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The Persistent Pesticide: A Review of Organophosphate Poisoning

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Patient Case

A 61-year-old male with a past medical history of alcoholism and depression presented to the emergency department an hour after ingesting a bottle of diazinon. Vital signs included: blood pressure 160/85 mmHg; heart rate 60 beats per minute; and an oxygen saturation of 97%. On physical examination, pupils were mid-sized and reactive. Copious salivation was noted, and respirations were rhonchorous. Heart sounds were within normal limits. Abdomen was soft, non-tender and non-distended. Bowel sounds were positive. Neurologically the patient was lethargic, but responsive to verbal stimuli. Routine laboratory assessments were normal including undetectable acetaminophen and salicylate levels.

Is organophosphate (OP) poisoning a common occurrence?

Organophosphate (OP) poisoning is an ubiquitous problem, associated with more than 200,000 deaths every year.[1] In the developing world, these events are more prevalent and associated with higher mortality rates.[2,3] However, the widespread availability of OP-containing household and occupational products provides significant opportunity for intentional poisoning *(Table 1)*. Severe poisoning is associated with substantial morbidity and mortality, as demonstrated by a fatality rate that greatly exceeds that of pharmaceutical ingestions.[1]

What is the pathophysiology of OP poisoning?

Acetylcholine is a stimulatory neurotransmitter found in red blood cells, the neuromuscular junction and the peripheral/central nervous systems. Acetylcholinesterase (AChE) is responsible for the degradation of acetylcholine. OPs inhibit AChE by phosphorylating its active site, effectively inactivating the enzyme and leading to acetylcholine accumulation. The rate and degree of AChE inhibition is dependent on the structure of the OP. Oxon OPs, such as dichlorovos (No-Pest®), are biologically active and capable of inhibiting AChE shortly after administration.[4] Conversely, thion OPs, such as diazinon (Spectracide®) and parathion (Supertox®), are biologically inactive and require hepatic activation to the corresponding oxon form to produce an AChE inhibitory effect.[5] As a result, the inhibitory effects of a thion OP can be delayed when compared to an oxon OP.

OPs initially form a non-covalent electrostatic bond at the AChE active site. When the first alkyl chain is cleaved form eth OP, a relatively weak covalent bond forms. Both the electrostatic and initial covalent bond are reversible in nature and the rate of spontaneous reactivation is dependent on the OP's chemical properties.[6] However, if a second alkyl side chain is lost (second "leaving group" leaves), an irreversible, covalent bond evolves. This phenomenon is more commonly known as "aging" and an OP's aging rate is dependent on its structure

Continued on page 2

Program Announcements

UNY: Combined Medical Examiner/Toxicology Case Conference, Center for Forensic Science 1/10, 4/11,7/11, 10/10 1:30-3:30pm

Albany Medical Center ½ day in Toxicology April 2013, (WEBEX available) more information to follow.

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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Continued from page 1

(Table 2).[6] After "aging" occurs, the affected AChE enzyme is permanently inactivated, cannot be regenerated with antidotal therapy, and new enzyme synthesis is required for return of physiologically functional enzyme activity.

What are the acute clinical manifestations of OP poisoning?

Acetylcholine plays an important role at the neuromuscular junction, the autonomic ganglia, and the central/peripheral nervous systems. Given this widespread distribution, it is not surprising that acute OP poisoning affects a number of organ systems. Typically, these effects are grouped based on the affected receptors and include muscarinic, nicotinic and central nervous system (CNS) effects.

Excessive muscarinic receptor stimulation produces the classical manifestations of OP poisoning. The mnemonics SLUDGE (salivation, lacrimation, urination, diarrhea, gastrointestinal cramps, and emesis) and DUMBBELS (defecation, urination, miosis, bradycardia, bronchorrhea, emesis, lacrimation, and salivation) are used to recall some of these effects. Typically these symptoms are the first to develop.[7] Some series note miosis as the most common finding, observed in approximately 80% of cases.[8, 9] However, the effects of bronchorrhea, bradycardia and bronchospasm have greater clinical significance despite a lower incidence of occurrence, since most deaths in OP poisonings are secondary to respiratory failure.

The nicotinic features of acute OP poisoning occur due to accumulation of acetylcholine at nicotinic acetylcholine receptors. Typically, these effects are more likely to occur after significant poisonings and include the following: 1) general weakness; 2) fasciculations; 3) sinus tachycardia; 4) mydriasis and 5) hypertension. The "days of the week" mnemonic is used to recall these nicotinic findings: 1) **M**onday – Mydriasis; 2) **T**uesday – Tachycardia; 3) **W**ednesday – Weakness; 4) t**H**ursday – Hypertension; and 5) **F**riday – Fasciculations. After severe poisoning, generalized weakness can include the respiratory muscles and assisted ventilation may be required. It is worth noting that a number of the muscarinic and nicotinic features tend to overlap due to action at the ganglia. As a result, patients may present with a mixed picture. It is very important to obtain an accurate patient history and maintain a vigilant clinical suspicion when evaluating a potential OP patient.

Due to muscarinic and nicotinic effects, as well as the general accumulation of acetylcholine in the CNS, patients can also present with rapidly declining mental status and lethargy. Seizures and convulsions are the most significant CNS findings, but are generally uncommon after an OP exposure.

How are the acute manifestations of OP poisoning managed?

Decontamination is essential in the initial management of an acutely poisoned OP patient. All clothing should be removed and aggressive irrigation should be performed if topical exposure is suspected. Leather-containing materials should be discarded, as OPs cannot be removed from these products. The same measures of aggressive decontamination should also be considered after an oral ingestion, as many OPs tend to be excreted in bodily fluids. Case reports of secondary exposure have been after vomiting noted after oral ingestions, so care should be taken to protect hospital staff from accidental exposures.[10, 11] Interventions include limiting patient contact to essential personnel, maintaining adequate room ventilation, use of protective equipment and treating bodily fluids as chemical spills.[10, 11] Gut decontamination via gastric lavage may be considered if the exposure occurred within 30 minutes of presentation and the patient is not already vomiting.[12] Activated charcoal may limit further absorption and may be considered if the patient has a protected airway.[12]

OP-poisoned patients can develop respiratory depression secondary to the combination of CNS depression, nicotinic-mediated diaphragmatic weakness, bronchospasm and profuse amounts of respiratory secretions. Moderate-to-severe poisoning may require supplemental oxygen and, in extreme circumstances, endotracheal intubation. Copious secretions can be managed by antagonizing the OP's muscarinic effects with an anticholinergic agent, such as atropine. A doubling dose strategy (atropine 1 – 3 mg IV, doubling the dose every 5 minutes until effect) is shown to reduce mortality more effectively when compared to a fixed-dosing strategy (atropine 2 – 5 mg every 10 – 15 minutes).[13] Given the mixed clinical picture seen with the muscarinic and nicotinic symptoms in OP poisoning, tachycardia and mydriasis should not prohibit atropine administration. Instead, atropine therapy should be guided by the patient's respiratory status and the dose should be titrated until respiratory secretions dry, and wheezing and rhonchi improve.[14]

Atropine does not reverse the nicotinic symptoms associated with OP poisoning. Pralidoxime reactivates OP-inhibited AChE by removing the OP from the enzyme, reactivating the AChE enzyme and improving and/or preventing nicotinic symptoms. The World Health Organization (WHO) recommends that pralidoxime be dosed as a 30 mg/kg bolus followed by an 8 mg/kg/hr infusion in adults.[15] Variations in pralidoxime efficacy are potentially related to the "aging" phenomenon.[16] OPs that age more slowly, such as diethoxy OPs, are more likely to be reactivated by pralidoxime; OPs that age more rapidly, such as dimethoxy OPs, are less likely to be reactivated. A recent Cochrane Review concluded that there is insufficient evidence to indicate whether pralidoxime is beneficial or harmful.[17] The antidote should likely be used, or at least considered, in every OP poisoned patient, understanding that it may not be universally effective. The therapy should be continued until weakness, fasciculations or other

Continued on page 10

Vivitrol®

Contributed by: Michael Hodgman, MD, Upstate NY Poison Center, Syracuse, NY

Case

A 69 year old male was sent by EMS from a primary care clinic with acute delirium, agitation, vomiting and incontinence. The physician at the clinic reported that the symptoms began acutely after he received his first intramuscular injection (IM) of a medication for management of opioid dependancy.

The patient's past history included substance abuse, chronic kidney disease, hypertension, depression, anxiety and multiple orthopedic procedures with chronic pain. Current medications were furosemide, duloxetine, metoprolol, amlodipine and pantoprazole.

EMS reported a restless elderly male with vomiting and incontinence. Pulse was 120 bpm, they were unable to obtain a blood pressure or accurate respiratory rate. In route to the emergency department he received ondansetron and naloxone IM and subcutaneous epinephrine (the rationale for naloxone and epinephrine was unclear).

On arrival to the emergency department the patient was diaphoretic, restless and thrashing. Blood pressure was 145/73 mm Hg, pulse 110-130 bpm and temperature 37.4° C tympanic. A respiratory rate could not be accurately assessed. Finger stick glucose was 199 mg/dL. Pupils were midsize and reactive, the chest exam revealed scattered wheezes and the neurologic exam showed purposeful use of all extremities with no clonus or rigidity. He was non-verbal, did not respond to voice and resisted all attempts at restraint.

Laboratory Data

- Sodium 143 meq/L, Potassium 3.3 meq/L, Chloride 102 meq/L, bicarbonate 25 meq/L, BUN 27 mg/dL and creatinine 2.0 mg/dL. Glucose was 180 mg/dL, CK 89 IU/L.
- Ethanol, salicylate, and acetaminophen were not detected.
- CT head no acute
- UTOX: positive for THC, opiates and PCP
- EKG: sinus tachycardia, narrow QRS, no ischemic changes

What is the likely etiology of this patient's acute delirium?

Given the temporal relationship to medication administration this appears to be an acute reaction to the medication administered. The physician at the clinic reported the patient appeared well prior to the medication. Routine laboratory studies and imaging do not suggest any other etiology for the patient's acute delirium.

What agents are used to manage an opioid dependent person?

Management of the opioid dependent person may involve substitution treatment, abstinence based therapy, alternative therapy with another class of medication as well as detoxification.

Opioid replacement therapy has been a traditional approach to opioid addiction going back over a century. The central analgesic, euphoric and respiratory depressant effects of opioids are mediated primarily by mu receptors. The mu receptor also appears to play a significant role in opioid withdrawal. Knock out mice lacking the mu receptor and habituated to morphine do not demonstrate withdrawal after administration of naloxone [1].

Methadone has been the standard opioid used as replacement therapy since the 1960s. First synthesized in Germany in the 1930s, studies at Rockefeller University in the 1960s demonstrated efficacy in the management of opioid addiction. Methadone has a long duration of action, allowing once daily or even less frequent dosing for treatment of dependency. At larger doses it blocks the reinforcing euphoria from parenterally used opioids [2]. A reduction in the illicit use of opioids, a reduction in criminal behavior and incarceration, reduced rates of infectious complications from intravenous drug abuse and reduced mortality are all attributed to methadone maintenance therapy [3]. Some detoxification programs use a tapering dose of methadone over days to weeks, with abstinence the goal at the completion of detoxification.

Buprenorphine is a potent, partial mu agonist also used for opioid dependency. It possesses a high affinity for the mu receptor but without full agonist activity. A ceiling analgesic effect is observed and a bell shaped dose response curve suggests antagonist effects at higher doses [4, 5]. A highly lipophilic drug, buprenorphine has a plasma elimination half-life of about 3-5 hours, but because of its very high affinity and slow dissociation from mu receptor its duration of action is prolonged, with a terminal elimination half life of over 24 hours [6]. Buprenorphine can block the effects of other pure opioid agonists, displacing full opioid agonists from the mu receptor and precipitating withdrawal [4, 6, 7, 8]. Because of this risk buprenorphine should always be initiated in a supervised medical setting.

Buprenorphine is administered parenterally or sublingually. Enteral oral bioavailability is poorer than sublingual. Buprenorphine is available for sublingual administration either singly as Subutex®, or as a combination product with naloxone, Suboxone®. Naloxone is added to deter diversion and intravenous use (Oral naloxone has very poor bioavailability and when properly used has no impact on the efficacy of Suboxone®). Suboxone® and Subutex® have been approved

Continued on page 4

Continued from page 3

for the treatment of opioid dependency. Buprenorphine is also available parenterally for use as an analgesic (Buprenex®). Although this patient's current clinical picture might be related to acute withdrawal after injection of Buprenex®, this preparation is not approved for the treatment or management of opioid dependence.

What are other drugs used for opioid dependency?

Clonidine, an alpha-2 agonist, is used to ameliorate symptoms associated with opioid withdrawal [9]. Opioid withdrawal is associated with noradrenergic hyperactivity in several areas of the brain, including the locus coeruleus and caudal medulla neurons projecting to the bed nucleus of the stria terminalis. Stimulation of presynaptic alpha-2 receptors in these regions reduces noradrenergic output by these neurons [10, 11]. Clonidine toxicity presents similar to opioid toxicity with sedation, miosis, hypotension, bradycadia and depressed respirations, not consistent with this patient's acute delirium and agitation.

Tramadol and gabapentin have also been used to manage withdrawal symptoms. Tramadol is an analgesic with weak agonism at mu opioid receptors, over 3 magnitudes less than that of morphine [12]. The (+)-O-desmethyltramadol metabolite, a product of CYP 2D6, has a greater affinity for mu receptors and is responsible for most of tramadol's activity at mu receptors [13]. Tramadol has been investigated for the management of opioid withdrawal, with several very small studies suggesting that it is a viable alternative to buprenorphine or methadone [14, 15, 16]. Gabapentin has also been reported to attenuate the symptoms of opioid withdrawal in several small studies [17, 18]. Neither agent, however, has been extensively investigated for this indication. Tramadol toxicity can include sedation, seizures and serotonergic. Gabapentin is usually sedating following oral overdose. This patient's clinical picture is not consistent with the use of either these drugs.

Mitragynia speciosa Korth, commonly known as Kratom, is a plant found in SE Asia that is used to treat opioid withdrawal [19, 20]. Mitragynine and 7-alpha-mitragynine are alkaloid components of Kratom that have agonist activity at opioid as well as a number of other receptors, including alpha-2 receptors. The plant may be chewed, smoked or consumed as a tea. At lower doses Kratom is a mild stimulant. The larger doses used to manage opioid withdrawal also have analgesic and sedating effects [19]. Misuse of Kratom has been associated with seizures [21, 22].

Ibogaine, found in the root bark of an African shrub, *Tabernanthe iboga*, is also used to treat opioid and other addictions. Ibogaine and its CYP 2D6 metabolite noribogaine act at opioid receptors [23]. Ibogaine is a schedule I drug in the United States although it is readily available on line and through treatment programs outside the U.S. [24]. An indole compound, ibogaine can lead to dream like states and hallucinations. Nausea and vomiting are common side effects. Other adverse events include QT prolongation, arrhythmias, anxiety, and dysphoria [25, 26, 27, 28, 29]. Ibogaine is unlikely to be the cause of this patient's acute delirium as it is taken orally.

Ayahuasca is a tea prepared from several plants used by indigenous communities in South America for religious practices and as a traditional medicine. Ayahuasca is prepared from *Banisteriopsis caapi* as well as other plants, typically *Psychotropia* sps., in particular *Psychotropia viridis*. *P. viridis* contains N,N-dimethyltryptamine (DMT), a hallucinogen similar to psilocybin. The oral bioavailability of DMT is nil because of extensive first pass metabolism. *Banisteriopsis caapi* contains harmine and related alkaloids. These are potent monoamine oxidase inhibitors that block the first pass metabolism of DMT, allowing systemic availability [30]. In a structured social and support environment Ayahuasca has been purported to reduce alcoholism and other substance abuse problems [31]. Although DMT is a schedule 1 drug in the US *Psychotropia viridis* is readily available online. An adverse reaction to this hallucinogen could include delirium and agitation and would be consistent with our patient's presentation, although the route of exposure is not consistent.

Other remedies that have been used to treat substance abuse and withdrawal include ginseng and kava [32]. Ginseng abuse may result in anxiety, insomnia, hypertension and diarrhea while Kava is sedating [33]. We have recently cared for several patients abusing high doses of loperamide to control symptoms of opioid withdrawal. This patient's presentation with agitation and delirium is not consistent with any of these products.

Further discussion with physician revealed he had received an IM dose dose of Vivitrol for treatment of his opioid dependence.

What is Vivitrol?

Vivitrol is a sustained release microsphere formulation of naltrexone administered by deep intramuscular (IM) injection every 4 weeks. Naltrexone is a potent competitive opioid receptor antagonist with a 5 to 7 fold greater affinity for mu receptors than naloxone. It also exhibits greater affinity at delta and kappa receptors [34]. Vivitrol incorporates naltrexone into microspheres of a polylactide-co-glycolide polymer that slowly releases a dose of 380 mg naltrexone over weeks as the polymer is degraded. It received FDA approval for the treatment of alcohol dependence in 2006. Approval for the treatment of opioid dependence following opioid detoxification was granted in 2010.

Naltrexone is metabolized hepatically to 6-beta-naltrexol. After oral dosing extensive first pass metabolism limits the bioavailability of naltrexone. 6-Beta-naltrexol is a potent peripheral opioid antagonist but has poor central antagonist effects, probably due to poor entry into the CNS [35, 36, 37]. Both naltrexone and 6-beta naltrexol are extensively glucuronidated and renally eliminated. After oral dosing the apparent

Continued on page 5

Continued from page 4

serum half lives of naltrexone and 6 beta naltrexol are about 10 and 11 hours respectively, although a very prolonged terminal elimination phase for naltrexone of 96 hours has been measured in adults [38]. This is consistent with the prolonged opioid antagonism observed. In one study subjective effects to 6 mg hydromorphone were blocked 5 days after the last oral dose of naltrexone although a modest reduction in respiratory rate was observed [39].

After IM administration of Vivitrol there is an early serum peak of naltrexone within hours followed by a second peak about 2 days later. After that there is sustained plateau level of naltrexone for several weeks followed by a slow decline of serum naltrexone concentrations. Naltrexone levels of over 2 ng/mL are maintained for nearly 5 weeks after injection of 380 mg Vivitrol. The elimination t 1/2 of naltrexone administered as Vivitrol is about 5 days, with the terminal elimination of naltrexone dependent on the degradation of the microsphere polymer [40].

Can the opioid antagonism of naltrexone be overcome?

Naltrexone levels of 2 ng/mL are sufficient to block the effects of 25 mg IV heroin [38]. Oral doses of naltrexone 25 mg daily results in levels above 2 ng/mL and at 100 mg daily levels are at least 3 to 4 fold higher. Either of these doses were effective at blocking the effects of 6 mg of hydromorphone administered IM over 45 minutes [39]. Follow IM injection of a different sustain release naltrexone product levels were > 1 ng/mL at 4 weeks and were sufficient to block the subjective effects of a cumulative dose of 13.5 mg hydromorphone given over 2 hours [41].

An adult with a regular heroin habit insufflated 500 mg of pharmaceutical grade heroin (diamorphine) 6 days after a 1 g naltrexone implant. No objective opioid effects were observed despite serum morphine and 6-monoacetyl morphine levels of 525 and 164 ng/mL respectively. Serum naltrexone and 6-beta naltrexol levels were 2.8 and 9.0 ng/mL respectively. Another adult had no objective response to 100 mg diamorphine 3 weeks after a 1 g naltrexone implant, although he reported felling relaxed. Naltrexone and 6-beta naltrexone levels were 5 and 12 ng/mL respectively [42].

These reports suggest that large doses of opioid agonists would be needed to overcome naltrexone antagonism, particularly soon after dosing when naltrexone levels would be higher than in the studies cited above. Several case reports illustrate this. An abstinent 31 year old heroin addict with a subcutaneous implant of 1000 mg naltrexone (Prodetoxon®, marketed in Russia) was able to overcome opioid blockade by injecting a 12 fold higher than usual dose of heroin (based on number of packets used) [43]. A 17 yo female with polydrug abuse found she could overcome receptor block 3 weeks after her last injection of Vivitrol by insufflating of an unknown amount of oxycodone, and in fact experienced withdrawal following her next Vivitrol injection [44].

Contraindications to the use of this product include current opioid dependence or withdrawal. The manufacturer recommends urine opioid screening and/ or a naloxone challenge test prior to administration of this long acting opioid antagonist. Complications reported after the use of this product include acute withdrawal, opioid overdose near the end of the dosing interval, local reactions at the site of infection, including abscess, and hypersensitivity reactions to either naltrexone or the vehicle [45].

How common is delirium with opioid withdrawal?

The typical features of withdrawal precipitated by abstinence include malaise, anxiety, restlessness, insomnia, yawning, lacrimation, rhinorrhea, sweating, nausea, vomiting, myalgia, cramps, diarrhea and piloerection. Alertness is typically preserved and delirium is not a usual feature of withdrawal due to abstinence.

Delirium has been observed with antagonist-precipitated withdrawal. A 27 yo injection drug user experienced agitation, delirium and incontinence after imbibing a drink spiked with naltrexone [46]. A 28 yo male exhibited restlessness, posturing, unresponsiveness and incontinence after an oral dose of naltrexone [47]. Several other case reports describe acute agitation, confusion or hallucinations and the need for deep sedation to manage symptomatology [48, 49]. In a small series of patients using naltrexone as part of rapid opioid detoxification nearly 25% of patients exhibited delirium [50]. Delusional thoughts have also been reported [51].

Other complications reported following rapid opioid withdrawal under general anesthesia include pulmonary edema, protracted vomiting, esophageal tear, mediastinitis, and seizure like activity. Subsequent sedative drug overdoses have also been reported, presumably related to excessive use to treat withdrawal symptoms [52, 53].

Treatment of a patient with an acute reaction to naltrexone depot is challenging. Previous cases that involved implantation of a naltrexone pellet afforded the option of surgical removal of the implant. As a depot given by deep IM injection the option of surgical removal would be a more difficult undertaking with a greater risk of complications.

Case management and outcome

Intravenous access was established and the patient received 40 mg of diazepam over 20 minutes without any improvement in delirium or agitation. Sedation was achieved with an escalating dose of propofol over about one hour following paralysis and intubation.

Over the next 24 hours he required several doses of labetolol for hypertension. He was extubated 23 hours after presentation. Over the next 7 days he required intermittent doses of lorazepam, 8 mg total over one week, mostly at night for anxiety and insomnia. The patient reported that he had recently

Continued on page 6

Continued from page 5

been using methadone obtained from a friend for treatment of his chronic pain. He refused rehabilitation services.

The patient's urine toxicology screen showed THC, PCP and opiates. The immunoassay is not sensitive to methadone, suggesting recent use of an opioid other than methadone as well. The etiology of the positive PCP result was unclear. There was no history PCP use and none of his reported medications should have cross-reacted with that immunoassay. Venlafaxine has been reported to cause a false positive PCP screen [54]. Although pharmacologically similar, the structures of venlafaxine and duloxetine differ. There are no reported cases of duloxetine as the cause of a false positive PCP screen. This patient's acute delirium could be explained by PCP intoxication although his normal mental state on presentation to the physician's office and rapid onset of symptoms following the Vivitrol injection more strongly support that as the etiology.

In effect, this patient underwent an unplanned rapid opioid detoxification. Serious complications have occurred from rapid opioid detoxification, including death [52,53,55,56,57,58,59]. Fortunately this patient did well and surprisingly had no ongoing withdrawal symptoms beyond perhaps insomnia.

What errors occurred in this case?

Prior to administering Vivitrol a focused history should include details of any recent opioid use. Urine toxicology screening, with the limitations of such tests recognized, may be performed. A positive urine screen for opiates would make suspect the patient's claim of recent abstinence. And finally, the use of a shorter acting antagonist such as naloxone is recommended prior to Vivitrol. If there is any withdrawal precipitated by naloxone Vivitrol would be contraindicated.

A MedWatch report of this case was submitted.

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Continued on page 9

Opioid-Induced Hearing Loss: A Trend to Keep Listening For?

Kathryn T. Kopec, DO, and Lewis S. Nelson, MD

What possible toxicologic causes should be considered for sudden-onset hearing loss?

Are treatments available—and what is the long-term prognosis?

An 18-year-old man presents to the emergency department via EMS after his mother had difficulty awakening him that morning. Paramedics administered naloxone in the field and the patient had an immediate response. The patient arrives in the emergency department awake and diaphoretic and reports being unable to hear. He attended a party the previous evening, where the patient states that all he drank was alcohol. His initial vital signs are: blood pressure, 79/53 mm Hg; heart rate, 115 beats/min; respiratory rate, 14 breaths/min; temperature, 98.6˚F/37˚C. His oxygen saturation is 92% on room air. The patient's physical examination is significant only for bilateral hearing loss; he has a positive Rinne test and no lateralization with a Weber test. A detailed neurologic examination is otherwise normal. Laboratory abnormalities include a white blood cell count of 37,000/µL; creatine kinase, 3,455 U/L; aspartate aminotransferase, 4,470 U/L; alanine aminotransferase, 2,747 U/L; lactate, 8.6 mmol/L; potassium, 7.6 mmol/L; creatinine, 3.4 mg/dL; and an anion gap of 19 mmol/L. The ECG shows sinus tachycardia with left axis deviation and normal intervals. He receives normal saline boluses, which improve his vital sign abnormalities, and he is admitted to the hospital.

How is hearing loss categorized?

The perception of sound occurs when sound waves are transmitted via the external ear to the bones of the middle ear and on to the cochlea. These mechanical sound waves are converted to neurologic signals through potassium influx in the organ of Corti, leading to neurotransmitter release at the vestibulocochlear nerve. The subsequent neurologic signal is conducted to the pons and the auditory cortex of the temporal lobe.[1]

There are two principal types of hearing loss, conductive and sensorineural. Conductive hearing loss occurs secondary to damage to or obstruction of the mechanical components of the middle and external ear. The most common causes of conductive hearing loss are cerumen impaction, otitis media or externa, foreign bodies, or otosclerosis. Sensorineural hearing loss occurs because of dysfunction at the level of the cochlea or dysfunction along the vestibulocochlear nerve and neuronal pathway. The most common causes of sensorineural hearing loss include cochlear injuries, cochlear ischemia, viral infections, autoimmune disorders, and ototoxic drug exposure.[2,3] Sensorineural hearing loss also commonly occurs with aging.

Ototoxicity is a well-described adverse effect from various medications, most commonly including salicylates, quinine, loop diuretics, aminoglycosides, NSAIDs, antineoplastic agents, and antimalarials *(Table)*.[2]

How do toxins cause hearing loss?

The various mechanisms for drug-induced ototoxicity are still not fully elucidated. Ototoxic drugs typically cause sensorineural hearing loss, commonly due to dysfunction within the cochlea. Damage tends to occur at two specific areas of the cochlea, the outer hair cells of the organ of Corti or the stria vascularis.[4] These areas appear to be sensitive to variations in electrolyte shifts, low blood flow, hypoxia, and free radical exposure.[1]

Medications that damage the hair cells of the organ of Corti include cisplatin, loop diuretics, salicylates, and aminoglycosides. Mechanisms of organ of Corti ototoxicity include apoptotic cell death, alteration in the outer hair cell turgor, interference with oxidative metabolism, and blocking of transduction secondary to alterations in calcium release.[4]

Among the medications that have been associated with ototoxicity secondary to damage at the stria vascularis are loop diuretics, salicylates, vincristine, vinblastine, and bromates. The stria vascularis is composed of cells that maintain the influx/efflux of potassium into and out of the cochlea. Interference with the Na^+/K^+-ATPase pump, edema, inhibition of adenyl cyclase, and damage from free radicals are various proposed mechanisms of ototoxicity at this site.[4]

Some medications, such as aminoglycosides and diuretics, can cause both ototoxicity and nephrotoxicity. Since the renal tubules and the stria vascularis both help maintain electrochemical gradients through various ion channels and electrogenic pumps, they share a similar response to toxins that interfere with these actions.[4]

Case Continuation

The patient's acetaminophen and salicylate levels were negative, and his urine drug screen was positive for opioids.

Continued on page 8

Opioid-Induced Hearing Loss: A Trend to Keep Listening For?

Continued from page 7

On further questioning, the patient reported having snorted two lines of crushed morphine tablets at the party the previous evening.

How common is opioid-induced deafness?

There are no accurate data on the prevalence of opioidinduced hearing loss. The first case reports are from the 1970s, although an increasing number of reports of this phenomenon, in particular from hydrocodone, have been noted in the literature over the past decade. This may suggest an increasing incidence of this phenomenon associated with escalating prescription opioid use, or it may simply be a reporting bias.

Hearing loss can be associated with acute opioid use, typically in overdose, or with chronic use. Hearing loss associated with chronic opioid abuse tends to have slow onset, but once initiated becomes rapidly progressive and is often irreversible. It is usually bilateral and is sensorineural in origin.[5] The majority of the patients reported to have hearing loss associated with acute opioid overdose have shown spontaneous resolution of the hearing deficit within days to weeks, although a few reports have described prolonged hearing loss.[2] Some patients with opioid-related hearing loss have received cochlear implants to restore their hearing, but there is little other successful therapy.[6]

Although hearing loss associated with opioid use and abuse is being diagnosed more frequently, it is likely that the condition often remains undiagnosed. Emergency physicians do not routinely question chronic opioid users or patients with acute opioid overdose about hearing loss, nor do they question patients with hearing loss about opioid use. Therefore, patients (and providers) may not make the connection to the opioid use. There are also legal and insurance-related ramifications associated with opioid use that could prevent patients from seeking medical attention.

What are the proposed mechanisms behind opioid-induced hearing loss?

The mechanisms underlying opioid-induced hearing loss are not fully understood and may differ between acute and chronic users. The most widely proposed mechanism is alteration in the function of the hair cells of the inner ear.[5] Since hearing loss has been reported with a wide range of opioids, it is assumed to be mediated by an opioid receptor subtype. All three opioid receptor subtypes are present in the cochlea; there have been some data implicating the κ opioid receptor.[7]

Table: Selected Medications Associated with Ototoxicity

Aminoglycosides	Loop diuretics	Quinine
Ampicillin	Macrolides	Rifampin
Bleomycin	Monoamine oxidase inhibitors	Salicylate
Chloramphenicol	NSAIDs	Tetracyclines
Chloroquine	Omeprazole	Valproic acid
Cimetidine	Opioids	Vancomycin
Cisplatin	Polymyxin B and E	Vinblastine
Cyclosporine	Quinidine	Vincristine

Although hearing loss associated with opioid use and abuse is being diagnosed more frequently, it is likely that the condition often remains undiagnosed.

Genetic polymorphism of various drug-metabolizing enzymes leading to altered pharmacokinetics has been suggested as a possible contributor to opioid-induced hearing loss in chronic users.[6,7] While metabolism may play a role, not all of the opioids have the same metabolites, suggesting this may be a class effect of opioids not necessarily related to metabolites or specific opioids.[6] Some cases of hearing loss not involving overdose occur in the setting of acute relapse of opioid use following abstention. This raises the possibility of resensitization of the opioid receptors in the cochlea or a hypersensitization of the system secondary to the withdrawal period.[8]

In patients with acute opioid overdose,[2,3,7-10] deafness may be due to temporal lobe or vestibulocochlear system ischemia.[9] Various case reports have noted that often these patients present in the morning following a night of abusing opioids. It is likely that a brief hypotensive or hypoventilatory event in these individuals led to hypoxemia and cochlear ischemia.[9] However, not all of the reported patients suffered significant damage to other end-organs, although the markedly abnormal laboratory tests suggested a prolonged "down-time" in the current patient. Regardless, although ischemic multiple organ system damage is widely described following opioid overdose, the association with hearing loss is not universal.

In some cases, an adulterant such as quinine may also contribute to hearing loss. For example, quinine is used to "cut" heroin, as the similar bitter taste allows sellers to surreptitiously expand the supply.[3,7,10] Naloxone administration does not appear to be associated with hearing loss.

Continued on page 9

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Opioid-Induced Hearing Loss: A Trend to Keep Listening For?

Continued from page 8

Case Conclusion

The patient received norepinephrine briefly for hypotension, although his hemodynamics rapidly stabilized. He required hemodialysis for 1 week, and all of his laboratory abnormalities normalized. The patient regained his hearing after 2 days. He was scheduled for outpatient ENT follow-up.

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Continued from page 5

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Continued from page 2

nicotinic symptoms have resolved. Finally, pralidoxime is not an atropine substitute. Pralidoxime should always be used in conjunction with atropine.

Animal models have suggested that prophylactic administration of diazepam reduces seizure incidence after exposure to nerve agents.18, 19 Based on this research, the military has included diazepam in the auto-injector kits used by soldiers for nerve agent exposures. While seizures are generally more unlikely after exposure to OP pesticides, diazepam is only necessary if seizures develop in an OP-poisoned patient.

Continuation of the current case

Atropine and pralidoxime were started in the Emergency Department. A total of 8 mg of atropine was administered before improvements in respiratory secretions were noted. Diarrhea, salivation and diaphoresis resolved. Vital signs included: blood pressure, 180/90 mmHg; heat rate, 84 beats per minute. Airway was patent and maintained with supplemental oxygen. Mental status was sleepy but oriented. The patient was transferred to an Intensive Care Unit for continued care.

Over the next few days, the patient remained hemodynamically stable, and respiratory status was maintained with supplemental oxygen. The patient continued to have intermittent cholinergic symptoms, including bronchorrhea and diarrhea, and was placed on scheduled atropine bolus doses. Pralidoxime was discontinued 72 hours after-ingestion, as the patient had a period of greater than 24 hours without any OP-related symptoms. Approximately 48 hours after pralidoxime discontinuation, episodes of diarrhea were noted and atropine was given. Relapsing cholinergic symptoms were observed over the next few days and complaints of weakness were noted. On Day 13 agonal respirations and bradycardia, unresponsive to atropine, developed, so endotracheal intubation was required.

Why are symptoms still being observed in this case of OP poisoning?

A decline in clinical status was noted after the patient appeared to be improving. All of the noted symptoms could potentially be explained by OP redistribution from fat stores, as they were either cholinergic or nicotinic in nature. In these cases, pralidoxime should be restarted, along with additional doses of atropine, as indicated by clinical signs and symptoms. Approximately 10 to 40% of acute OP poisonings develop delayed weakness in the proximal limbs, neck flexors and muscles of respiration.[20, 21] This constellation of symptoms is known as the intermediate syndrome (IMS), and its etiology is poorly understood. Some researchers have cited insufficient pralidoxime therapy and tissue redistribution as potential causes, though these opinions are not universally shared.[20, 22] Our patient demonstrated worsening general weakness and labored breathing, both of which are potentially consistent with intermediate syndrome. However, evolution typically occurs 24 to 96 hours post-ingestion and after the resolution of the initial cholinergic symptoms.[20, 21] In our patient symptoms potentially consistent with intermediate syndrome occurred 7 days later, far longer than the values previously reported.

Management includes respiratory support with endotracheal intubation as clinically indicated. Interestingly, it has been noted that intermediate syndrome resolves in the following order: 1) decrease in respiratory difficulty; 2) return in proximal limb strength and 3) resolution of neck flexor weakness.[22, 24] Atropine and pralidoxime administration does not lead to symptomatic improvement in this clinical syndrome and are generally not recommended.[20, 22] Symptom resolution typically occurs 5 – 18 days after evolution.[22 - 24]

What other long-term complications have been associated with OP poisoning?

OP-induced delayed polyneuropathy (OPIDN) has been previously noted. It should be distinguished that this phenomenon is noted only with select OPs.[25] In exposures at risk, lower limb cramps or other sensory/motor complaints are observed 1 to 5 weeks after recovery from a symptomatic OP exposure. These complaints rapidly evolve into an ascending paralysis that seems to occur more frequently in the lower limbs.[22, 24] Eventually the flaccid paralysis resolves and hypertonicity is seen.[22, 24] Historically, these symptoms are known as "Ginger Jake Paralysis", since thousands of Americans during prohibition became weak or paralyzed after drinking an alcohol-containing ginger extract (Ginger Jake) that had been contaminated with the OP triorthocresyl phosphate (TOPC).[26] These cases typically developed permanent spasticity and an abnormal gait known as "Jake leg" or "Jake walk". The environmental protection agency performs testing to estimate the risk of a given OP to cause OPEDN using a hen bioassay.

Case conclusion

The patient remained intubated and generalized weakness was noted throughout the remainder of the patient's hospitalization. A consulting neurologist had suspicions that the patient may have a more complicated neurological picture. On Day 18 the patient was transferred from the consulting institution to a different medical center for a more complete neurological evaluation, where he was lost to follow up.

Conclusion

OPs can have significant toxicity. The symptoms associated with acute OP poisoning are generally grouped as muscarinic, nicotinic and CNS effects. Initial management includes decontamination and protecting hospital staff from secondary OP exposure. Respiratory depression can occur due to CNS depression, diaphragmatic weakness, bronchospasm and copious amounts of respiratory secretions (bronchorrhea). Supplemental oxygen is often required, and severe cases can

Continued on page 11

Continued from page 10

require endotracheal intubation. Doubling doses of atropine should be used to antagonize cholinergic- induced respiratory secretions. Pralidoxime is used to treat nicotinic symptoms and to lower the atropine requirement. Relapsing symptoms can be seen after exposure to highly lipophilic OPs.

The treatment of OP poisoning continues to be a challenging and difficult endeavor. Although these poisonings are more prevalent in developing nations, they should be considered in patients with an array of cholinergic symptoms and a history of intentional overdose.

Table 1: Potential sources of organophosphate pesticides

Household	Pet shampoos; Pet sprays; Flea collars; Pesticides; Roach/insect bait; Head lice shampoos
Occupational	Pesticides; Crop dusting; Livestock dipping; Exterminators; House fumigation
Terrorism	Nerve agents (sarin, VX gas, etc.) are organophosphates

Table 2: Common organophosphate compounds

Dimethoxy Organophosphates (Age more quickly)	**Diethoxy Organophosphates (Age more slowly)**
Dichlorovos (No-Pest®)	Chlorpyrifos (Brodan®)
Dimethoate (Cygon 400®)	Coumaphos (Muscatox®)
Fenthion (DMTP®)	Diazinon (Spectracide®)
Malathion (Ortho malathion®)	Dichlorofenthion (Nemacide®)
Methyl parathion (A-Gro®)	Parathion (Supertox®)

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