
SIDE EFFECTS OF GLAUCOMA MEDICATIONS

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ABSTRACT

The safety profile of the different glaucoma medications is an important issue when initiating therapy in glaucomatous patients. The decision on which medication to prescribe depends not only on the type of glaucoma, but also on the patient's medical history and needs a detailed knowledge of the potential side-effects of each medication. Medications side effects may be an important cause of non adherence for the individual patient

The properties of the drugs, the composition of the glaucoma eyedrops and the dynamics of ocular drug absorption must be considered. The ocular surface changes induced by long-term antiglaucomatous treatment especially by their preservatives are a major cause of intolerance or poor tolerance to glaucoma eyedrops. Moreover topically applied ophthalmic medications can attain sufficient serum levels through absorption into conjunctival and nasal mucosas to have systemic effects and to potentially interact with other drugs.

Then this presentation will deal with the ocular and systemic side-effects which can be encountered with the different classes of the currently available glaucoma topical medications.

Recommendations than can be applied to reduce both frequency and severity of side-effects of glaucoma medications will be stressed on. Concurrently patients should be fully informed not only about their disease but also the medications they used and what side-effects they have to expect.

RÉSUMÉ

Le profil d'innocuité des différentes médicaments antiglaucomateuses est un paramètre déterminant au moment de l'instauration d'un traitement chez tout patient glaucomateux. Le choix des médicaments dépend non seulement du type de glaucome, mais aussi des antécédents médicaux de chaque patient et implique une connaissance détaillée des effets secondaires potentiels de chaque médication. La survenue d'effets secondaires liés aux médicaments est une cause potentielle importante de non observance du patient glaucomateux à son traitement.

Les propriétés des médicaments, la composition des collyres et la pharmacocinétique de l'absorption des médicaments oculaires sont à considérer en 1^{er} lieu. Les modifications des tissus de surface induites par les traitements au long terme mais surtout par leur agent conservateur représentent une cause majeure d'intolérance ou de mauvaise tolérance des collyres administrés. En outre, les médicaments locaux peuvent atteindre, via une absorption par les muqueuses conjonctivales et nasales, des taux sériques suffisants pour induire des réactions systémiques secondaires et potentiellement interagir avec d'autres médicaments.

Après ce rappel général, cet article passe en revue les effets secondaires oculaires et systémiques susceptibles d'être observés avec les différentes classes pharmacologiques des médicaments actuellement prescrites.

Les recommandations et précautions à appliquer pour réduire à la fois la fréquence et la gravité des effets secondaires liés aux collyres antiglaucomateux sont développées. Il est indispensable que les patients soient informés non seulement sur leur maladie, mais aussi sur les médicaments qu'ils reçoivent et la nature des effets secondaires auxquels ils doivent s'attendre.

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INTRODUCTION

In addition to their mechanism of action, effectiveness, cost and convenience, the safety of the different glaucoma medications is a major issue both when initiating and continuing therapy in glaucomatous patients for the long term (26).

Medical treatment has been proven to be an effective way of controlling glaucoma, Compliance is of major importance to get the full, potential protective effects against visual field defects (67). Among other considerations, tolerance of topical treatment is a crucial issue and medications side effects may be, among other barriers, an important cause of non adherence for the individual patient (26, 67).

Glaucoma drug side effects are frequent but their definite frequency is probably underestimated (8). Based on a mail survey including a large representative French sample, J.P. Nordmann and coworkers found that two-thirds of the questioned patients had side effects but the vision related Quality of Life (QoL) of patients with topical antiglaucomatous drug side effects was lower with poor treatment satisfaction, poorer compliance and additional visits to their ophthalmologist (56).

Side effects of glaucoma medications can be categorized in 3 groups. In addition to well-known ocular and systemic side effects, drug-drug interactions corresponding to potential interactions of glaucoma medications with other systemic drugs are the third component of this concern and beyond the scope of this review (33).

Some preliminary general considerations are crucial to clarify the nature itself of the glaucoma drug side effects.

1. PRINCIPLES OF OCULAR THERAPEUTICS

The chief advantages of topical application which is the most common route of administration are convenience, simplicity, non-invasive nature, and the patient's ability to self administer. The properties of drugs include efficacy, potency, and therapeutic index which corresponds to the ratio comparing the efficacy of a drug to the magnitude of adverse side effects. Receptor selectivity, corneal penetration, protein/melanin

binding and pharmacokinetics are some other important drug properties to be considered (65). Except for the proper active ingredient, each topical medication contains excipients, represented by preservative, buffers, viscosity agents, vehicle and so on, to make the drug more effective. The pH of a formulation not only affects the patient's comfort, but also corneal penetration and ocular absorption. Its tonicity is impacted by the active drug, preservative and vehicle. Agents such as various forms of methylcellulose, polycarbophil and polyvinyl alcohol, increase corneal contact time by increasing viscosity, bioavailability of the drug and delaying the phenomenon of washout. Preservatives are added to multidose ocular medications in order to minimize microbial contamination and prevent from decomposition of the active drug. Among preservatives, benzalkonium chloride (BAC) is the most frequently used and acts non-specifically on cells it encounters. It is stable and has a long shelf life (65).

The large majority of topical glaucoma medications are formulated as aqueous solutions, which are easiest for patients to administer, and generally cause the least amount of blurred vision upon instillation. The downside of this formulation is that aqueous solution quickly drains into the lacrimal system. Moreover, pharmacokinetic studies have shown that only 1% to 7% of an instilled dose penetrates the cornea and that the maximal tear film concentration is achieved with a 20 μ l drop. Any volume in excess of this amount simply overslows the eye or will drain in the nasolacrimal duct.

Finally the flow of tears tends to decrease with age and to increase on irritation, as with the application of ocular medications. As a consequence, the drug concentration in the eye as well as the absorption into the cornea decreases through a dilution effect (65).

Another major point to be stressed on concerns the

2. OCULAR SURFACE CHANGES INDUCED BY ANTIGLAUCOMA MEDICATIONS

The dry-eye condition is an inflammatory disease of the conjunctiva that may predispose toward conjunctival hyper-reactivity to topical drugs. Twenty years ago, it was shown for the

first time that the dry-eye condition could be caused by long-term antiglaucomatous therapy and especially by their preservative (13,32). Since that time, it has been extensively demonstrated that preservatives decrease the stability of the precorneal tear film through a detergent effect on the lipid layer and a decrease of the density of goblet cells in the conjunctival epithelium. According to their nature, they induce an allergic reaction but more frequently a cytotoxic reaction (10, 16, 51, 55, 77, 82). These side effects are dose dependent and increase with the frequency of instillations. Moreover, these changes have been demonstrated to represent a significant risk factor for failure of filtration surgery (11).

Subtle signs of ocular toxicity, such as reduced Break up Time, Superficial punctate Keratitis (SPK) indicate chronic cell injury that can have long term consequences (4). To a greater extent, the long term use of these agents can result in a form of conjunctival scarring known as drug induced pemphigoid (34). In impression cytology specimens, C. Baudouin and co-workers have found abnormal expression of inflammatory and allergy markers (HLA-DR antigens and receptors to IgE CD23) in chronically treated patients without clinical inflammation and confirmed that the toxic or immunoinflammatory effect on the ocular surface is to a large part caused by BAC (3, 4, 61, 63). These changes could probably also concern the trabeculum structures (4). In a recent study dealing with the study of the inflammatory profile and mucin detection of conjunctival specimens analyzed by flow cytometry and in agreement with others papers, they also concluded that the use of long-term preserved beta-blockers in glaucoma patients was associated with a direct subclinical epithelial toxicity in the conjunctiva comparatively with drops that did not contain BAC (3, 4, 47). In a large retrospective epidemiological study survey, Pisella, Poulouen and Baudouin further found that symptoms of foreign body sensation, dry eye sensation, tearing and eyelid itching as well as signs of ocular toxicity to preservatives, were significantly more common with preservatives eye-drops than without and that most adverse reactions induced by preservative glaucoma medication were dose-dependent and reversible after removing preservatives (62, 63).

Indomethacin 0.1% and fluorometholone 0.1% eyedrops could be effective in reducing sub-clinical conjunctival inflammation before filtering surgery (5).

Among other practical implications, these findings involve that adding another medication to an already complex regimen is associated with an increase of the contact time of conjunctival tissues to preservatives (53).

Meanwhile and except for beta-blockers, all commercially currently available antiglaucoma eyedrops contain BAC with different dosages.

3. ALLERGY TO GLAUCOMA MEDICATIONS

By inducing discomfort and inconvenience, repeated allergies represent a load to patients and are a factor of discouraging from compliance. Ocular medication allergy typically causes well known symptoms of pruritus, red eye, tearing, follicular conjunctival reaction, contact dermatitis of the eyelids, occasionally chemosis or lid swelling. The patient with evidence of ocular allergy on multiple medications represents a particularly difficult situation to deal with. The preservative toxicity has been previously discussed (34, 62). Some patients develop allergy to the preservatives benzalkonium chloride or EDTA in the preparation and/or also to any ophthalmic preparation. Dipivefrin, brimonidine, apraclonidine, dorzolamide, and brinzolamide are the most frequent offending glaucoma medications. On the other hand, adrenergic antagonists and miotics as well as prostaglandin analogs cause a lower rate of ocular allergy (39, 65).

4. SYSTEMIC ABSORPTION OF GLAUCOMA MEDICATIONS

Finally, topically ophthalmic medications can reach sufficient levels through absorption into conjunctival, nasal, oropharyngeal, and gastrointestinal mucosa to have systemic effects and to interact with other drugs (65). In fact, topical administration to the eye has been linked to intravenous rather than oral administration because a high percentage of the absorbed drug avoids hepatic first-pass metabolism. The induced systemic side effects and interactions are

especially dangerous because the majority of glaucomatous patients are elderly, may have multiple systemic illnesses and are taking many other medications (78). When systemically absorbed, many antiglaucoma medications affect the sympathetic and parasympathetic nervous system of patients and can cause cardiovascular or respiratory toxicity. There is a considerable variation in the degree of systemic absorption between individuals (65). Although very unfrequent, some patients can develop hypersensitivity and manifest systemic side effects to all glaucoma medications they have been prescribed whatever the concentration and the frequency.

MEDICATIONS OPTIONS AND THEIR SIDE EFFECTS

The currently available therapeutic options to treat glaucoma patients include five different drug classes: the alpha-adrenergic agonists, the beta-adrenergic antagonists, the parasympathomimetics or cholinergic agents, the carbonic anhydrase inhibitors, and the prostaglandin analogs. Whatever their pharmacological class, every single currently available medication has potential ocular and/or systemic adverse effects.

Adverse effects associated with glaucoma medications can be of immediate onset or can occur much later. Rechallenge allows to firmly confirm the causality of the medication in the incriminated adverse effects but is ethically impossible or in the practice only possible in a minority of the cases.

Prior to 1978, only 3 classes of medications were available for the treatment of chronic glaucoma (65, 70).

Among them, topical miotics were generally effective but, among their numerous and mostly ocular side effects, they were, in most cases, poorly tolerated because of induced myopia, poor night vision, fluctuating vision, or headache (*Table 1*).

Topical epinephrine or its analogs were useful, but frequently associated with rebound hyperemia, allergic blepharoconjunctivitis but also with tachycardia, nervousness, elevated blood pressure (*Table 2*).

Table 1: Major ocular and systemic side effects of parasympathomimetics (cholinergic drugs): **direct-acting** (pilocarpine) and **indirect-acting agents** (demecarium bromide, ecothiophate bromide, physostigmine)

OCULAR SIDE EFFECTS
<i>Direct and indirect-acting agents</i>
Stinging, burning, lacrimation
Miosis, poor night vision
Pseudomyopia (fluctuating vision)
Browache
Retinal detachment
Ciliary spasm
Increased pupillary block
Increased permeability of the aqueous-blood barrier
<i>Indirect-acting agents</i>
Conjunctival thickening
Iris cysts
Cataract
SYSTEMIC SIDE EFFECTS
<i>Direct and indirect-acting agents</i>
Intestinal cramps
Diarrhea
Bronchospasm
<i>Indirect-acting agents</i>
Cardiac irregularities

Oral carbonic anhydrase inhibitors such as acetazolamide were also very effective but they induced numerous and unacceptable side effects such as lethargy, malaise-anorexia-depression, fatigue, gastrointestinal disturbances, hypokalemia, and renal lithiasis. Roughly two-thirds of patients complained of paresthesias, but that generally improved with time. Sulfa-allergic urticaria but especially Stevens-Johnson syndrome, and aplastic anemia were rare but severe problems (Table 3).

Since 1980, many new alternatives to treat chronic glaucoma are at the disposal of the clinicians.

BETA-BLOCKING AGENTS OR BETA-ADRENERGIC ANTAGONISTS

Beta-adrenergic antagonists revolutionized the medical therapy of glaucoma at the end of the '70's. For the first time a topical medication was available that had few visual or ocular side effects. Over 20 years later, beta-blockers are still among the most prescribed antiglaucoma drugs all over the world and remain a first choice treatment. However the initial hope of a side effect-free class of drugs has turned out to be

Table 2: Summary of the most frequent side effects induced by non-selective adrenergic agonists (dipivefrin 0.1%; epinephrine 0.25-2.0%).

OCULAR SIDE EFFECTS
Conjunctival rebound hyperemia
Conjunctival pigmented deposits
Allergic blepharoconjunctivitis

SYSTEMIC SIDE EFFECTS
Tachycardia
Arrhythmia
Elevated blood pressure

Table 3: Major side effects of systemic carbonic anhydrase inhibitors (acetazolamide, dichlorphenamide)

Paresthesias (2/3)
Gastrointestinal symptoms and disturbances: nausea, vomiting, diarrhoea, gastralgia
Malaise- anorexia-depression
Lethargy
Fatigue
Taste alteration: Tinnitus, hearing dysfunction
Decreased libido
Kidney stones
Blood dyscrasia
Metabolic acidosis
Electrolytic imbalance (hypokaliemia)

Adverse reaction to sulfonamide derivatives
Anaphylaxis
Fever rash, multiform erythema
Stevens-Johnson syndrome
Bone-marrow depression
Thrombocytopenic purpura
Hemolytic anemia
Leukopenia, pancytopenia, agranulocytosis

erroneous and has caused it to fall out of favour as the only first choice drug in glaucoma management in recent years. Although the topical side effects of the beta-blocking eye drops were relatively unfrequent, their long-term systemic adverse effects have been shown to be numerous, sometimes severe, and, yet, frequent subtle. There are four FDA-approved non-selective and one β_1 -adrenergic selective β -blocking agents. They induce a 20-25% IOP decrease, can be used once or twice daily and demonstrate a very favourable ocular tolerability, a low rate of ocular allergy, stinging, follicular conjunctivitis, and contact dermatitis, even after many years of treatment.

Ocular side effects (65, 70)

The most common ocular complaint with their use is a transient stinging and burning.

Other commonly reported symptoms include transient blurred vision, reversible myopia, foreign body sensation, photophobia, itching, and ocular irritation, as well as cystoid macular edema.

Objective ocular signs consist of superficial punctate keratitis, keratitis sicca, corneal hypoaesthesia, lid ptosis, and allergic blepharoconjunctivitis due for the most part to the preservatives and ingredients other than the drug itself. Iritis and uveitis had been reported with levobunolol hydrochloride and metipranolol, although no definitive causal relationship with this particular molecule could be established. Lastly owing to their membrane stabilizing effect, patients on beta-blockers may exhibit a corneal anaesthetic effect and an ability to inhibit corneal epithelial cell migration.

Systemic side effects

It has been estimated that roughly 80% of an eyedrop can pass through the nasal nasolacrimal duct and into the nasal mucosa and its microvasculature. Eighty per cent of one 50 μ l drop of a 0.5% solution contains 200 μ g of active ingredient. Considering that these eyedrops are commonly used in both eyes once or twice a day, and that patients often squeeze more than one drop upon instillation, the systemic implications can be dangerous (65). Subjects lacking of the cytochrome P 450 enzyme CYP2D6 allowing betablockers to be metabolized could have greater risk to develop systemic side effects due to higher plasma concentrations of timolol following topical administration of the drug (23).

Importantly many of systemic side effects may only develop through an accumulation effect. Moreover, because some side effects may be very mild and subtle and do not manifest until months or years after the treatment is initiated, a careful monitoring is needed even in patients who experienced no initial side effects (65,70). Some of the following side effects can be theoretically decreased with the use of gel forming solutions whose more viscous formulation increases corneal contact time and penetration and decrease systemic absorption (22,72).

Exacerbation of asthma and chronic obstructive pulmonary disease due to induced bronchospasm are well known side effects. To a minor degree for betaxolol as a selective beta-blocker, these agents must be avoided in patients with a history of reactive airway diseases, such as asthma, emphysema, and chronic bronchitis (40,43,44,78). Less well known and moreover still controversial is the fact that, even in patients with no history of asthma or obstructive airway disease, long-term application of a non selective beta-blocker can be associated with a reduction in pulmonary function and even more by a subclinical increase in bronchial reactivity which may not be completely reversible on withdrawal of the medication. For that reason, they theoretically had to be avoided in patients who smoke. By manifesting only by a nocturnal coughing in some unfrequent cases, this induced reduction of pulmonary function can be very misleading (31,69,71).

Bradycardia is another potential side effect, as well as other forms of conduction defects. In younger patients, tolerance to exercise and endurance may be decreased. By lowering myocardial contractility and cardiac output, beta-blockers can exacerbate congestive heart failure, although this effect is currently controversial (29,52,65,70). They can *lower blood pressure* and are potentially associated with nocturnal hypotension, which may be a risk factor in progression of glaucomatous optic nerve damage (36,65,70). Moreover, they can theoretically induce *vasospasm* by leaving alpha receptors, which mediate vasoconstriction, free to bind epinephrine that is freely circulating in the blood (65,70).

Most of the non selective betablockers have the potential to adversely affect the *plasma cholesterol levels*, which may increase the risk of coronary artery disease (42,65,70).

In term of psychological effects, they can cause or worsen clinical *depression* after prolonged use (65,68,70). This is believed to result from blocking of the neurotransmitter pathways in the central nervous system and a decrease of the concentration of catecholamines and serotonin. Mood alterations, insomnia, memory loss, hallucinations and decreased libido could be more frequent than generally acknowledged. Topical beta-blockers could be also a risk fac-

tor for falls in the elderly. By potentially masking some of the usual signs of hypoglycaemia and delaying the physiological response to insulin, they are a relative contraindication in patients with *diabetes* (65,70).

Timolol and other topical beta-blockers should be avoided during pregnancy and in nursing mothers, as they do cross into breast milk (65,70).

The most frequent ocular and systemic side effects induced by beta-blocking agents are summarized on *table 4*.

PROSTAGLANDIN ANALOGS

Hypotensive lipids, named as eicosanoids, include latanoprost, travoprost and bimatoprost. Due to their potent IOP lowering effect, they are currently, with beta-blockers, used as drug of choice for first-line therapy. By achieving this effect at minimal concentrations that are orders of magnitude much lower than other medications, they induce relatively few systemic side effects. However because they have not been available as long as many of the other agents, their ultimate safety profile is relatively unknown and can justify for some authors, their caution use in young patients (25,60,65). Except for minor differences, the different commercially available prostaglandin analogs are both comparable with respect to their ocular and systemic side effects (65,70).

Ocular side effects

Ocular side effects include to some different degrees hyperemia, foreign body sensation, hypertrichosis, increased lower eyelid pigmentation with darkening of the periocular skin and "cernes", and superficial punctate keratopathy (26, 37, 57,60,65). The incidence of hyperemia varies among the different studies and molecules(from 5% to 68%). It mainly occurs in the first weeks of therapy, with a progressive but non constant decrease over time. This side class related effect may represent a cosmetic problem to the patient, possibly leading to non-or poor compliance. Allergic reactions occur in 1% of adult patients (35,41). Increased eyelash thickness, length and number appear to be related to the drug's ability to induce growth and hypertrophy in resting follicles (6,58).

Table 4: Major side effects of Beta-adrenergic antagonists

Non-selective: timolol 0.1%, 0.25%, 0.50%; levobunolol 0.25%, 0.50%;metipranolol 0.1%, 0.3%, 0.6%).

Beta-1 selective: betaxolol 0.50%.

with ISA (+): carteolol 1%, 2%.

OCULAR SIDE EFFECTS

- Stinging, burning
- Transient blurred vision
- Foreign body sensation, itching, hyperemia
- Photophobia
- Epithelial keratopathy
- Corneal anaesthetic effect

SYSTEMIC SIDE EFFECTS

Pulmonary system

- Bronchospasm
- Airways obstruction
- Dyspnea
- Coughing

Cardiovascular system

- Bradycardia
- Arrhythmia
- Heart failure
- Syncope
- Hypotension
- Nocturnal hypotension
- Vasospasm
- Increased plasma cholesterol levels

Central Nervous System

- Amnesia
- Confusion
- Depression
- Headaches
- Impotence
- Insomnia
- Hallucinations
- Mood alterations
- Risk factor for falls in the elderly?

Gastrointestinal

- Nausea, vomiting, diarrhea

Diabetes

- Masked hypoglycaemia in insulin dependent diabetes mellitus

Beta-1 selective (betaxolol) has a better tolerance in most patients sensitive to non-selective agents.

Of some concern is the ability of these agents to cause an increase in the melanin granule population in the melanocytes in the iris stroma, resulting in permanent hyperchromia of the iris. Iris color changes develop in 7% to approximately 30% of patients. Although no cellular proliferation or other dangerous sequelae of this effect have been seen, long-term consequences of prostaglandin use especially in young

patients still need to be evaluated. Nonhomogeneous mixed color iris, i.e green-brown, or blue-grey-brown iris are more prone to develop permanent increased iris pigmentation with the prostaglandin analogs (65). This effect starts relatively early after initiation of therapy (18 to 24 weeks) but would unfrequently develop after month 36 (1). Latanoprost has been demonstrated to be associated with the most important rate of iris pigmentation, with 16% at 12 months compared with 3% for travoprost and less than 2% for bimatoprost (1,65).

Although these associations have not been proven to be causal, the use of latanoprost has been reported to be associated with exacerbation of uveitis (46) and cystoid macular edema in predisposed patients, i.e in pseudo- and aphakic patients with lens rupture capsule (30,76,80), as well as some reports of iritis with choroidal effusion (50-66).

More significant but uncommon side effects include reactivation of herpes simplex or herpes simplex-like keratopathy as well as development of reversible iris cyst mimicking iris melanoma (12,18).

Whether the topical application of prostaglandines onto the cornea reduces the central corneal thickness or not has to be further confirmed (79).

Relatively subtle differences exist between the 3 existing prostaglandins. As previously mentioned, latanoprost has revealed to induce the lowest rate of hyperemia but the higher rate of iris color changes. Hypertrichosis is more pronounced and frequent with travoprost. Bimatoprost has less incidence of iris discoloration (about 1.5% of the patients), but a significantly higher rate of hyperemia and periocular "cernes" than any drug in this class (45).

Systemic adverse effects

Systemic side effects induced by latanoprost and other prostaglandin analogs are unfrequent and typically minor. They consist in migraine headaches, muscle or joint aches, through a probable role of prostaglandins in the mediation of sensory (pain) perception, flu-like-symptoms, non ocular eczema and allergy, and upper respiratory signs (48,64,65). Although studies carried out in asthmatic volunteers with topical PGF2 alpha did not show any respiratory side effects, topical prostaglandins analogs

should be avoided in patients with severe corticoid-dependent asthma (65). Although prostaglandin F2alpha is also a known vasoconstrictor, no definite vasoconstrictive effect of prostaglandin analogs on the retinal and optic nerve head has been published yet (65).

Side effects in children are uncommon. However parents should be warned of possible sleep disturbance, sweating, ocular hyperemia, irritation, increased iris pigmentation and lashes before starting latanoprost treatment (24).

Except for the second trimester of pregnancy, latanoprost and travoprost should be avoided in pregnant women, because prostaglandins are known to induce labor. Bimatoprost does not seem to have an effect on uterine muscle in vitro, but its effects in vivo have to be further clarified (15).

Table 5 summarizes the ocular and systemic side effects of prostaglandin analogs.

Table 5: Side effects of prostaglandin derivatives and prostamides.

OCULAR SIDE EFFECTS

Conjunctival hyperemia (5% to 68%) (transient and usually mild)

Burning, stinging, foreign body sensation, itching

Allergic reactions (1%)

Eyelash changes (reversible)

Increased lower eyelid pigmentation

Epithelial keratopathy

Increased iris pigmentation

in 7% to 30%

in patients with green-brown, blue/gray- brown, yellow-brown irides

Cystoid macular edema in aphakes/pseudophakes

- with a posterior lens capsule rupture or

- in patients with known risk for macular edema

Reactivation of herpes keratitis

Anterior uveitis

SYSTEMIC SIDE EFFECTS

Migraine

Muscle/joint pain

Flu-like symptoms

Non-ocular eczema

Upper respiratory signs: dyspnea, asthma, exacerbation of asthma

Caution in corticoid-dependent asthmatic patients!

ALPHA-ADRENERGIC AGONISTS

In this class, apraclonidine (Iopidine® 0.50%, 1%, Alcon) is a relatively non selective alpha-adrenergic agent. Its high rate of tachyphylaxis and its high incidence of allergy have made it less useful for long-term therapy (33,65, 83). Brimonidine is a selective alpha-2 adrenergic agonist which has about the same efficiency than topical beta-blockers. It works by both increasing uveoscleral outflow and by decreasing aqueous formation (17,33,65).

Ocular side effects related to this molecule include the typical rebound hyperaemia of adrenergic agonists along with conjunctival follicle formation (17,65). Allergy has been reported in 4 to 26% of patients (17,20,21). An history of eyedrop allergy and of reduction of the tear film production could be more frequently associated with the development of a brimonidine induced ocular allergy (49,57). That brimonidine should be considered as a possible cause of drug-induced uveitis with or without concurrent allergic conjunctivitis is less known (7). It has been also suggested that the delayed development of a follicular conjunctivitis could be frequently associated with a loss of IOP control and recommended that patients on brimonidine eyedrops should be instructed to report promptly to their ophthalmologist the onset of redness of their eyes so that their glaucoma treatment could be adjusted (81).

The frequency of *systemic side effects* induced by brimonidine varies in adult series from 20% to 50% and could be more frequent in elderly patients (20,21). These include dry mouth in nearly one-third of patients. Headaches, fatigue, dizziness, drowsiness (which can be both attributed to the drug's lipophilicity and induced hypotension) have been reported to various degrees and represent potentially significant problems (20,21). Somnolence could interfere with driving or professional activities. Except for young children, cardiovascular and pulmonary side effects are rare in adults (83).

Brimonidine should be avoided in newborns, young infants and children with juvenile glaucoma younger than 12 years, because of some reports of apneic spells and cyanosis, hypothermia, hypotony related to Central Nervous System depression due to the immaturity of the blood-brain barrier (9,25).

Ocular and systemic side effects of brimonidine are summarized on table 6.

Table 6: *Side effects of alpha-2 selective adrenergic agonists (apraclonidine 0.5-1%, brimonidine).*

OCULAR SIDE EFFECTS

- Rebound hyperemia
- Lid elevation
- Pupil dilatation (for apraclonidine)
- Allergy (up to 26% for brimonidine, up to 36% for apraclonidine)
- Uveitis ± allergic conjunctivitis ± IOP increase (brimonidine)

SYSTEMIC SIDE EFFECTS

- Dry mouth
- Headaches
- Fatigue
- Drowsiness
- Dizziness
- Decrease in systolic blood pressure

TOPICAL CARBONIC ANHYDRASE INHIBITORS (IAC)

Although dorzolamide and brinzolamide are slightly less efficacious in lowering IOP than their oral counterparts, their systemic side effects are greatly decreased (65, 73).

Ocular side effects

Dorzolamide is known to induce stinging and burning upon instillation in more than one-third of patients because of its low pH (at 5.8), but also ocular dryness, superficial punctate keratitis and blurred vision. However pain symptoms become generally fewer following chronic dosing and are generally characterized as mild. Brinzolamide in suspension allows buffering to a more neutral pH, which increases patient comfort but with a white deposit or debris on the eyelids (33,65,75).

For both drugs, allergic reactions may be seen, most related with sulfamide-allergy. Because topical IAC inhibit carbonic anhydrase which is required for the pumping action of the corneal endothelium, corneal decompensation may occur in patients with already compromised endothelium and pre-existing corneal edema (65). Induced myopia, prolonged hypotony following filtering surgery, choroidal detachment and angle-closure glaucoma due to a forward rota-

tion of the ciliary body, have been reported in some rare cases (26,33,65).

Systemic side effects

A percentage of the medication is absorbed and binds to erythrocytes. A metallic, bitter or distorted taste, especially with carbonated beverages, are noticed by approximately 25% of the patients. This rarely precludes chronic therapy and is generally easily decreased with digital punctal occlusion.

Rarely, transient gastrointestinal symptoms are seen. Headaches, dizziness and sometimes depression have been reported with topical IAC. Rare cases of nephrolithiasis have been reported, although a causal relationship has not firmly established with any of topical IAC.

Caution is advised when used in patients with sulfa allergy which must be systematically searched for on initiation of therapy.

Serious side effects are rare and a causal relationship has not been firmly established for any of these. Aplastic anemia and Stevens-Johnson syndrome remain a theoretical risk as with any sulfamide-derived drug, even with topically ACI agents, although these have been never described until now. In return, excessive fatigue and especially sensation of weakness of the inferior limbs are probably more frequent than usually recognized and must be periodically searched for (19,26,33,65).

Ocular and systemic side effects of topical ACI are summarized on table 7.

COMBINATION PRODUCTS

Carteopil®, Cosopt®, Normoglacon® and Xalacom® represent the four currently commercially available combination products.

As fixed combinations, there is theoretically less chance of washout effect, fewer long-term ocular side effects because of fewer preservatives than when using concomitant therapy. However the contraindications and adverse reactions are similar to those of each individual agent (1,2,38,59,74).

CONCLUSIONS

Drug side effects are frequent and can have a major impact on glaucoma management. Very often, patients do not establish a relationship

Table 7: *Side effects of topical carbonic anhydrase inhibitors (brinzolamide 1%, dorzolamide 2%).*

OCULAR SIDE EFFECTS

- Burning
- Stinging
- Dryness
- Superficial punctate keratitis
- Blurred vision
- Tearing
- Allergy (sulfonamide derivatives)
- Corneal decompensation
- Myopia, prolonged hypotony,
- Choroidal detachment, angle closure glaucoma

SYSTEMIC SIDE EFFECTS

- Bitter taste (25%)
- Gastrointestinal disorders
- Headaches
- Dizziness
- Depression
- Fatigue
- Urticaria, pruritus

between presented side effects, especially systemic side effects, and the instilled drug (14). Therefore we have to be aware of the potential ocular and systemic side effects of the different available medications, although they are less frequent with new meds such as prostaglandins. Patients must be informed on their disease, the medications they use and what side effects they have to expect. Without being suggested, they will be questioned during each visit about potential side effects.

The goal of glaucoma treatment should be obtained with the least possible side effects, the least possible dosing frequency and the lowest patient cost (26,33,65).

Systemic levels of glaucoma medication can be reduced by using lower frequency (daily vs twice or thrice daily) and lower concentrations of medication (i.e timolol 0.25% versus 0.50%).

Punctal occlusion and lacrimal sac compression can further reduce absorption. Practically many patients neglect, will not be able to do or forget this recommendation. Removing excess fluid from lid margins combined with simple eyelid closure during at least one minute which will increase ocular contact time and decrease systemic absorption of topical medications, can work just about as well (27,65).

All current systemic and ocular medications should be noted to plan appropriate therapy and to avoid potential adverse effects, dupli-

cation of therapy, and adverse drug interactions (33,65).

Obtaining a history of allergies and systemic and ocular medication intolerances will guide glaucoma medications choice and avoid the possibility of placing the patient on a medication to which he or she is allergic or have had a previous intolerance or adverse event (80). Major concerns deal with the preservatives contained within topical eye drop preparations. For patients at risk for ocular surface damage and to improve the long-term local tolerance of medications, it is recommended to choose medications with either low levels of BAC or alternative preservative or preservative-free solutions (54). Monodoses of free preservatives are currently available for some beta-blockers. Unfortunately, they are relatively expensive and still non reimbursed to the patient for some of them. Whenever adjunctive therapy is needed, it is important to consider the use of preservative-free preparations/delivery systems and/or fixed combinations. Anyway we must encourage Pharmaceutics and Public Health Services to develop alternative free-preservative drugs for each pharmacologic class.

Finally we also have a role in mentioning some unusual adverse effects to the manufacturer of the medication (28).

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