

Safety of ophthalmic drug therapy: focus on adverse effects

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Summary:

In spite of high quality requirements concerning ophthalmic preparations (sterility, isotonicity, a pH close to the lacrimal fluid, lack of insoluble contaminations) they are not devoid of side effects. Their application to the conjunctival sac, onto the surface of the eye or under the eyelid may cause local adverse effects such as redness, eye irritation, transient increases in intraocular pressure, blurred vision as well as systemic adverse effects due to drug penetration into the lacrimal system. The latter effects are frequently forgotten by physicians, even though they may be sometimes more dangerous for the patient than local ones. Therapeutic efficacy of ophthalmic drugs within a specific group (e.g. ophthalmic NSAIDs) is generally similar and the question whether a particular drug is suitable for the individual patient is determined by the side effects. Sometimes the side effects (local or systemic) can be the reason for discontinuation of treatment by the patient, which can have a negative influence on treatment efficiency. This article provides a critical review of local and systemic adverse effects of ophthalmic drugs. The information on side effects of ophthalmic drugs and contraindications for their administration are presented in a comprehensive table, which can be very helpful for the reader to see which ocular drugs induce characteristic side effects and therefore are not recommended in a specific disease.

Key words: ocular drugs, eye drops, adverse effects, absorption, preservatives, benzalkonium chloride.

Drugs used in the treatment of eye diseases are a special group of preparations, which have to face the growing demands for their high quality since the eye — the organ to which they are directly applied — is one of the most sensitive sites of drug administration to external agents. Ophthalmic drugs introduced into the conjunctival sac, on the surface of the eye or the eyelid may, besides to the desired pharmacological effect, cause numerous adverse reactions, which considerably reduce the therapeutic efficacy of the drug. Thus, preparations used in ophthalmology should be sterile, isotonic, have a pH close to the pH of the tear fluid and should not contain insoluble impurities [1,2].

Ophthalmic drugs are primarily used topically in the form of drops or ointments as well as fluids injected via subconjunctival, retrobulbar or peribulbar and intravitreal routes. The topical administration of the ophthalmic drugs allows to obtain a higher concentration of active substances at the action site, i.e. in the eyeball, and to reduce the risk of systemic side effects of used drugs. The oral administration is used rarely, as in the case of immunosuppressive agents applied in uveitis, retinitis or optic neuritis, or antiglaucoma (diuretic) agent acetazolamide [3].

The drug is absorbed after its application to the conjunctival sac. The possible routes of drug absorption after ocular delivery are schematically shown in Figure 1. Transcorneal and transconjunctival/scleral absorptions are the desired routes for localized ocular drug effects. If the topically used ophthalmic drug is not supposed to penetrate (or to a very small extent) into the eyeball, it must be hydrophilic, or have only slight lipophilic properties.

In these cases, only water-soluble compounds should be chosen from a particular group of drugs. On the other hand, drugs which are to act in the eyeball should have amphiphilic properties to be able to penetrate both the hydrophilic and lipophilic compartments (such as the cornea and the anterior chamber of the eye) [3,4].

The drug applied to the conjunctival sac may also penetrate the systemic circulation, primarily through the absorption from the nasal mucosa (nasolacrimal drainage contributes to the systemic absorption of ophthalmic drugs applied to the conjunctival sac), and may locally penetrate the cornea and conjunctiva. Following transcorneal absorption, the aqueous humor accumulates the drug, which is then distributed to intraocular structures, as well as potentially to the systemic circulation by the trabecular meshwork pathway. Absorption from the nasal mucosa avoids hepatic and intestinal first-pass metabolism and may lead to significant systemic side effects after the conjunctival application, especially in the case of chronic use [2-4].

The potential toxicity of most drugs used in ophthalmology, which are administered topically to the eye, is associated with hypersensitivity or direct toxic effect on the cornea, conjunctiva, periocular skin and nasal mucosa.

Moreover, all ophthalmic drugs are potentially absorbed into the systemic circulation, so they can cause systemic side effects. Therefore, it should be kept in mind that the prescribed ophthalmic drug, which the patient has to use topically, may exert systemic side effects. For example, in many cases the administration of eye drops containing β -adrenergic receptor antagonists (β -blockers) may cause systemic side effects typical for this group of drugs, including even death of the patient (see Table 1).

Although the eye-drops used in short-term treatment are well tolerated, they may give temporary side effects, such as redness, eye irritation, transient increase in intraocular pressure, blurred vision, burning sensation and dry eye, which however do not require discontinuation of therapy. In the case of long-term treatment, the risk of side effects increases and has influence on the course of treatment. Sometimes it can be the reason for discontinuation of treatment, e.g. while taking preparations for the treatment of glaucoma (see Table 1).

Toxicity of these preparations results from the contraction of the ciliary body, or through the action on the cholinergic receptors. This may induce myopia and refraction fluctuations caused by shrinkage of the pupil and the ciliary body in accordance with the increasing and decreasing action of the drugs between their applications. Headaches that occur after the drug application are associated with the shrinkage of the iris and the ciliary body. Derivatives of epinephrine can cause the so-called rebound effect - contraction and dilation of the vessels, leading to redness. Ocular and skin allergies are also frequently found after applying epinephrine in eye-drops and its prodrugs: apraclonidine and brimonidine. Systemic absorption of epinephrine derivatives and β -blockers, as was mentioned above, carries the risk of inducing any side effects that occur after direct systemic administration. Regular use of carbonic anhydrase inhibitors may cause malaise, fatigue, depression, paresthesia, and kidney stones. Administration of antiglaucoma agents in eye-drops minimizes the relatively high frequency of side effects.

To sum up, the available pharmacological strategies of e.g. glaucoma treatment allow to slow down the progression of the disease¹⁾, however

¹⁾ Practically all currently used antiglaucoma drugs tend to lower intraocular pressure (IOP). They operate according to the accepted therapeutic strategy, which assumes that any reduction of elevated IOP — one of the risk factors, will delay the development of pathology. However, elevated IOP is a relative matter, for in many patients diagnosed with glaucoma there is no evidence of elevated IOP. The main cause of the disease is neurodegeneration of retinal ganglion cells and their axons, or nerve fibers, of unknown etiology. Currently, we do not know how to oppose the progressive process of neurodegeneration — so the symptomatic treatment is used in the form of IOP-lowering drugs.

the effect of this treatment on quality of patient's life must be always taken into consideration in relation to the existing potential risk of adverse reactions induced by therapy [4-7].

In order to avoid the systemic side effects of ophthalmic drugs the patient should respect the fundamental principles of their usage. During the drug application, the patient's head should be tilted back, and then after pulling away the lower lid 1 drop or ointment (corresponding to the head of one match) should be instilled into the conjunctival sac. During the delivery, the patient must not touch the eyelashes or lids with a drug container to prevent contamination of the bottle or tube. It is important to press the inside corner of closed eyelids for about 2 minutes immediately after the application of the drug. The eye closure and the pressure on the lacrimal sac are extremely important in order to minimize the systemic absorption of the administered drug. Moreover, a single dose of eye drops should be included in the one-drop volume (about 50 μ l) because the volume of the tear fluid in the eye is only about 10 μ l (up to 30 μ l). Therefore, the application of a greater volume of one drop will lead to its flowing out on the skin or to the nasolacrimal system, which in the latter case is associated with an increased risk of systemic side effects [8].

In some eye preparations, side effects may also be due in part to the presence of preservatives, whose main task is to maintain sterility of an ophthalmic drug during storage and use, despite the non-sterile usage by the patient. According to the current Polish Pharmacopoeia IX, a preservative should have a broad spectrum of antimicrobial activity, be chemically and thermally stable, compatible with the other ingredients of the formulation and should not cause any side effects [9].

Unfortunately, until now no preservative has been discovered, which would be in line with the above requirements. Eye drops and lotions for contact lenses may contain preservatives, such as benzalkonium chloride (BAK), chlorobutanol, thimerosal, chelating agents and lots of others. Both in vitro and in vivo studies on animals have shown cytotoxic effect of preser-

vatives on the external (conjunctiva, cornea) and internal (lens, trabecular mesh, retina) structures of the eye [4, 10, 11]. Particularly, BAK may cause a punctate keratopathy or toxic ulcerative keratopathy. Thimerosal is nowadays rather rarely used because of the development of frequent allergic reactions. Some preservatives, such as merfen and beta-phenylethyl alcohol, show non-compliance with poly-(2-hydroxyethyl methacrylate) (PHEMA), a component of soft lenses, and they should not be present in solutions used for storing and cleaning contact lenses, which can be preserved with acetate or chlorhexidine gluconate.

A certain rule can be noticed while observing the studies on an ideal preservative which have been performed until now that the better the conservative safety profile for the eye is, in comparison to the most widely used preservative, BAK, the weaker the required criteria for preservatives it meets [12]. Therefore, the best solution would be to eliminate preservatives in eye drops, which would reduce the incidence of adverse events and decrease the necessity of treatment discontinuation. As a result, a more efficient treatment would be achieved and the patients' quality of life would be improved, especially of those suffering from chronic diseases, who are sometimes forced to use ophthalmic preparations for their whole life.

This possibility is provided by new forms of ophthalmic drugs such as one-dose packages, the so-called minims, or special structures - drug dispensing systems in the form of membrane filter papers with a very small pore size (of about 0.22 μ m) or silver-plated items, which frequently guarantee sterility without the addition of preservatives. This type of eye preparations should become in the nearest future the gold standard treatment for many eye diseases such as glaucoma. However, now, they are far more expensive than conventional dosage forms such as eye drops or ointments, and therefore, they are not being chosen by patients, particularly in the case of long-term treatment.

The table below (Table 1) shows the potentially important local and systemic side effects of various drugs used in ophthalmic therapy [5-7].

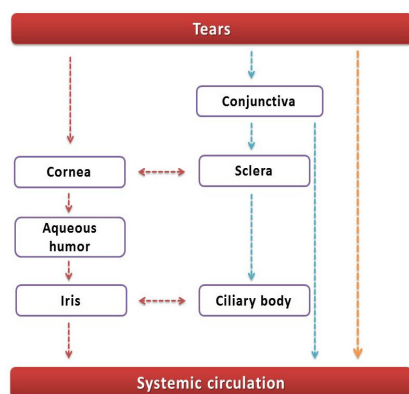


Figure 1: Possible absorption pathways of an ophthalmic drug following topical application to the eye (diagram according to [4], modified)

Legend:

-> the corneal; -> according conjunctival/scleral; -> nasolacrimal absorption pathway

The institution involved in the collection and exchange of information concerning the toxic effects of drugs in ophthalmology, the National Registry of Drug-Induced Ocular Side Effects, is worth mentioning. The principal goal of this organization is to collect the knowledge of the possible side effects of ophthalmic drugs. To report an adverse drug reaction one should contact the Casey Eye Institute at Oregon Health and Science University, 3375 SW Terwilliger Blvd., Portland, OR 97201, fax: 503-494-4286 or e-mail: www.eyedrugregistry.com[8].

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Table 1: The most important local and systemic side effects of drugs used in ophthalmology therapy

Drugs	The most important local and systemic side effects	Contraindications
Mydriatic agents		
1) Non-cycloplegic sympathomimetics	Phenylephrine conjunctival hyperemia and burning eye pain, glaucoma attack, cycloplegia, conjunctival epithelial keratosis with lacrimal point closure and epiphora stimulation of the sympathetic nervous system*	Hypersensitivity, pregnancy and breast-feeding, glaucoma with narrow angle glaucoma, hypertension, pheochromocytoma, advanced atherosclerosis
2) Paralyzing accommodation (cycloplegics)** muscarinic antagonists	Atropine Tropicamide increased intraocular pressure, blurred vision, conjunctivitis irritation, photophobia facial flushing, nasal dryness, dry mouth, visual hallucinations, restlessness, psychosis, hyperthermia, tachycardia	glaucoma with narrow angle glaucoma, hypersensitivity to the drug, rhinitis sicca
Miotic agents		
Cholinergic agonists	Pilocarpine Carbachol ↑ tension during accommodation — drug-induced myopia, photophobia, miosis impairing vision, ocular hyperemia, tearing, epithelial corneal dystrophy, retinal detachment, vasodilatation of conjunctiva and episclera — increased bleeding during surgery bradycardia, ↓ pressure, ↑ secretion of urine, saliva, sweat, tears, gastric juice; bronchospasm, intestinal spasms, ↑ bladder pressures, psychomotor agitation	inflammation of the iris and ciliary body, corneal damage, cataracts, heart failure, asthma, hyperthyroidism, peptic ulcers, intestinal obstruction, abnormal urination, breast-feeding
Drugs lowering intraocular pressure		
1) Cholinergic agonists	Pilocarpine Carbachol see above	see above

Drugs		The most important local and systemic side effects	Contraindications
2) β -Adrenolytics	Timolol Metipranolol Carteolol Betaksolo Pindolol ¹	burning, conjunctivitis, keratitis, blepharitis, blurred vision, drooping eyelids, symptom of "dry eye" bradycardia, arrhythmia, hypotension, hypoxia of the brain and limbs, impaired atrioventricular conduction, congestive heart failure, cardiac arrest, bronchospasm, respiratory failure, dyspnea-especially non-selective, \uparrow triglycerides, headache, dizziness, weakness, depression, alopecia	hypersensitivity to drug constituents (e.g., benzalkonium chloride), bronchial asthma, severe chronic obstructive pulmonary disease, sinus bradycardia, atrioventricular block II and III, heart failure, used cautiously in patients with diabetes mellitus and hypothyroidism
3) Adrenomimetics	Brimonidine	ocular dryness, ocular burning, blurred vision, a sensation of a foreign body in the eyes dry mouth, fatigue, headache, hypotension, orthostatic hypotension, insomnia	hypersensitivity, children under 2 years of age, patients taking antidepressants: monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants
4) Carbonic anhydrase inhibitors	Dorzolamide Brinzolamide Acetazolamide	burning, stabbing, itchy eyes, blurred vision, tearing, conjunctivitis, blepharitis, iritis and cyclitis; after absorption systemic side effects: paresthesia, \uparrow urination, facial flushing, polydipsia, bitter taste, headache, dizziness, hearing loss, tinnitus, drowsiness, fatigue, metabolic acidosis	hypersensitivity to drug constituents (e.g., benzalkonium chloride), intolerance to sulfonamides, liver failure, kidney disease, pregnancy and breast-feeding, hyperchloremic acidosis
5) Prostaglandin analogs	Latanoprost Bimatoprost Trawoprost Tafluprost Unoproston!	eye pain, foreign body sensation, \uparrow pigmentation of the iris, burning, blurred vision, redness and swelling of the conjunctiva, inflammation, corneal erosion, punctate keratitis, eyelid dermatitis, cystoid macular edema	hypersensitivity to drug constituents (e.g. propylene glycol)
6) Osmotic diuretics	Mannitol	bleeding into the subdural space, exacerbation of heart failure, acidosis, electrolyte loss	renal failure, congestive heart failure, pulmonary edema, intracranial bleeding, severe dehydration, metabolic edema

Drugs used to treat microbial diseases in the eye

Antibacterial agents	Aminoglycosides Amikacin Gentamicin Neomycin Tobramycin	swelling and itching of the eyelids, conjunctival erythema, punctate keratitis, erythema, tearing, secondary superinfection, long-term treatment with gentamicin may cause thrombocytopenic purpura, hallucinations	hypersensitivity to ingredients
	Macrolides Erythromycin Azithromycin	hypersensitivity reactions, secondary superinfection, increasing resistance (to erythromycin)	sensitivity
	Tetracyclines Oxytetracycline - ingredient of Atecortin	transient burning sensation around the eyes, tearing, conjunctival redness, blurred vision, secondary infections caused by refractory bacteria and fungi	hypersensitivity, tuberculous infection, viral and fungal infections, glaucoma

Drugs		The most important local and systemic side effects	Contraindications
Antibacterial agents	Polimyxins Polimyxin B – ingredient of Atecortin drops	as above	sensitivity
	Gramicidin – ingredient of Dicortineff drops	itching and burning of conjunctiva, secondary superinfection, cataract	sensitivity
Sulfonamides	Sulfacetamide	temporary irritation of the eye, blurred vision, superinfection with resistant organisms, bitter taste in the mouth, severe allergic reactions such as aplastic anemia	hypersensitivity, infants under 2 months of age
Fluoroquinolones	Ciprofloxacin Levofloxacin Moxifloxacin Norfloxacin Oflxacin	mild eye irritation: burning, itching	hypersensitivity to ingredients such as benzalkonium chloride
Antiviral agents	Acyclovir Ganciclovir Denotivir	transient burning and itching, keratopathy	hypersensitivity to ingredients such as benzalkonium chloride
Antiseptic and astringent agents Zink compounds	Zinc sulphate – ingredient of Oculosan, Cincol	dryness of eye mucous membranes	hypersensitivity, dry eye syndrome, children under two years of age
Argentum compounds	Argentum nitricum	conjunctival irritation, argyria	sensitivity
Drugs used to treat ocular inflammatory diseases			
Glucocorticosteroids	Hydrocortisone Dexamethasone Fludrocortisone Fluorometolone	burning, eye irritation, impaired visual acuity, steroid glaucoma, cataracts, corneal ulcers	hypersensitivity to drug components, cases of undiagnosed red eye, tuberculosis infections, viral and fungal infections, purulent conditions, corneal injuries and ulcers, glaucoma unhealed wounds
	Prednizolone Loteprednole	after long-term use (especially in children) impaired water and electrolyte balance, hypertension, edema, obesity, myopathy, osteopenia, osteoporosis, stomach ulcers, bowel perforation, impaired wound healing, metabolic disturbances, steroid-induced diabetes, reduced immunity, inhibition of the hypothalamic-pituitary-adrenal axis	
Nonsteroidal antiinflammatory drugs	Indomethacin Diclofenac	burning sensation, ↑ intraocular pressure, sensitivity, bleeding into the eye tissues contact dermatitis, gastric and duodenal ulcers, bronchial asthma attack and anaphylactic reactions in allergic people	hypersensitivity to the drug, blood clotting disorders, asthma, active peptic ulcer disease, severe liver and kidney failure, pregnancy (after 5 months)

Drugs		The most important local and systemic side effects	Contraindications
Drugs used to treat allergic inflammation			
Antihistamines			
• H ₁ antihistamines	I generation Ketotifen Epinastine II generation Emedastine Azelastine	local irritation of the eye, dry eye and foreign body sensation, blurred vision and disturbance of eye function, mydriasis, ↑ intraocular pressure systemic side effects (mostly the first generation drugs): headache, drowsiness, rash, dry mucous membranes	hypersensitivity to the drug, glaucoma with narrow angle glaucoma, hypertension, hyperthyroidism, cardiac arrhythmias, pregnancy
• Cromolyn sodium		local eye irritation	hypersensitivity, soft lenses (caused by benzalkonium chloride)
• Olopatadine			
Lodoxamide		local eye irritation, systemic side effects as above	hypersensitivity
Decongestants			
α - adrenergic agonists	Naphazoline Tetrahydrozoline	xerophthalmia, mydriasis, ↑ intraocular pressure CNS disorders, high blood pressure, abnormal heart rate, breathing difficulties, headaches	hypersensitivity to the drug, glaucoma with narrow angle glaucoma, dry eye syndrome, hypertension, hyperthyroidism, children under 2 years of age
Anesthetics used in ophthalmic procedures			
	Proxymetacaine	mucous membrane irritation, cornea damage, loss of eye effects on the cardiovascular system and the central nervous system ***, allergic reactions	epithelial damage, hypersensitivity, soft lenses (caused by benzalkonium chloride)
Drugs which are supposed to improve tissue metabolism and regeneration			
	Pirenoxinum Potassium iodide Natrium iodide Solcoseryl Dexpanthenol Vitamin A	transient blurred vision, local allergic symptoms enlarged thyroid gland, acne (iodide preparations)	hypersensitivity to iodine preparations (e.g. Vitreolent) thyroid dysfunction, pregnancy and lactation, children
Agents used to treat dry eye			
	Polyvinyl alcohol Hyaluronan Hypromellose Dextran 70 Polyacrylic acid Carbomer Polyvidone	allergic reactions to preservatives in preparations such as cetrimide, polidronium chloride	hypersensitivity to constituents of the preparation
Agents used to assist in ocular diagnosis			
Dyes	Fluorescein	blurred vision, glaucoma with damage to the optic nerve, cataract, secondary ocular infection, perforation of the eye-ball, allergic reactions	hypersensitivity to constituents of the preparation, tuberculosis, viral and fungal infections of the eye

Drugs		The most important local and systemic side effects	Contraindications
Drugs and biological agents used in ophthalmic surgery			
Viscoelastic substances	Hyaluronic acid Hyaluronan Hypromellose Poliacrylamides Collagen Chondroiten sulfate	↑ intraocular pressure, allergic reactions	hypersensitivity
Drugs used to treat age related macular degeneration			
Angiogenesis inhibitors	Bewacizumab Ranibizumab Pegaptanib	eye irritation, ↑ intraocular pressure, conjunctival hemorrhage, corneal edema	eye infections, hypersensitivity to the drug
Photodynamic therapy	Verteporfin	blurred vision, allergic reactions nausea, weakness, back pain, hypercholesterolemia	porphyria, severe liver damage, hypersensitivity to constituents of the preparation

* Too high doses can cause stimulation of the sympathetic nervous system with such symptoms as: anxiety, tremor, weakness, headache, dizziness, pale skin, respiratory disorders, cardiac arrhythmias, retrosternal pain, palpitations and hypertension. Cardiovascular symptoms may be more pronounced in patients with hyperthyroidism, hypertension, ischemic heart disease.

** Note that the dark irises are more resistant to mydriasis, and therefore the drug can be easily overdosed.

*** Symptoms of poisoning from the central nervous system: a metallic taste in the mouth, feeling light-headed, agitation, anxiety, euphoria, tremor, confusion, headache, dizziness, nausea, tinnitus, blurred vision, vomiting, feeling hot, cold or numbness, loss of consciousness, convulsions, depression; from the cardiovascular system: hypotension, bradycardia, and in extremely severe cases, cardiac arrest.

! preparations not registered in Poland.

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