

Ototoxicity: The Hidden Menace

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Abstract Otolaryngology, although considered a surgical specialty, also covers many diseases that are not cured by surgery. These are treated medically and thus the otolaryngologist should have a good knowledge of drug treatments. It also entails ability to recognize, when an ENT symptom may be caused by one of the patient's medications, particularly as this is easily remedied by changing the drug. Although most of us know the common drugs that can cause otological side effects, there are many others that we may not be aware of. Here we have tried to consolidate a list of some commonly used drugs having otological side effects.

Keywords Ototoxicity · Ototoxic drugs · Hearing loss

Adverse drug events may not be recognized if physicians assume that pharmacologic therapy is always beneficial. It is just as important for clinicians to recognize the presence of an adverse drug event as it is to diagnose a serious disease [1]. Otologic side effects of drugs are more common than people imagine. Each year, the side effects of ototoxic drugs disrupt millions of people's lives and leave a trail of upheaval in their wake. The exact incidence of ototoxic side effects is not known, we apparently only see the tip of the iceberg. For extremely

ototoxic drug such as cisplatin the chances of incurring hearing loss is almost 100% while it is estimated to be 63% with Aminoglycosides [2]. Ototoxicity is defined as: 'the tendency of certain therapeutic agents and other chemical substances to cause functional impairment and cellular degeneration of the tissues of the inner ear, and especially of the end-organs and neurons of the cochlear and vestibular divisions of the eighth cranial nerve [3].' Organ specific drug toxicity such as ototoxicity may result from a unique susceptibility of the injured tissue to the drug, accumulation of the drug within the organ, or a combination of both factors. Inner ear injury may result from reversible inhibition of normal physiological functions, such as endolymph formation, which if inhibited for prolonged periods of time results in degeneration of tissue dependent upon the particular physiological function. Direct toxic effects on the sensory end organs (i.e., hair cells) also play a role in drug induced toxicity. Some drugs also appear to have central effects, delaying brain stem auditory impulses or altering higher central processing so that patients wrongly complain of hearing loss which in turn is wrongly ascribed to an ototoxic action. For example, carbamazepine appears to dampen cortical responses to sound with an increased latency this effect may relate to the altered hearing that is sometimes noted in patients taking this drug. Some of the most important drugs are also potentially nephrotoxic, thus it is highly desirable to adjust the dose of an ototoxic drug on the basis of renal function test. Ototoxicity is not necessarily limited only to parenteral administration. Hearing loss has occurred with neomycin following irrigation of surgical wounds, superficial dressing of severe burns, aerosol inhalation, rectal and colonic irrigation, or even after oral administration [4]. Certain risk factors are associated with an increased incidence of

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Table 1 Drugs causing hearing loss as a side effect

Drug category	Class of drug	Subclass of drug	Examples
Anti infective	Antibiotics	Aminoglycosides	Neomycin, gentamicin, amikacin, netilmicin
		Macrolides	Erythromycin, azithromycin, clarithromycin
		Quinolones	Ofloxacin, ciprofloxacin, levofloxacin
		Others	Tetracyclines, vancomycin, teicoplanin, framycetin, colistin, imipenem with cilastin
	Antivirals	Ganciclovir, zalcitabine, ribavirin + interferon	
	Antifungals	Amphotericin, flucytosine	
	Antimalarials	Chloroquine, mefloquine, quinine	
	Antituberculous	Capreomycin	
	Analgesics	Non steroidal	Aspirin, indomethacin, ibuprofen, diclofenac,
	Anti-inflammatory	Ketorolac, sulindac, naproxen,	
	Cytotoxics	Platinum compounds	Cisplatin, carboplatin, oxaloplatin
Anticancer drugs		Vinca alkaloids	Vindesine, vinblastine, vincristine
		Others	Bexarotene, taxane
		Cardiac and vascular drugs	Diuretics
		Carbonic anhydrase inhibitor	Acetazolamide
		Beta blockers	Metoprolol, sotalol, practolol, bisoprolol
		ACE inhibitor	Ramipril
Neurologic drugs	Anticonvulsant	Sodium valproate	
	Anti-Parkinson's	Entacapone	
Others	Immunosuppressant	Tacrolimus	
	Antirheumatoid	Hydroxychloroquine	
	Local anaesthetics	Ropivacaine	

drug induced ototoxicity. They include increased drug concentrations and/or prolonged exposure of the inner ear to the drug, dehydration, fever, noise exposure, preexisting sensorineural hearing loss, bacteremia, heredity, prior exposure to ototoxic agents, renal failure, presence of infected emboli, hypoxia and possibly old age [5–7]. Ototoxic synergism occurs if several ototoxic drugs are administered concurrently, potentiation of the ototoxicity is likely to occur, even when the dose of either drug is within the recommended limits [8]. Before prescribing any drug with ototoxic potential these group of high risk patients must be kept in mind. If possible, baseline audiometric and vestibular function test should be performed. Many ototoxic drugs begin destroying hearing at the highest frequencies first, and as the exposure continues, lower frequencies become involved. Since hearing is traditionally only tested up to 8 kHz, most initial cases of hearing loss from ototoxic drugs are never revealed by standard audiometric testing. High frequency audiometry can reveal the early effects of ototoxic drugs before tinnitus appears or hearing damage is visible on a conventional audiogram (250–8,000 Hz). Testing high frequencies between 125 and 20,000 Hz is time consuming and of course, adds additional expense

to the evaluation. Fortunately, researchers have recently discovered a five frequency slope that is very sensitive to the ravage of ototoxic drugs. The beauty of this five frequency slope testing is that it is highly sensitive to initial ototoxic hearing loss [9]. Despite these general reservations about using the label 'ototoxic' rather freely, it is clear that several classes of drugs do damage the inner ear. There are at least 743 drugs that are known to be ototoxic [10]. Toxic effects on the structure of inner ear include ototoxicity resulting from adverse effects on the cochlea, producing hearing loss, and/or the vestibular apparatus, producing vertigo, ataxia, light headedness and other symptoms. Symptoms of ototoxicity vary considerably from drug to drug and person to person. They range from mild imbalance to total incapacitation and from tinnitus to total hearing loss. The primary warning symptoms of drug induced ototoxicity are tinnitus, hearing loss or disequilibrium. Although some of the side effects are irreversible others are reversible, and it is therefore worthwhile looking for alternatives. In addition, some drugs only cause their symptoms in high doses, and reducing the dose may remove the side effect. At present, there are no treatments that can reverse the damage. Our aim, however, must be to prevent or

Table 2 Drugs causing tinnitus as a side effect

Drug category	Class of drug	Subclass of drug	Examples	
Anti infective	Antibiotics	Aminoglycosides	Tobramycin, netilmicin, amikacin	
		Macrolides	Clarithromycin, azithromycin	
		Quinolones	Ciprofloxacin, ofloxacin, norfloxacin	
		Others	Tetracyclines, vancomycin, teicoplanin, cotrimoxazole, cefpodoxime, linezolid	
	Antivirals		Ganciclovir, zalcitabine,	
	Antifungals		Amphotericin	
	Antimalarials		Mefloquine, Quinine	
	Antituberculous		Capreomycin	
	Analgesics diclofenac	Non steroidal		Aspirin, indomethacin, ibuprofen, diclofenac,
		Anti-inflammatory		Ketorolac, sulindac, naproxen, celecoxib
Anticancer drugs	Cytotoxics	Platinum compounds,	Cisplatin, carboplatin	
Cardiac and vascular drugs		Vinca alkaloids	Vindesine	
		Others	Bexarotene, paclitaxel	
		Diuretics	Loop diuretics	Frusemide, torasemide
		Potassium sparing diuretic	Amiloride	
			Carbonic anhydrase inhibitor	Acetazolamide
		Beta blockers		Metoprolol, timolol
		Alpha blockers		Prazocin
		ACE inhibitor		Ramipril, Enalapril,trandolapril
		AT-II receptor		Irbesartan
		Antagonist		
		Anti arrhythmic		Flecainide, quinidine, adenosine
		Calcium channel blockers		Diltiazem, ncardepine
	Neurologic drugs	Anticonvulsant		Carbamazepine, fosphenytoin
		Anti-depressant	Tricyclics	Imipramine, amitriptyline
SSRI			Citalopram	
Antimigraine		5HT-1 antagonist	Almotriptan	
Hypnotics		Benzodiazepine	(on withdrawal)	
Others	Immunosuppressant		Tacrolimus	
	Antirheumatoid		Hydroxychloroquine	
	Local anaesthetics		Lignocaine	
	Hypoglycaemics		Tolbutamide	
	Antihistamines		Chlorpheniramine	

diminish adverse effects secondary to ototoxic drugs. This can be achieved by avoiding or discontinuing the ototoxic drug if a satisfactory alternative is available. It is not possible for a doctor to know all the possible drugs having a certain symptom as a side effect. The list of drugs given here can be used as a quick reference (Table 1, 2, 3) [11]. The list contains only commonly used drugs that can produce either otologic symptom. Physicians should be familiar with the common adverse effects of the drugs they use and when in doubt should consult the literature.

Conclusion

Drugs can be remarkably beneficial, prolonging life and improving its quality by reducing the symptoms. The beneficial effects of drugs are coupled with the inescapable risk of untoward effects. Otologic side effects of drugs are not uncommon and patients presenting to the otolaryngologist will often be taking drugs for the treatment of unrelated problem. Hence it is important to consider the medication of the patient presenting for the first time with an otologic symptom.

Table 3 Drugs causing vertigo or dizziness as a side effect

Drug category	Class of drug	Subclass of drug	Examples
Anti infective	Antibiotics	Aminoglycosides	Tobramycin, gentamicin, amikacin, netilmicin
		Macrolides	Erythromycin, azithromycin, clarithromycin
		Quinolones	Ofloxacin, ciprofloxacin, levofloxacin, norflox
		Penicillins	Piperacillin, amoxicillin
		Cephalosporins	Cefopodoxime, cefadroxil, ceftazidime, cefixime, cefalexin, cefaclor, ceftazolin, ceftriaxone, cephradine
		Others	Tetracyclines, vancomycin, teicoplanin, metronidazole, tinidazole, clindamycin, cotrimaxazole, linezolid, pentamidine
	Antivirals		Ganciclovir, zalcitabine, acyclovir, zidovudine, amantadine, ritonavir, lopinavir, indinavir
	Antifungals		Fluconazole, flucytosine, itraconazole, terbinafine, gresiofulvin
	Antimalarials		Hydroxychloroquine, mefloquine, lumefantane
	Antituberculous		Isoniazid, rifampicin, capreomycin, cycloserine
Analgesics	Antihelminthics		Piperazine
	Non steroidal		Aspirin, indomethacin, ibuprofen, diclofenac
	Anti-inflammatory		Ketorolac, sulindac, naproxen, celecoxib, mefenamic acid, aceclofenac, rofecoxib
	Opioids		Morphine, codeine, alfentamil, pethidine, tramadol, dextropropoxyphene
Anticancer drugs	Cytotoxics	Platinum compounds	Cisplatin,
		Vinca alkaloids	Vinblastine
		Antimetabolites	Capecitabine, methotrexate, cytarabine
		Others	Etoposide, hydroxyurea, procarbazine, docetaxel
Cardiac and vascular drugs	Diuretics	Loop diuretics	Frusemide, bumetanide, torasemide
		Thiazides	Indapamide, metolazone, bendrofluazide
		Carbonic anhydrase inhibitor	Acetazolamide, dorzolamide
		Potassium sparing	Amiloride, spironolactone
	Beta blockers		Metoprolol, timolol, propranolol, atenolol, pindolol, sotalol, labetalol, carvedilol
	Alpha blockers		Prazocin, terazosin, doxazocin, tamsulosin,
	ACE inhibitor		Ramipril, Enalapril, trandolapril, captopril, perindopril, lisinopril,
	AT-II receptor antagonist		Irbesartan, losartan, candesartan, valsartan
	Anti arrhythmic		Flecainide, quinidine, adenosine, digoxin, amiodarone, bretylium, disopyramide
	Calcium channel blockers		Amlodipine, nifedipine, verapamil
Nitrates		Isosorbide mononitrate, glyceryl trinitrate	

Table 3 continued

Drug category	Class of drug	Subclass of drug	Examples
Neurologic drugs	Anticonvulsant		Sodium valproate, carbamazepine, phenytoin, gabapentin, tiagabine, lamotrigine, ethosuccimide
	Anti-depressant	Tricyclics	Imipramine, amitriptyline, amoxapine,
		SSRI	Citalopram, fluoxetine, sertraline
		MAO inhibitors	Moclobemide
	Antimigraine	5HT-1 antagonist	Almotriptan, sumatriptan
	Hypnotics	Benzodiazepine	Clonazepam, lorazepam, diazepam, midazolam, alprazolam,
		Other hypnotics	Zopiclone, zolpidem
	Anti-Parkinson's		Entacapone, selegiline, biperiden, bromocriptine, pramipexole
	Antipsychotics		Thioridazine, olanzapine, clozapine, chlorpromazine, haloperidol, serindole
	Drugs for dementia		Memantine, galantamine, donepezil,
Muscle relaxant		Dantrolene, baclofen, tizanidine	
Endocrine and metabolic	Hypoglycemics		Glipizide, glimepiride, pioglitazone, insulin
	Corticosteroids		Dexamethasone, fludrocortisone
	Bisphosphonates		Pamidronate, zoledronate
Gastro intestinal drugs	Antiemetics		Metoclopramide, ondansetron, nabilone, trifluorperazine, tropisetron
	Antiulcer	H ₂ antagonist	Ranitidine, cimetidine, famotidine
		Proton pump inhibitors	Omeprazole, lansoprazole, pantoprazole, Promethazine, cetirizine, cyclizine
			Fenofibrate, simvastatin, colestipol
	Lipid regulating		
Others	Immunosuppressant		Tacrolimus, azathioprine, mycophenolate
	Antirheumatoid		Leflunomide, etanercept, azathioprine
	Anti gout		Allopurinol
	Local anaesthetics		Ropivacaine, lignocaine
	Antihistamines		Chlorpheniramine, fexofenadine, promethazine, cetirizine, cyclizine
	Antimuscarinics		Atropine, hyoscine, dicyclomine
	Antiasthmatics		Salbutamol, montelukast, salmeterol

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