Meta-analysis of randomised controlled trials comparing latanoprost with timolol in the treatment of patients with open angle glaucoma or ocular hypertension

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Authors’ objectives
To evaluate the efficacy and tolerance of latanoprost in comparison with timolol for open angle glaucoma and ocular hypertension.

Searching
MEDLINE, EMBASE and the Science Citation Index were searched from 1966 to July 2000. The search terms and strategies were described in the report. The bibliographies of studies and reviews were checked. The manufacturers’ databases, including the Pharmacia Upjohn ophthalmology database and the Merck glaucoma database, were searched. Once the searches had been completed, a list of identified trials was sent to the manufacturers in order that any additional trials might be identified.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion. Single- and double-blind, parallel and crossover studies were included.

Specific interventions included in the review
Studies of latanoprost versus timolol were eligible for inclusion. In most of the included studies latanoprost eye drops 0.005% were used once or twice a day; one study used 0.006% twice a day, while another study used 0.0015% twice a day and 0.005% once a day in a crossover design. The comparator was twice daily 0.5% timolol eye drops. The included studies lasted from one week to 12 months.

Participants included in the review
Studies in patients with primary or secondary open angle glaucoma, or ocular hypertension were eligible for inclusion. The majority of the patients in the included studies had primary open angle glaucoma or ocular hypertension. The mean age of the participants in the studies ranged from 46 to 67 years. The studies were conducted in various countries in North America, Asia and Europe.

Outcomes assessed in the review
The main efficacy outcome was the percentage reduction in intraocular pressure (IOP). The outcomes for side-effects included risk of hyperaemia, conjunctivitis and increased iris pigmentation. The reduction in systemic blood-pressure (hypotension) and heart rate (bradycardia) were also assessed.

How were decisions on the relevance of primary studies made?
The authors state that they read the titles and abstracts of citations retrieved, suggesting that more than one reviewer was involved, but no other details of the selection process were reported.

Assessment of study quality
Validity was assessed using the criteria proposed by Jadad et al. (see Other Publications of Related Interest no.1). In addition, blinding was differentiated as double, single or open-label, and the trials were categorised as parallel or crossover. The authors do not state how the papers were assessed for validity, or how many of the reviewers performed the validity assessment.

Data extraction
Two reviewers independently extracted the data using a standard form and resolved any disagreements by discussion. The data extracted were: author, year, study design, location, duration, the number of participants, age, gender, type of glaucoma and percentage withdrawals. For the latanoprost group and the timolol group in each study, the baseline mean IOP and the end point mean IOP were extracted along with their associated standard errors. The mean value of IOP measured in the morning, noon and afternoon was used in the analyses, except for one trial which only measured IOP in the morning. The data on local and systemic side-effects were extracted and the relative risk (RR), risk difference and the number-needed-to-harm (NNH) were estimated using intention-to-treat analysis. When the event rates were zero, 0.5 was added to each cell in the 2x2 table.

Methods of synthesis
How were the studies combined?
A meta-analysis was used to pool the difference in the percentage reduction in IOP from baseline between latanoprost and timolol. The studies were weighted by the inverse of the variance (see Other Publications of Related Interest no.2). For adverse effects, the RR and risk difference were pooled using the method of DerSimonian and Laird (see Other Publications of Related Interest no.3). A random-effects model was used in the presence of unexplained statistical heterogeneity. The NNH and 95% confidence intervals (CIs) were estimated using the method of Cook and Sackett (see Other Publications of Related Interest no.4). Publication bias was not investigated.

How were differences between studies investigated?
The Q-statistic was used to assess statistical heterogeneity in the meta-analyses. Using the main efficacy outcome, differences between those studies that administered latanoprost in the evening, morning or twice daily were investigated by subgroup analyses that pooled individual treatment arms across the trials. Sensitivity analyses were conducted on the main efficacy outcome to look for differences by study design and withdrawal rates (greater than 10% versus less than 10%).

Results of the review
Eleven RCTs (n=1,256) were included.

The difference in the percentage reduction in IOP with latanoprost in comparison with timolol was 6.9 (95% CI: 0.4, 13.4) at one week (3 trials, n=81), 3.8 (95% CI: 1.2, 6.3) at one month (3 trials, n=524), 5.0 (95% CI: 2.8, 7.3) at 3 months (5 trials, n=841), and 5.0 (95% CI: 2.8, 7.3) at 6 months (4 trials, n=865). All differences were statistically significant. A random-effects model was apparently used to pool the data at one, 3 and 6 months because of statistical heterogeneity (p<0.001), but the tabulated information and the graph appeared to be inconsistent in that respect. Only one trial (n=36) provided data at 12 months (4.9, 95% CI: -5.9, 15.8) that showed no statistically-significant difference. The sensitivity analyses showed no statistical difference between the different study designs or between trials with greater than 10% versus less than 10% withdrawal rates.

Compared with timolol, the RR of hyperaemia was 2.2 (95% CI: 1.33, 3.65) and the NNH was 21 (95% CI: 14, 42) with latanoprost (6 trials, n=1,089). Iris pigmentation occurred in 21 of the 478 patients treated with latanoprost and in none of the 387 patients treated with timolol (4 trials; RR 8.0, 95% CI: 1.87, 34.3; NNH 36, 95% CI: 22, 91). No significant difference was shown for conjunctivitis (3 trials, n=739), hypotension (one trial, n=294) or bradycardia (one trial, n=178). Heterogeneity was not reported.

One trial (n=268) reported a reduction in heart rate of 4 beats per minute (bpm) (95% CI: 2, 6) at 3 and 6 months in the timolol group (p<0.01), compared with one bpm (95% CI: -2, 4) at 6 months in the latanoprost group. One other trial (n=294) showed no difference in bpm with timolol at 6 months.

One crossover trial compared an evening with a morning regimen of latanoprost. Only the first period data were considered, supposedly to reduce carryover effect, and these showed no statistically-significant difference in IOP reduction at 3 months (4.6%, standard error 2.6, p=0.08). The authors appear to have achieved a statistically-significant difference between the evening and morning regimens by pooling indirect comparisons.

Once-daily versus twice-daily latanoprost was not directly compared in any of the included trials. The authors appear to have pooled once-daily latanoprost data from three of the included trials with data from another RCT (n=50) that
compared once- versus twice-daily latanoprost (0.006%) with concomitant timolol in both groups. No statistically-significant difference was shown.

Cost information
Based on UK costs and assuming no difference in effectiveness, the authors estimated that once-daily latanoprost would be three times more expensive than timolol twice a day.

Authors’ conclusions
The meta-analysis suggests that latanoprost is more effective than timolol in lowering IOP, but since latanoprost often causes iris pigmentation careful lifetime evaluation is justified.

CRD commentary
The review addressed a clear question in terms of the participants, intervention, comparator, outcomes and study design. Appropriate databases were searched and unpublished data were sought. No language restriction was mentioned. There were insufficient details to assess whether the study selection process was open to reviewer bias. The data were extracted in a way that should have minimised bias and errors. Some characteristics of the included trials were presented in tabular format.

The internal validity of the included trials was assessed systematically, although quality features specific to crossover trials were not considered. Sensitivity analyses were used to look for differences in effect by study design, but the number of studies was too small to draw meaningful conclusions. The data appear to have been pooled appropriately for the main outcomes, but the methods do not explain whether both treatment periods of the crossover trials were used in any of the analyses. It was also unclear whether statistical heterogeneity was examined appropriately. This could not be checked because the number of participants and events in each study were not reported according to treatment group. No details about the presence or absence of co-morbidities among the participants in the included trials were reported, to aid interpretation of the side-effects findings. The analyses of the effects of different latanoprost regimens were not robust.

The authors' main conclusions are consistent with the evidence presented, but their conclusions concerning different regimens are probably not reliable. The conclusions on side-effects other than hyperaemia and iris pigmentation are based on very few data.

Implications of the review for practice and research
Practice: The authors state that latanoprost is a suitable alternative if timolol is contraindicated. However, ongoing surveillance of iris pigmentation is necessary.

Research: The authors state that a rigorous economic evaluation of latanoprost and timolol is needed.

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