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A Rise in Fentanyl-Laced Heroin Deaths

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A 25-year-old male was found deceased in a stairwell. An autopsy was performed on the Medical Examiner's Office. External examination revealed areas suspicious for old injection scars and recent injection marks on the upper extremities. On internal examination, there was frothy white foam in the trachea, and the lungs were markedly heavy with pulmonary edema. Toxicological analysis of femoral blood and urine samples was positive for fentanyl, 6-monoacetyl morphine, and free morphine. This was just one of eight confirmed cases of fentanyl-laced heroin overdose death diagnosed at the Onondaga County Medical Examiner's Office (OCMEO) in 2014. In the first four months of 2015, preliminary data indicates at least 15 known heroin-related deaths at the OCMEO, and 7 of those involving both fentanyl and heroin.

As in the case presented, the most common route of administration of fentanyl-laced heroin has been intravenous injection. Other routes of administration include subcutaneous or intradermal injection (also known as skin popping), and insufflation or snorting. Virtually all cases have had autopsy findings of pulmonary edema (including froth at the nose/mouth and in the trachea), with some also having findings of cerebral edema.

Heroin and Fentanyl

Both heroin and fentanyl exert their effects through opioid receptors located in the brain, spinal cord, and smooth muscle cells of the body. Activation of these receptors modulates the release of neurotransmitters. For example, the euphoria people experience with some opioids, like heroin, is linked to the release of dopamine in the mesolimbic system[1]. One important effect of opioids on the brain is the depression of respiratory centers within the brainstem. This is a dose dependent effect

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Program Announcements

UNY: Please mark your calendars for the **Nineteenth Annual Toxicology Teaching Day** 11/4/15 in Syracuse. Email *morer@upstate.edu* for more information.

NYC: Consultants Case Conference • The first Thursday of the Month from 2-4pm

Please call administrative telephone numbers for more information and to attend remotely.

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which becomes more severe at higher doses and with higher potency, leading to a reduction in respiratory rate and preventing the body from responding to increases in carbon dioxide. The eventual outcome is a state of anoxia, buildup of fluid within the lungs (pulmonary edema), and death. The increase in carbon dioxide also leads to cerebral vasodilation which in turn leads to an increase in intracranial pressure and cerebral edema. Other effects of opioids include suppression of the cough reflex, nausea and vomiting through the activation of brainstem chemoreceptors, bradycardia, decreased gastrointestinal activity, miosis, urinary retention through increased sphincter tone, and sedation. Tolerance to some of these effects, such as nausea and feelings of euphoria, can develop over time. Other effects don't develop much tolerance over time, such as constipation and miosis[2]. *(Figure 1.)*

DEGREE OF TOLERANCE DEVELOPED	HIGH	MODERATE	LOW
Opioid Effect	Analgesia	Bradycardia	Miosis
	Euphoria		Constipation
	Sedation		
	Respiratory Depression		
	Nausea and vomiting		
	Cough suppression		

Figure 1: Tolerance Development of Opioid Effects [2]

Heroin is also known as diacetylmorphine. It is essentially a morphine prodrug which has a low affinity for opioid receptors until it is metabolized to 6-monoacetylmorphine (6-MAM) and morphine. Both 6-MAM and morphine have a high affinity for opioid receptors, leading to the effects we expect from opioid receptor activation. Despite its low affinity for opioid receptors, heroin is still two times more potent than morphine. It is also more lipophilic than morphine thanks to its two acetyl groups which allow it to cross the blood-brain barrier and exert its effects on the brain within seconds of administration[3]. Of interest, 6-MAM has an extremely short half-life in the bloodstream (minutes), and is more often detected in urine or vitreous fluid during postmortem toxicology testing.

Fentanyl is a synthetic opioid. It is 100-200 times more potent than morphine and 50-100 times more potent than heroin. Like heroin, it is highly lipophilic, and easily crosses the blood-brain barrier, exerting its effects on the brain within seconds. Unlike heroin, it is readily active and has a high affinity for opioid receptors.[1] While pharmaceutical fentanyl is used clinically for relief of severe pain, illicitly-produced fentanyl is being combined with heroin to produce a more potent illicit drug product with a more intense "high".

What areas have had increases in fentanyl and heroin related deaths?

In recent years, there has been an increase in fentanyl-laced heroin deaths in several states, particularly in the Northeast. According to the Office of National Drug Control Policy 2015 Threat Assessment Report, there have been increases in illicit fentanyl-related deaths in several counties. The report doesn't specify which deaths were fentanyl only and which involved fentanyl-laced heroin, but it provides a good picture of the changes in fentanyl-related deaths over time, and the rise in illicitly-produced fentanyl. This data along with that in other reports is presented in Figure 2.

In New York state, Dutchess County had been averaging 1-3 fentanyl related deaths per year from 2009-2012, but reported 7 in the span of one month from November to December of 2013. Erie County had 7 fentanyl related deaths in 2012 and 32 in 2013. In Nassau County, there were 3 fentanyl related deaths in 2012 and 12 in 2013 [4].

Dutchess County, New York	1-3 deaths/year	2009-2012
	7 deaths	Nov-Dec 2013
Erie County, New York	7 deaths	2012
	32 deaths	2013
Nassau County, New York	3 deaths	2012
	12 deaths	2013
State of New Jersey	31 deaths	2011
	41 deaths	2012
	49 deaths	2013
Essex County, Massachusetts	66 deaths	2013
	120 deaths	2014

Figure 2: Increases in the Number of Fentanyl-related Overdose Deaths in Several Counties and States [4,5,6]

Looking at other states, New Jersey also saw an uptick in fentanyl-related deaths in 2011-2013 [5]. In Essex County, Massachusetts, fentanyl deaths recently nearly doubled: 66 fentanyl-related deaths were reported for 2013, and 120 from January to November of 2014 [6]. The Centers for Disease Control (CDC) reported that in Rhode Island, the number of fentanyl-related overdose deaths in 2014 was double that of previous years with 52 fentanyl-related deaths out of a total of 165 fatal drug overdoses for that year [7].

Why the rise in overdose deaths?

A glimpse at the past may give us some clues as to what can be done and why there has been a recent rise in

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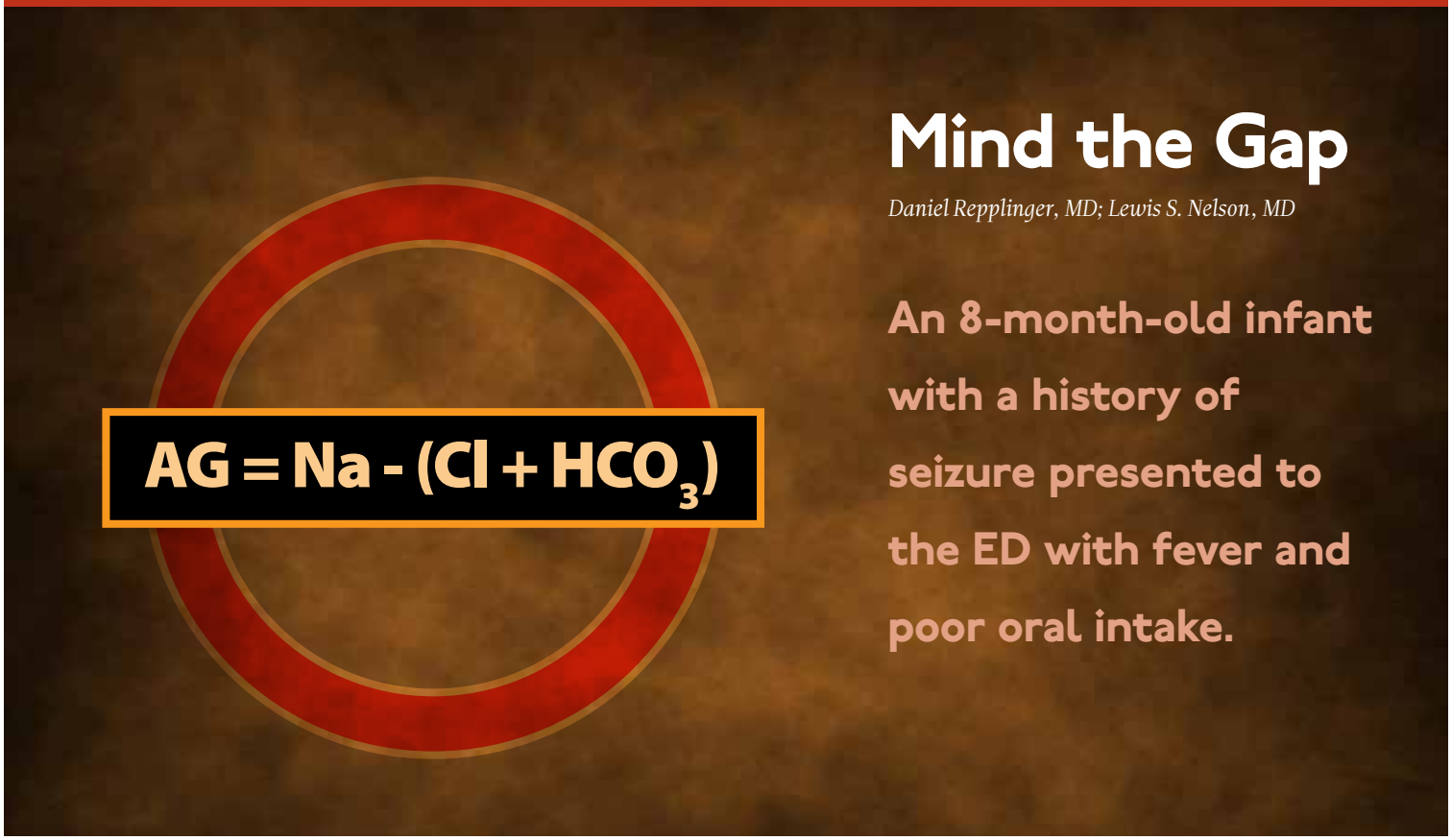

Mind the Gap

Daniel Repplinger, MD; Lewis S. Nelson, MD

An 8-month-old infant with a history of seizure presented to the ED with fever and poor oral intake.

Case

An 8-month-old boy with a history of hypotonia, developmental delay, and seizure disorder refractory to multiple anticonvulsant medications, was presented to the ED with a 2-week history of intermittent fever and poor oral intake. His current medications included sodium bromide 185 mg orally twice daily for his seizure disorder.

On physical examination, the boy appeared small for his age, with diffuse hypotonia and diminished reflexes. He was able to track with his eyes but was otherwise unresponsive. No rash was present. Results of initial laboratory studies were: sodium 144 mEq/L; potassium, 4.8 mEq/L; chloride, 179 mEq/L; bicarbonate, 21 mEq/L; blood urea nitrogen, 6 mg/dL; creatinine, 0.1 mg/dL; and glucose, 63 mg/dL. His anion gap (AG) was -56.

What does the anion gap represent?

The AG is a valuable clinical calculation derived from the measured extracellular electrolytes and provides an index of acidbase status.[1] Due to the necessity of electroneutrality, the sum of positive charges (cations) in the extracellular fluid must be balanced exactly with the sum of negative charges (anions). However, to routinely measure all of the cations and anions in the serum would be time-consuming and is also unnecessary. Because most clinical laboratories commonly only measure one relevant cation (sodium) and two anions (chloride and bicarbonate), the positive and negative sums are not completely balanced. The AG therefore refers to this difference (ie, AG = Na – [Cl + HCO_3]).

Of course, electroneutrality exists in vivo, and is accomplished by the presence of unmeasured anions (UA) (eg, lactate and phosphate) and unmeasured cations (UC) (eg, potassium and calcium) not accounted for in the AG (ie, AG = UA – UC). In other words, the sum of measured plus the unmeasured anions must equal the sum of the measured plus unmeasured cations.

What causes a low or negative anion gap?

While most healthcare providers are well versed in the clinical significance of an elevated AG (eg, MUDPILES [methanol, uremia, diabetic ketoacidosis, propylene glycol or phenformin, iron or isoniazid, lactate, ethylene glycol, salicylates]), the meaning of a low or negative AG is underappreciated. There are several scenarios that could potentially yield a low or negative AG, including decreased concentration of UA, increased concentrations of nonsodium cations (UC), and

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Mind the Gap

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overestimation of serum chloride.

Decreased Concentration of Unmeasured Anions. This most commonly occurs by two mechanisms: dilution of the extracellular fluid or hypoalbuminemia. The addition of water to the extracellular fluid will cause a proportionate dilution of all the measured electrolytes. Since the concentration of measured cations is higher than the measured anions, there is a small and relatively insignificant decrease in the AG.

Alternatively, hypoalbuminemia results in a low AG due to the change in UA; albumin is negatively charged. At physiologic pH, the overwhelming majority of serum proteins are anionic and counter-balanced by the positive charge of sodium. Albumin, the most abundant serum protein, accounts for approximately 75% of the normal AG. Hypoalbuminemic states, such as cirrhosis or nephrotic syndrome, can therefore cause low AG due to the retention of chloride to replace the lost negative charge. The albumin concentration can be corrected to calculate the AG.[2]

Nonsodium Cations. There are a number of clinical conditions that result in the retention of nonsodium cations. For example, the excess positively charged paraproteins associated with IgG myeloma raise the UC concentration, resulting in a low AG. Similarly, elevations of unmeasured cationic electrolytes, such as calcium and magnesium, may also result in a lower AG. Significant changes in AG, though, are caused only by profound (and often life-threatening) hypercalcemia or hypermagnesemia.

Overestimation of Serum Chloride. Overestimation of serum chloride most commonly occurs in the clinical scenario of bromide exposure. In normal physiologic conditions, chloride is the only halide present in the extracellular fluid. With intake of brominated products, chloride may be partially replaced by bromide. As there is greater renal tubular avidity for bromide, chronic ingestion of bromide results in a gradual rise in serum bromide concentrations with a proportional fall in chloride. However, and more importantly, bromide interferes with a number of laboratory techniques measuring chloride concentrations, resulting in a spuriously elevated chloride, or *pseudohyperchloremia*. Because the measured sodium and bicarbonate concentrations will remain unchanged, this falsely elevated chloride measurement will result in a negative AG.

What causes the falsely elevated chloride?

All of the current laboratory techniques for measurement of serum chloride concentration can potentially result in a falsely elevated value. However, the degree of pseudohyperchloremia will depend on the specific assay used for measurement. The ion-selective electrode method used by many common laboratory analyzers appears to have the greatest interference on chloride measurement in the presence of bromide. This is simply due to the molecular similarity of bromide and chloride. Conversely, the coulometry method, often used as a reference standard, has the least interference of current laboratory methods.[3] This is because coulometry does not completely rely on molecular structure to measure concentration, but rather it measures the amount of energy produced or consumed in an electrolysis reaction. Iodide, another halide compound, has also been described as a cause of pseudohyperchloremia, whereas fluoride does not seem to have significant interference.[4]

How are patients exposed to bromide salts?

Bromide salts, specifically sodium bromide, are infrequently used to treat seizure disorders, but are generally reserved for patients with epilepsy refractory to other, less toxic anticonvulsant medications. During the era when bromide salts were more commonly used to treat epilepsy, bromide intoxication, or bromism, was frequently observed.

Bromism may manifest as a constellation of nonspecific neurological and psychiatric symptoms. These most commonly include headache, weakness, agitation, confusion, and hallucinations. In more severe cases of bromism, stupor and coma may occur.[3,5]

Although bromide salts are no longer commonly prescribed, a number of products still contain brominated ingredients. Symptoms of bromide intoxication can occur with chronic use of a cough syrup containing dextromethorphan hydrobromide as well as the brominated vegetable oils found in some soft drinks.[5]

How is bromism treated?

The treatment of bromism involves preventing further exposure to bromide and promoting bromide excretion. Bromide has a long half-life (10-12 days), and in patients with normal renal function, it is possible to reduce this half-life to approximately 3 days with hydration and diuresis with sodium chloride.[3] Alternatively, in patients with impaired renal function or severe intoxication, hemodialysis has been used effectively.[5]

Case Conclusion

The patient was admitted for observation and treated with intravenous sodium chloride. After consultation with his neurologist, he was discharged home in the care of his parents, who were advised to continue him on sodium bromide 185 mg orally twice daily since his seizures were refractory to other anticonvulsant medications.

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heroin and illicit fentanyl overdose deaths. From 2005-2007, there was an illicit fentanyl and heroin epidemic in several states.

A case findings and surveillance system implemented by the CDC and Drug Enforcement Agency (DEA) in response to the identification of non-pharmaceutical fentanyl on the drug market in April of 2006 ultimately identified a total of 1,013 cases of illicit fentanyl related deaths between 2005-2007 in New Jersey, Maryland, Illinois, Michigan, and Pennsylvania. In response to these findings, public health agencies formed task forces which alerted health care providers, law enforcement, and drug users of the dangers of illicit fentanyl use. Outreach programs on overdose prevention were also formed and law enforcement focused on shutting down illicit fentanyl production facilities. Following these efforts there was a steady decline in the number of cases of illicit fentanyl and heroin overdose deaths.

The availability and subsequent use of illicit fentanyl was linked to a rise in supply which was thought to have been brought about by a new method of producing illicit fentanyl called the "Siegfried Method". This method of production did not require any special equipment or high degree of knowledge and the instructions could be easily found on the internet. Additionally, the main chemical used to produce illicit fentanyl, N-phenyl-4-piperidone, wasn't regulated, making it easy to obtain. N-phenyl-4-piperidone became regulated by the DEA in 2007, slowing the production of illicit fentanyl [8].

Why add fentanyl to the heroin market?

Heroin administration by itself already has the potential to cause fatal overdoses, but the addition of the even more potent fentanyl, increases that risk. To understand the possible reasons for the addition of illicit fentanyl to the heroin market, it is important to have some understanding of the economic forces around this particular drug trade.

Typically in states east of the Mississippi River, heroin is supplied by South American producers, whereas states west of the Mississippi River are supplied by Mexican producers. Since the 2000s, there has been a steady reduction in the supply of heroin coming from South America, particularly from Colombia. Since 2002, a decline has been observed in the purity of heroin within the North Eastern States. From 2002-2007, in New York, New Jersey, and Pennsylvania, heroin purity declined from an average of 70% to 50%. The overall decline in purity is reflected in a reduced quality of heroin available to buyers and users, who experience a reduced sense of euphoria or "high", leading to dissatisfaction with the purchased product. Even with the addictive quality of heroin, illicit drug purveyors lose customers particularly because of the availability of alternatives to illicit heroin, such as prescription opiates or access to methadone clinics.

Studies have shown that buyers and users tend to react to changing purity with substitution of their heroin use with alternatives if heroin is not providing their desired effects. With this dilemma, sellers try to maintain the potency of their product with the addition of illicit fentanyl. With fentanyl-laced heroin, customers and users are still buying a less pure heroin batch, but they experience strong drug-induced effects (primarily from the fentanyl) so they remain satisfied with their purchase [9].

Summary

The increases in illicit fentanyl-related deaths in several states in the past few years suggest a resurgence of the addition of fentanyl into the heroin drug market. With N-phenyl-4-piperidone now regulated, it is possible that individuals have identified methods to produce illicit fentanyl with compounds that remain unregulated and easily available. Other factors which may be contributing to this new rise in overdose deaths may include a continued decline in the production of South American heroin and subsequent reduction in the purity of heroin within the eastern United States. Regardless of the reasons for the rise, it is clear that the use of illicit fentanyl results in fatal consequences, particularly due to its very high potency.

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