Oxymorphone Insufflation Associated with Acute Sensorineural Hearing Loss: Case Files of the University of Massachusetts Medical Toxicology Fellowship

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Case Presentation

A 37-year-old male was found supine and minimally responsive in his mother's basement. Emergency medical services reported miotic pupils, bradypnea, and depressed mental status that improved significantly after administration of naloxone 1 mg intramuscularly. In the emergency department, the patient had stable vital signs and normal mental status. He reported having consumed alcohol earlier, then snorting crushed Opana® (oxymorphone: Endo Pharmaceuticals Inc; Chadds Ford, PA, USA) shortly before being found unresponsive. The patient purchased the oxymorphone on the Internet and was unsure if he used the immediate- or the extended-release formulation.

In the emergency department, the patient felt well, except for acute subjective bilateral hearing loss described as feeling like he was "in a tunnel." He denied any associated trauma, headaches, changes in vision, tinnitus, or ataxia. His physical exam was unremarkable except for subjective bilateral hearing loss observed by both the patient and the examiners. No formal audiologic testing was performed.

What Is the Differential Diagnosis of Sensorineural Hearing Loss?

The differential diagnosis of sensorineural hearing loss (see Table 1) is extensive and includes medications, organic solvents, heavy metals, structural lesions, neurologic disease, infectious etiologies, psychiatric disease, and trauma, and it can be idiopathic [1–3]. Noise exposure is recognized as one of the most common causes of hearing loss, affecting both people exposed to loud environments on a regular basis, as well as singular exposures like gunshots [4]. Acoustic trauma causes damage to the middle and inner ear and is often permanent.

Several xenobiotic substances are ototoxic. Classically recognized among these are aminoglycoside antibiotics and platinum chemotherapeutics such as cisplatin. Hearing loss associated with these therapeutic agents may be permanent and affects a significant proportion of treated individuals. As many as 33 % of patients treated with aminoglycosides experience ototoxicity [5], while 60 % of children treated with cisplatin suffer from permanent bilateral hearing loss [6]. Imatinib, a chemotherapeutic tyrosine kinase inhibitor, has also been associated with hearing loss in a case report of a young man receiving treatment for chronic myeloid leukemia [7]. Loop diuretics have also been associated with both reversible and irreversible sensorineural hearing loss [8]. A recent review of the literature suggests that antimalarial therapeutics, and possibly the falciparum parasite itself, cause hearing loss [9].

Vancomycin and macrolide antibiotics (e.g., clarithromycin) are also associated with sensorineural hearing loss [10, 11]. In the case of macrolides, this deafness is thought to be reversible, dose-related, and possibly due to dysfunction of the outer hair cells [11]. Iopamidol, a low osmolar intravenous contrast dye, is linked to bilateral permanent hearing loss after abdominal aortic angiography [12].

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Table 1 Differential diagnosis for acute ototoxicity [1–3]

Xenobiotics
Antibiotics (aminoglycosides, macrolides, vancomycin)
Anticonvulsants (valproic acid)
Anti-inflammatory (NSAIDs)
Anti-hypertensives (enalapril)
Antimalarial (quinine)
Antineoplastics (cisplatin)
Heavy Metals (cobalt, mercury)
Loop diuretics (furosemide)
Organic solvents (carbon disulfide, styrene, trichloroethylene, toluene)
Other (imatinib, iopamidol)
Structural/Neurologic Disease
Acoustic neuroma
Demyelinating disease
Meniere's disease
Neoplasm (posterior cranial fossa)
Paraneoplastic syndrome
Spinal tap (secondary to decrease in ICP)
Stroke
Trauma (noise, temporal bone fracture, perilymphatic fistula)
Vestibular schwannoma
Infectious
Encephalitis
Lyme disease
Syphilis
Psychiatric
Conversion disorder
Idiopathic

Organic solvents have been linked to ototoxic effects in laborers across the globe, but it is unclear if there is a direct causation or simply an association with significant noise in the workplace. Carbon disulfide, styrene, trichloroethylene, and toluene have been associated with hearing loss in humans [13]. In animal models, ethyl benzene, *n*-hexane, and xylene demonstrate ototoxic properties [13, 14]. Numerous studies have also explored hearing loss in workers exposed to mixtures of organic solvents, as may commonly occur in industrial workplaces [13]. Animal models have shown a synergistic effect between noise and organic solvent exposure on hearing loss, but this effect has not been demonstrated in humans [13].

Heavy metals like mercury and cobalt are ototoxic agents as well. Mercury's irreversible damage to both the peripheral and central auditory systems following acute and long-term exposures does not appear to be dose-dependent [15]. Previously, patients receiving cobalt chloride as a therapeutic to treat refractory anemia experienced tinnitus and deafness [16]. Currently, cobalt ototoxicity has been suggested in patients with cobalt chromium alloy prosthetic joint implants. These

patients may suffer from a release of metal ions due to deterioration of the prosthesis leading to progressive hearing loss and tinnitus [16].

What Other Kinds of Auditory Toxic Effects Have Been Reported?

Tinnitus is a type of auditory hallucination that describes the perception of sound in the absence of external environmental stimuli [17]. It is a common hallucination, with 50 million adults reporting it in a recent US health census [17]. Tinnitus is associated with sensorineural hearing loss, noise exposure, allergies, congenital defects, and medications [17, 18]. Cisplatin, quinine, and salicylates have all been shown to cause tinnitus [17].

Musical hallucinations are a type of auditory hallucination with a lower incidence than that of tinnitus [19]. They are considered to be a disorder of sound processing and present as the perception of music in the absence of external stimuli [19]. Musical hallucinations are associated with sensorineural hearing loss [20]. Elderly age, female sex, and psychiatric conditions such as obsessive-compulsive disorder, schizophrenia and depression, neurologic disease, and some medications also are associated with the development of these sensory disturbances [20, 21]. The mechanism behind musical hallucinations is unclear, but they may result from a cholinergic deficit, as anticholinergic medications have been reported to cause musical hallucinations [22].

Multiple case reports describe the development of musical hallucinations after medication (e.g., salicylates, propranolol, voriconazole, steroids, tricyclic antidepressants, amantidine, and dipyridamole) administration [23–30]. Whiplash injury and abdominal pain have also been associated with these hallucinations [31, 32].

Opioids (e.g., tramadol, morphine sulfate, and oxycodone) are associated with musical hallucinations as well [30, 33, 34]. Although the exact mechanism of opioid-associated hearing loss (OAHL) and musical hallucinations are unclear, all three opioid receptor types exist in mammalian cochlea [33].

Case Continuation

The patient reported a past medical history significant for chronic back pain and opioid abuse. He took oxycodone/acetaminophen combination tablets as prescribed by his physician for management of back pain, and he purchased other opioids on the Internet for additional pain control. He denied ever having previous episodes of hearing loss in the setting of his chronic oxycodone/acetaminophen use.

The patient's initial serum ethanol level was 113 mg/dL. Urine GCMS was significant for the presence of cannabinoids,

citalopram, diphenhydramine, ibuprofen, nicotine, and oxcarbazepine. Serum oxymorphone concentration was 1,274 ng/mL and serum oxycodone level was 1,055 ng/mL. His serum acetaminophen level was undetectable (lower detection limit=10 µg/mL).

What Is Known About Opioid-Associated Hearing Loss?

Hearing loss is generally divided into three types: conductive, sensorineural, and mixed. Conductive hearing loss is due to a mechanical obstruction or damage to the outer or middle ear, resulting in disruption of the transmission of sound. Cerumen impaction, foreign bodies, and otitis media are all examples of conductive hearing loss [35]. Sensorineural hearing loss is due to damage of the inner ear (cochlea) itself, or disruption of the pathways from the inner ear to the auditory cortex. Of the three types of hearing loss, OAHL has been demonstrated to be sensorineural in all cases where patients had audiometric evaluation [35].

A number of opioids have previously been reported to cause OAHL, but our case appears to be the first report of OAHL attributed to oxymorphone. Oxymorphone is a semi-synthetic mu-opioid receptor agonist that is derived from thebaine [36]. Oxymorphone has been shown to be the major active metabolite of oxycodone and is a schedule II narcotic. It is available in both immediate- and extended-release oral formulations. Oxymorphone 10 mg has been shown to be equivalent to oxycodone 20 mg and oral morphine sulfate 30 mg in terms of its analgesic effects [37]. Its potency is due to its high lipid solubility, allowing it to reach its maximum plasma concentration in a shorter amount of time [36]. Oxymorphone can be abused by insufflation of crushed tablets, which increases its bioavailability from 10 % by the oral

route to 40 % by the intranasal route [36, 38]. The bioavailability of oxymorphone is also significantly increased by coingestion of ethanol [36].

Other opiates and opioids associated with hearing loss in case reports include codeine, dextropropoxyphene, heroin, hydrocodone, methadone, morphine, and propoxyphene (see Table 2) [35, 39–41]. Hearing loss has been demonstrated with both acute ingestion as well as chronic use [35]. Despite the growing number of case reports in the literature, the mechanism behind OAHL has yet to be elucidated. In a cochlear culture model study, ototoxicity of hydrocodone/acetaminophen co-formulation was in fact secondary to high levels of acetaminophen causing damage to inner and outer hair cells [42]. However, isolated acetaminophen toxicity is well described, and we were unable to find any reports of clinically demonstrated acetaminophen-related hearing loss [42–44]. Two reviews have demonstrated successful treatment of irreversible OAHL attributed to codeine and hydrocodone with cochlear implantation [43, 44]. The efficacy of cochlear implantation suggests that the mechanism of OAHL is likely to heavily involve the cochlea [44].

Case Conclusion

Approximately 5 h after arrival to the emergency department, the patient reported complete resolution of his bilateral hearing loss. He was admitted to the inpatient service for 24 h of observation.

Follow-up serum concentrations of oxymorphone and oxycodone were 34 and 16 ng/mL, respectively, at 22 h after arrival. His hospital course was uncomplicated and he was discharged to home with complete resolution of his symptoms.

Table 2 Case reports of opioid associated hearing loss [35, 39, 41, 45–54]

Reference	Substance ingested	Symptoms	Outcome
Harrell 1978	Propoxyphene	Bilateral hearing loss	Unknown
Mulch 1979	Heroin	Bilateral hearing loss	Resolved
Polpathapee 1984	Heroin	Bilateral hearing loss	Permanent hearing loss
Oh 2000	Hydrocodone/acetaminophen	Bilateral hearing loss	Hearing restored with cochlear implant
(2nd case)	Hydrocodone/acetaminophen	Bilateral hearing loss	Permanent hearing loss
Ishiyama 2001	Heroin	Bilateral hearing loss	Resolved
Kortequeue 2005	Heroin	Right sided hearing loss	No change at 3-month follow-up
Blakley 2008	Codeine/acetaminophen	Bilateral hearing loss	Unknown
Fowler 2008	Heroin/cocaine	Bilateral hearing loss	Unknown
Schrock 2008	Heroin	Bilateral hearing loss	High-frequency deficit at 3 days
van Gaalen 2009	Methadone	Bilateral hearing loss	Resolved
Christenson 2010	Methadone	Bilateral hearing loss	Unknown
(2nd case)	Methadone	Bilateral hearing loss	Resolved
Shaw 2011	Methadone	Bilateral hearing loss	Resolved
Kopec 2012	Morphine	Bilateral hearing loss	Resolved

The patient subsequently returned to the emergency department multiple times for unintentional narcotic overdoses. During each of these visits, he denied any repeated episodes of hearing loss.

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