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NBOMe Drugs

Use of Dangerous New Hallucinogens Grows Despite Risks of Toxicity

By Uttam Garg, PhD, and Stephen Thornton, MD

In recent years many new classes of designer drugs, including synthetic marijuana, bath salts, and NBOMe, have emerged on the illicit drug market. These drugs have gained popularity because they are not detected by routine drug screening systems and are readily available online or from street retailers known as "head," "smart," "C-store," or "coffee" shops.

The use of NBOMe drugs has been reported only since 2010. Sold under street names such as N-bomb, smiles, legal acid, 25I, 25C, and 25B, NBOMe compounds are available as powder or laced on blotter paper. They are often marketed as "cheap LSD" because of their potent hallucinogenic properties, but in contrast to LSD's effects, which are almost entirely hallucinogenic, NBOMe drugs also have sympathomimetic activity.

These drugs are derivatives of N-methoxybenzyl (hence "NBOMe"), specifically from the 2C-X family of 2,5-dimethoxyphenethylamines (1,2). They were first synthesized in 2003 by chemist Ralf Heim during his graduate research at the Free University of Berlin as a pharmacological tool to study the 5-HT_{2A} serotonin receptor. Later, David Nichols' lab at Purdue University researched the structural-activity relationships of NBOMe compounds (3).

Since then, a large number of NBOMe compounds have been synthesized using various substitutions (Table 1). The most commonly reported drugs are 25B-NBOMe, 25C-NBOMe, and 25I-NBOMe. Figure 1 shows their molecular structures and those of related 2C-X compounds.

Like other 2C drugs, NBOMe compounds produce their hallucinogenic and other psychoactive effects through the activation of 5-HT_{2A} serotonin receptors, which are modulators of several neurotransmitters. The addition of an N-methoxybenzyl group to 2C-X drugs dramatically increases their affinity for 5-HT_{2A} receptors and their ability to cross the blood–brain barrier.

Epidemiology

Very limited data exists on the epidemiology of NBOMe use. Many media reports have attributed deaths to NBOMe abuse throughout the world, including in Australia, the United States, the United Kingdom, Russia, and Poland. The drugs have become popular enough to draw law enforcement attention in various countries.

The history of human use of these drugs seems to begin in 2010, when they first became available online. Recently, the Global Drug Survey reported findings of an online poll of 22,289 respondents on the use of 25B-NBOMe, 25C-NBOMe, 25I-NBOMe, and similar drugs (4). Conducted in late 2012, the survey estimated the place of use by the currency used to purchase them: U.K., 34% of respondents; Australia, 36%; U.S. 17%; Euro-Zone, 10%; and Canada, 3%. Most respondents were male (69%) with a mean age of 31.4 years. Many were experienced hallucinogen users: 39% reported using LSD; 43% had used magic mushrooms; and 26% had used ketamine. Tables 2 and 3 summarize their responses regarding NBOMe and related drugs. The results should be interpreted with caution because they are based on self-reported data.

Pharmacology and Metabolism

No human clinical studies have been performed on the pharmacology, metabolism, and safety of

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NBOMe compounds. Animal studies and human case reports indicate that these drugs are highly potent, with anecdotal reports that 50–250 µg are effective doses when administered nasally or sublingually. Doses on blotter paper range from 200 to 1000 µg (4).

Information on NBOMe metabolism is also scarce. The parent compounds undergo O-demethylation or N-acetylation of the aromatic ring followed by glucuronidation or sulfation. The parent compounds and phase II metabolites have been detected in urine (5–7). These drugs are also metabolized by deamination to the corresponding aldehydes, followed by formation of corresponding acids or alcohols by oxidation or reduction. Serum concentrations in severely intoxicated individuals ranged from 0.25 to 2.78 ng/mL (6).

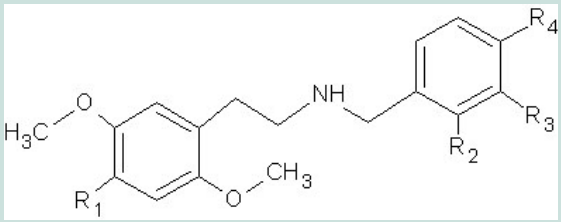
Laboratory Analysis

Currently, no commercial immunoassays are available that detect NBOMe drugs. Many of these compounds can be purchased from commercial sources to use for method development.

Gas chromatography-mass spectrometry (GC-MS) and liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods have been described to assay these compounds. One GC-MS study analyzed 33 NBOMe compounds (2). The method involved DB-1, 30 m x 0.25 mm inner diameter (ID) fused-silica capillary columns coated with 0.25-µm of 100% dimethylpolysiloxane. The initial oven temperature was 100 °C and temperature ramp was 6 °C/min, with a final temperature of 300 °C and a hold time of 5.67 min. The injector and mass selective detector (MSD) temperatures were 280 °C and 230 °C, respectively. The elution order (retention time) was 4-methoxybenzyl > 3-methoxybenzyl > 2-methoxybenzyl for each NBOMe series. In general, the NBOMe compounds produced a base peak ion at m/z 121 due to cleavage of the benzyl moiety and an ion at m/z 150 due to α-cleavage of the phenethylamine moiety. Tropylium ion at m/z 91 was also seen. This ion was significantly more abundant in 2-methoxybenzyl–substituted compounds than in 3- and 4-methoxybenzyl–substituted analogs. The relative abundances of the molecular ions were extremely low, ranging from 0.05 to 1.0%.

Several LC-MS/MS methods have been described in the literature (6,8–10). In a recent paper, nine NBOMe compounds were determined in urine specimens (8). The method involved solid-phase ex-

Table 1. Substitutions of Various Groups Enable Synthesis of Many NBOMe Compounds (2)



Compound	R_1	R_2	R_3	R_4
25H-NB20Me	H	OCH_3	H	H
25H-NB30Me	H	H	OCH_3	H
25H-NB40Me	H	H	H	OCH_3
25B-NB20Me	Br	OCH_3	H	H
25B-NB30Me	Br	H	OCH_3	H
25B-NB40Me	Br	H	H	OCH_3
25C-NB20Me	Cl	OCH_3	H	H
25C-NB30Me	Cl	H	OCH_3	H
25C-NB40Me	Cl	H	H	OCH_3
25D-NB20Me	CH_3	OCH_3	H	H
25D-NB30Me	CH_3	H	OCH_3	H
25D-NB40Me	CH_3	H	H	OCH_3
25E-NB20Me	C_2H_5	OCH_3	H	H
25E-NB30Me	C_2H_5	H	OCH_3	H
25E-NB40Me	C_2H_5	H	H	OCH_3
25I-NB20Me	I	OCH_3	H	H
25I-NB30Me	I	H	OCH_3	H
25I-NB40Me	I	H	H	OCH_3
25N-NB20Me	$N0_2$	OCH_3	H	H
25N-NB30Me	$N0_2$	H	OCH_3	H
25N-NB40Me	$N0_2$	H	H	OCH_3
25P-NB20Me	$CH_2CH_2CH_3$	OCH_3	H	H
25P-NB30Me	$CH_2CH_2CH_3$	H	OCH_3	H
25P-NB40Me	$CH_2CH_2CH_3$	H	H	OCH_3
25T2-NB20Me	CH_3CH_2S	OCH_3	H	H
25T2-NB30Me	CH_3CH_2S	H	OCH_3	H
25T2-NB40Me	CH_3CH_2S	H	H	OCH_3
25T4-NB20Me	$(CH_3)_2CHS$	OCH_3	H	H
25T4-NB30Me	$(CH_3)_2CHS$	H	OCH_3	H
25T4-NB40Me	$(CH_3)_2CHS$	H	H	OCH_3
25T7-NB20Me	$CH_3(CH_2)_2S$	OCH_3	H	H
25T7-NB30Me	$CH_3(CH_2)_2S$	H	OCH_3	H
25T7-NB40Me	$CH_3(CH_2)_2S$	H	H	OCH_3

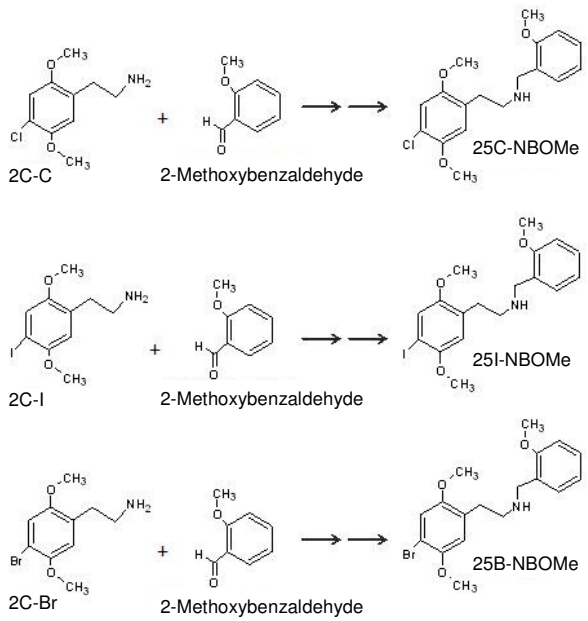


Figure 1. Molecular Structures and Synthesis of NBOMe Compounds, Including 2C-X Precursors
Figure courtesy of the author

traction, a biphenyl column, ammonium acetate/formic acid and methanol mobile phases, electrospray ionization, and multiple reaction monitoring. The transition ions for the NBOMe compounds studied in this paper are shown in Table 4. The authors also described solid-phase extraction and an LC-MS/MS method for analysis of 25I-NBOMe in whole blood, brain tissue, bile, liver tissue, and gastric contents. Many laboratories now use high performance liquid chromatography–time-of-flight (HPLC-TOF) mass spectrometry for screening large numbers of synthetic drugs, including NBOMe.

Zuba et al. used GC-MS, LC-MS, Fourier transform infrared spectroscopy, and nuclear magnetic resonance to identify NBOMe compounds on blotter papers (1). Their GC-MS method was similar to the one described above. Their LC-TOF mass spectrometry method involved chromatographic separation using a C18 (7.5 cm x 2.1 mm x 2.7 µm) column (Supelco) and mobile phases of 0.1% formic acid/water and 0.1% formic acid/methanol with gradient elution. The instrument was operated in positive ion electrospray ionization mode.

Legal Status

Several countries, including the U.S., U.K., Australia, New Zealand, Israel, Russia, and Sweden, have passed regulations to temporarily or permanently ban many NBOMe compounds. From June 2011 to June 2013, the System to Retrieve Information from Drug Evidence and the National Forensic Laboratory Information System reported many incidents of powder or blotter paper laced with NBOMe compounds, including 849 reports of 25I-NBOMe, 171 reports of 25C-NBOMe, and 24 reports of 25B-NBOMe. On Nov. 15, 2013, the U.S. Drug Enforcement Administration added 25I-NBOMe, 25C-NBOMe, and 25B-NBOMe to Schedule I under the Federal Controlled Substances Act (11).

Table 2. Prevalence of Hallucinogenic Drug Use among 22,289 Respondents to Online Global Drug Survey (4)

	Ever used		Last 12 mos.		Last month	
	N	%	N	%	N	%
LSD	8774	39.4	3340	15	1149	5.2
Magic mushrooms	9604	43.1	3586	16.1	1180	5.3
Ketamine	5784	26.0	2505	11.2	1182	5.3
2C-I	1054	4.7	419	1.9	65	0.3
2C-B	1866	8.4	879	3.9	242	1.1
2C-E	777	3.5	338	1.5	58	0.3
2C-C	180	0.8	91	0.4	18	0.1
25B-NBOMe	65	0.3	47	0.2	24	0.1
25C-NB0Me	267	1.2	233	1.0	112	0.5
251-NBOMe	442	2.0	406	1.8	177	0.8
Any NBOMe drug	582	2.6	526	2.4	189	0.8
Any 2C-X drug	2526	11.3	1263	5.7	348	1.6

Table 3. Prevalence of Use of Selected Psychoactive Substances in Past 12 Months from Online Survey of 22,289 Respondents (4)

	N	%
Cannabis, any form	13,965	62.7
MDMA, any form	7971	35.8
Cocaine	5290	23.7
Synthetic cannabis, herbal	1021	4.5
Mephedrone	871	3.9
Methoxetamine	545	2.4
Any NBOMe drug	526	2.4
Benzo-fury (5/6-APB)	316	1.4
Methylone	279	1.2
Synthetic cannabis, powder	175	0.8
MDPV	95	0.4
N-Ethyl ketamine	44	0.2
Flephedrone (4-FMC)	20	0.1

Clinical Toxicity

The first cases of toxicity from laboratory-confirmed exposures to NBOMe compounds were reported in the medical literature in 2012 (12). Since then, many other reports have highlighted the potentially severe toxicity associated with these drugs (7,10,13–15).

The most commonly reported symptom, sinus tachycardia, is present in all published case reports. There have been no reports of QRS prolongation, QT prolongation, or any arrhythmias. Hypertension is commonly reported. Both the tachycardia and hypertension are likely due to the structural similarity the NBOMe compounds share with amphetamines and cathinones. Agitation and hallucinations are frequently reported and can be severe. An American case series described "psychomotor agitation" in four cases, while a case series from the U.K. found that six patients presented with agitation or hallucinations. Seizures appear to be common. In several cases, patients had multiple or refractory seizures that required a combination of medications to control. Serotonin syndrome and clonus have been reported, which is not surprising considering the potent serotonergic activity of the NBOMe compounds.

Hyperpyrexia is common, with Hill et al. reporting six cases with temperatures greater than 38.0 °C (13). Polkis et al. noted a temperature of 40 °C after 25B-NBOMe use (10). Rhabdomyolysis is another reported complication that is likely due to the combination of agitation and seizures. Acute kidney failure requiring renal replacement therapy has occurred.

Treatment of the toxicity caused by NBOMe compounds focuses on aggressive supportive care and treatment of symptoms (7,10,12,13,15). Intravenous fluid hydration is common, especially when rhabdomyolysis is present. Benzodiazepines are frequently used to control the agitation and seizures, with lorazepam the most common. Dexmedetomidine has also been used to control agitation, with propofol used in refractory cases. In one case, a neuromuscular blocker (pancuronium) was required, and cyproheptadine has also been tried to treat possible serotonin syndrome.

Several deaths have been reported. Poklis et al. described a 19-year-old male who suffered fatal traumatic injuries while reportedly under the influence of 25I-NBOMe (9). HPLC-MS/MS confirmed 25I-NBOMe, with blood and urine levels of 405 pg/mL and 2.86 ng/mL, respectively. In another report, a 21-year-old male and a 15-year-old female suffered nontraumatic, sudden deaths after reportedly using 25I-NBOMe (17). Blood and urine samples were positive for 25I-NBOMe by LC-MS/MS, but concentrations were not reported.

Table 4. Transition Ions in NBOMe Compounds Identified by Multiple Reaction Monitoring (MRM) (8)

NBOMe compound	MRM, transition ions (m/z)
25H-NBOMe	302 > 121 302 > 91
25CC-NBOMe	336 > 121 336 > 91
25I-NBF	416 > 291 416 >109
25D-NBOMe	316 > 121 316 > 91
25B-NBOMe	380 > 121 380 > 91
25T-NBOMe	348 > 121 348 > 91
25I-NBMD	442 > 135 442 > 77
25G-NBOMe	330 > 121 330 > 91
25I-NBOMe	428 > 121 428 > 91

Conclusion

NBOMe drugs are very new, with limited data on their epidemiology and pharmacology. They are potent, with effective doses of only a few hundred micrograms. They are not detected by routine drug screening, and their concentrations in body fluids are quite low. Their toxicity stems from their hallucinogenic and sympathomimetic effects. With no known specific antidote, treatment is based on aggressive supportive care and alleviation of symptoms. A number of deaths have been attributed to NBOMe toxicity. Further studies are needed to elucidate their short- and long-term toxicity.

Learning Objectives

After completing this article, the reader will be able to describe the emerging trend of NBOMe abuse and describe the laboratory and clinical aspects of NBOMe drugs.

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Uttam Garg, PhD, DABCC, DABFT, FACB, is director of the clinical chemistry and toxicology laboratories at Children's Mercy Hospitals and Clinics and professor of pathology at the University of Missouri School of Medicine in Kansas City, Mo. He is a member of the Clinical & Forensic Toxicology News *editorial advisory board. Email: ugarg@cmh.edu. Stephen Thornton, MD, FACEP, is a board-certified medical toxicologist and emergency medicine physician who is the medical director for the University of Kansas Hospital Poison Control Center in Kansas City, Kan. Email: sthornton@kumc.edu*

Forensic Toxicology Update

AACC Press Issues New Edition

AACC Press has released a fourth edition of the popular text, *Principles of Forensic Toxicology*. This revised edition includes a new section on special topics and updated chapters on drug testing, methods validation, alcohol, GHB, and metals.

The first section provides an introduction to postmortem forensic toxicology, human performance forensic toxicology, forensic drug testing, and pharmacokinetics and pharmacodynamics. Newly added chapters cover testing for pain management and performance-enhancing drugs.

The second section is devoted to analytical principles, including both theory and applications of a wide variety of methodologies. The third section discusses commonly encountered analytes, including legal and illegal drugs and substances.

The newly added fourth section includes chapters on in-vitro stability of drugs, postmortem redistribution, postmortem chemistry, pharmacogenomics, and testing of hair and meconium.

Edited by Barry Levine, the 550-page softcover costs $99 ($79 for AACC members) and can be ordered from www.aacc.org.

Case Study

When Should Clinicians Consider a Malicious Cause for Hypoglycemia?

By John Mills, PhD, and Hemamalini Ketha, PhD

A 52-year-old male presented at his regional hospital for evaluation of recurring episodes of hypoglycemia of undetermined etiology. Limited records from his local hospital noted that his elevated insulin concentrations and hypoglycemia had led to a diagnosis of autoimmune hypoglycemia and a prescription for 50 mg prednisone and 100 µg octreotide taken daily. The diagnosis was questionable, however, because tests did not detect insulin antibodies and the patient had no evidence of autoimmune disease.

The patient was not diabetic but did have a recent history of glucose concentrations as low as 45 mg/dL. His medical history was significant for renal dysfunction (creatinine: 1.5 mg/dL) and hyperlipidemia (total cholesterol: 332 mg/dL). He had had a coronary artery bypass graft following a myocardial infarction about 9 months prior to his current presentation.

The patient described several episodes of hypoglycemia and apparent grand mal seizures during the past 8 months, despite the octreotide and prednisone therapy. During evaluation, his blood glucose concentrations were 100–120 mg/dL. A 72-hour fasting study of his hypoglycemic response found that his plasma glucose was maintained at 61 mg/dL at 72 hours, inconsistent with a hypoglycemic disorder. Tests for C-peptide, β-hydroxybutyrate, and insulin were normal, and a non-insulin hypoglycemic agent screen was negative. A glucagon stimulation test revealed no overt impairment of hypoglycemic counter-regulation (glucose increase from 61 mg/dL to 72 mg/dL).

Exploratory Surgery

At this time, his physicians considered an insulinoma possible, so they ordered a selective intra-arterial calcium stimulation study. A faint blush in the tail of the pancreas suggested the possibility of an adenoma in the mid-portion. However, CT found no evidence of a focal mass or insulinoma. Exploratory surgery to further evaluate the presence of an insulinoma was scheduled and the patient was discharged.

A month later, the surgery revealed no palpable masses. Intraoperative ultrasound also found no pancreatic lesions, only heterogeneous fatty infiltration of the pancreas with no focal mass.

Suspicious Hypoglycemia

Postoperatively, the patient's blood glucose was stable for the first 48 hours, but after transfer to an observation unit, he experienced hypoglycemic episodes in which his glucose concentrations plummeted to as low as 23 mg/dL. Additional tests performed while he was hypoglycemic included C-peptide (<33 pmol/L), proinsulin (<0.6 pmol/L), and insulin (11,140 µIU/mL). These results—low C-peptide and proinsulin in the face of extremely high insulin—led to suspicion of exogenous insulin administration.

In response to further questions, the patient reported several instances when he was awakened at night by stinging sensations and found red, tender areas in the morning. Investigators confronted the patient's wife, who denied administering insulin to her spouse but eventually agreed to a search of her belongings. The search found insulin vials, at which point the wife confessed to injecting exogenous insulin into the victim and was taken into custody for attempted murder.

Insulin as a Weapon

The use of insulin as a murder weapon has been documented as far back as the 1950s with the infamous case of Kenneth Barlow, an unemployed nurse who claimed to have discovered his second wife dead in the bathtub. Two empty syringes were found in the Barlow home. Close examination of the body revealed a hypodermic injection site on each buttock, and tissue samples from the injection sites contained insulin. With this evidence, Barlow was found guilty of using insulin as a murder weapon. Not surprisingly, given the easy access to insulin, homicide by insulin is not particularly uncommon (1).

Hypoglycemia Follow-up

But before considering that a hypoglycemic event or death is due to exogenous insulin, clinicians should rule out a variety of more likely causes, including insulinoma, autoimmune hypoglycemia, IGF-secreting tumors, oral hypoglycemic agents, and critical illness.

Performing tests at the time of a hypoglycemic episode is the best way to establish the causes of hypoglycemia in nondiabetic patients. Whipple's triad, a group of symptoms indicating a hypoglycemic disorder, includes: symptoms consistent with hypoglycemia; low plasma glucose concentration measured with a precise method (not a home glucose monitor) when symptomatic; and relief of symptoms after the plasma glucose level is raised.

If the patient is asymptomatic during evaluation, one diagnostic strategy involves replicating condi-

tions in which hypoglycemia is expected. The most reliable test of this nature is a supervised fast of up to 72 hours. A hypoglycemic event is documented if the fasting glucose concentration falls below 55 mg/dL. In this patient, the fasting test was inconsistent with a hypoglycemic disorder, and no evidence of hypoglycemia or exogenous insulin was observed.

Given these results, the patient's physicians considered the possibility of an insulinoma. These rare islet-cell tumors are usually small, solitary, and intrapancreatic. Surgical resection is curative. Small insulinomas, those less than 2 cm, are challenging to localize using conventional imaging modalities. Selective intra-arterial calcium injection with hepatic venous sampling for insulin was developed to localize insulin-secreting tumors, based on the premise that tumor cells differ from normal cells in their response to calcium injection (2). In this case the calcium stimulation test was faintly positive but imaging studies did not corroborate these findings. Because of these inconclusive results, the patient underwent an abdominal exploration and extended distal pancreatectomy and splenectomy.

Exogenous Insulin

The medical team suspected exogenous insulin only when the patient had unexplained hypoglycemia and other anomalous test results while in the hospital. In healthy nondiabetic victims, the clinical presentation of poisoning is not always obvious, but once exogenous insulin is identified, the interpretation of past events becomes straightforward. Identification of deliberate insulin poisoning of a diabetic victim is significantly more complex; the presence of exogenous insulin alone may be insufficient to draw definite conclusions Thus, quantitation of insulin is required for evidence of misuse of insulin.

The most challenging situation occurs when insulin analysis must be done postmortem to prove the cause of death. Measurement of insulin in postmortem blood has limited diagnostic value because of the unpredictable nature of thanatochemical processes. No correlation has been found between insulin dosage and postmortem concentrations, or with the timing of administration (3). In postmortem samples from patients who received exogenous insulin, levels ranged from 10–240 μIU/mL; in cases of homicide-by-insulin, levels have been >600 μIU/mL, which is well above control postmortem samples (4,5). Yet there is no definitive concentration that indicates a fatal dose. The biggest challenge with postmortem analysis is hemolysis because insulin-degrading enzyme is released from lysed red blood cells, leading to a significant reduction in insulin.

Further confounding interpretation, death following a lethal dose of insulin is typically not immediate. Hypoglycemic coma ensues about an hour after insulin injection, typically followed by irreversible brain damage within 6 hours. The length of survival depends on the type and dose of insulin, and where and how the dose is administered. The length of survival is difficult to ascertain, particularly when there is a delay in obtaining samples. Whereas the absence of exogenous insulin is not informative in postmortem analysis, its detection can be meaningful. Investigation of vitreous humor for the presence of exogenous insulin has been successful in numerous cases.

Insulin Testing

Insulin quantitation is typically performed using any of several commercial immunoassays. The advent of recombinant insulin analogs has made identifying factitious hypoglycemia particularly problematic because a lack of cross-reactivity means many immunoassays do not detect them (6). In recent years, liquid chromatography-tandem mass spectrometry (LC-MS/MS) has been recognized as the most reliable method for identification of insulin variants. This methodology uses molecular weights to identify recombinant analogs (7). However, LC-MS/MS testing for insulin is not widely available. Therefore, understanding the cross-reactivity and limitations of immunoassays is crucial for clinical evaluation and forensic interpretation.

Missing a patient's hyperinsulinemia due to inappropriate test ordering or interpretation has significant consequences because it can trigger costly imaging studies, additional laboratory work-up, and confusion. Endogenous insulin is synthesized as a prohormone, undergoes proteolytic cleavage, and is secreted alongside a proteolytic fragment, C-peptide. Exogenous preparations of insulin do not contain C-peptide. Endogenous insulin has a half-life of 5–10 minutes, whereas C-peptide has a half-life of roughly 30 minutes. Therefore, under normal conditions, the ratio of insulin/C-peptide is <1; however, when exogenous insulin is given, the absence of C-peptide leads to an insulin/C-peptide ratio >1. When considering the source of nondiabetic hypoglycemia, C-peptide should be measured in tandem with insulin before investigation of a possible insulinoma. Proinsulin is also elevated in cases of insulinoma but absent with exogenous insulin, similar to C-peptide (8).

Case Summary

In this case, the victim had a history of hypoglycemic episodes of unknown etiology. Although the patient's hypoglycemia was recognized early, there

was a failure to investigate the possibility of insulin poisoning in the clinical management of the patient. Had this possibility been explored sooner, the victim could have avoided invasive medical procedures and been removed more quickly from a life-threatening situation.

Learning Objectives

After completing this article, the reader will be able to recognize the limitations of insulin immunoassays to confirm exogenous insulin administration and recommend the laboratory tests required to distinguish hypoglycemia from factitious hypoglycemia.

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John R. Mills, PhD, and Hemamalini Ketha, PhD, are clinical chemistry fellows in the department of laboratory medicine and pathology at the Mayo Clinic in Rochester, Minn. Email: mills.john2@mayo.edu and ketha.hemamalini@mayo.edu.

The authors have nothing to disclose.

Case Study

Excipients Can Cause Recurrent Pneumonia in Intravenous Drug Users

By Haiying Chen, MD, MS, and Barbarajean Magnani, PhD, MD

When patients present with recurrent pneumonia, the underlying cause can be difficult to diagnose. The intravenous injection of oral medications or impure heroin is a possible to cause to consider. This abuse of oral medications has been reported since 1950, and here we report a case in which it led to recurrent pneumonia.

A 23-year-old male had three episodes of pneumonia in the past year with no etiology identified. His symptoms included fever (up to 39 °C), cough, shortness of breath, and chest pain. His medical history was significant for a forearm abscess that he said was possibly due to a "bee sting" and a positive hepatitis C serology.

He worked as a certified nursing assistant and had smoked one pack of cigarettes per day for the past seven years. He denied alcohol abuse or illicit drug use upon hospital admission.

Examination and Test Results

A physical examination revealed multiple tattoos. A chest X-ray showed bilateral interstitial and parenchymal opacities. A urine toxicology screen was positive for opiates, which could have been caused by the morphine administered for his chest pain. Blood cultures and bronchial alveolar lavage cultures were both negative. He was started on broad-spectrum antibiotics empirically and his symptoms improved quickly.

Because of his history of recurrent pneumonia, he was scheduled for a lung biopsy. A microscopic examination of the biopsy showed prominent desquamative changes with intra-alveolar, hemosiderin-laden macrophages consistent with desquamative interstitial pneumonitis.

In addition, the interstitium contained abundant foreign material that showed a Maltese cross pattern under polarized light (Figure 1). The sample stained positive in a periodic acid–Schiff (PAS) stain, consistent with starch granules. Both these findings are classically associated with intravenous injection of illicit drugs. When confronted with that possibility, the patient admitted to intravenous injection of both Percocet (using crushed tablets of the combination of oxycodone and acetaminophen intended for oral use) and heroin.

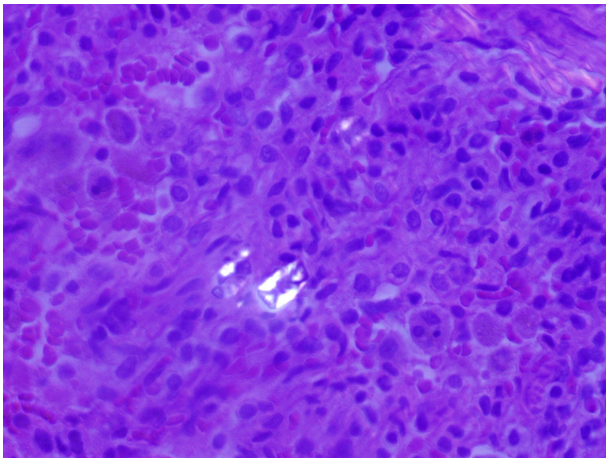

Figure 1. Maltese cross pattern. Birefringent foreign material in the lung biopsy appears white, outlining a pattern that resembles a Maltese cross.
Figure courtesy of the author

Discussion

Some drug abusers dissolve oral medications in solution because injection into their veins provides a more intense high than they can achieve through oral intake. Oral formulations contain excipients not designed to be injected, so this practice can introduce them into the bloodstream. Heroin use poses a similar danger because dealers often cut their product with adulterants to increase its bulk to provide a larger financial margin.

Sometimes these excipients and fillers become trapped in pulmonary capillaries and cause pneumonia. One study reported that these materials are found most often in the lungs, followed by the spleen, liver, lymph nodes in the hepatic portal area, and bone marrow (1).

The most common fillers are talc (magnesium trisilicate), cellulose, and starch. Talc and cellulose often cause granulomatous reactions. Starch granules tend to be digested by pulmonary macrophages quickly, and cause only a minimal tissue response (2).

These materials are birefringent when viewed using polarized light microscopy: Talc appears as needle-shaped or irregularly shaped crystals; cellulose appears as elongated rods; and starch granules classically show a Maltese cross pattern. Talc is negative in a PAS stain, whereas starch and cellulose stain positive (3).

In the present case, the foreign material had a Maltese cross pattern and stained positive for PAS, so it was most likely starch. The absence of a granulomatous reaction in the biopsy also suggested that the foreign material was starch.

There were several hints in the patient's clinical history pointing to intravenous drug abuse. The patient had an unexplained positive hepatitis C serology, a forearm abscess without a clear etiology, multiple tattoos (tattoos can be used to hide needle tracks), and a positive urine toxicology result for opiates. The clinicians suspected drug abuse and the lung biopsy confirmed their suspicion.

Conclusion

In patients with recurrent pneumonia and a clinical suspicion of intravenous drug abuse, intravenous injection of oral medication should be considered. A lung biopsy can help to render the correct diagnosis.

Learning Objective

After completing this article, the reader will be able to identify various causes of recurrent pneumonia in chronic drug abusers related to excipient material found during biopsy.

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Haiying Chen, MD, MS, is a pathology resident at Tufts Medical Center in Boston. Email: hchen@tuftsmedicalcenter.org. Barbarajean Magnani, PhD, MD, is the chair and pathologist-in-chief of the department of pathology and laboratory medicine at Tufts Medical Center. She is a member of the Clinical & Forensic Toxicology News *editorial advisory board. Email: bjmagnani@tuftsmedicalcenter.org*

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Pocket Guide to Abused Drugs

Abused Drugs III: A Laboratory Pocket Guide incorporates an encyclopedic listing of more than 200 drugs commonly seen in overdose, with information from molecular structures to pharmacokinetics. Compiled by John Wilson, the 131-page softcover is available for $20 ($16 for AACC members) from www.aacc.org.

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Learning objectives vary by article, but in general, after completing *Clinical & Forensic Toxicology News*, the reader will be able to:

- Describe emerging and changing trends in drug abuse, including new designer drugs, usage patterns, and contaminants/adulterants.
- Identify potential analytes (drugs, metabolites, biomarkers) of clinical and/or forensic significance.
- Evaluate methodologies for their utility and limitations relative to the needs of toxicology labs.
- Discuss relevant regulations, such as analytical performance requirements, or the legality of new drugs of abuse.
- Explain the analytical and regulatory issues unique to specific applications, including postmortem toxicology, workplace drug testing, and drug screening.
- Describe the medical implications of drug abuse, toxicity associated with therapeutic agents, and exposure to other toxicants.

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