Systemic adverse effects of topical ocular treatments

Key points

- Some eyedrops, gels or ointments may cause adverse effects as serious as those observed with systemic therapies.
- Because of their relatively poor penetration into eye tissue, ophthalmic drugs usually contain high concentrations of their active ingredient.
- Asking patients about these drugs to prevent interactions is useful when prescribing a new systemic treatment.
- Conversely, it is advisable to ask about ophthalmic drugs during the etiological investigation of possible iatrogenic effects.

The risk of general toxicity of topical ophthalmic medication has long been underestimated. The first reports appeared in general medicine journals in the 1960s, at the same time as very active and therefore potentially iatrogenic new pharmacological treatments were being introduced1,2.

The common use of eyedrops, ophthalmic gels and ointments may mask their potential unwanted side effects, which can under some circumstances become as toxic as systemic treatments2-4. Medications can be absorbed through many routes, and most of the ingredients included in topical eye treatments are likely to enter the bloodstream at high concentrations. When problems arise, patients usually forget to mention their eyedrops. Physicians must be familiar with the secondary effects of these local ophthalmic treatments to take proper care of their patients.

Adverse and iatrogenic effects: ophthalmologic concern

The World Health Organization defines adverse effects as any noxious, unwanted, or otherwise unintended reaction linked to a therapeutic dose of medication. More broadly, the concept of iatrogenic effects deals with all the circumstances of an incident caused by a medication prescribed in either the diagnostic or therapeutic phases5. Unavoidable iatrogenic effects, linked to the concept of treatment risks and individual sensitivity, must be distinguished from avoidable iatrogenic effects, very often associated with poor compliance with the drug insert (indications, warnings and precautions) or misuse of the treatments6. These errors are the responsibility not only of physicians, but also of other healthcare professionals and caregivers, as well as patients, especially in cases of improper use or self-prescription; the latter is more common, precisely because the agent is intended only for local application.

Mechanisms of systemic adverse effects following local ophthalmologic treatments

It has been estimated that only 1 to 5% of the active drug included in an eyedrop penetrates the eye7,8. This means that up to 80% of this active ingredient may reach the general circulation. The poor bioavailability of most topical eye treatments, due mainly to the complexity of eye penetration (figure 1), requires the use of high doses of the active ingredient within eye solutions, gels and ointments, with higher risks of systemic transfer. In addition, the volume of an eyedrop is about 50 µL, which is greater than the estimated 30 µL storage capacity within the tear meniscus at the border of the inferior eyelid7,9,10. About 20 µL, that is, 40% of a standard eyedrop does not touch the cornea, the principal route of penetration into the eye, but goes directly to the highly vascular tear drainage apparatus7.

Intraocular penetration routes for eyedrops and other solutions

More than 80% of the active ingredient that actually penetrates into the eye passes through the cornea11. Penetration depends upon complex mechanisms (figure 2). The corneal epithelium can be compared to a...
complex lipid membrane that carries non-ionized molecules, while the corneal stroma can be pictured as a watery structure more permeable to ionized molecules. As a result, the quantity of active ingredient passing through the cornea depends upon the relative balance between its ionized and non-ionized forms (dissociation coefficient) and between the lipid and water environments. Molecules in eyedrops may be absorbed through the lymphatic channels of the conjunctiva. Although this is unimportant in healthy eyes, inflammation and consequent conjunctival hyperemia may magnify its effect. The structure of the sclera allows greater permeability to hydrophilic molecules than the cornea and provides direct access to the vitreous cavity. However, the surrounding conjunctiva prevents all but a small part of the ingredient from entering the eye this way.

FACTORS REGULATING OCULAR BIOAVAILABILITY

Both the physical qualities of the medication and clinical state of the eye determine the bioavailability of the active ingredient. Many eyedrops and eyewashes are suspensions in which insoluble solid substances stimulate the corneal nerve endings during instillation, encouraging the eye to water and thereby reducing penetration of the active ingredient. Conversely, solutions are frequently salt-based and the active ingredient thus ionized; this limits penetration through the corneal epithelium (figure 1). The development of ophthalmic gels allows significant contact with the cornea and therefore increases ocular bioavailability for an equivalent concentration of active constituent. Other factors also determine transcorneal drug penetration: concentration of the active ingredient (correlated with contact time and absorption...
speed), its molecular weight (weak diffusion of large molecules, such as polypeptide antibiotics) and electrochemical properties (see box), level of binding to proteins contained in tears, and tear evaporation rate.\(^5,11,19\).

Drug metabolism in the corneal area can also affect bioavailability\(^10\). Some eye solutions are prodrugs that allow a better balance between transepithelial and trans-stromal passage. A classic example is dipivefrin, an epinephrine-derived ester that is 600 times more lipophilic than native epinephrine. After passing through the epithelium, dipivefrin is hydrolyzed by corneal esterases to yield epinephrine. The final bioavailability of this molecule is 17 times greater than that of an eyedrop that contains simple epinephrine and thus produces similar therapeutic properties in the eye with fewer undesirable cardiovascular effects\(^10,20,21\).

The addition of an antiseptic to eye solutions facilitates transcorneal drug penetration because its epithelial toxicity alters the ocular surface\(^22\). The clinical state of the eye also determines ocular pharmacokinetics. Transcorneal drug penetration is greater when the epithelium is altered or the corneal stroma is edematous\(^10,11\). For example, some antiviral eyedrops do not penetrate into the corneal stroma except in case of severe herpetic keratitis\(^23\). Similarly, the toxic effect of preservatives on the epithelium improves transcorneal penetration of the drug being preserved\(^22\). Conjunctival hyperemia and inflammation may also improve lymphatic passage\(^1\) and nonproductive absorption through the conjunctival vessels\(^10\). Similarly, increasing the protein concentration within the anterior chamber of the eye may modify the balance in the drug/protein complex, and either lead to a depot-type drug delivery system or increase active drug turnover\(^10\).

**ROUTES TO THE GENERAL CIRCULATION FOR ACTIVE INGREDIENTS**

The main route by which active ingredients pass into the systemic circulation is the tear drainage apparatus\(^10,14\). The excess 20µL from a standard eyedrop (see box) are rapidly pumped by the lacrimal puncta and pass into the lacrimal canaliculi and then successively into the lacrimal sac, the nasolacrimal duct and finally the nasal cavity. The active ingredients are there absorbed by the mucous vessels and distributed into the general circulation but avoid the first passage through the liver.\(^5,9,10\) A second drop, instilled immediately after the first, sends a still higher proportion of active ingredient into the nasal mucosa.

Absorption through the conjunctiva accounts for a part of the systemic passage of the drug, since its surface of exchange is about 17cm\(^2\) in comparison to approximately 1cm\(^2\) for the cornea. The rate of this so-called passive absorption depends on the biochemical properties of the product.\(^10\).

Finally, a portion of the active ingredient that penetrates into the eye may also pass into systemic circulation after absorption through the uveal vessels (iris or ciliary body) or by the aqueous humor outgoing flux (filtration through the trabecula into the episcleral vessels before reaching the general circulation\(^9\)).

**How to reduce adverse systemic effects of ophthalmic medications**

A few simple rules help limit the incidence of iatrogenic effects related to topical ophthalmic medication. It is necessary to comply with the contraindications, to use weak concentrations for the most fragile patients and to wait at least 5 to 10 minutes between 2 drops, to prevent increased passage through the tear drainage apparatus\(^5,9\). In addition, closing the inferior lacrimal punctum at or immediately after instillation increases contact time with the cornea and limits the passage of the active ingredient into the lacrimal channel\(^1,24,25\). This punctal occlusion is produced by pressing a finger into the area beneath the medial extremity surrounding the inferior eyelid. Reducing the drop volume to approximately 10µL may also help limit adverse systemic effects\(^9,26\).

Besides these practical measures, pharmacological progress has already helped to optimize some treatments. One illustration is prodrugs, which only become effective after ocular absorption (see the example of dipivefrin above). It is also sometimes possible to modify the molecule to limit its penetration at the site of maximum toxicity. Apraclonidine is a clonidine-derived local treatment for glaucoma and carries an NH\(^+\) group on its aromatic ring. This chemical modification limits the passage through the blood-brain barrier once the molecule has reached the general circulation\(^27\) and thus reduces the central adverse effects of apraclonidine, compared with a clonidine-based solution\(^28\).

Increased product contact time with the cornea is gained with gels, which thus provide clinical efficacy identical to that of solution for a lower concentration of active ingredient. Research programs are developing gels that can increase their viscosity after instillation, reacting to physicochemical tear properties, such as presence of bivalent ions, pH or temperature.\(^19,29\) Similarly, it is possible to use inserts in the conjunctival cul-de-sac to deliver the active ingredient at a minimal but effective and continuous dose. Beta-blockers as gels or inserts, for example, reduce cardiac frequency less than classic ocular solutions.\(^17,18,30,31\)

Some research teams are working on delivery systems based on ion exchange resins, cyclodextrins, nanoparticles, or liposomes.\(^19,29,32\). Again the common characte-
Systemic adverse effects of topical ophthalmic medications

Box
Adverse reactions associated with anti-glaucoma treatments

Most frequent or serious adverse reactions associated with topical β-blockers

Central nervous system effects (32% of serious adverse effects [SAE] associated with timolol)46
- Depression, anxiety, confusion, fatigue, hallucinations, dysarthria

Cardiac and vascular effects (30% of SAE associated with timolol)46
- Bradycardia, arrhythmia, heart failure, syncope, hypotension

Respiratory effects (15% of SAE associated with timolol)46
- Dyspnea, airway obstruction, pulmonary failure

Dermatologic effects (6% of SAE associated with timolol)46
- Maculopapular rash, alopecia, hives

Gastro-intestinal effects (3% of SAE associated with timolol)46
- Diarrhea, nausea, cramping

Miscellaneous
- Raynaud’s syndrome
- Sexual impotence, decrease of libido
- Arthropathy
- Modifications of serum lipid levels (increase of HDL-cholesterol)
- Reduced warning of diabetic hypoglycaemic crisis
- Exacerbation of myasthenia gravis or psoriasis
- Exacerbation of hyperthyroidism if stopped suddenly

At least theoretically, some adverse effects may be prevented by using β-blockers with a high level of cardioselectivity or with intrinsic sympathetic activity3,37-39,47

Most frequent or serious adverse reactions associated with topical adrenergic anti-glaucoma treatments

Rarely serious but frequent27,48
- Dry mouth, dry nose (30% of patients)
- Fatigue, mild sedation,
- Headache
- Systemic hypotension and bradycardia (low risk)
- Thymic disorders - Bradycardia, hypothermia and apnea in infants < 1 year-old (particularly with brimonidine?)
- Drug interaction with drugs that block the uptake of epinephrine or norepinephrine or that inhibit monoamine oxidase

Adverse reactions associated with topical carbonic anhydrase inhibitors

Rarely serious49
- Bitter taste
- Gastrointestinal disorders (during the first days of treatment)
- Headache, vertigo, paresthesia
- Allergic reactions (carbonic anhydrase inhibitors are sulfa-related products) hives, neutropenia, theoretical risk of medullar aplasia or cutaneous bullae

Adverse reactions associated with topical prostaglandin analogues

Rare, compared with frequent local adverse effects50
- Headache and migraine
- Recurrence of infection with herpes simplex or varicella-zoster viruses (extraocular reactivations have been rarely reported)
- Sometimes dry mouth, muscle pain, bitter taste, cutaneous allergy

At least theoretically
- Risk of delivery during the third trimester
- Risk of exacerbation of steroid-dependant asthma
Adverse reactions associated with topical parasympathomimetic drugs

In case of overdosage

- Nausea, vomiting, salivation, sweat
- Bradycardia
- Hallucinations, coma

Anti-inflammatory and anti-infectious topical treatments

Adverse reactions associated with topical steroids

Eye lotions or ointments

- Decrease in level of plasmatic cortisol after frequent instillations of dexamethasone 0.1% during several days\textsuperscript{51,54} but modidies neither the circadian cycle of cortisol secretion\textsuperscript{51} nor corticotropic regulation\textsuperscript{52}.
- Iatrogenic hypercorticism is very rare owing to the very frequent use of topical steroids in ophthalmology. Some cases have been reported \textsuperscript{2,55,56}
- Hypocorticism induced by steroid deprivation when reducing dosage is rare (progressive tapering of topical steroids is advisable to avoid exacerbation of the inflammation)

Peri-ocular injections

- One sub-Tenon’s injection of dexamethasone 4 mg induces a systemic steroid effect estimated at about 2/3 of that observed after an oral dosage of 7.5 mg of dexamethasone (prednisone-equivalent: 60mg)\textsuperscript{57}

Adverse reactions associated with topical nonsteroid anti-inflammatory drugs (NSAIDS)

Rarely

- Cutaneous allergy (pruritus, redness) or photosensitivity
- Risk of airway-obstruction in NSAIDS-sensitized patients\textsuperscript{58,59}

Adverse reactions associated with topical antibiotics and antivirals

No adverse affect with the exception of:

- Chloramphenicol
  - Immuno-allergic hematological accidents. See discussion in\textsuperscript{3,60,61}
- Quinolones
  - Bitter taste
- Rifampicine
  - Risk of asthma or anaphylactic reaction if sensitization to sulfites
- Association of polymyxine B and neomycine
  - Diffuse cutaneous allergy

No systemic adverse effect with topical antivirals

Mydriatic and cycloplegic agents

Adverse reactions associated with topical parasympatholytic muscarinic mydriatics

In infants and children Pseudo-ocular syndrome

In male elderly (particularly in case of a prostate blockage)

- Acute urinary retention

Overdosage (multiple instillations or accidental ingestion)

- More frequent in infants, children, elderly and patients with neurological disorders (particularly Down’s syndrome)
  - Dryness of the skin and mouth, dermal flushing, fever, irritability
  - Confusional psychosis, ataxia, hallucinations, convulsion, coma
  - Tachycardia with normal blood pressure, arrhythmia, death
  - « Hot as a hare, red as a beet, dry as a bone, blind as a bat, mad as a hatter »

Note 1: Overdoses may be treated with physostigmine (0.02mg/kg of body weight);
Note 2: These drugs pass through the placenta and the breast milk, thus they should be used cautiously in pregnant women and nursing mothers

Adverse reactions associated with topical adrenergic mydriatics or adrenergic contained in some prescription-over-the-counter (used for eye discomfort)

- Tachycardia, trembling, headache
- If overdosage (more frequent in infants children and elderly)
- Acute hypertension with cardio-vascular and neurological complications\textsuperscript{62}
- Ventricular arrhythmia, angina, death
Systemic adverse effects of topical ophthalmic medications

The principal adverse effects after instillation of ophthalmic solutions, ointments and gels are summarized in the box. They are not exhaustive but only indicate the most frequent and most severe systemic adverse effects in clinical practice. Two examples are particularly representative: β-blockers because of their toxicity on cardiovascular and respiratory systems and mydriatics since they are used routinely to examine the fundus oculi.

For the 800,000 glaucoma patients in France and 2.5 million in the USA, β-blockers are incontestably the most frequent cause of iatrogenic effects secondary to ophthalmic treatment. The risk is increased by possible drug interactions, including overdosage, with the systemic treatments given to these patients, mostly elderly; β-blockers in eyedrops pass into the systemic circulation at a high rate, since 2 drops per day leads to stimulation of systemic β-receptors similar to that observed with oral treatment. These topical anti-glaucoma treatments reduce heart rate and expiratory outflow significantly, especially in high-risk patients. An analysis of data from the United States food and drug administration and the National registry of drug-induced ocular side effects showed an incidence of serious or lethal β-blocker-related adverse effects of respectively 1/100,000 and 1/1,000,000 retail dispensed prescriptions between 1978 and 1985. These results probably underestimate the real figures, because of the lack of exact diagnosis in many cases of iatrogenic disease and the underreporting of drug-related serious adverse effects in databases. The iatrogenic risks of β-blockers should not, however, make us forget that uncontrolled glaucoma causes blindness.

Mydriatic drops are applied either as a treatment, for example in inflammatory ocular diseases to prevent synechiae between the iris and the lens, or as a diagnostic tool, for access to the eye fundus. Despite their inoffensive appearance and daily use, these drugs have various potential adverse effects, including pseudo-obstructive syndrome in children, acute retention of urine in patients with prostatic adenoma and severe cardiovascular and neurological disorders. It is thus advisable to avoid the simultaneous use of parasympathomimetic and adrenergic mydriatics in fragile patients, children or elderly, because this risks an increase in systemic adverse effects. Finally, accidental oral absorption of mydriatic drugs, notably with young children, exposes them to a risk of severe neurological complications. It is therefore wise to advise parents to keep eyedrops out of the reach of children.

This brief review of the adverse effects related to topical ophthalmic agents demonstrates the need for closer examination of new symptoms that may be drug-related. Patients often tend not to consider eyedrops as potentially toxic and not to spontaneously mention them to their doctor. Physicians must systematically ask patients about eye treatment during the etiological investigation of any new symptom that might be iatrogenic, and above all, when prescribing new drugs, to prevent possible drug interactions.

Références
