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OREGON PUBLIC HEALTH DIVISION • OREGON HEALTH AUTHORITY

# YOU CAN'T ALWAYS GET WHAT YOU WANT: DESIGNER DRUGS, METHEMOGLOBINEMIA AND THE INTERNET

They thought they were going out for a good time. On an August evening in 2011, a 30-something Oregon man (patient A) collapsed in a fast food restaurant and was taken by ambulance to a local emergency room. He reported feeling lightheaded and nauseated 15 minutes after sharing a soft drink with his friend (patient B). He was cyanotic* and confused. His pulse oximetry reading was 86% despite 100% oxygen by nonrebreather mask.

Blood drawn for lab testing was chocolate-brown. Arterial blood gas: pH 7.43, $pCO_2$ 35 mm Hg, $pO_2$ 222 mm Hg, bicarbonate 23 mmol/L, $SaO_2$ 96.7%. His methemoglobin level was 66.7% (normal, 1%–3%) and peaked six hours after ingestion at 79.6%.

Patient B, also a 30-something male, had shared the soft drink with patient A and was also deeply cyanotic in the ER. His methemoglobin level was 49.5% and peaked eight hours after ingestion at 74.4%.

The Oregon Poison Center (OPC) was consulted and advised treatment with methylene blue.[1] Methemoglobin is an oxidized form of hemoglobin, and a metabolite of methylene blue reduces methemoglobin to hemoglobin.

After several doses of methylene blue, both patients' methemoglobin levels began to fall. Alas, so did their hemoglobin levels. Patient B's hemoglobin fell from 14 g/dL to 10 g/dL, but he left AMA without further treatment. Patient A's fell from 14 to 6 g/dL; low haptoglobin and LDH>2000 suggested acute oxidant-stress-induced hemolysis. Glucose-6-phosphate dehydrogenase (G6PD) concentration was normal. Several blood transfusions and multiple plasmapheresis sessions later, his hemoglobin stabilized.

Chemicals of two classes cause methemoglobinemia: nitrates and aromatic amines. Local anesthetics like benzocaine, and sulfonamide antibiotics like dapsone, are common culprits. But the list is long and varied, and includes cyclophosphamide, chloroquine, and aniline dyes.[2]

## PUBLIC HEALTH INVESTIGATION

Under interrogation by the ER physician, patients A and B confessed to having bought "2C-E," a psychoactive recreational chemical, from a Chinese web site. FDA tested the yellow liquid and found aniline — a commonly used industrial solvent — and no trace of 2C-E. When ingested, aniline causes methemoglobinemia that can lead to hemolytic anemia.[3]

The patients denied sharing the product with others. Nonetheless, out of concern that aniline might have been mislabeled and sold to others seeking 2C-E, investigators from the Oregon Public Health Division (OPHD) and OPC actively searched for unexplained cases of methemoglobinemia since January 2011. OPC queried poison center directors nationally and searched the National Poison Data System for reports of aniline poisoning. OPHD notified CDC and looked for cases using Oregon's Health Alert Network and CDC's Epidemic Information Exchange. No additional cases were identified.

## DESIGNER DRUGS

Despite the passage in 1986 of the Controlled Substances Analogue Enforcement Act (CSAEA),[4] use of novel psychoactive recreational drugs has mushroomed† in the United States. To circumvent CSAEA, manufacturers design drugs that have structures distinct from regulated substances but that retain psychoactive effects. These products may evade surveillance and regulation through advertisement using code words like "research chemicals," "plant food," "pond cleaner," or "bath salts."

Designer drugs have seductive names like "Meow Meow," "K2 Spice," and "Vanilla Sky."[5] They are peddled domestically in smoke shops and gas stations, and through the Internet from domestic and international sources. They are ingested, smoked or inhaled. Designer drugs come in three popular flavors: synthetic amphetamines, synthetic cathinones, and synthetic cannabinoids.

*Synthetic amphetamines* include the "2C" family of phenethylamine derivatives, which produce psychedelic effects similar to those of methamphetamine. Drugs of this class, which include "ecstasy" — 3,4-methylenedioxymethamphetamine (MDMA) were designed and popularized by Berkeley chemist Andrew Shulgin, PhD.[6]

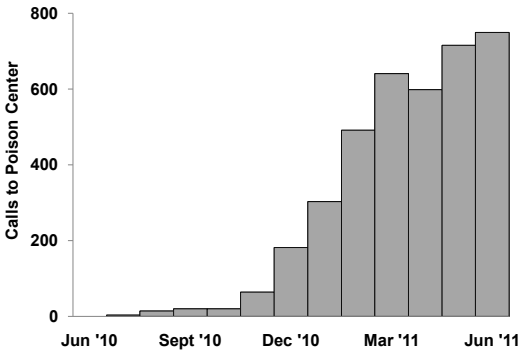
*Synthetic cathinones* are β-keto phenethylamine derivatives related to the psychoactive substance in *khat,* a narcotic leaf chewed in East Africa; they are sold as "plant food" or "bath salts."

*Synthetic cannabinoids*, which mimic the effects of δ-9-tetrahydrocannabinol, are sold as "herbal incense" products (e.g., "spice," "JWH").

## THE INTERNET: NOT FOR AMATEURS

The availability of psychoactive chemicals and other hazardous ingestibles for order over the Internet poses a risk for obtaining products (either advertently or in-) that are inherently toxic or that have been adulterated (whether intentionally or un-). From 2010 to 2011, calls to poison centers about exposures to "bath salts" increased nationally from 303 to 6,072 (Figure).[5] In Minnesota last year, teens at a party overdosed on 2C-E: several suf-

**Figure. "Bath salts": Exposure calls to poison control centers, United States, Jun 2010–Jun 2011**




* Per the ED physician, "blue as a smurf"

† Not just psilocybin derivatives.

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fered seizures, and one died. Several Oklahoma teens purchased 2C-E from a foreign Internet site, but instead got a more potent designer drug called "bromo-dragonfly." Two of them died, and several were hospitalized for seizures. In 2010, Michigan saw a sharp increase in ER visits for neurologic, psychiatric and cardiac sequelae of "bath salts."[7] In Wyoming in early March 2012, a cluster of nine people with abdominal and/or back pain was associated with ingestion of "spice"; three of them were hospitalized for acute renal failure.

During four months of surveillance in Oregon, OPC received 16 calls about human designer drug exposures, including nine about "bath salts." Patients were 16–43 years of age, and 10 of 16 were male. The substances were either inhaled or ingested, and adverse symptoms included agitation, hallucinations, tachycardia, hypertension and coma.[8] Seven required hospitalization. As designer drugs become more popular, expect more troubling stories.

## THE PERILS OF ANILINE

Strong oxidizing agents, including aniline metabolites, convert hemoglobin (with $Fe^{2+}$ in the heme group) into methemoglobin ($Fe^{3+}$), rendering it unable to bind oxygen. Methemoglobin concentrations >50% can cause syncope. Concentrations >70% can be lethal. Cyanosis is profound, and chocolate-brown blood seen at venipuncture is a tip-off to methemoglobinemia. The pulse oximetry reading is unreliable in the presence of methemoglobin, and will typically read 85% — a figure that won't budge despite 100% $F_iO_2$ or the antidote methylene blue. *For clinical management of methemoglobinemia, only the $SaO_2$ level on ABG co-oximeter is a reliable measure of oxygenation.*‡

Methemoglobin produced by aniline metabolites is often refractory to conversion back to hemoglobin by methylene blue. In addition, at high doses, methylene blue can be an oxidizing agent and cause hemolytic anemia. This side effect is more likely with G6PD deficiency.

## THE LAW

The DEA and State drug control agencies have recognized the need to monitor and, when necessary, to control these chemicals. The CSAEA bans many analogues of controlled substances, including the phenethylamines with their isomers and salts.[4] The Oregon Board of Pharmacy lists synthetic cannabinoids and cathinones as Schedule I controlled substances.§

## WHAT TO DO?

Be aware that in 2012, virtually any chemical produced in any country is available over the Internet, so it's *caveat emptor*! If you suspect that your patient has ingested a toxic substance, call Poison Control at 1-800-222-1222. In addition, report to the FDA immediately (1-888-INFO-FDA) any toxicity thought to have been caused by a commercial product. Nonemergent adverse events can be reported to the FDA district office consumer complaint coordinator during regular business hours (www.fda.gov/safety/reportaproblem/consumercomplaintcoordinators/default.htm). If the offending substance is available, save it for testing.

‡ The $SaO_2$ reading from the ABG co-oximeter is more reliable because pulse oximeters *derive* $SaO_2$ by measuring the relative absorbance of two wavelengths of light that distinguish oxyhemoglobin from deoxyhemoglobin. But since methemoglobin absorbs both wavelengths *equally*, the pulse oximeter incorrectly reports the $SaO_2$ as 85%.

§ Oregon Administrative Rule 955-080-0021

## FOR MORE INFORMATION

- Read the recent CDC article: Severe methemoglobinemia and hemolytic anemia from aniline purchased as 2C-E (4-ethyl-2,5-dimethoxyphenethylamine), a recreational drug, on the Internet — Oregon, 2011. MMWR 2012; 61:85–8. Available at www.cdc.gov/mmwr/preview/mmwrhtml/mm6105a1.htm.
- Oregon Poison Control: 1-800-222-1222

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