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

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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

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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. 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 opioid-induced 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.

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

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

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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]

➤➤*Fast Track*

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.

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. **EM**

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