Main topic issue No 3: 
 Fixed Combinations – Concept of Use

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Special Focus: Quality Use of Fixed Combinations

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Core Concepts
- Beta blockers (BBs) and alpha agonists (AAs) reduce aqueous formation by decreasing the rate of movement of water to the ciliary non-pigmented epithelial (NPE) aqueous surface.
- Carbonic anhydrase inhibitors (CAIs) reduce aqueous production by decreasing bicarbonate formation, thus preventing sodium and water movement from the non pigmented epithelial cells.
- Prostaglandin analogs (PGAs) increase uveoscleral outflow of aqueous. While all other PGAs activate the FP receptor, bimatoprost seems to act through a variant of this receptor.
- PGAs are the most potent hypotensive drugs available, reducing IOP up to 31-33% from baseline.
- PGAs reduce IOP for at least 24 hours, consistently flattening the circadian curve better than CAIs, AAs or BBs.
- Fixed dose combinations (FDCs) have advantages such as reduced preservative exposure, wash out effects and drug interactions.
- The non inferiority design of studies comparing FDCs with individual components might limit the evidence.
- Cost effectiveness studies differ greatly in methodology and in selected outcomes measures, making interdrug comparison difficult.

Action of components

Mechanism of action: Ocular hypotensive FDCs are products that include two active agents in the same bottle. All currently available FDCs include timolol – a nonselective beta-blocker at the concentration of 5 mg per ml (0.5%). The other drug is a PGA, including bimatoprost, latanoprost or travoprost; the alpha-agonist brimonidine, a CAI, (brinzolamide or dorzolamide); or the cholinergic agent pilocarpine at 2% or 4% concentrations (1).

Although mechanisms of action of these drugs are different, all of them reduce IOP either by reducing aqueous production (AP) or by facilitating aqueous outflow (AO). (3,4,5).

CAIs reversibly bind to the almost ubiquitous enzyme carbonic anhydrase II, hindering it from catalyzing its reaction (6). This reduces the production of bicarbonate and consequently aqueous humor formation.

PGAs increase uveoscleral outflow, the alternative route for aqueous outflow, and can be classified as AO facilitators (8). Among the different PGAs available as fixed combinations, latanoprost and travoprost activate the FP receptor. FP activation alters second messenger signaling, stimulating intracellular production of pro-metalloproteinase. These convert to metalloproteinase outside the cell, and degrade collagen fibres, making the ciliary extracellular matrix more porous and facilitating passage of aqueous. Bimatoprost could act through a variant of the FP receptor (9).

Finally, cholinergic agents like pilocarpine stimulate ciliary muscle contraction, thus stretching and opening the trabecular meshwork (10). This facilitates aqueous passage through the conventional pathway. Cholinergics do not block the effect of PGAs, as might be expected from their respective mechanisms of action (11).

Beyond these hypotensive effects, there may be IOP-independent actions for some agents: improvement in ocular hemodynamics by dorzolamide (12), or retinal neuroprotection with brimonidine (13). Further studies are needed to confirm the true added value of these compounds in glaucoma management.

Efficacy: Efficacy varies between drugs; it is the amount of IOP reduction from an untreated baseline, expressed as a percentage and/or absolute values, depending on the design and methodology of studies for that particular drug.

According to a meta-analysis (14), PGAs are the most powerful hypotensive drugs currently available, reducing IOP as much as 31–33% from baseline. Theoretically, FDCs containing PGA (PGA/FDC) should be the most effective two-drug combination, as they bring together an AP reducer plus an AO facilitator. When latanoprost/timolol FDC once daily was compared with dorzolamide/timolol FDC bid there were no statistically significant differences in IOP reduction (15,16). Conversely, travoprost/timolol FDC once daily compared with dorzolamide/timolol bid demonstrated statistical significance favouring the PGA/FDC, although the mean IOP differences between both FDCs was less than 1 mmHg (17).

Studies comparing the efficacy of the different PGA/FDCs, report statistically significant differences, in favour of bimatoprost/timolol FDC for IOP reduction, compared with latanoprost/timolol FDC (18) and travoprost/timolol FDC (19). While these differences are quantitatively small, even small amounts of IOP lowering could be relevant. A measurable direct relationship between IOP reduction and decreased risk of glaucoma progression has been estimated (20, 21). The clinical relevance for visual field preservation remains to be determined through adequately designed studies.

Also relevant is the duration of a drug’s hypotensive effect. As monotherapy, PGAs show a sustained IOP reduction lasting at least 24 hours, consistently flattening the day and night IOP curve, superior to BBs or CAIs (22). Non-PGA/FDCs, like dorzolamide/timolol FDC bid, have 24 hour IOP control comparable with latanoprost monotherapy daily and better than brimonidine monotherapy tid (23).
Similarly, dorzolamide/timolol FDC bid performed equally to latanoprost/timolol FDC daily. (24). One study has compared 24 hour-IOP efficacy of two different PGAFDCs. Travoprost/timolol FDC qd showed statistically significant differences in 24 hour IOP lowering at some individual time points ahead of latanoprost/timolol FDC qd (25). With PGAFDCs, both morning and evening instillation are effective, but evening dosing might yield statistically significant better 24-hour IOP control (25-27).

Limitations/additivity: FDCs have advantages and disadvantages. Benefits include: lower risk of a washout effect, less preservative-induced ocular damage and drug interactions, and increased compliance. (28,29) Regarding PGAFDC efficacy, concerns arise when studies are analyzed in depth. A recent meta-analysis (30), which included studies investigating the IOP lowering effect of PGA combined with BB therapy, has reported that differences in efficacy may relate to study design limitations such as the concept of non-inferiority of FDCs compared with the concomitant combination of their separate components (36,31,39,40,41). As all FDCs include timolol, a specific cardiopulmonary history including asthma or bradycardias must be excluded (42).

All PGA-FDCs have a reduced rate and severity of conjunctival hyperemia compared with each of the PGAs used alone (41, 43, 44). Similarly, the incidence of conjunctival allergy-like reaction from AAs, is lower for the brimonidine/timolol FDC than in monotherapy with brimonidine tid (45,46). Over the long term, latanoprost/timolol FDC is safe and effective over five years; more than two third of patients treated with this FDC, did not show increased iris pigmentation. (48)

Cost-effectiveness (CE): Some studies have addressed cost issues of glaucoma medical treatment with FDCs. Travoprost monotherapy was compared with a fixed combination of latanoprost/timolol as first-line therapies for ocular hypertension or glaucoma. (49) The authors estimated a reduction around half of the mean daily costs in favor of travoprost. These results do not support FDCs as a cost-effective first-line therapy, compared with PGA monotherapy. Travoprost/timolol FDC was shown to compare favorably with latanoprost/timolol FDC through an algorithmic approach that converted IOP data into visual field progression (50). Two European studies have analyzed the efficacy and cost implications comparing the three PGA-FDCs (51) with two non- PGA-FDCs (52). The authors reported brimonidine/timolol FDC bid to be more cost-effective than dorzolamide/timolol bid, and brimonidine/timolol FDC the most effective and least costly PGA-FDC in most of the evaluated countries. However, CE analyses of glaucoma management has limitations: some patient concerns such as life expectancy or disease stage, outcome measures selected, as well as differences in design and methodology. Such factors significantly influence results.

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37. EGS.
37. EGS.
37. EGS.
37. EGS.
Core Concepts

- Medications from the same pharmacological group should not be used in combination
- Therapeutic agents should act synergistically e.g. a drug that increases uveoscleral outflow should be combined with one that decreases aqueous inflow
- When initiating a combination therapy, attention needs to be given to the patient’s medical history
- Prostaglandin monotherapies are considered best clinical practice and should be the basis for combination therapies
- Fixed combinations may have the benefit of increased patient compliance and less exposure to preservatives, potentially improving patients’ quality of life

Introduction

The major risk factor for glaucoma is elevated intraocular pressure.

The only proven effective strategy for treating glaucoma is reducing intraocular pressure.

In most clinical situations, significant reduction of intraocular pressure is achieved by the application of topical medication.

The ideal treatment would be a single agent that is well tolerated, administered once daily with excellent efficacy.

However in some routine cases adequate reduction of the intraocular pressure towards the desired target pressure can only be achieved with the use of more than one agent.

The options of combination therapy are discussed centred on a typical glaucoma case history scenario.

Case Study:

JT, a 56 year old Caucasian with no family history of glaucoma, was referred by his optometrist. He was systematically well on no medications. His unaided visual acuity was 6/6 OU.

His intra-ocular pressures (IOP) were 32 mmHg OD and 28 mmHg OS (CCT 554nm and 557nm) and he had open angles on gonioscopy without pigment dispersion or pseudo-exfoliation.

The right optic disc had an inferior focal thinning of the neuro-retinal rim, and there was corresponding superior arcuate visual field loss.

The diagnosis was primary open angle glaucoma. A target intraocular pressure of 14–16 mmHg was suggested. Best clinical practice is to use a topical prostaglandin analogue as initial therapy. These agents are used once daily, and have minimal side effects (initial hyperemia, eyelashes longer, darker, thicker, and possible iris darkening long term.)

Daily treatment, often at night-time is presumed to improve compliance, as well reduce exposure to topical preservatives. A therapeutic trial of Gtt latanoprost at night time (1 drop) to the right eye was initiated.

6 weeks later the respective IOP measurements were 26 mmHg OD and 27 mmHg OS.

To reach target IOP, medical therapy needed to be changed: what are the options available? To switch within the same class of ocular hypotensive (prostaglandin) or to add an additional agent from another class?

We switched “within same class of drug” to of Gtt brimatoprost, (1 drop) at bedtime only for the right eye.

8 weeks later IOP were 22 OD and 26 OS. As target IOP had not yet been reached, additional therapy is required.

The clinical photos of the Humphrey Visual fields are depicted on page 6 (figure 1) and 7 (figure 2). The optic disc photographs are shown on page 8 (figure 3).

This case history illustrates a common scenario in medical treatment of glaucoma: one hypotensive agent results in insufficient IOP lowering. While there are several options available, the treating physician must tailor treatment to the individual accounting for multiple factors, including concurrent systemic medical conditions.

When more than one topical ocular hypotensive agent is commonly required in glaucoma management, what are the options?

Two agents can be combined together into one solution (“Fixed Combination”), or the two agents can be instilled simultaneously but separately (“Unfixed Combination”).

All currently available fixed combination medications use timolol as the second agent.

<table>
<thead>
<tr>
<th>Medication Combination</th>
<th>Country of Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Timolol + Dorzolamide Cosopt®</td>
<td>MSD Pfizer</td>
</tr>
<tr>
<td>Timolol + Latanoprost Xalacom®</td>
<td>Allergan</td>
</tr>
<tr>
<td>Timolol + Travoprost Duotrat®</td>
<td>Alcon</td>
</tr>
<tr>
<td>Timolol + Bimataprost Ganfort®</td>
<td>Allergan</td>
</tr>
<tr>
<td>Timolol + Brimonidine Combigan®</td>
<td>Allergan</td>
</tr>
<tr>
<td>Timolol + Pilocarpine</td>
<td>Only available in a few countries</td>
</tr>
</tbody>
</table>

Add-on topical therapies fall into three categories:

- a) Beta blockers;
- b) Alpha agonists;
- c) Carbonic anhydrase inhibitors.

Each of these medications has its own potential side effects and precautions; in particular topical beta blockers may exacerbate asthma/reactive airways disease, heart disease, and have other central nervous system side effects. Attention must be given to the patient’s past medical history.

Topical alpha analogues are contraindicated in children, and their use may be limited by local allergic reactions.

Topical carbonic anhydrase inhibitors have little systemic side effects (occasional after-taste), but may cause local discomfort.

When a medication is added to an ongoing regimen, there are multiple options.

The following overview lists advantages and disadvantages of fixed combination therapy with un-fixed combined therapy:
Major advantages
1) Presumed improved compliance with reduced total daily instillation frequency;
2) Reduced exposure to topical preservatives;
3) Avoidance of the need to wait at least five minutes between drops from different bottles;
4) Reduced local side effects (especially hyperemia) when timolol is combined with brimonidine and any of the prostaglandin agents;
5) All this contributes to improved quality of life, an important often neglected factor in the treatment of glaucoma patients.

Major disadvantages
1) No avoidance of possible systemic and local side effects of component agents;
2) No avoidance of possible tachyphylaxis (especially with topical beta blockers);
3) The additive hypotensive effect may not meet target IOP;
4) The two agents might be slightly more effective if used in an unfixed combination (little evidence).

Implementing a combination therapy
General Principles
Medications from the same pharmacological group should not be used in combination: There is a variably additive effect across all pharmacological groups of ocular hypotensive agents, which requires any combination to be tested for each patient. No patient should use a fixed combination unless they have been shown to have inadequate IOP reduction from each agent alone, and to have an additive effect from both together.

Adherence
Even though we cannot measure accurately true compliance in everyday treatment situations as opposed to carefully crafted randomized double masked trials, we suspect it to be reduced. Indirect measurements of drug purchased from the pharmacy demonstrate that even with single daily dosage regimen the adherence was found to be as low as 50%.

These findings were confirmed by another study group that additionally found adherence further decreased if 2 medications were applied (32%).

Table 2.2 of the SEAGIG guidelines outlines the mechanisms of action of the different drug classes (reproduced with permission)

<table>
<thead>
<tr>
<th>Mechanism of action</th>
<th>Drug class</th>
<th>Preparations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase in aqueous outflow</td>
<td>PGAs</td>
<td>Latanoprost, Travoprost, Bimatoprost, Unoprostone</td>
</tr>
<tr>
<td>Increase uveoscheral outflow with Brimonidine and Prostaglandin agents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decrease in aqueous inflow</td>
<td>β-Blockers</td>
<td>β1-Non-selective Timolol, Levoburolol, Carteolol, β1-Selective Betaxolol</td>
</tr>
<tr>
<td>Increase trabecular outflow</td>
<td>α2-adrenergic agonists</td>
<td>Brimonidine, Apraclonidine</td>
</tr>
<tr>
<td></td>
<td>CAIs</td>
<td>Systemic Acetazolamide, Methazolamide, Dichlorphenamide, Topical Dorzolamide, Brinzolamide</td>
</tr>
</tbody>
</table>

Side Effects
Fixed combination therapy brimonidine + timolol appears to have a reduced incidence of allergic reaction compared with unfixed combined therapy. Initial reports of this phenomena were anec-
Having considered all above points the case history continued as follows:

This patient was keen to keep therapy simple, so after further discussion treatment with a fixed combination prostaglandin analogue + timolol with evening dosing was prescribed.

After instilling Gtt travoprost/timolol fixed combination (1 drop) at night in the right eye for 8 weeks, IOP were right 17 mmHg on the right and 21 mmHg on the left. Subsequently both eyes were treated with the same medication.

What is the best adjunctive therapy?

Additive medical decisions must be individualized to minimize side effects and maximize compliance.

When one topical medication is combined with a second, the rationale underpinning the choice of drugs is based on the knowledge of the mechanism of actions. It would make sense to combine a drug that increases aqueous outflow by increased uveoscleral outflow, (prostaglandin analogue) with a second drug that decreases aqueous inflow (a beta Blocker). Drugs of the same class would not be expected to have an additive or synergistic effect when used as a combined preparation. Another alternative is the combination of two drugs that both decrease aqueous inflow; the two available options representing this therapeutic approach combines a beta blocker either an alpha adrenergic agonist (Combigan), or with a carbonic anhydrase inhibitor (Cosopt).

Conclusion

The use of a typical glaucoma case history scenario provided the framework for discussion of the available options of combination therapy for reduction of intraocular pressure.

One of the main principles is the concomitant use of therapeutic agents that act synergistically to reduce intraocular pressure.

There are potential benefits from combination therapy that need to be balanced by the convenience of single agents as opposed to multiple agents, and must be tailored to the individual patient circumstances in order to achieve the desired target intraocular pressure.
Figure 3: Case study – Optic disc photographs (OD above, OS below).

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Clinical Issues: Fixed Combinations in Treatment Algorithms and Guidelines

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Core Concepts

- Glaucoma treatment should be started with a topical monotherapy
- If the first choice monotherapy is not effective or tolerable, a switch to a different monotherapy is to be considered
- If the first choice monotherapy is effective, but does not yield target IOP, an adjunctive therapy is to be considered
- When two or more actives are necessary a fixed combination should be considered.
- Fixed combinations may offer several advantages, such as improved efficacy and tolerability – through less exposure to preservatives – as well as improved patient compliance and quality of life.

There’s a general consensus to start glaucoma medical therapy with one topical intraocular pressure (IOP) lowering medication. If the first choice monotherapy alone is not effective to reduce IOP or is not tolerated, it is preferable to switch to another molecule that is initiated as monotherapy. Adjunctive therapy should be considered whenever a monotherapy does not reach target IOP or the target must be lowered as the disease is progressing (1,2) (Fig.1). Usually fixed-combinations are not ideal as a first choice product, unless an large reduction in IOP is needed quickly.

In such cases, fixed-combination drug preparations may have advantages if compared with two separate instillations of the same agents (1) (Fig.1).

Improved compliance. Compliance with any given medical therapy in glaucoma, like other chronic diseases, is better when regimens are simple rather than complex (3). In most patients it is not recommended to use more than two drugs in two separate bottles or to add more than one single drug to a fixed-combination. Besides complexity, the higher costs from more bottles seem to promote non-compliance and reduce persistence (4).

Reduced daily amount of exposure to preservatives and side effects: There may be a direct correlation between the presence of preservatives and the surface symptoms provoked by anti-glaucoma therapy (5); reducing such exposure could improve the patient’s comfort and thus compliance. Long-term use of topical drugs may be detrimental as a dose- and time-dependent consequence to benzalkonium chloride exposure (5). Such changes may reduce the success rate of subsequent filtration surgery (6). Although no definitive data exist, at least some of the currently available fixed combination have shown a better safety profile and tolerability when compared with the same molecules used separately (1,7).

Possibly more efficacy. Several open-label replacement studies have suggested an additional IOP lowering effect when switching from dorzolamide and a beta-blocker to the fixed-combination dorzolamide/timolol, but no definitive data is available (7). Increased compliance and elimination of the dilution effect if drops are instilled from different bottles without sufficient time between, could explain such fixed-combination benefit.

A substantial proportion of patients on a multiple drops regimen wait less than 3 minutes before instilling the second medication. The dilution effect occurs when patients consecutively instill multiple eye drops too closely, so that the first drop is washed away by the second drop before the first can achieve maximal ocular penetration and thus efficacy (8).

Possible cost savings. The cost of a fixed combination is not necessarily less than the sum of the two separate medications (7).
Glaucoma is a chronic, asymptomatic disease that requires long-term, potentially costly treatment. Medical treatment often causes side effects, with no subjective improvement in visual function. Unsurprisingly, non-adherence is so frequent among our patients. One additional factor increasing non-adherence rates is the frequent need for more than one medication to control their intraocular pressure (IOP). Among the patients on medications in the Ocular Hypertension Treatment Study, 40% required 2 or more medications to obtain a mean IOP reduction of 20%. When IOP reduction is greater, such as in the Collaborative Initial Glaucoma Treatment Study, where patients achieved a mean IOP reduction of 40%, 75% of those in the medical treatment group were using 2 or more agents.

One of the most important factors associated with non-adherence is the medical regimen. Patel & Spaeth demonstrated that while 49% of patients using one medication for the treatment of glaucoma were compliant, only 32% of those using two medications were. The more medications we prescribe for one patient, the higher the chances of non-adherence.

Using multiple agents can also lead to an undesirable "washout effect". Although we ask patients to wait at least 5 minutes between dosing different medications, few of them actually do. If a patient waits only 30 seconds between dosing multiple agents, the IOP reduction of one medication can be washed out by the other agents.

Conclusions
When two or more active molecules are necessary to obtain an adequate IOP, fixed-dose combination eye drops may offer advantages for patients, while maintaining at least the same effect on IOP than separate instillation of the same two products. Reducing the number of daily drops may improve compliance and quality of life, save costs and reduce detrimental effects to the ocular surface.

REFERENCES

Practical Tips:
Fixed Combinations and Patient’s Perspective
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Core concepts
• Glaucoma is an asymptomatic disease and motivating patients to adhere to treatment is a well known issue
• Studies have shown that only about 50% of patients adhere to monotherapy and even less patients adhere to a therapy scheme including to 2 medications; as a consequence this has a negative effect on drug efficacy and treatment success
• In combination therapy use of multiple agents can lead to washout effects and increase exposure to toxic effects of preservatives
• Use of fixed combinations decreases such issues and ultimately have a positive effect on patients’ quality of life.

One of the most important aspects for patients.

Good quality of life, which is one of the important tool in order to maintain a efficacy, fixed combinations represent an ing drops and bottles without losing ef-
side effects and therapy costs. By reduc-
ing disease, other factors alone or in combi-
may affect patients’ quality
of life: inconvenience of the treatment,
ber of daily drops may improve compli-
ance and quality of life, save costs and re-
duce detrimental effects to the ocular
surface.

Quality of life. The goal of glaucoma treat-
tment is to maintain the patient’s vi-
sual function and related quality of life
(1). Besides the functional loss and hav-
ing the diagnosis of a potentially blind-
disease, other factors alone or in combi-
i

than the cost of the single components. However, fixed combinations reduce the number of purchased bottles, which may reduce costs for patients whose prescription drug coverage requires a co-payment for each prescription filled.
instilled at the same time, 24.5 % when they were instilled 2 minutes apart, and 27.3 % when the interval between drops was 5 minutes\(^1\).

Recently, interest has increased concerning ocular surface disease in glaucoma patients on medical treatment. Several medications increase toxic effects to the ocular surface, which may be secondary to eye drop preservatives (especially benzalkonium chloride, BAK)\(^2\).

In terms of efficacy, most randomized, clinical trials that compared fixed with unfixed combinations showed better IOP control with the latter. While randomized, controlled trials are the best way to assess efficacy and safety of medications, they do not provide insight into the impact on adherence, since all patients are closely monitored and encouraged to use their medications correctly. “Real-world” studies, in which glaucoma patients are switched from unfixed to fixed-combination therapy, demonstrate further reductions in IOP, probably as a consequence of increased adherence to therapy\(^3\)\(^,\)\(^4\).

In conclusion, fixed combinations may increase adherence and improve the patient’s quality of life by decreasing the number of instillations required per day and by reducing the toxic effects induced by preservatives. Finally, they may even improve the IOP reduction compared with unfixed combinations, especially in non-adherent patients. These benefits have encouraged some ophthalmologists to use fixed combinations as first-line therapy. We do not recommend this approach: patients should be started on monotherapy, with other medications being substituted or added in a stepwise fashion as needed to achieve target IOP. Before using a fixed combination, the ophthalmologist needs to confirm the efficacy and safety of each of its constituent compounds for the individual patient.

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STATEMENT OF NEED AND PROGRAM DESCRIPTION
Recent months and years have seen significant advances in our understanding of glaucoma. Much has been learned, not only about damage mechanisms and pathogenesis, but also about diagnosis and management. Treatment options – both medical and surgical – continue to expand. This program will review this new knowledge with an emphasis on incorporating recent insights into day-to-day practice.

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