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Dangers in the use of systemic and local drugs expressed in eye disorders – a literature review

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Abstract

Introduction and purpose

Medications that have been available for many years are commonly used to treat various illnesses. However, nearly all of them can also have toxic effects on other organs, including the eyes, in addition to their therapeutic benefits. In this review, we discuss chosen drug-induced eye disorders, their specific clinical characteristics, and the mechanisms by which certain drugs can damage the ocular system. Isotretinoin and certain chemotherapy drugs are known to contribute to the development of dry eye syndrome. Atimalarial drugs, amiodarone, nonsteroidal anti-inflammatory drugs and chlorpromazine cause the formation of corneal deposits. Prolonged use of glucocorticoids leads to the development of characteristic posterior subcapsular cataracts. The development of cataracts can also be caused by the use of antipsychotic medications. Paradoxically, drugs used topically to treat glaucoma or other eye diseases may trigger an acute attack of angle-closure glaucoma.

Materials and methods

The methodology for conducting literature search involved utilizing medical subject headings terms to explore PubMed. Search terms included: “drug-induced dry eye disease”, “drug-induced cataract”, “drug-induced glaucoma”, “drug-induced corneal damage”.

Conclusions

Educating patients about the potential ocular side effects of newly introduced treatment is crucial so that they can quickly consult an ophthalmologist if symptoms occur. Adjusting the dosage or discontinuing the drug may alleviate ocular symptoms, but these changes must be considered in light of the overall risk posed by the underlying disease. Every treatment should aim to offer the patient maximum benefits while minimizing any adverse impact on their quality of life.

Keywords: “drug-induced dry eye disease”, “drug-induced cataract”, “drug-induced glaucoma”, “drug-induced corneal damage”.

Introduction

Medical advancements introduce new types of medications that can stop the progression of diseases or prevent their detrimental effects. [1] Systemically administered drugs may affect the eye, leading to various abnormalities. The same mechanisms by which drugs control cellular processes to inhibit disease can also cause damage in other parts of the body. Toxic reactions of systemic therapies to organs are easily detectable in the eye. Pharmacological therapy for various diseases can lead to numerous eye conditions, such as dry eye syndrome, inflammation of different parts of the eye, cataracts, and glaucoma. Medications can also cause visual field disturbances or blurred vision, often resulting in damage to the retina or visual nerves, and may even lead to blindness. [2,3]

Additional topical medications in drop form may come into contact with the ocular surface and cornea, such as anti-inflammatory drugs, local anesthetics, glaucoma medications, fluoroquinolones, and preservatives. [4]

Objective of the work

The aim of this review is to focus on the adverse effects of some systemic therapies manifesting themselves in eye diseases.

Description of the state of knowledge

Drug-induced dry eye disease

Dry eye syndrome, also known as keratoconjunctivitis sicca, is a prevalent eye condition affecting one in seven individuals aged 48 and older. It results from a disruption in the tear film formation, either due to abnormal tear secretion or an irregular composition of the tear film. Maintaining the correct parameters of the tear film is essential for proper vision, as it, along with the cornea, forms the optical window that allows light to focus on the retina. It also participates in moisturizing the eye and removing impurities from its surface. Symptoms of dry eye syndrome include burning sensations in the eyes, a feeling of a foreign body under the eyelids, blurred vision, and even pain. As a result, patients experience a reduced quality of life. [5] Risk factors associated with this syndrome include advanced age, female sex, exposure to viral environments, autoimmune diseases, and systemic treatments. [6]

- **Systemic isotretinoin**

  Isotretinoin, also known as 13-cis-retinoic acid, is a vitamin A analogue frequently used to treat acne vulgaris. Its primary mechanism involves causing atrophy of the sebaceous glands. Additionally, it reduces and alters the structure of the meibomian glands in the eyelids, which produce the lipids and proteins that prevent tear evaporation. [1]

  Tanriverdi et al. conducted a study on 88 patients who underwent systemic isotretinoin treatment for 4-8 months. The study aimed to analyze changes in the meibomian glands and tear film layer in these patients. The following procedures were performed: a general ophthalmological examination, assessment of non-invasive and invasive tear break-up time, corneal staining, and evaluation of eyelid margin abnormalities. These tests were conducted before, during, and after the treatment. The study found that the appearance and quality of the meibomian glands, tear film layer, and ocular surface disease index (OSDI) scores worsened in patients taking systemic isotretinoin during treatment. Although these results gradually began to improve after discontinuing the medication, they still remained below baseline levels even 12 months post-treatment. [7]

  Another study similarly evaluated alterations in the ocular surface and tear film function in patients undergoing systemic isotretinoin treatment. The research involved 120 eyes from 60 patients. Each patient underwent a standard ophthalmological assessment, including a biomicroscopic examination of the meibomian glands, measurement of tear film breakup time (BUT), and subjective evaluations using the OSDI questionnaire. The study's significant differences in the OSDI score, alterations in the appearance of the meibomian glands, and the average BUT value led to the conclusion that systemic isotretinoin treatment could induce changes in the tear film and dry eye symptoms.

The OSDI questionnaire, which does not necessitate a specialized ophthalmological examination, stands as the simplest test for evaluating the severity of dry eye syndrome in this patient group. [8]

In a study conducted by Koca et al., a comparison was made between patients with acne vulgaris and healthy volunteers based on all the aforementioned studies. The results of the study suggest a higher susceptibility to dry eye among individuals with acne vulgaris, as indicated by both subjective assessments using the OSDI questionnaire and objective tests such as non-invasive tear film breakup or morphological evaluations of the meibomian glands. [9]

Given the prevalence of acne vulgaris and the effectiveness of isotretinoin treatment, dermatologists should advise patients taking isotretinoin systemically to use over-the-counter lubricating eye drops. If you experience any disturbing symptoms of blepharitis, you should consult an ophthalmologist. [1]

- **Cancer therapy**

  Chemotherapy drugs commonly used to treat various cancers may cause symptoms of dry eye syndrome. [1] The effects of systemic therapy with taxanes, paclitaxel and docetaxel on the cerebral organ were investigated. During therapy, 1.1% of patients encountered ophthalmic side effects, with the most prevalent being meibomian gland dysfunction resulting in sicca syndrome. Additional side effects comprised cystoid macular edema, tubular obstruction, as well as diplopia, blepharitis, and eyelash loss. While these occurrences are infrequent, these conditions can be effectively managed with targeted ophthalmic therapies, allowing patients to continue taxane therapy, thereby extending their lives. [10]

  Aromatase inhibitors (AIs) are hormonal therapy supplements recommended for women diagnosed with hormone receptor-positive breast cancer or ovarian cancer. [1] In a retrospective study of patients receiving AI therapy for the aforementioned conditions, the majority reported experiencing blurred vision, while less than one-third reported irritation or a foreign body sensation. Additional symptoms included redness, tearing, and photosensitivity. Over 70% of individuals presented with blepharitis, and 10% were diagnosed with dry eye syndrome. This study suggests that aromatase inhibitors might play a role in dry eye symptomatology. [11]

  In another clinical study, the incidence of dry eye symptoms in breast cancer patients treated with AI was 64%. Increased tear osmolarity and atrophy of the meibomian glands were demonstrated in this group of patients. [12]

Drug-induced corneal damage

Various drugs, whether administered topically, often as drops, or systemically, can cause corneal damage. The presentation varies significantly depending on the drug type, concentration, duration of use, and other factors. Potential effects include opacification of the corneal stroma, changes in the corneal epithelium characterized by deposits that may manifest as swirl keratopathy (also known as vortex or verticillata keratopathy), punctate keratopathy, or crystalline deposits. [13,14]

Most drugs that damage the cornea epithelium are both amphiphilic and cationic. Due to their hydrophobic ring structure and hydrophilic side chain with a charged cationic amino group, they cause the formation of a swirl pattern of deposits. This phenomenon, called phospholipidosis, occurs because of the accumulation of phospholipids. These include antimalarials drugs and amiodarone. [13,14]

- **Antimalarial drugs**
  Chloroquine has been recognized for a long time to cause corneal deposits. When examined with dilated pupils, up to 95% of patients taking chloroquine exhibit these changes. [15] Other antimalarial drugs that can cause side effects include hydroxychloroquine, mepacrine, tafenoquine, and amodiaquine. The deposits most often are first deposited in dots and then merge into curved, linear, irregular whorls. Amodiaquine causes keratopathy characterized by "a distinct swirl of blue-gray opacities." [13] A significant study on tafenoquine's safety, tolerability, and effectiveness for malaria prevention found that mild vortex keratopathy was observed in up to 93% of patients taking the drug. This condition persisted for up to a year after stopping treatment but did not affect visual acuity. [16] Chloroquine can also cause bull's eye maculopathy due to its accumulation in the retinal pigment epithelium, leading to retinal damage and potentially resulting in blindness. [17]

- **Amiodarone**
  Amiodarone, a commonly used antiarrhythmic medication, works by blocking potassium channels. [13] 95% of patients showed corneal epithelial abnormalities upon slit lamp examination. The primary symptom is bilateral vortex keratopathy, characterized by deposits arranged in a vortex pattern. These deposits typically manifest within a short timeframe, approximately two weeks after initiating amiodarone therapy. Further examination using transmission electron microscopy reveals lipid deposits within intracytoplasmic inclusions, observable in the conjunctiva and lens. [18,19] In approximately half of the patients, lens opacities may develop due to deposits. However, these deposits do not typically necessitate discontinuation of amiodarone therapy, as visual acuity remains stable in the majority of cases. These changes typically resolve within 3 to 20 months after stopping treatment. Additionally, other ocular complications such as retinopathy and optic neuropathy associated with amiodarone treatment are rarely reported. [20]

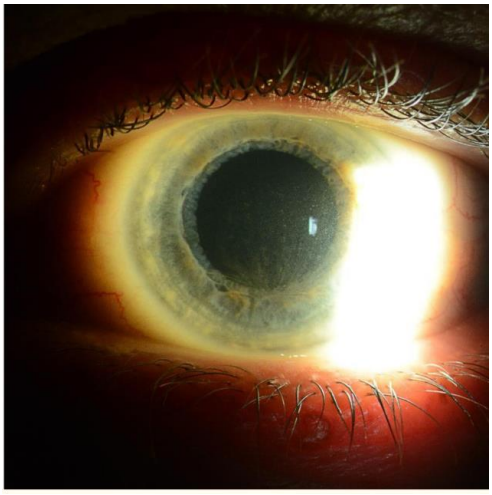

Figure 1.
Amiodarone-induced vortex keratopathy. [19]

- **Nonsteroidal anti-inflammatory drugs**
  Several cases of vortex keratopathy, described as intracellular deposits in the epithelium, have been reported following the use of nonsteroidal anti-inflammatory drugs. These deposits can form rapidly, sometimes within a few days of starting high-dose treatment, but they disappear just as quickly once the treatment is discontinued. [21] Corneal surface deposits related to naproxen treatment appeared as parallel lines resembling a fingerprint and cleared up quickly after the treatment was discontinued. [22]

- **Chlorpromazine**
  Chlorpromazine is an antipsychotic drug used in schizophrenia and other psychoses. [13] Case reports of patients receiving high doses of the drug over an extended period have documented skin discoloration and ocular manifestations, including scattered deposits in the corneal stroma and endothelium, anterior subcapsular cataracts, and abnormal pigmentation of the conjunctiva, eyelids, and even the retina. [13,23,24] Currently, it is not a first-line drug, so such side effects are rarely observed. [24]

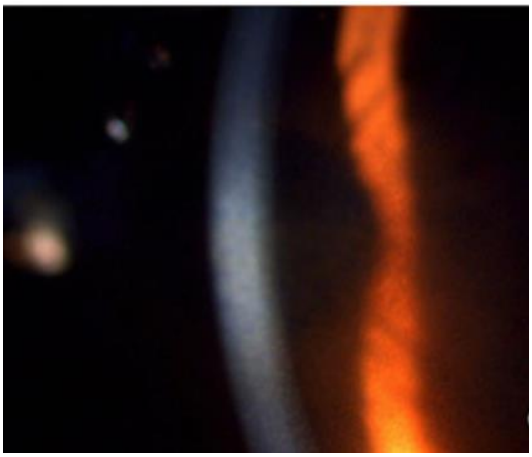

Figure 2
Numerous fine deposits on the corneal surface are visible under the slit lamp. [23]

Drug-induced cataract

Cataract is an eye disease primarily affecting older individuals and progressing with age, characterized by clouding of the lens that leads to a loss of visual acuity. The development of cataracts can be influenced by various medications. [25]

- **Glucocorticoids**
  Glucocorticoids are commonly used to treat various conditions, such as asthma and for immunosuppression. One complication of steroid therapy is the development of cataracts. A study on chicken embryos revealed that administering these drugs induced cataracts in over 90% of cases, likely due to oxidative stress. [26] The most common type of cataract in patients taking chronic glucocorticoids is a posterior subcapsular cataract. This typically affects young people, including preschool children, who have not yet developed age-related cataracts. [27] There have been cases where the use of topical intranasal steroids has led to the rapid development of bilateral posterior subcapsular cataracts. [28,29]

A clinical study assessing the risk of posterior subcapsular and cortical cataracts found that the increased risk of these cataracts occurred only in individuals using both inhaled and oral steroids. [30] The primary treatment method is cataract surgery, which carries a higher risk of complications compared to standard age-related cataract removal and thus should be performed by an experienced surgeon. [27]

- **Antipsychotic**
  First-generation antipsychotic drugs, such as chlorpromazine, are still used in some countries because of their low cost. Gowda et al. described a case series of 7 patients taking chlorpromazine who developed ocular complications. After various durations of chlorpromazine use, they developed anterior capsular cataracts and corneal endothelial deposits in both eyes, leading to visual disturbances. [31] Due to concerns about the newer group of atypical antipsychotics, a study was conducted to compare the two generations. Patients were divided into two groups: those using typical antipsychotic drugs and those using atypical drugs. Cataracts were found in 33% of all patients, with a higher incidence in the first group. However, among patients taking atypical drugs, cataracts were also present in 18% of cases. The main type observed was anterior capsule cataract. [32]

Ocular drug-induced glaucoma

Glaucoma, characterized by increased intraocular pressure and secondary optic neuropathy. It can be categorized into closed-angle and open-angle glaucoma based on the condition of the iris-corneal angle. Glaucoma may arise from the use of specific medications either directly applied to the eye. If left untreated, drug-induced glaucoma can result in vision loss. [33] Most often, drugs that stimulate the sympathetic system or inhibit the parasympathetic system cause pupil dilation, leading to a narrowing of the filtration angle, difficulties in the circulation of aqueous humor and an increase in intraocular pressure, known as an acute attack of angle-closure glaucoma. [34]

- **Antiglaucoma drugs**
  Topically applied antiglaucoma drugs in ophthalmology, such as pilocarpine, cholinergic agents, and local anticholinesterases, may paradoxically induce an acute attack of glaucoma by moving the iris-lens apparatus forward and closing the filtration angle. [35] Another glaucoma drug, latanoprost, may work in a similar way. While its primary function is to increase uveoscleral flow, it can cause swelling of the ciliary body, leading to the closure of the filtration angle. [36]

- **Mydriatics**
  To perform a fundus examination, the pupils must be dilated by the topical administration of anticholinergic drugs such as atropine or cycloplegic agents like tropicamide. [33] Various studies have shown conflicting evidence about their effect on acute glaucoma attacks. A study involving individuals with a narrow iridocorneal angle reported that using tropicamide to dilate the pupil can significantly increase intraocular pressure.

While, a large systematic review of studies published in the twentieth century shows that the risk associated with using tropicamide alone is nearly zero. This procedure is safe for all patients who require a thorough examination of the retina. [38]

- **Botulinum toxin**
  Botulinum neurotoxin targets the neuromuscular junctions of skeletal muscles, resulting in temporary muscle weakness by blocking the release of acetylcholine. [33] A case is described of a patient who received a series of botulinum toxin injections to treat blepharospasm. Due to the drug's diffusion into the area of the ciliary ganglion, it paralyzed the pupillary sphincter muscle. The resulting strong and constant pupil dilation led to an acute attack of angle-closure glaucoma. [39]

Conclusion

Scientific evidence indicates that many systemic and topically therapeutic agents are linked to alterations in the ocular apparatus, including symptoms of dry eye, corneal deposits, cataract and glaucoma. Physicians should remain vigilant and educate patients about potential drug-induced ocular disorders. It is usually not necessary to modify or discontinue therapy, but you may find that changing your dose will reduce possible side effects. Patients may not be aware of their predisposition to complications, such as individuals with a narrow iridocorneal angle who may inadvertently use medications that precipitate an acute glaucoma attack. If patients experience concerning eye symptoms after initiating a new therapy, they should promptly seek evaluation by an ophthalmologist. If there's a sudden decline in visual acuity or onset of blindness following medication intake, seeking immediate attention at an ophthalmologist's emergency department is crucial. Conditions like an acute glaucoma attack can potentially result in irreversible vision loss.

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Software, validation, formal analysis, investigation, resources, writing original draft preparation: Paweł Ziemba, Aleksandra Janocha,
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