NEW DEVELOPMENTS IN GLAUCOMA MEDICAL TREATMENT

NUEVOS DESARROLLOS EN EL TRATAMIENTO MÉDICO DEL GLAUCOMA

MUÑOZ-NEGRETÉ FJ¹, PÉREZ-LÓPEZ M², WON KIM H-R², REBOLLEDA G¹

ABSTRACT

The medical treatment of glaucoma has undergone significant development in recent years. Research in this field is focused on improving pre-existing drugs and on the development of new molecules. In relation to commercial drugs, there is a trend to improve local tolerance, using less toxic preservatives as in the case of sofZIA in travoprost, and eliminating the preservatives as in tafluprost. The development of new, fixed combinations of commercial drugs could also enhance their administration and therapeutic compliance.

There is also intense research activity in the search for new therapeutic groups for glaucoma treatment. Calcium channel-blockers such as lomerizine do not seem to affect systemic hypotension, while topical calcium-blockers like flunarizine and iganidipine are also under research. Endothelin 1 antagonists such as sulfisoxazole and bunazosine could be also useful in the treatment of glaucoma. In the renin angiotensin system, angiotensin (1-7) and olmesartan are under investigation for use in glaucoma patients. Trabecular drugs such as Rho-kinase inhibitors could be effective on the pathogenic mechanism of primary open angle glaucoma.

Finally, topical mifepristone, an antagonist of glucocorticoid receptors, is under evaluation for corticosteroid-induced elevated intraocular pressure (Arch Soc Esp Oftalmol 2009; 84: 491-500).

RESUMEN

El tratamiento médico del glaucoma ha presentado una gran evolución en los últimos años. Las investigaciones que se están desarrollando en este campo se basan en el perfeccionamiento de productos actuales con preservantes menos tóxicos, como es el caso del preservante sofZia que se ha asociado al travoprost, y la eliminación del uso de conservantes, como sucede con el tafluprost. También el desarrollo de nuevas combinaciones fijas de fármacos comercializados podría facilitar su administración y el cumplimiento terapéutico.

Por otro lado, se están investigando nuevas moléculas que puedan ser de utilidad en el tratamiento médico del glaucoma. Entre estos podemos destacar las investigaciones sobre antagonistas del calcio como la lomerizina, que parece no producir hipotensión sistémica, y productos que se están investigando para uso tópico ocular como la flunarizina y la iganidipina. También se están investigando inhibidores de la endotelina 1, como el sulfisoxazol y la bunazosina. Dentro del sistema renina-angiotensina se están evaluando la Angiotensina (1-7) y el olmesartan. La investigación de drogas trabeculares, como los inhibidores de la Rho-kinasa, podrían actuar sobre el mecanismo patogénico del glauco-
High intra-ocular pressure (IOP) is one of the main risk factors in the development of glaucoma. Initial management consists in reducing IOP by means of drugs. Since pilocarpin began to be utilized in 1870 for the treatment of glaucoma, researchers have focused intensely on this pathology with the aim of discovering new and more powerful active principles with long effects and increased safety and tolerance.

At present, new products are focused on variations of pre-existing active principles with the aim of improving local tolerance, mainly with the addition of new preservatives or preservative-free formulations as well as the description of new pharmacological groups, some of which have action mechanisms that are different to that of existing products. The aim of this revision is to review the most relevant novelties produced in the pharmacological treatment of glaucoma, as can be seen in table I.

**Table I. Future anti-glaucomatous products in research**

1) Prostaglandin analogs  
   a) AR-102  
   b) PF-03187207  

2) Calcium Antagonists  
   a) Lomerizine  
   b) Topical flunarizine  
   c) I ganidipine  

3) Endothelin antagonists  
   a) Sul f s oxazole  
   b) topical bunazosine  

4) Agonists/antagonists of Renin-Angiotensin receptors  
   a) Topical olmesartan  
   b) Angiotensin (1-7)  

5) Rho-kinase (ROCK) inhibitors  
   a) Topical Y-27632  

6) Antagonists of steroids receptors  
   a) Topical mifepristone

**PROSTAGLANDIN AGONISTS**

The use of prostaglandin analogs as ocular hypotensors for treating glaucoma was proposed in the early eighties by Camras and Brito (1). Since then, Prostaglandin FP receptor agonists found in the market, latanoprost (Xalatan®, Pfizer, S.A. Madrid, Spain), bimatoprost (Lumigan®, Allergan S.A., Tres Cantos, Madrid, Spain) and Travoprost (Travatan®, Alcon Cusí, S.A., El Masnou, Barcelona, Spain) have exhibited high ocular pressure-reducing properties above those of topical betablockers both in patients with open Angle primary glaucoma as in closed angle glaucoma patients (2,3). If we add the low prevalence of systemic complications, it is easy to understand the current pre-eminence of said anti-glaucoma drugs.

The manufacturers of said products are trying to improve their tolerance introducing changes in the formulation, such as in the case of Travatan® (Alcon, Fort Worth, Texas, USA) in which benzalconium chloride is substituted by sofZia, an ionized preservative exhibiting lower toxicity on the ocular surface without diminishing the pressure-reducing efficacy of the preparation (4). There is a unique case of a patient who developed cystoid macular edema after switching treatment from latanoprost to Travatan-Z. The authors stated that this defect could be related more to the preservative than to the active ingredient (5).

Soon to appear in the Spanish market are generic prostaglandin analogs. Even though in theory at least these analogs should be just as effective as the original products, a study recently published in India observed that the generic preparation of Latanoprost (Latoprost®) had less effective pressure-reducing properties than Xalata®, with similar local adverse effects. This will have to be analyzed when generic prostaglandin analogs appear in the market in our country (6).
The list of prostaglandin analogs in the market is completed with new products aiming at enhancing the pharmacological potency and diminishing ocular iatrogenia, minimizing the use of preservatives. Tafluprost (Saflutan®, Merck Sharp & Dohme, S.A., Madrid, Spain) is a recently approved FP-receptor agonist, an isopropyl ester which, when making contact with the ocular surface, is rapidly hydrolyzed by corneal sterases and turns into a clinically active metabolite. It exhibits great affinity with FP receptors. The pre-clinical trial has shown that its pressure-reducing effect is greater than that of latanoprost in rats and mice with normal ocular pressure (7). Likewise, its topical application in cats has demonstrated increased retinal blood flow, above that of latanoprost, which suggests a similar effect in glaucoma patients in which it could improve ocular perfusion (8).

It is known that prostaglandin analogs cause iris pigmentation, growth of eyelashes and conjunctival hyperemia. Even though these effects are foreseeable with the use of the new prostanoid, it has been observed that, in contrast with latanoprost, tafluprost does not increase melanogenesis of melanic cells cultured in vitro (9). Long-term clinical trials are required to determine whether tafluprost produces less hyper-pigmentation of the iris in humans than the rest of prostaglandin analogs in the market.

On the other hand, the presentation of preservative-free Tafluprost could become an additional advantage in what concerns ocular toxicity compared to traditional prostaglandin analogs which associate benzalkonium chloride (10). However, in a placebo-controlled study Sutton et al have found a greater prevalence of conjunctival hyperemia and photophobia in the group of patients treated with tafluprost against the group that was given Latanoprost (11).

Additional prostaglandin analogs in research stage are AR-102 (Aerie Pharmaceuticals Inc) and PF-03187207 (Pfizer and NicOx) (12). As regards the former, pre-clinical studies indicate it could be 150 times more effective and 30 times more potent for FP receptors than latanoprost. Pre-clinical trials are encouraging and refer higher pressure-reducing efficacy, longer duration of effects against latanoprost and greater tolerance against travoprost. As regards PF-03187207, an F2-alpha prostaglandin analog which associates nitric oxide-donating properties, after initial clinical trials it has been decided to cancel its marketing.

**CALCIUM ANTAGONISTS**

The development of certain optic nerve diseases has been related to insufficient ocular blood flow. In the case of glaucoma, it could develop partly due to a compromise of circulation at the optic nerve head associated to increased IOP. Calcium antagonist drugs, broadly used for treating arterial high pressure and coronary diseases, reduce the tone of blood vessels by inhibiting the entry of calcium in the cells, which causes a relaxation of the smooth muscle and a regional increase of blood flow in various tissues. A number of researchers suggest that the systemic use of calcium antagonists could improve the prognosis of at least a part of glaucoma patient due to the increase of ocular blood flow and a neuro-protective effect on retina ganglionary cells because hypoxia of said cells seems to be at least partially related to increased intra-cellular calcium levels. However, the use of these products in glaucoma is controversial because a recent publication affirmed that the use of calcium antagonists could be linked to a higher rate of open angle primary glaucoma, which could exclude its use (previously recommended by some authors) for this type of glaucoma (13).

Lomerizine is a mixed calcium antagonist which acts over calcium T- and L-receptors. It has exhibited a selective improvement of retinal and optic nerve head blood flow both in rabbits and humans (14) and neuro-protective effect in rabbits (15) and rats (16) with hardly any significant effects on systemic pressure and heartbeat frequency (14). As such, it can be considered as a vessel dilator at the ocular tissue level without systemic pressure-reducing effects. Its apparent selectiveness of brain arteries increases hopes that the vascular effect of this drug in the eye will be more selective at the level of neural tissue (which seems confirmed by the fact that lomerizine increases retinal and optic nerve head blood flow without modifying the choroidal flow). The relative lack of influence on systemic pressure could make lomerizine more adequate for ophthalmic use than other calcium antagonists, although it could also cause secondary effects such as drowsiness or facial reddening.

Flunarizine is a mixed calcium antagonist which, like lomerizine, acts on calcium T- and L-receptors and also as antagonist for sodium channels. Its action mechanism seems to consist in the inhibition of dopamine capture and union to dopa-
mine receptors, mainly the D2 type. As other DA receptor antagonists, flunarizine interacts with sigma receptors in the iris and ciliary body of the rabbit eye, related to the production and drainage of aqueous humor. Its topical application seems to reduce IOP in normotensive rabbit eyes as well as in eyes with hypertension induced by alpha-chymotrypsin (17) and in dogs (18).

In turn, iganidipin is a new dihydropyridine derivative of calcium antagonists which is relatively water soluble. It is the only currently available calcium antagonist in the form of ophthalmic solution (19). Its topical administration increases ipsilateral optic nerve head blood flow in rabbits and monkeys (20,21) and inhibits the contraction of blood vessels induced by endothelin-1 (19).

In general, the use of calcium antagonists could cause the appearance of side effects derived from the blockage of calcium channels at the level of peripheral arteries such as hypotension, palpitations, reflex tachycardia, peripheral edemas and vertigo. At present there is evidence showing that the effect of lomerizine on blood pressure is lower than in the remainder of calcium antagonists because it selectively inhibits the access of Ca++/KCl channel-dependent calcium more potently at the level of the brain arteries than the mesenteric arteries.

**ENDOTHELIN ANTAGONISTS**

Endothelins are a family of isopeptides (ET1, ET2 and ET3) encoded by several genes located in different loci. ET1 and ET2 act as power vasoconstrictors in comparison with ET3 which acts as a comparatively weak vasoconstrictor. In addition to the vasoactive effects, said endothelins produce multiple effects in non-vascular tissue including nervous tissue. They act at the level of ETa and ETb receptors (22,23). Of these, receptor ETa exhibits selective affinity for ET1 while ETb exhibits the same affinity for all three isoforms. Receptor ETa is mainly associated to the blood vessels smooth muscle (24) and its activation produces vasoconstriction, whereas receptor ETb is more abundant in astrocytes (25).

It has been demonstrated that endothelins play an important role in homeostasis both of the anterior and posterior chamber of the eye. In the anterior segment high levels of ET1 and ET3 have been detected at the level of the iris, ciliar body and aqueous humor, while receptors Eta and ETb have been located at the level of the iris, ciliar muscle and ciliary processes in rats, rabbits and humans. It seems that ET1 plays a role in IOP regulation (26). In the posterior segment immunoreactive ET1 and ET3 have been detected, and their ARNm at the level of the choroids and the retina.

In addition to intervening in ocular homeostasis, endothelins could play a role in the pathogenesis of glaucoma (27). Thus, high ET1 levels have been detected in the aqueous humor and plasma of humans, dogs and rats with glaucoma.

Recent studies endeavor to assess the capacity of endothelin receptor antagonists to act as neuro-protective agents and propose several action mechanisms. At the vascular level, in ischemia situations ET1 is released, causing vasoconstriction in the optic nerve head, which could be followed by ischemia and cell death. To this we must add that with increased IOP the ET1 levels in the optic nerve head also increase (28). Accordingly, endothelin antagonists could protect neurons by preventing post-ischemia hypoperfusion of the retina and vasoconstriction of the optic nerve head. On the other hand, at the non-vascular level and in ischemia conditions, quiescent astrocytes in the brain, the retina and optic nerve head undergo an astrogliosis process which produces the release of toxic mediators and neuronal death (29). In this case, endothelin antagonists would also act inhibiting said cascade.

**Sulfinoxazol** is a non-selective antagonist of endothelin. Experimental studies in rats have recently proved that the use of the antagonist protects the retina against ischemic damage in processes like glaucoma, reducing electro-retinogram alterations and normalizing changes in the acetylcholintransferase levels, synthethase nitric oxide, Thy-1(a specific marker of retina ganglionary cells) and FGF-2 (trophic factor produced by glial cells in stress conditions), typical of ischemia conditions (30).

**Bunazosin** is a powerful selective antagonist of alpha-1 adrenergic receptors. It has been observed that after instilling bunazosin in normotensive rabbits, it penetrates locally and reaches the retina at a sufficient concentration to attenuate vasoconstriction of retinal arteries induced by phenylephrine or endothelin-1. In adult humans the topical application of bunazosin increases the blood flow rate in the optic nerve, the retina and choroids without altering arterial pressure or heartbeat frequency. These
qualities could determine its usefulness in ischemic retinal diseases and glaucoma cases with vascular component (31).

**AGONISTS/ANTAGONISTS OF ANGIOTENSIN RECEPTORS**

The role played by the retina-angiotensin system (RAS) in controlling systemic arterial pressure and ionic homeostasis of the internal medium is well known. It has been recently demonstrated that angiotensin II not only has a powerful action for vasoconstricting and stimulating the release of aldosterone but it also acts as a growth and immunomodulating factor in cell proliferation, fibrosis and apoptosis processes. Even though its action in adrenal, renal and vascular tissues is well known, many of the RAS system components have been identified in human and animal eyes. Specifically, said components express in the ciliar body, the tissue responsible for producing the aqueous humor. Its presence and relevance in the trabecular mesh is the object of study. Authors like Shen et al (32) have evidenced a pro-proliferative and pro-fibrotic role of Angiotensin II at said level in animal models. However and in contrast with what could be expected in these findings, Yan Ke et al did not find statistically significant differences in angiotensin II levels in patients with normotensive glaucoma compared to controls (33).

Just like angiotensin 1 and 2 are not able to cross the blood-brain barrier, they cannot reach the vitreous when the blood-retina barrier is intact (34). For this reason, in recent years several studies have been developed for assessing the action of RAS in the ocular system.

As far back as the late eighties, the topical application of angiotensin-converting enzyme was proved to diminish IOP in patients with ocular high pressure and open angle primary glaucoma (35).

After evidencing the influence of angiotensin II on the uveo-scleral drainage mediated by receptors AT1 (36), Wang et al (37) utilized olmesartan (CS-088), an antagonist of AT1-type angiotensin receptors topically in monkeys with laser-induced unilateral glaucoma and observed a reduction of the dosage-dependent IOP.

A new RAS metabolite, angiotensin (1-7), the product of the action of carboxi- and endo-peptidases on two forms of angiotensin, 1 and 2, has demonstrated to have the contrary effects of its precursor because it acts as a biologically active vasodilator and anti-proliferative factor (38-41). It seems that these actions are mediated by a Mas receptor linked to the G protein which is exclusive of the angiotensin (1-7) ligand and without activity in the presence of angiotensin II.

A recently published study (42) has assessed the effect of angiotensin II and its Angiotensin (1-7) metabolite on intraocular IOP and changes in the aqueous humor flow, utilizing an animal model with ocular normotension. It was observed how the topical as well as intravitreal application of angiotensin II was accompanied by a significant increase of the resistance to the release of aqueous humor, without involving IOP changes. This effect was reverted with an AT1 antagonist such as olmesartan. In turn, angiotensin (1-7) reduced IOP, probably through the Mas receptors, without registering changes in the aqueous humor release flow. This suggests that its action mechanism mediated by Mas receptors could be related more to the inhibition of aqueous humor production than to the increase of its release or drainage.

**RHO-KINASE INHIBITORS (ROCK)**

In the majority of glaucoma forms, increased IOP seems to be the result of a difficulty in the drainage of aqueous humor in the trabecular mesh and Schlemm’s canal. A number of studies have attempted to identify the actual pathogenic mechanism that determines changes in the trabecular mesh which modulate the filtration of aqueous humor and the drugs which could modify said mechanism. The trabecular mesh has properties similar to those of smooth muscles and its contracting capacity could allow for the regulation of the release of aqueous humor through it, either via changes in the size of mesh drainage spaces, the permeability of Schlemm’s canal or the extra-cellular matrix.

Rho guanosin triphosphatase (Rho GTPasa) is a transmembrane protein of the Ras Superfamily which, through its effector, Rho Kinase protein (ROCK) controls cellular activities such as muscle contraction, the organization of the cyto-skeleton, cellular adhesion or in vitro cultured cell migration from the trabecular mesh. Ponugoti et al have observed that the inhibition of the Rho-Kinase protein produces changes in the morphology of trabe-
cular cells and the inter-cellular unions. It also inhibits the phosphorylation of light mioseine chains, which correlates with an improvement in the release of aqueous humor (43). Subsequently, Koga et al (44) studied the behavior of in vitro cultures human trabecular mesh cells with Y-27632, a selective ROCK inhibitor. The findings were partially contradictory with what other authors beside themselves had found previously, i.e., that Rho-Kinase inhibitors induced changes in cellular morphology, increasing cell adherence and citoplasmatic projections and accelerating cellular migration. Accordingly, the IOP reduction associated to topical treatment with Y-27632 described by Inatani et al (45) and previously documented in animal studies could be explained by these induced changes in the cellular activity of the trabecular mesh.

Following the above line of research and encouraged by the absence of cellular toxicity associated to Y-27632 in previous studies, Rao et al (46) evidenced additional properties of ROCK inhibitors such as increased ocular blood flow, survival of retinal ganglionary cells and axon regeneration. Honjo et al (47) have researched their capacity to regulate the fibroblastic activity in Tenon’s capsule after penetrating glaucoma surgery in rabbits. They found that post-op topical instillation of this product had positive effects on the prevention of fibrosis of the filtration ampoule.

Therefore, ROCK inhibitors could act in the treatment of glaucoma through a new action mechanism which we could name «trabecular mechanism» which would more directly target the true pathogeny of glaucoma than the drugs we utilize at present.

**ANTAGONISTS OF STEROID RECEPTORS**

Mifepristone is a specific antagonist of glucocorticoid receptors which, when topically applied to rabbits, produces a modest IOP reduction. In experiments it was observed that animals treated with mifepristone and subsequently dexametasone did not exhibit IOP increases (48).

Studies have also been made to determine the possibility of interactions between progesterone and mifepristone and the repercussion thereof on IOP of rabbit eyes. It was observed that the isolated administration of medrisone (progesterone) causes a significant increase of IOP the first three weeks whereas, when medrisone is administered simultaneously with mifepristone, IOP initially increases but returns to baseline levels after 2 weeks. The IOP levels also go down when mifepristone is administered 2 weeks after medrisone (49). Thus, it seems that the use of mifepristone antagonizes the effects of progesterone over intra-ocular pressure.

A formulation of topical mifepristone (RU486) is at present in phase 2 study as a treatment for raising IOP secondary to the use of corticoids (12).

**NEURO-PROTECTIVE DRUGS**

Oral memantine, approved for use in Alzheimer’s disease, has been studied as a neuro-protective agent in glaucoma although finally it wasn’t approved (12). Neurotech labs are researching the use of intravitreal implants for sustained release of growth factors to the posterior pole (12).

**FIXED COMBINATIONS**

All the fixed combinations of anti-glaucoumatous drugs in the market contain 0.5% timolole maleate, which has been combined with prostaglandin analogs such as latanoprost (Xalacom®, Pfizer, Madrid, Spain), travoprost (Duotrav®, Alcon Cusi, S.A., El Masnou, Barcelona, Spain) and bimatoprost (Ganfort®, Allergan S.A., Tres Cantos, Madrid, Spain), with alpha2-agonists such as brimonidine (Combigan®, Allergan S.A., Tres Cantos, Madrid, Spain) and topical carbonic anhidrase inhibitors such as dorzolamide (Cosopt®, Merck Sharp & Dohme, S.A., Madrid, Spain) and brinzolamide (Azarga®, Alcon Cusi, S.A., El Masnou, Barcelona, Spain), the latest product in its kind to appear in the market in Spain.

A randomized study comprising over 500 patients has demonstrated that this combination is more efficient than each component thereof. No adverse effects at the cardiovascular level have been referred, although this is biased by the sample selection criteria which excluded patients with contraindications for betablockers (50). A recent comparative study of the two fixed combinations which contain carbonic anhidrase inhibitors has shown comparable efficacy. As regards adverse effects, more discomfort and ocular irritation has been
found with the fixed combination which includes dorzolamide and more blurred vision with the one containing brinzolamide, as occurred previously with these two components when applied in isolation without betablockers (51).

In México a fixed combination has been placed on the market comprising three active products: timolole, brimonidine and dorzolamide (Krytantek on the market comprising three active products: timolole, dorzolamide and prostanoid FP-receptor agonistic activity as an ocular hypotensive drug. Exp Eye Res 2004; 78: 767-776.


51. Manni G, Denis P, Chew P, Sharpe ED, Orengo-Nania S, Coote MA, et al. The safety and efficacy of brinzolamide 1%/timolol 0.5% fixed combination vs dorzolamide 2%/timolol 0.5% in patients with open-angle glaucoma or ocular hypertension. J Glaucoma 2009; 18: 293-300.