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 preservative, 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 systemically well on no medications. His unaided visual acuity was 6/6 OU.

His intra-ocular pressures (IOP) were 22 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.

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 uveoschleral outflow</td>
<td>Cholinergics</td>
<td>Pilocarpine, Carbachol</td>
</tr>
<tr>
<td>Increase trabecular outflow</td>
<td>β1-Blockers</td>
<td>Timolol, Levoburolol, Betaxolol, Betatropine</td>
</tr>
<tr>
<td></td>
<td>β1-Selective</td>
<td>Carteolol</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Betaxolol</td>
</tr>
<tr>
<td></td>
<td></td>
<td>α2-adrenergic agonists</td>
</tr>
<tr>
<td></td>
<td>CAIs</td>
<td>Systemic Acetazolamide, Methazolamide, Dichlorphenamide</td>
</tr>
<tr>
<td></td>
<td></td>
<td>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-

---

Figure 1: Case study – Humphrey Visual Field Test 24-2, right eye.
and reflect differing methodologies for the studies.¹

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.
REFERENCES


