, and always lags behind the clinical problems caused by the drug. The popularity of a specific drug or its analogues is difficult to predict before abuse is already widespread. In most instances, reference materials on designer drugs are profoundly inadequate so analytical comparison by toxicologists is severely limited.¹ Some potential users of designer drugs perceive that these substitutes are likely of higher quality and less harmful than street drugs. Shops that sell “bath salts” and online legal high sellers often claim the main ingredient in products is naphyrone which is one of the first ‘legal highs’ to be marketed as a ‘new legal alternative’ to mephedrone.^{5, 7} A major issue in assessing the causes and effects of designer drugs is determining the purity of the substance. Synthesis and production of the substances are often produced in illicit laboratories with little or no quality control. These drugs may be cut or mixed with other psychoactive substances such as heroin, ketamine, and ephedrine.⁵ In addition, samples of the same drug may contain many different kinds of chemicals.^{8,9} Chemical analysis has shown that packages with the same label often vary significantly in content. NRG-1 is purported to contain naphyrone only. However, gas chromatography/mass spectrometry analysis of samples revealed many different stimulants including naphyrone, caffeine, mephedrone, methylone, butylone, and flephedrone, alone or in various combinations. Although naphyrone was present in some of the samples, it was not present in all.¹⁰

CASE REPORT

A 34-year old male was brought by his girlfriend to the urgent care clinic. The patient complained of extreme restlessness, agitation, hallucinations, and teeth-grinding for the past 4 hours. Hallucinations consisted of seeing shadows moving and hearing voices calling his name. After obtaining naphyrone (NRG-1) over the Internet, he snorted half a packet 8 hours ago and the remainder 5 hours ago. The patient denied drinking alcohol or consuming other controlled or illicit substances during the previous 24 hours, but had a 22 year smoking history and increased alcohol use over the past months. He has never received treatment for alcohol or chemical dependence, and denies taking any controlled or illicit substances prior to taking “bath salts” earlier today. The past medical history, including review of symptoms, was non-contributive. Physical examination revealed a blood pressure of 164/92 mm Hg, sinus tachycardia, dilated pupils with sluggish response to light, and bruxism (teeth grinding). Laboratory results were unremarkable. The working diagnoses for the patient were:

1) naphyrone or other stimulant abuse and toxicity; 2) unknown stimulant abuse - composition of insufflated substance unconfirmed 3) alcohol abuse; and 4) tobacco abuse

PHARMACOLOGICAL EFFECTS

Naphyrone, also known as O-2482 and naphthylpyrovalerone, is considered a successor to the designer bath salt mephedrone. Naphyrone is derived from pyrovalerone and acts as a triple reuptake inhibitor, producing stimulant effects.¹⁰ As a pyrovalerone derivative, due to its myriad of actions on serotonin, dopamine and norepinephrine levels in the brain, naphyrone can cause a wide spectrum of effects similar to those observed with amphetamine use. Mephedrone is a cathinone analogue and has a chemical structure very similar to amphetamine (synchronium). Amphetamine releases catecholamines (especially dopamine) from synaptic vesicles in nerve terminals. Elevated catecholamine levels may lead to increased arousal and a decrease in fatigue. Amphetamine interacts with N-methyl-D-aspartate (NMDA) receptors on serotonergic neurons¹¹. Peripheral nervous system effects include inotropic and chronotropic effects on the heart and peripheral vasculature.¹¹

Central effects include enhanced vigilance and alertness, euphoria, sensory stimulation, hyperthermia, seizures, and anorexia. Possible peripheral effects include tachypnea, tachycardia, hypertension, bruxism, and hyponatremia. Psychotic effects can include hallucinations, agitation, paranoia, and anxiety.¹⁰ No safety or toxicity data are available on the drug¹² or its metabolites¹³, and effects must be anticipated based on experience with similar substances with more-established research findings. The acute effects of MDMA and naphyrone, when taken orally, have an onset of approximately 30 minutes. These symptoms include anxiety, tachycardia, diaphoresis, bruxism, dry mouth, and increased psychomotor activity. Within 1 hour, these sympathomimetic effects are replaced with euphoria, feelings of relaxation, and increased communications and feelings of empathy. Although overt visual or auditory hallucinations are not common, patients report mild visual distortions such as halos and increased tactile enhancements. The effects plateau for approximately 90 minutes and then diminish over 3-4 hours. Users may attempt to prolong these effects by taking additional doses of the drug or by ingesting other drugs or alcohol.³ A number of severe clinical complications are possible as a result of naphyrone toxicity and include sudden death, serotonin syndrome, hyperpyrexia, acute panic disorder, isolated liver

failure and hepatic encephalopathy, rhabdomyolysis, and hyponatremia with cerebral edema.^{14,15} (see Table 1)

Table 1

Major Acute Complications Associated with Naphyrone Toxicity¹⁵

Table 1. Major Acute Complications Associated with Naphyrone Toxicity ¹⁵	
>	Sudden death
>	Hyponatremia with cerebral edema
>	Cerebrovascular accident
>	Hyperthermia resulting in rhabdomyolysis and multiple organ failure
>	Acute anxiety and panic disorder
>	Acute liver failure with hepatic encephalopathy
>	Serotonin syndrome

¹⁵ Adapted from Hall AP, Henry JA. Acute toxic effects of ‘ecstasy’ (MDMA) and related compounds: overview of pathophysiology and clinical management. *Brit J Anaesth* 2006;96: 678-685.

MANAGEMENT

Diagnostic Testing

The diagnosis of naphyrone or other stimulant toxicity is based on history and clinical presentation due to the lack of a confirmatory urine drug screen for this substance. However, a urine drug screen may indicate the presence of other substances.¹⁵ The substances tested in a standard 12-panel urine drug screen include methadone, methamphetamine, ecstasy, marijuana, benzodiazepines, barbiturates, amphetamine, opiates, oxycodone, propoxyphene, cocaine, and buprenorphine.¹⁶ Confirmation of the presence of other abusable substances is important in both making a diagnosis and in anticipating possible complications. A blood alcohol level should also be obtained since many individuals drink alcohol at the same time they ingest these substances. Other diagnostic tests are useful in identification and prevention of complications. Serum electrolytes, blood urea nitrogen (BUN), and creatinine results may reveal hyponatremia or impaired renal function. Elevated serum liver function tests may suggest hepatic failure, and high creatine phosphokinase (CK) levels can indicate the occurrence of rhabdomyolysis.¹⁵ An electrocardiogram may show cardiac dysrhythmias, and is warranted since patients with underlying cardiac or pulmonary disease are especially at risk for development of arrhythmias and heart failure. ³ Patients manifesting significant or prolonged hyperthermia require coagulation studies to exclude disseminated intravascular coagulopathy (DIC).⁵

Non-pharmacological Interventions

During the acute toxicity phase, the focus of non-

pharmacological intervention is the management of anxiety and agitation. Monitoring and observation in a quiet, non-stimulating environment may reduce anxiety. The peak action of the drug is at 90 minutes and effects last for 3-4 hours; therefore, all patients should be observed for at least 4 hours after drug ingestion. Any person interacting with the patient should communicate in a calm, clear, non-judgmental, and non-threatening manner. Address physical concerns related to hunger, warmth, and pain in a timely manner. Supportive family members or others may be encouraged to stay at the bedside.¹⁷

Pharmacological Interventions

Since evidence regarding the treatment of naphyrone is almost non-existent and some NRG-1 samples contain other stimulant substances¹⁸, pharmacological interventions must be based on clinical presentation and adapted from more established evidence-based treatments for similar toxic agents such as amphetamine and 3,4-methylenedioxymethamphetamine (MDMA). The symptoms of toxicity and severity vary for person to person and with the amount and combinations of drugs ingested. The objectives for management of acute toxicity in the emergency department include: 1) treatment of agitation and anxiety with diazepam or lorazepam¹⁵ ; 2) relief of muscle spasms and/or cramping with benzodiazepines such as diazepam or lorazepam; 3) treatment of hyperthermia with rapid cooling using cool compresses or a cooling blanket with the goal to cool the core temperature to 101° Fahrenheit (avoid shivering), in severe cases may need deep sedation, paralysis and ventilation; 4) prevention of rhabdomyolysis (breakdown of muscle fibers) with intravenous fluids; 5) control of seizures with benzodiazepines; and 6) control of cardiovascular and hemodynamic disturbances with antihypertensive such as labetalol, nitroprusside, phentolamine, or nitroglycerin. ⁵ (see Table 2 for a summary of clinical management). Admission to the hospital should be considered if significant hyperthermia, severe hyponatremia, respiratory depression, cardiovascular instability, altered mental status, seizures or acute renal failure are present. ⁵

Table 2

Clinical Management of Acute Stimulant Toxicity¹⁵

Table 2. Clinical Management of Acute Stimulant Toxicity ¹⁵	
Monitoring	
<ul style="list-style-type: none"> ➤ Observe for at least 4 hours ➤ Monitor pulse, blood pressure, cardiac monitoring, and core temperature 	
Diagnostics	
<ul style="list-style-type: none"> ➤ 12 lead electrocardiogram ➤ Electrolytes, BUN, creatinine, creatine phosphokinase, liver function tests; consider coagulation studies ➤ Urine drug screen (to determine presence of other illicit substances) ➤ Blood alcohol level 	
Treatment	
<ul style="list-style-type: none"> ➤ Seizures: diazepam or lorazepam intravenously (IV), rectally, or intramuscularly ➤ Anxiety or agitation: diazepam or lorazepam orally or IV ➤ Hyponatremia: fluid restriction; consider hypertonic saline if severe (monitor serum sodium levels to avoid rapid or over correction) ➤ Hypotension: intravascular volume expansion (monitor for hyponatremia) ➤ Metabolic acidosis: consider sodium bicarbonate if severe ➤ Severe hypertension: consider labetalol, nitroprusside, phentolamine, or nitroglycerin ➤ Hyperthermia: simple cooling methods (cool compresses or a cooling blanket); if temperature greater than 101° Fahrenheit, consider dantrolene and critical care measures (sedation, intubation, and paralysis). Avoid shivering. ➤ Organ system failure: conventional support - promote diuresis of 1-2 ml/kg/hour with mannitol or furosemide; respiratory and cardiovascular support; establish invasive monitoring access and a hemodialysis catheter if multi-organ failure is expected 	

¹⁵ Adapted from Hall AP, Henry JA. Acute toxic effects of ecstasy (MDMA) and related compounds: overview or pathophysiology and clinical management. *Brit J Anaesth*. 2006;96: 678-685.

REFERRALS/EDUCATION/FOLLOW UP

This patient did not have the severe symptoms such as hyperthermia, cardiac or liver failure, or acute psychosis and did not require hospitalization and could be discharged for outpatient follow up. The patient was advised by the Advanced Practice Nurse (APN) to avoid further stimulant or recreational drug use, encouraged to return to urgent care if symptoms re-emerged, and referred to a residential drug treatment program. While full recovery from acute toxicity is likely, recidivism is high among acute or chronic stimulant abusers. Stimulant abuse remission rates range, depending on study and definition, from 16-45%.¹⁹ Aggressive sociological and psychological interventions such as inpatient detox/rehabilitation programs or outpatient drug abuse counseling to treat dependence and change lifestyle are necessary to reduce the high relapse rate.³

SUMMARY

This case is representative of the healthcare challenges related to designer drugs. Confirmatory drug tests may not be available in an urgent care setting, and evidence-based guidelines for the treatment of toxicity are almost non-existent. The clinician must rely mainly on clinical

presentation for diagnosis and adapt existing treatments from experience with other stimulant substances in the management of designer drug toxicity.

The APN should be suspicious of designer drug abuse with a suggestive clinical presentation, vigilant in the assessment of changes in condition, mindful of possible complications, and prepared for immediate intervention. Despite the growing use of “bath salts” and other designer drugs, serious acute illness remains relatively rare. However, when complications occur they can be life threatening. A full history of substance abuse (prescription, illicit, alcohol, tobacco) is critical to obtain. Patient education related to prognosis and treatment options, as well as referral for substance abuse counseling and treatment, are important elements of a comprehensive management plan.

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