SCIENTIFIC REPORT

Long term effect of latanoprost on intraocular pressure in normal tension glaucoma

A Ang, M A Reddy, L Shepstone, D C Broadway

....

Aim: To determine the long term effect of latanoprost on the intraocular pressure (IOP) of patients with normal tension glaucoma (NTG).

Methods: Newly diagnosed patients with NTG were recruited into the study and had their baseline IOPs measured hourly between 8 am and 5 pm using a handheld electronic Tonopen. Patients with fixation threatening field defects were placed immediately into the treatment group while those with non-fixation threatening field defects were randomised into either the treatment group or the control group (no treatment). Treatment consisted of once daily topical latanoprost 0.005%. After a minimum period of 6 months, the patients underwent a second period of IOP phasing.

Results: 76 newly diagnosed patients with NTG were recruited—26 had fixation threatening disease, 25 were randomised to treatment, and 25 randomised to the control group. The average duration of treatment was 11 months. The average and maximum diurnal IOP for the patients randomised to treatment were statistically significantly lower than for the control patients at follow up (p<0.05). The treated group as a whole demonstrated a 17% decrease in the average diurnal IOP and a 19% decrease in the maximum diurnal IOP when compared to baseline IOP. 41% of those treated achieved a decrease of at least 20%, but only 10% of patients achieved a decrease of at least 30%.

Conclusion: Latanoprost had a sustained hypotensive effect in eyes with NTG and 41% of treated patients achieved a reasonable response. However, in the majority of eyes with NTG, latanoprost monotherapy may be insufficient in producing a desirable 30% reduction in IOP.

About 25% of white patients with glaucoma have normal tension glaucoma (NTG).[1] In such patients, a 30% reduction in intraocular pressure (IOP) can slow the rate of progressive visual field loss.[2][3] Fistulising surgery is an effective method of lowering IOP but is associated with potential complications which can mask the overall visual benefit gained by the IOP reduction.[2] Medical therapy provides a potentially safer alternative but had been disappointing in previous studies.[4][5] With the introduction of new antiglaucoma drugs such as latanoprost, the concept of medical therapy for NTG needs to be reassessed.

An effect of latanoprost in patients with NTG has been reported previously in short term studies (≤2 months) with small numbers of subjects.[6–9] This study was conducted to determine the longer term effect of latanoprost on the IOP of patients with newly diagnosed NTG.

PATIENTS AND METHODS

Patients attending the glaucoma clinic in the Department of Ophthalmology (Norfolk and Norwich University Hospital) with features of NTG were enrolled into the study between January and June 2000. All patients underwent a full ophthalmic examination including Snellen visual acuity, refraction, an automated (Humphrey 24-2 SITA Standard) visual field analysis and slit lamp biomicroscopy. In addition, central corneal thickness was measured using an ultrasonic pachymeter (the BVI Pocket Pachymeter; Spectrum Ophthalmics, Macclesfield, UK). The mean of five reasonably consistent readings (plus or minus 5 μm) from each eye was taken as the central corneal thickness for the present study.

A diagnosis of NTG was made if (1) glaucomatous optic disc changes and visual field defects characteristic of glaucoma (as defined by the Collaborative Normal Tension Glaucoma Study) were present in one or both eyes of the patient, and (2) no recorded IOP greater than 22 mm Hg in either eye during a routine period of daytime IOP phasing (one spike of 24 mm Hg being allowed). Only patients performing reliable visual field analyses (that is, false positive rate of <15%, false negative rate of <30%, and fixation loss rate of <15%) were invited to take part in the study.

Demographic data collected for each patient included age, sex, racial origin, family history of glaucoma, previous medical and ophthalmic history, smoking and drug history. Patients were excluded if they were taking systemic medications with any potential effect on visual field (such as vigabatrin), had undergone previous intraocular surgery, or had a history of systemic or ocular pathology that could have had an effect on the optic disc, visual field, or IOP. Patients taking systemic β blockers were not excluded if treatment had been started before enrolment into the study and the dosage had remained stable throughout.

Following diagnosis of NTG, patients with field defects threatening fixation were placed immediately into the treatment group. Patients with non-fixation threatening field defects were randomised into either the treatment group or a control group by the flip of a coin. Treatment consisted of one drop of topical latanoprost 0.005% a day, taken between 9 pm and 11 pm. Patients in the control group were left untreated.

After a minimum period of 6 months, each study patient underwent a second period of daytime IOP phasing. Throughout the study period patients were monitored according to clinical need and anyone showing signs of definite progressive visual field loss had their second session of IOP phasing expedited so that they could exit the study.

At both periods of daytime IOP phasing each patient had 10 IOP recordings made hourly between 8 am and 5 pm using an electronic, handheld tonometer (Tonopen XL,

....

Abbreviations: AIOP, average IOP; CCT, central corneal thickness; IOP, intraocular pressure; MIOP, maximum IOP; NTG, normal tension glaucoma; RMSE, root mean squared error

Bio-Rad, Glendale, CA, USA). Only readings with a measurement error of 5% or less were accepted. The measurements of IOP were made by one of two observers masked to the treatment status of the patient (authors AA and MAR).

The study was approved by the Norwich District ethics committee and all patients underwent informed consent.

Statistical methods

Only patients who were randomised to the study were included in any formal analysis comparing the treated group to the control group. The primary end points of interest were the average IOP (AIOP) and maximum IOP (MIOP) in one treated eye (selected at random when both eyes had been treated) over the 10 readings at follow up. The AIOP was calculated as the average of the IOP readings obtained during phasing for the selected eye. A two sample *t* test was used to test for a difference in the mean follow up AIOP and MIOP between the two randomised groups (after checking that the variables concerned had a normal distribution). A general linear model was employed to calculate the mean follow up AIOP and MIOP adjusted for differences in baseline variables. The estimated ''root mean squared error'' (RMSE) was used as an estimate for a common standard deviation for the two treatment groups.

Of secondary interest, the range of IOP (that is, the maximum value of IOP minus the minimum value for each eye) at follow up between the two randomised groups was also compared using a two sample *t* test with adjustments for baseline differences as above.
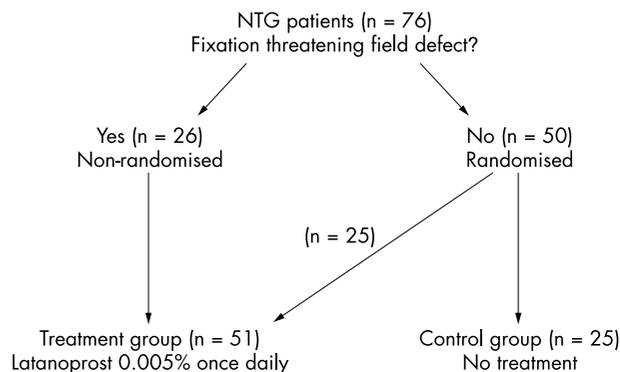

Figure 1 Chart of participant flow. NTG = normal tension glaucoma.

Comparisons of the AIOP and MIOP before and after treatment within the group of all treated patients were made by expressing the change in IOP as a percentage of the baseline value. A subgroup analysis was performed using the general linear model to explore the interactions between the various clinical factors and the response to latanoprost. Pearson's correlation coefficient was calculated to determine the correlation between the baseline AIOP and the reduction in IOP with treatment.

A sample size of 53 randomised eyes was calculated to have 80% power to detect a 1.5 mm Hg difference in the mean AIOP between the two randomised groups at the required

Table 1 Baseline characteristics of the treatment groups

|	Control (n = 25)	Latanoprost (randomised) (n = 25)	Latanoprost (non-randomised) (n = 26)
Sex			
Male	14 (56%)	16 (64%)	15 (58%)
Female	11 (44%)	9 (36%)	11 (42%)
Age (years)			
Mean	71.5	65.7	74.0
SD	10.6	11.7	9.3
Smoking status			
Non-smoker	14 (56%)	11 (46%)	10 (42%)
Ex-smoker	11 (44%)	8 (33%)	13 (54%)
Current smoker	0	5 (21%)	1 (4%)
Unknown	0	1	2
Currently using			
α Blockers	2 (8%)	0	2 (8%)
β Blockers	3 (12%)	3 (12%)	4 (15%)
Treated eye			
Left	13 (52%)	14 (56%)	14 (54%)
Right	12 (48%)	11 (44%)	12 (46%)
Disease duration (months)			
Mean	12.1	12.4	13.3
SD	4.7	5.5	7.3
Average baseline IOP (mm Hg)			
Mean	14.4	17.5	16.4
SD	2.5	1.8	2.6
Maximum baseline IOP (mm Hg)			
Mean	17.6	20.8	19.6
SD	3.0	2.1	2.7
Range of baseline IOP (mm Hg)			
Mean	6.2	6.5	6.1
SD	2.6	1.9	2.0
Length of treatment (months)			
Mean	NA	11.0	11.6
Median		9	10
SD		5.3	6.4
Time until follow up (months)			
Mean	11.1	11.4	12.8
SD	4.2	5.4	6.3
Central corneal thickness (μm)			
Mean	532.0	521.6	522.2
SD	27.9	34.4	33.4
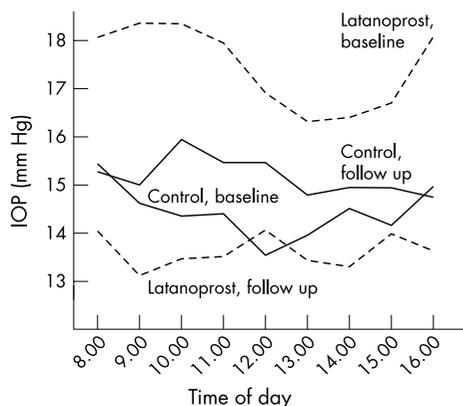
Figure 2 Diurnal IOP curves of randomised treated (broken line) and control (solid line) groups at baseline and follow up.

level of significance (standard deviation = 3.8 mm Hg, $\alpha = 0.05$). A p value of less than 0.05 was considered to be statistically significant.

On a selected number of randomly chosen patients, IOP measurements were performed by both observers using the same handheld electronic tonometer. Using the methodology as described by Bland and Altman, limits of agreement of the repeated measurements were calculated.[10] This was to ensure that the IOP measurements between the two observers were comparable.

All calculations were performed using SAS, version 8.2 (SAS institute Inc, Cary, NC, USA).

RESULTS

Twelve patients out of the 95 invited to participate dropped out before the first round of phasing (10 declined for personal reasons, one patient died, and one patient moved away). Of the remaining 83 patients, 28 had fixation threatening field defects and were started on treatment. Twenty six patients were randomised to receive treatment while 29 were randomised to the control group. Seven patients (two non-randomised patients, one randomised latanoprost patient, and four controls) failed to undergo their follow up phasing because of either personal reasons (one developed carcinoma, and one moved away) or for medical reasons (one developed uveitis, one developed keratitis, and three started systemic β blockers during the study period).

The flow of patients who completed the study is as shown in figure 1. No patients were switched between the groups and none of the patients had their phasing expedited because of progression of NTG. However, at both baseline and follow

up, IOP readings were not available for the 5 pm reading for approximately 50% of the individuals studied (at baseline, 5 pm data were available for 17 controls and 11 randomised latanoprost patients and at follow up data were available for 13 and 10 patients respectively) because of the development of ocular irritation in those patients concerned towards the end of the phasing period, so that the final IOP was not measured. Therefore, the AIOP was calculated as the average of the first nine readings.

The baseline characteristics for the three patient groups are shown in table 1. The baseline AIOP and MIOP were greater in the randomised latanoprost group than in the control group (17.5 mm Hg v 14.4 mm Hg and 20.8 mm Hg v 17.6 mm Hg respectively). Other differences included the average age and smoking status of the patients. The central corneal thickness (CCT) was similar in the three groups.

The mean treatment duration in the randomised latanoprost group was 11 months (range 6–27 months, median 9 months) and in the non-randomised latanoprost group 11.6 months (range 6–26 months, median 10 months).

Figure 2 shows the mean diurnal curves for both randomised groups at baseline and at follow up. At baseline, the curves appeared similar in shape between the two groups. Both groups tended to exhibit higher pressures in the morning, decreasing around noon, and then increasing again by late afternoon.

The randomised latanoprost group had a statistically significantly lower mean AIOP and MIOP than the control group at follow up (1.5 mm Hg and 1.8 mm Hg respectively). After adjustment for baseline differences, the estimated mean differences increased to 2.7 mm Hg for both variables (tables 2 and 3). Further adjustment, by age and smoking status, did not alter the magnitude of this difference to any significant extent. No statistically significant difference was found in the IOP range (table 4).

The mean AIOP in the treated group (randomised and non-randomised patients) was reduced from 16.9 mm Hg to 14.1 mm Hg (17%) while the mean MIOP was reduced from 20.3 mm Hg to 16.4 mm Hg (19%). Patients randomised to treatment had their mean AIOP and MIOP reduced by 22% (from 17.5 mm Hg to 13.7 mm Hg) and 24% (from 20.9 mm Hg to 15.8 mm Hg) respectively. In comparison, non-randomised patients exhibited a reduction of mean AIOP of 12% (from 16.4 mm Hg to 14.5 mm Hg) and a reduction of mean MIOP of 14% (from 19.7 mm Hg to 16.9 mm Hg).

The reduction in IOP obtained with latanoprost treatment correlated with the baseline AIOP (fig 3). This correlation was significant ($r^2 = 0.31$, p = 0.01). When considering other potential factors that may have had an effect on the

Table 2 Follow up average intraocular pressure

	Control (n = 25)	Latanoprost (n = 25)	Difference	95% CI†	Significance
Average follow up IOP					
Mean (mm Hg)	15.2	13.7	1.55	0.27 to 2.83	p = 0.020
SD	2.4	2.1			
Adjusted analyses					
Baseline IOP					
Adjusted mean (mm Hg)	15.8	13.1	2.68	1.20 to 4.16	p<0.001
RMSE*	2.1	2.1			
Baseline IOP + age					
Adjusted mean (mm Hg)	15.7	13.1	2.63	1.07 to 4.19	p = 0.002
RMSE*	2.2	2.2			
Baseline IOP + age + smoking					
Adjusted mean (mm Hg)	16.1	13.2	2.94	1.36 to 4.52	p<0.001
RMSE*	2.1	2.1			

*Root mean squared error.
†Confidence interval.

Table 3 Follow up maximum intraocular pressure

	Control (n = 25)	Latanoprost (n = 25)	Difference	95% CI†	Significance
Maximum follow up IOP					
Mean (mm Hg)	17.5	15.7	1.8	0.31 to 3.29	p = 0.019
SD	3.0	2.2			
Adjusted analyses					
Baseline IOP					
Adjusted mean (mm Hg)	17.9	15.2	2.71	0.94 to 4.49	p = 0.0041
RMSE*	2.6	2.6			
Baseline IOP + age					
Adjusted mean (mm Hg)	17.8	15.3	2.45	0.65 to 4.25	p = 0.009
RMSE*	2.6	2.6			
Baseline IOP + age + smoking					
Adjusted mean (mm Hg)	18.1	15.5	2.58	0.73 to 4.44	p = 0.008
RMSE*	2.6	2.6			

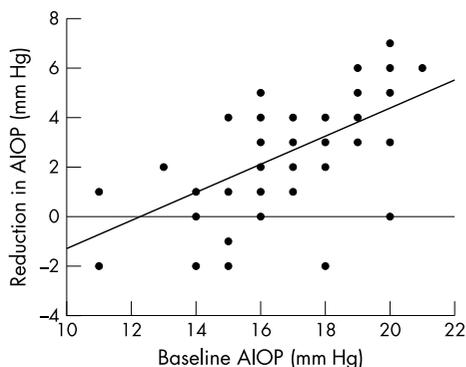*Root mean squared error.
†Confidence interval.

Figure 3 Scattergraph demonstrating the relation of magnitude of average IOP (AIOP) reduction versus baseline AIOP in the treated group as a whole (randomised and non-randomised).

hypotensive effect of latanoprost, only age of patient was found to interact significantly with treatment. This was significant irrespective of whether AIOP (p = 0.017) or MIOP (p = 0.004) was considered. In both cases the difference in IOP between the control and randomised treated group increased with increasing age. There was no significant relation found between CCT and baseline IOP.

Fifteen pairs of repeated IOP measurements were compared for the calculation of limits of agreement between the two observers. The mean difference of the measurements was 0.3 mm Hg and the 95% confidence interval was −0.2 mm Hg to 0.7 mm Hg. The limits of agreement were −1.3 mm Hg to 1.7 mm Hg.

DISCUSSION

In the Collaborative Normal-Tension Glaucoma Study (CNTGS), pilocarpine 2% alone achieved the required 30% IOP reduction in eight of 30 patients with NTG.[2][3] Potential side effects and high frequency of application (four times daily) has reduced the popularity of pilocarpine especially in the presence of newer generation glaucoma medications. Latanoprost is a ''new generation'' drug that has recently been evaluated as a potential therapy for patients with NTG in short term studies.[6–9]

In the present study, patients with fixation threatening disease were not randomised as it was considered unethical to withhold treatment from them. Although not included in formal analyses (to avoid the introduction of bias), data from the non-randomised eyes were presented in an observational, descriptive manner since such data provide potentially useful information about the hypotensive effect of latanoprost in eyes with NTG.

In an effort to minimise observer error, the IOP measurements in the study were made objectively with the handheld electronic tonometer. Good agreement between the electronic tonometer and the Goldmann applanation tonometer had previously been found although this was not evaluated in this study.[11][12] Differences in the technique of using the electronic tonometer between the two observers could have introduced some error. Fortunately, interobserver limits of agreement were found to be good when tested.

At baseline, the randomised latanoprost group had a higher average AIOP and MIOP in comparison with the control group. This bias occurred despite the randomisation process and was possibly a reflection of the relatively small number of subjects in the study. Despite the baseline

Table 4 Follow up range intraocular pressure

	Control (n = 25)	Latanoprost (n = 25)	Difference	95% CI†	Significance
Range follow up IOP					
Mean (mm Hg)	4.7	4.2	0.56	−0.39 to 1.51	p = 0.245
SD	2.1	1.0			
Adjusted analyses					
Baseline IOP					
Adjusted mean (mm Hg)	4.8	4.0	0.85	−0.34 to 2.04	p = 0.162
RMSE*	1.7	1.7			
Baseline IOP + age					
Adjusted mean (mm Hg)	4.7	4.2	0.52	−0.67 to 1.71	p = 0.386
RMSE*	1.6	1.6			
Baseline IOP + age + smoking					
Adjusted mean (mm Hg)	4.7	4.2	0.50	−0.66 to 1.66	p = 0.391
RMSE*	1.6	1.6			

*Root mean squared error.
†Confidence interval.

differences, AIOP and MIOP were statistically significantly lower in the randomised latanoprost group following treatment (1.5 mm Hg and 1.8 mm Hg respectively). The mean differences were estimated to be 2.7 mm Hg when adjustments were made for baseline disparities, confirming the significant hypotensive effect of latanoprost in NTG. The treatment duration was for at least 6 months and averaged 11 months, indicating that the ocular hypotensive effect of latanoprost is sustained in NTG.

The average reductions of IOP achieved were 17% for AIOP and 19% for MIOP in the treated group (randomised and non-randomised latanoprost patients). Other investigators had achieved similar IOP reductions of 18–21.4% after shorter follow up periods.[6–8] In the present study, 41% (21 of 51) of those treated achieved a minimum reduction of 20% in the AIOP but only 10% (five of 51) achieved a minimum reduction of 30%. Taking a 20% IOP reduction as a reasonable response, about four of 10 treated patients would achieve this target on treatment with latanoprost alone.

Patients randomised to treatment appeared to respond better to latanoprost than non-randomised patients. The reason for this phenomenon is unclear but may be partly accounted for by the higher baseline AIOP and MIOP, wider IOP range, and smaller standard deviation between values in the randomised latanoprost group. Alternatively, there may have been a difference in compliance between the patients. Unfortunately compliance was not formally assessed in this study. It is also possible that eyes with a more advanced, fixation threatening disease are more resistant to latanoprost. A subgroup analysis however did not find any significant interaction between the visual field mean defect (which is an indicator of disease severity) and response to latanoprost. Interestingly, age of patient had a significant effect on response to latanoprost. This has not been documented previously and may be of clinical importance when managing patients with NTG.

As reported in previous studies, response to latanoprost appeared to be better with higher baseline IOP.[6 8 9] Another more likely explanation for this phenomenon was regression to the mean, whereby higher initial IOP measurements were more likely to "regress to the mean" on repeat measurement and therefore was independent of the action of latanoprost.

There was a trend towards a flattening of the diurnal curve with treatment (fig 2). However, no statistically significant change in IOP range was found. This may be a reflection of the small numbers involved in the study.

The average CCT of the patients involved in the study was 525 μm. Copt et al found a similar average CCT in their NTG patients which were less than their primary open angle glaucoma and ocular hypertensive counterparts.[13] In our study, no significant relation was found between CCT and measured IOP.

There were some potential weaknesses in the present study. Firstly, no placebo was used in the control group and thus the patients were not masked to their treatment status. The observers, however, were masked to the treatment status. This minimised the potential bias introduced into the study since it would have been unlikely for there to have been a placebo effect on IOP. Secondly, as mentioned, compliance with treatment was not objectively assessed in the treated group.

In conclusion, a sustained ocular hypotensive effect of latanoprost in eyes with NTG was found after an average treatment period of nearly 1 year. Forty one per cent of those treated achieved a reasonable IOP reduction of at least 20% but only a relatively small proportion of NTG patients (10%) treated with latanoprost monotherapy achieved the 30% reduction in IOP advocated by the CNTGS Group.[2 3]

. . . .

Authors' affiliations
A Ang, M A Reddy, D C Broadway, Norfolk and Norwich University Hospital, Colney Lane, Norwich NR4 7UY, UK
L Shepstone, School of Medicine, Health Policy and Practice, University of East Anglia, Norwich NR4 7TJ, UK

Commercial interest: None.

Correspondence to: Mr David Broadway, Department of Ophthalmology, Norfolk and Norwich University Hospital, Colney Lane, Norwich NR4 7UY, UK; david.broadway@nnuh.nhs.uk

Accepted for publication 4 September 2003

REFERENCES
1 **Klein BE**, Klein R, Sponsel WE, et al. Prevalence of glaucoma. The Beaver Dam Eye Study. Ophthalmology 1992;**99**:1499–504.
2 **Collaborative Normal-Tension Glaucoma Study Group**. The effectiveness of intraocular pressure reduction in the treatment of normal-tension glaucoma. Am J Ophthalmol 1998;**126**:498–505.
3 **Collaborative Normal-Tension Glaucoma Study Group**. Comparison of glaucomatous progression between untreated patients with normal-tension glaucoma and patients with therapeutically reduced intraocular pressures. Am J Ophthalmol 1998;**126**:487–97.
4 **Nyman K**. Intraocular pressure reduction with topically administered pilocarpine, timolol and betaxolol in normal tension glaucoma. Acta Ophthalmol (Copenh) 1993;**71**:686–90.
5 **Sacca SC**, Macri A, Rolando M, et al. Effect of betaxolol on primary open-angle glaucoma and normal-tension glaucoma patients. J Ocul Pharmacol Ther 1998;**14**:191–201.
6 **McKibbin M**, Menage MJ. The effect of once-daily latanoprost on intraocular pressure and pulsatile ocular blood flow in normal tension glaucoma. Eye 1999;**13**(Pt 1):31–4.
7 **Greve EL**, Rulo AH, Drance SM, et al. Reduced intraocular pressure and increased ocular perfusion pressure in normal tension glaucoma: a review of short-term studies with three dose regimens of latanoprost treatment. Surv Ophthalmol 1997;**41**(Suppl 2):S89–92.
8 **Rulo AH**, Greve EL, Geijssen HC, et al. Reduction of intraocular pressure with treatment of latanoprost once daily in patients with normal-pressure glaucoma. Ophthalmology 1996;**103**:1276–82.
9 **Tamada Y**, Taniguchi T, Murase H, et al. Intraocular pressure-lowering efficacy of latanoprost in patients with normal-tension glaucoma or primary open-angle glaucoma. J Ocul Pharmacol Ther 2001;**17**:19–25.
10 **Bland JM**, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986;**1**:307–10.
11 **Viestenz A**, Lausen B, Junemann AM, et al. [Comparison of precision of the TonoPenXL with the Goldmann and Draeger applanation tonometer in a sitting and recumbent position of the patients—a clinical study on 251 eyes]. Klin Monatsbl Augenheilkd 2002;**219**:785–90.
12 **Bandyopadhyay M**, Raychaudhuri A, Lahiri SK, et al. Comparison of Goldmann applanation tonometry with the Tonopen for measuring intraocular pressure in a population-based glaucoma survey in rural West Bengal. Ophthalmic Epidemiol 2002;**9**:215–24.
13 **Copt RP**, Thomas R, Mermoud A. Corneal thickness in ocular hypertension, primary open-angle glaucoma, and normal tension glaucoma. Arch Ophthalmol 1999;**117**:14–16.