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ADVERSE DRUG REACTIONS IN AUDIOLOGY, PHONIATRICS, AND OTORHINOLARYNGOLOGY

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Abstract

Introduction: Due to the growing number of registered medicinal products, it is important to know about their mechanisms of action and adverse side effects. This also applies when diagnosing an otorhinolaryngology patient. The aim of this study was to review the literature and summarise various active substances and their relevant adverse effects.

Material and methods: Available literature data and summary of product characteristics were analysed. The following adverse reactions were studied: dizziness, hoarseness, oral candidiasis, pharyngitis, ototoxicity, painful swelling of the salivary glands, nasal congestion, dysgeusia, nosebleeds, tinnitus, dry nose, and difficulty swallowing. To classify adverse reactions the MeDRA classification was used.

Results: A list of individual adverse reactions and active substances that may cause them was prepared, along with the mechanism of causing a given adverse reaction. Dizziness was found to be caused by the largest number of drugs analyzed. The most severe adverse effects were irreversible ototoxicity (e.g., caused by intravenous aminoglycoside antibiotics) and embryotoxicity.

Conclusions: Adverse effects of medicinal substances important in otorhinolaryngology, audiology, and phoniatrics are multifactorial, but knowledge of them is necessary to make a correct diagnosis.

Keywords: adverse drug reactions • ototoxicity • tinnitus • vertigo • ENT diagnosis

DZIAŁANIA NIEPOŻĄDANE LEKÓW W AUDIOLOGII, FONIATRII I OTORYNOLARYNGOLOGII

Streszczenie

Wprowadzenie: Wraz ze wzrastającą liczbą zarejestrowanych produktów leczniczych rośnie potrzeba znajomości ich mechanizmów działania oraz możliwych działań niepożądanych – szczególnie w procesie diagnostyczno-terapeutycznym w otorynolaryngologii, audiologii i foniatrii. Celem niniejszego badania była analiza aktualnych danych dotyczących działań niepożądanych istotnych w ww. specjalizacjach.

Materiał i metody: Przeprowadzono przegląd dostępnych danych literaturowych oraz charakterystyk produktów leczniczych (ChPL). Analizie poddano działania niepożądane, takie jak: zawroty głowy, chrypka, kandydoza jamy ustnej, zapalenie gardła, ototoksyczność, bolesny obrzęk ślinianek, niedrożność nosa, zaburzenia czucia smaku, krwawienia z nosa, szumy uszne, suchość nosa oraz trudności z przełykaniem. Do klasyfikacji działań niepożądanych zastosowano system MedDRA.

Wyniki: Opracowano szczegółową listę konkretnych działań niepożądanych oraz substancji czynnych, które mogą je wywoływać, wraz z opisem mechanizmów ich powstawania. Najczęściej raportowanymi działaniami niepożądanymi ważnymi dla diagnostyki otorynolaryngologicznej, audiologicznej i foniatrycznej były zawroty głowy. Najcięższym działaniem niepożądanymi okazała się nieodwracalna ototoksyczność (np. wywoływana przez dożylne antybiotyki aminoglikozydowe).

Wnioski: Działania niepożądane substancji leczniczych istotnych w otorynolaryngologii, audiologii i foniatrii mają charakter wielokierunkowy, a ich znajomość jest niezbędna do postawienia trafnej diagnozy.

Słowa kluczowe: działania niepożądane leków • ototoksyczność • szumy uszne • zawroty głowy • diagnostyka otorynolaryngologiczna

Introduction

Because of the growing number of registered medicinal products, it is important to know the mechanisms of action of each product and its possible adverse effects. When diagnosing a patient with otorhinolaryngological or audiological conditions, the practitioner needs to be aware of the potential adverse effects that medicinal products may be having. According to national and international classifications, adverse reactions of medicinal products can be divided according to their seriousness. Serious adverse reactions are those that may result in: (1) death or life-threatening; (2) teratogenicity and embryotoxicity, associated with the occurrence of congenital defects or perinatal damage; (3) the need for hospitalization or prolongation of the patient's hospitalization; (4) permanent damage, thereby leading to disability; and (5) other serious side effects. The last classification categorizes side effects based on their frequency. This type of classification is primarily used in materials related to medicinal products – package leaflets, summary of product characteristics, and the classification of adverse reactions during clinical trials. They are then divided according to the classification of systems and organs – MedDRA dictionary (*Medical Glossary of Side Effects*). According to this classification, the frequency of adverse reactions is classified as follows:

1. Very common (≥ 1/10), i.e., more than 1 in 10 patients treated.
2. Common (≥ 1/100 to < 1/10), i.e., less than in 10 patients but more often than 1 in 100 patients treated.
3. Uncommon (≥ 1/1000 to < 1/100), i.e., less than 100 patients but more than 1000 patients treated.
4. Rare (≥ 1/10,000 to < 1/1000), i.e., less than 1000 patients but more than 10,000 patients treated.
5. Very rare (< 1/10,000), i.e., less than in 1 in 10,000 patients treated.
6. Not known [1,2].

Subsequent classification of adverse reactions to medicinal products encompasses those involving patient-dependent factors, as well as those dependent on the medicinal product (active substance) and environmental factors. Drug-related factors include:

1. Occurrence of adverse reactions despite the correct dose and method of administration.
2. The occurrence of overdose adverse reactions associated with a single high dose or another route of administration other than indicated.
3. Occurrence of adverse reactions related to chronic use of the active substance.
4. Risk of interactions. There are three types of interactions:
   - drug–drug interaction
   - drug–food ingredient interaction (including dietary supplements)
   - drug–stimulant interaction (tobacco smoke, alcohol, psychoactive substances, narcotics).

Risk factors for patient-related adverse drug reactions include:

1. Clinical characteristics of the patient (e.g., age, gender, race, BMI, renal failure, liver failure).
2. Immune reactions (e.g., allergic, most often antigen–antibody, sometimes late-cell hypersensitivity).
3. Genetically determined (e.g., characteristics of the patient in terms of drug metabolism rate).

Another classification of side effects divides them according to the type of reaction they cause. Type A side effects (*Augmented*) are dose-dependent and predictable side effects related to the mechanism of action of a drug; they usually cause low mortality. Type B side effects (*Bizarre*) are an adverse reaction which is independent of the dose used (the dose may be consistent with the characteristics of the medicinal product but cause a type B side effect). Type B side effects are rare and unpredictable; they are not related to the mechanism of action of the drug, and usually have a high mortality rate. Type C side effects (*Protect*) are adverse reactions depending on the duration of use of the drug and are related to the dose used. Type D side effects (*Delayed*) involve side effects observed during long-term treatment, although they do not always depend on the duration of drug use. Type E side effects (*End of use*) are side effects associated with the discontinuation of a drug. Type F side effects (*Therapy failure*) are adverse effects associated with failure of the therapy.

Due to intensive development and the introduction of new active substances to the market, the European Medical Agency obliges drug manufacturers to introduce an inverted black triangle marking for some of them, which means that the medicinal product needs to be monitored even more closely for adverse effects.

The aim of the study is to review the literature and summarize product characteristics, and in this way develop a list of various active substances and their adverse effects that may occur in patients, which might be important in forming a diagnosis within the fields of otorhinolaryngology and audiology.

Material and methods

This list is for reference only. Available literature and the summary of product characteristics were used to analyse the material. The following adverse reactions, which are important from the otorhinolaryngological point of view, were studied: dizziness, hoarseness, oral candidiasis, pharyngitis, ototoxicity, painful swelling of the salivary glands, nasal congestion, dysgeusia, nosebleeds, tinnitus, dry nose, and difficulty swallowing. For the classification of adverse reactions and their nomenclature, the MeDRA (*Medical Dictionary for Regulatory Activities*) classification was utilized.

Results

Based on the analyzed material, a list of individual adverse reactions and active substances that may cause them, along with the mechanisms behind each adverse reaction, was prepared. They are presented in **Table 1**.

Discussion

Significant adverse drug reactions relevant to the diagnosis of diseases in the fields of otorhinolaryngology, audiology,

Table 1. Adverse reactions associated with otorhinolaryngology (adverse reactions affecting hearing, balance, throat, larynx, and nose) and mechanisms of their formation [1–20]

No.	Type of side effect	Active substance that may cause the side effect
1.	Difficulty in swallowing	tetracycline
		clindamycin
		iron preparations
		bisphosphonates
		non-steroidal anti-inflammatory drugs (NSAIDs)
		antipsychotics (e.g., haloperidol, chlorpromazine)
2.	Dry oral mucous membranes	lithium
		tricyclic antidepressants
		anticholinergic drugs
		H_1 receptor blockers
		opioid analgesics
3.	Embryotoxicity (caused by the use of medications during pregnancy)	isotretinoin
		aminoglycoside antibiotics
		warfarin
4.	Hoarseness	inhaled glucocorticoids
5.	Nasal congestion	mepolizumab
6.	Nose bleeds	clopidogrel
		new generation oral anticoagulants (NOAK)
		vitamin K antagonists
7.	Oral candidiasis	glucocorticoids
8.	Ototoxicity	chemicals used in industry: toluene, styrene
		salicylates
		aminoglycosides antibiotics
		diuretics (loop diuretics)
		topical preparations containing neomycin/polymyxin B
		quinine, chloroquine
		macrolides
		vincristine
		chemotherapy drugs: cisplatin, fluorouracil, bleomycin
		phosphodiesterase type 5 inhibitor: sildenafil
		glycopeptide antibiotics: vancomycin
		oral contraceptives
		iodine-containing agents
9.	Painful swelling of the salivary glands	iodine compounds
10.	Pharyngitis	mepolizumab
		sulfonamides
		eptinezumab

Table 1 continued. Adverse reactions associated with otorhinolaryngology (adverse reactions affecting hearing, balance, throat, larynx, and nose) and mechanisms of their formation [1–20]

No.	Type of side effect	Active substance that may cause the side effect
11.	Taste disturbances	angiotensin-converting enzyme (ACEI) inhibitors
		terbinafine
		lithium
		calcium antagonists
		metronidazole (bitter-metallic taste)
		levodopa
		carbamazepine
		metformin
		some cytostatics, e.g., cisplatin, carboplatin
		zaleplon, zolpidem, zopiclone, eszopiclone
		iodine
		maribavir
12.	Tinnitus	isoniazid
		quinine
		salicylates
		doksazosin
		beta-blockers
		amlodipine
		ramipril
		tadalfil, sildenafil
		paroxetine, sertraline, escitalopram, fluoxetine (SSRI)
		sofosbuvir, ledipasavir
		etoposide
		abatacerpt
13.	Vertigo	hypnotics
		aminoglycoside antibiotics
		gyrase inhibitors
		beta-blockers
		opioid analgesics
		angiotensin-converting enzyme inhibitors
		antiarrhythmics
		anticonvulsants
		psychotropic drugs
		proton pump inhibitors
		bupropion
		varenicline
		trazodone

Table 1 continued. Adverse reactions associated with otorhinolaryngology (adverse reactions affecting hearing, balance, throat, larynx, and nose) and mechanisms of their formation [1–20]

No.	Type of side effect	Active substance that may cause the side effect
13.	Vertigo	agomelatine
		triptans
		nitrates
		buspiron
		gabapentin
		pregabalin
		brivaracetam
		macrolides
		tolperizone
		tizanidine
		baclofen
		dantrolene
		mefloquine
		H_2 blockers
		fexinidazole
		acyclovir
		aprepitant
		galcanezumab (common)
		antiarrhythmic drugs

and phoniatrics should be reported to the manufacturer or the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products. Depending on the severity of the adverse reaction, the time-frame of its reporting extends from the moment of becoming aware of its occurrence to later times.

Dizziness is often classified as a neurological side effect, and can have different origins. It is often seen at the beginning of therapy in patients suffering from hypertension or taking antiarrhythmics or cardiac glycosides, which can cause cardiac arrhythmias and dizziness. Dizziness can also be caused by a hypoglycemic episode. This is particularly important in patients with diabetes who are using drugs to treat the condition (e.g., insulin, sulfonylureas).

Hoarseness and candidiasis of the oral cavity are complications resulting from the negative effects of oral-inhaled glucocorticoids in patients suffering from asthma or chronic obstructive pulmonary disease. Oral candidiasis is mainly associated with immunosuppressive glucocorticoid activity; reducing the likelihood of side effects can be achieved by taking drugs from this group before a meal. In addition, after using these medications it is worth brushing the teeth and rinsing the mouth with water.

Taste disturbances, or complete loss of taste, were reported to physicians during and after the COVID-19 pandemic. Some of the side effects can be a complete loss of taste, unpleasant sensations of specific tastes, and lowering the taste threshold. They can be temporary, although they can also accompany the patient throughout the therapy. In some cases, switching to another drug may be considered (e.g., in the case of long-term treatment, switching from one drug from the group of angiotensin-converting enzyme inhibitors to another drug from this group or to one from the so-called spartan group).

Ototoxicity is a dangerous side effect of medications because some of them can cause irreversible damage to the hearing organ. Factors that may increase the toxicity of drugs include: renal failure; age of the patient (geriatric and pediatric populations are particularly vulnerable); history of inner ear diseases; use of the drug for a long time or in high doses; individual sensitivity of the patient; dehydration; fever; and concomitant use of other ototoxic agents (e.g., aminoglycosides and loop diuretics).

Some drugs cause reversible hearing disorders, while others are irreversible (e.g., aminoglycoside antibiotics). To reduce the ototoxicity of cisplatin, in recent years a medicinal product with INN-sodium thiosulfate has been approved. It is indicated for the prevention of cisplatin chemotherapy-induced ototoxicity in patients 1 month to < 18 years of age who have local, non-metastatic solid tumors. The mechanism of action of sodium

thiosulfate to protect against ototoxicity is not fully understood. However, it probably includes an increase in endogenous antioxidant levels, inhibition of intracellular oxidative stress, and a direct interaction between cisplatin and the thiol group to produce inactive platinum species. Concomitant incubation of sodium thiosulfate with cisplatin has resulted in a reduction in cisplatin cytotoxicity to cancer cells in vitro, and delayed addition of sodium thiosulfate to these cultures has prevented the achievement of a protective effect (based on the summary of product characteristics).

Difficulty swallowing can also be part of the diagnosis of patients by otorhinolaryngologists and phoniatricians. Swallowing disorders can be reduced by recommending that the patient use plenty of water while taking solid forms of the drug. In this way, it is possible to reduce the contact of the drug with the esophageal mucosa.

Tinnitus can be a side effect of medication and may go away on its own once the medication is discontinued. It is divided into objective and subjective tinnitus, as well as primary and secondary tinnitus (as in the case of tinnitus caused by drugs). The appearance of tinnitus in a patient who has started pharmacotherapy with a drug that can cause such an effect requires contact with a doctor and further diagnostics to confirm the cause.

In Poland, the obligation to report adverse reactions applies to healthcare professionals (e.g., doctors, dentists, pharmacists, nurses). Patients who have had an adverse reaction to a medicine can also report it themselves, or through their legal representative or guardian. The notification is made via a form on the website of the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products. Such a notification can also be made directly to the manufacturer of the medicinal product in question.

Conclusions

The adverse effects of medicinal substances important in otorhinolaryngology, audiology, and phoniatric diagnostics are multidimensional; however, knowing them is essential for making an accurate diagnosis for the patient.

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