Addition of pindolol to routine medical therapy: a clinical trial

REDMOND J. H. SMITH, TRUDY BLAMIREs, S. NAGASUBRAMANIAN, R. WATKINS, AND D. POINOOSAWMY

From the Glaucoma Clinic, Moorfields Eye Hospital, City Road, London EC1V 2PD

SUMMARY A double-blind study of pindolol eye drops 0.5% was carried out on 24 patients with primary open-angle glaucoma. Pressures were taken once weekly during three 3-week periods. In one of these periods placebo was given in both eyes, during another pindolol was given in one eye, and during another it was given in the other eye. A drop in pressure averaging 2.79% was found in eyes receiving pindolol compared with the period when they were receiving saline. Substantial placebo effects were found when in-trial pressures were compared with pretrial, but the placebo effects were avoided in the analysis of the pindolol effect. Blood pressure and pulse rates were not significantly affected. There was slight evidence of pindolol in one eye affecting the contralateral eye but little evidence of persistence of hypotensive effects after cessation of treatment.

The ocular hypotensive effect of pindolol has been described by various authors including Bonomi and Steindler¹ and S. E. Smith *et al.*²

The study about to be described was an appraisal of the pressure-lowering effect of topical pindolol while patients with chronic glaucoma continued to take their usual medication. Thus the protocol was similar to that employed by R. Smith *et al.*³ in respect of timolol. The arrangements were, however, not identical in that a double placebo period was introduced which had not been employed in the prior study.

Patients and methods

Twenty-four patients with chronic primary open-angle glaucoma were selected. They were already taking local medication but not acetazolamide. The majority were on pilocarpine plus guanethidine and adrenaline. They were asked if they were willing to try a new drug in addition to their existing treatment and their consent was obtained before entering them into the trial. The selection was limited to patients of 40 years or more, male or female, with a pulse rate of 61 or more and a blood pressure of at least 120/70 mmHg.

At an initial session the following data were

recorded: name, age, sex, intraocular pressure in each eye, date and time of measurement, visual acuity, blood pressure, and pulse rate. Existing therapy was continued and the Pharmacy issued 2 extra identical bottles, one containing normal saline and the other either normal saline or pindolol 0.5% (Moorfields formulation). Patients were instructed to instil one drop into the right eye from the bottle so marked and one into the left eye from the other bottle each morning and evening for one week, including the morning of the next visit. One week later the patients were reviewed and again on 2 more weekly visits. Then the therapy was altered for a further 3-week period and once more for a final 3-week period. All the examinations were carried out at about the same time of day in each patient.

The administration of pindolol or saline to one eye and saline to the other was arranged so that by the end of the trial each patient had had a 3-week period of drug in one eye and saline in the other, a period the other way round, and a period with saline in both eyes. It was arranged that one-third of the patients received double saline in the first, second, or last periods respectively. The trial was carried out double-blind, and the Pharmacy held the code, which was not broken until the trial was completed.

FORMULATION

Both pindolol and placebo drops were prepared in

Correspondence to Mr Redmond Smith.

the Hospital Pharmacy and put up in identical packs. The only information given was the trial number of the patient, the treatment period, and the eye for which the bottle was to be used (right or left). The name and concentration of preservative was given (benzalkonium chloride was used in both active and placebo drops). Batch numbers were varied in each treatment period, though all drops were prepared at the same time, to prevent identification of the active drug by means of the batch number.

AIMS AND OBJECTS

The objects of the trial were first to confirm that pindolol has a pressure-lowering effect in chronic open-angle glaucoma; secondly to find what effect, if any, pindolol has on the pressure of the contralateral untreated eye; thirdly to determine the duration of effect of pindolol after administration has been stopped; fourthly to determine the effect of topical pindolol on the pulse rate and blood pressure; and finally to see if there are any obvious short-term side effects.

Results

BASILINE DATA

The mean age of the patients was 63.8 with a range of 41 to 81 and a standard deviation of 9.01. The mean pretrial blood pressure was 149/88 mmHg, and the mean pretrial pulse rate 77.66. There were 6 females and 18 males.

INTRAOCULAR PRESSURE

It might be supposed that the simplest way to study the effect of pindolol on the intraocular pressure would be to take the mean of the pretrial pressures and of the pressures during the use of pindolol and compare them; and indeed if this is done a clear-cut difference is found, pretrial pressures averaging 24.89 mmHg and pressures on pindolol averaging

18.37, a difference of 6.52 mmHg or about a 25% drop in pressure (Table 1).

Unfortunately there is also a substantial reduction of pressure with the placebo drops, pretrial pressures again 24.89 and pressures on placebo averaging 21.10, a difference of 3.79 or 15%. This placebo effect may have been due to the more conscientious use of other medication in the patients under study.

On the assumption that the patient's compliance improved throughout the trial it would probably be better for all further comparisons to be made between

Table 2 Comparison between pressures of the 8 eyes which had double saline in the first period (SSIS) and the same eyes when on pindolol (SSIP)

Patient	SSIS		SSIP		Differences			
					Right eyes		Left eyes	
	R	L	R	L	S-P	(S-P) ²	S-P	(S-P) ²
3	26	26	19	18	7	49	8	64
	24	21	15	20	9	81	1	1
	27	24	20	21	7	49	3	9
6	38	28	27	26	11	121	2	4
	33	29	26	23	7	49	6	36
	35	28	26	25	9	81	3	9
8	22	22	20	17	2	4	5	25
	24	24	18	18	6	36	6	36
	22	22	18	18	4	16	4	16
11	14	16	11	14	3	9	2	4
	14	18	11	14	3	9	4	16
	16	17	13	14	3	9	3	9
13	16	19	18	25	-2	4	-6	36
	16	23	18	22	-2	4	1	1
	17	20	17	21	0	0	-1	1
16	26	22	18	17	8	64	5	25
	22	21	17	20	5	25	1	1
	22	23	17	21	5	25	2	2
19	19	15	16	14	3	9	1	1
	16	14	12	14	4	16	0	0
	16	14	15	14	1	1	0	0
24	26	36	26	27	0	0	9	81
	30	42	25	25	5	25	17	289
	28	38	26	29	2	4	9	81

Table 1 Comparison of pressures (mmHg), all eyes

Pretrial pressures		Pressures on pindolol	
n = 48.00 (observations)		n = 144.00 (observations)	
€ = 1195.00		€ = 2696.00	
m = 24.89	[D = 6.52]	m = 18.37	
s = 6.29		s = 4.41	
var = 38.80		var = 19.39	
Pretrial pressures		Pressures on double saline	
n = 48.00 (observations)		n = 144.00 (observations)	
€ = 1195.00		€ = 3039.00	
m = 24.89	[D = 3.79]	m = 21.10	
s = 6.29		s = 6.02	
var = 38.80		var = 36.10	

R Saline		Pindolol		L Saline		Pindolol	
n = 24.00		24.00		24.00		24.00	
€ = 549.00		449.00		562.00		477.00	
m = 22.87	[D = 4.17]	18.70		23.41	[D = 3.54]	19.87	
sD = 6.76		4.96		7.28		4.67	
var = 43.77		23.62		50.82		20.94	
Comparing means as paired data				Comparing means as paired data			
€RS-RP	= 100.00			€LS-LP	= 85.00		
€(RS-RP) ²	= 690.00			€(LS-LP) ²	= 747.00		
MD	= 4.17			MD	= 3.54		
S diff	= 3.37			S diff	= 4.31		
SEM diff	= 0.70			SEM diff	= 0.90		
t	= 5.95			t	= 3.93		
p	< 0.001			p	< 0.001		

Table 3 Comparison between pressures of the 8 eyes which had double saline in the second period (SS2S) and the same eyes when on pindolol (SS2P)

Patient	SS2S		SS2P		Differences			
					Right eyes		Left eyes	
	R	L	R	L	S-P	(S-P) ²	S-P	(S-P) ²
2	26	14	26	13	0	0	1	1
	24	13	26	13	-2	4	0	0
	30	10	27	13	3	9	-3	9
4	19	18	16	15	3	9	3	9
	18	17	19	16	-1	1	1	1
	18	17	17	18	1	1	-1	1
9	18	16	20	15	-2	4	1	1
	19	18	21	16	-2	4	2	4
	25	22	19	20	4	16	2	4
12	16	17	16	18	0	0	-1	1
	22	24	16	13	6	36	11	121
	18	18	18	15	0	0	3	9
14	31	32	28	28	3	9	4	16
	32	28	28	29	4	16	-1	1
	40	32	25	27	5	25	5	25
18	22	20	16	16	6	36	4	16
	23	19	16	16	7	49	3	9
	25	26	20	18	5	25	8	64
20	24	18	20	18	4	16	0	0
	25	19	20	20	5	25	-1	1
	24	20	22	17	2	4	3	9
22	12	24	12	16	0	0	8	64
	12	20	10	16	2	4	4	16
	12	21	10	17	2	4	4	16
R Saline		Pindolol		L Saline		Pindolol		
n = 24.00		24.00		24.00		24.00		
ε = 533.00		468.00		483.00		423.00		
m = 22.20 [D = 2.70]		19.50		20.13 [D = 2.51]		17.62		
sD = 6.70		5.24		5.40		4.47		
var = 43.08		26.33		27.94		19.15		
Comparing means as paired data				Comparing means as paired data				
εRS-RP = 55.00				εLS-LP = 60.00				
ε(RS-RP) ² = 297.00				ε(LS-LP) ² = 398.00				
MD = 2.70				MD = 2.51				
S diff = 2.67				S diff = 3.21				
SEM diff = 0.56				SEM diff = 0.67				
t = 4.82				t = 3.74				
p < 0.001				p < 0.01				

Table 4 Comparison between pressures of the 8 eyes which had double saline in the third period (SS3S) and the same eyes when on pindolol (SS3P)

Patient	SS3S		SS3P		Differences			
					Right eyes		Left eyes	
	R	L	R	L	S-P	(S-P) ²	S-P	(S-P) ²
1	17	16	17	18	0	0	-2	4
	18	16	15	18	3	9	-2	4
	18	15	15	17	3	9	-2	4
5	21	20	22	24	-1	1	-4	4
	21	19	20	18	1	1	1	1
	21	20	20	19	1	1	1	1
7	19	13	18	12	1	1	1	1
	20	16	18	12	2	4	4	16
	20	15	20	12	0	0	3	9
10	20	17	17	14	3	9	3	9
	24	20	22	18	2	4	2	4
	26	20	18	18	8	64	2	4
15	15	16	14	13	1	1	3	9
	14	16	14	14	0	0	2	4
	16	18	18	14	-2	4	4	16
17	26	20	21	15	5	25	5	25
	23	22	20	16	3	9	6	36
	25	22	20	20	5	25	2	4
21	15	26	18	24	-3	9	2	4
	16	26	14	24	2	4	2	4
	17	32	15	20	2	4	12	144
23	16	18	12	14	4	16	4	16
	14	14	11	17	3	9	-3	9
	16	17	16	15	0	0	2	4
R Saline		Pindolol		L Saline		Pindolol		
n = 24.00		24.00		24.00		24.00		
ε = 458.00		415.00		454.00		406.00		
m = 19.08		[D = 1.79] 17.29		18.92		[D = 2.01] 16.91		
sD = 3.71		3.05		4.36		3.67		
var = 13.24		8.95		19.24		12.90		
Comparing means as paired data				Comparing means as paired data				
εRS-RP = 43.00				εLS-LP = 48.00				
ε(RS-RP) ² = 209.00				ε(LS-LP) ² = 336.00				
MD = 1.79				MD = 2.01				
S diff = 2.34				S diff = 3.16				
SEM diff = 0.49				SEM diff = 0.66				
t = 3.65				t = 3.04				
p < 0.01				p < 0.01				

pressures 'on saline' (or 'on placebo') and pressures 'on pindolol,' pretrial pressures being totally eliminated from the statistics. But the problem with this approach is that cross-over and/or follow-on effects may be operating.

In order to eliminate cross-over or follow-on effects the 8 patients (16 eyes) who took saline in both eyes for the first 3-week period (the SS1 patients) may be studied separately. Table 2 shows the findings. In these patients the mean pressures during the 3 weeks of placebo were 22.87 mmHg for right eyes and 23.41

for left eyes. The mean pressures in these same eyes during their later 3-week pindolol periods were 18.7 and 19.87 respectively, a difference of 4.17 for right eyes and 3.54 for left, differences which appear to be statistically significant.

Ignoring any possible follow-on effects for the moment but avoiding cross-over effects we can also study the 'double saline second' and 'double saline third' groups. As in the 'double saline first' (or SS1) group there are 8 patients and 16 eyes in each group.

In the SS2 patients (Table 3) the mean pressures on

Addition of pindolol to routine medical therapy: a clinical trial

Table 5 Pressures on saline versus pressures on pindolol (all patients)

Double saline		Pindolol
ϵ	= 3039.00	2638.00
m	= 21.10	18.31
n (obs)	= 144.00	144.00
n (eyes)	= 48.00	48.00
SD	= 6.02	4.48
SD ²	= 36.24	20.07
var	= 36.10	19.99

placebo were 22.2 mmHg for right eyes and 20.13 for left, and the mean pressures on pindolol were 19.5 for right and 17.62 for left, a difference of 2.7 for right and 2.51 for left. In the SS3 patients (Table 4) the mean pressures on placebo were 19.08 mmHg for right eyes and 18.92 for left and the pressures on pindolol 17.29 and 16.91, differences of 1.79 and 2.01 for right and left eyes respectively. All these differences are significant at least at the 0.01 level of confidence. Pooling the figures we can say that the difference between all eyes on double saline and all eyes on pindolol is 2.79 mmHg (Table 5).

(It should be emphasised that the comparison between saline and pindolol in all the above examples refers to the comparison between the 'double saline' pressures and the pindolol pressures. Pressures 'on saline' obtained while the other eye was on pindolol

Table 6 Dosage schedule

Patient	Period 1		Period 2		Period 3	
	R	L	R	L	R	L
3	S	S	P	S	S	P
6	S	S	S	P	P	S
8	S	S	P	S	S	P
11	S	S	P	S	S	P
13	S	S	S	P	P	S
16	S	S	S	P	P	S
19	S	S	P	S	S	P
24	S	S	S	P	P	S
2	S	P	S	S	P	S
4	P	S	S	S	S	P
9	S	P	S	S	P	S
12	S	P	S	S	P	S
14	P	S	S	S	S	P
18	S	P	S	S	P	S
20	P	S	S	S	S	P
22	P	S	S	S	S	P
1	P	S	S	P	S	S
5	S	P	P	S	S	S
7	P	S	S	P	S	S
10	P	S	S	P	S	S
15	S	P	P	S	S	S
17	P	S	S	P	S	S
21	S	P	P	S	S	S
23	S	P	P	S	S	S

Table 7 SS2S eyes with prior pindolol versus without

SS2 with prior pindolol		SS2 without prior pindolol	
		R	L
2	{	—	14
		—	13
		—	10
		—	30
4	{	19	—
		18	—
		18	—
		—	16
9	{	—	18
		—	18
		—	19
		—	22
		—	17
12	{	—	24
		—	18
		—	18
14	{	31	—
		32	—
		40	—
		—	30
18	{	—	19
		—	26
		—	25
20	{	24	—
		25	—
		24	—
22	{	12	—
		12	—
		12	—
		—	21
n	=	24.00	24.00
ϵ	=	484.00	532.00
m	=	20.16	22.16
SD	=	7.21	4.71
var	=	49.88	21.30

[D = -2.0]

have not been used to avoid possible cross-over effects.)

POSSIBLE 'FOLLOW-ON' EFFECT

The term 'follow-on' effect refers to the possibility of the effects of pindolol persisting for some time after administration had ceased.

The mean pressures during the double placebo periods seem to get lower the later the period occurs in the trial. If we study the administration code (Table 6) it is apparent that in the SS2 group 8 of the 16 eyes concerned had received pindolol at some prior period. In order to test whether prior pindolol had affected the SS pressures it was found possible in the SS2 group to compare the pressures *during the saline period* of those eyes which had not and those eyes which had received prior pindolol—a comparison which could not be made either in the SS1 or the SS3 group.

Table 7 illustrates this analysis. SS2S eyes which had had prior pindolol showed a mean pressure of 20.16 mmHg, whereas eyes with no prior pindolol showed a mean pressure of 22.16—a difference of -2.0 mmHg. Each refers to 24 observations in only 8 eyes, and the difference might simply be due to

Table 8 SS2S eyes with and without prior pindolol

SS2S eyes 'with prior pindolol' while on pindolol		SS2S eyes 'without prior pindolol' while on pindolol	
R	L	R	L
2	{ — 13	26	—
	{ — 13	26	—
	{ — 13	27	—
4	{ 16 —	—	15
	{ 19 —	—	16
	{ 17 —	—	18
9	{ — 15	20	—
	{ — 16	21	—
	{ — 20	19	—
12	{ — 18	16	—
	{ — 13	16	—
	{ — 15	18	—
14	{ 18 —	—	28
	{ 28 —	—	29
	{ 28 —	—	27
18	{ — 16	16	—
	{ — 16	16	—
	{ — 18	20	—
20	{ 20 —	—	18
	{ 20 —	—	20
	{ 22 —	—	17
22	{ 12 —	—	16
	{ 10 —	—	16
	{ 10 —	—	17
n = 24.00		24.00	
ε = 406.00		418.00	
m = 16.91		19.91	
SD = 4.66		4.58	
var = 20.82		20.15	

[D = -3.0]

chance or to the fact that the 2 groups of 8 eyes were not comparable. The group with the higher pressures might tend to show higher pressures at other stages in the investigation. But this can be tested. It is possible next to compare these same eyes while on pindolol, when each should be at minimum pressure. If the same difference is found, it would be reasonable to assume that there was a constitutional difference and that there was therefore no likelihood of the -2.0 difference shown in Table 7 being of any particular significance. Table 8 supports this view, namely, that the eyes 'with prior pindolol' happened to be a relatively low pressure group compared with the SS2 eyes 'without prior pindolol,' since when the groups are compared at the time when each is actually on pindolol a difference of -3.0 mmHg is found.

Thus in these 8 patients at least it is possible to conclude that there is no evidence of a persistence of any hypotensive effect of pindolol ('follow-on' effect).

POSSIBLE 'CROSS-OVER' EFFECT

The term 'cross-over' effect refers to the possibility of pindolol drops in one eye affecting the pressure in the other eye.

Table 9 Comparison between 'double saline' and 'single saline' pressures (all eyes)

Right eye				Left eye			
SS	S			SS	S		
26	16	22	21	26	20	24	16
24	22	26	20	21	19	17	18
27	18	24	25	24	26	24	20
38	31	34	22	28	18	24	28
33	32	28	22	29	19	26	25
35	40	32	19	28	20	26	25
22	22	20	12	22	24	22	28
24	23	18	13	24	20	18	24
22	25	21	13	22	21	20	30
14	24	13	18	16	16	13	16
14	25	13	18	18	16	14	20
16	24	13	17	17	15	16	20
16	12	18	35	19	20	27	20
16	12	16	21	23	19	25	22
17	12	18	28	20	20	24	20
26	17	15	25	22	13	23	18
22	18	18	22	21	16	22	20
22	18	20	18	23	15	23	18
19	21	17	17	15	17	12	20
16	21	16	23	14	20	14	19
16	21	18	22	14	20	14	18
26	19	27	10	36	16	31	20
30	20	26	14	42	16	31	14
28	20	28	14	38	15	31	18
26	20	26	19	14	20	14	17
24	24	28	20	13	22	10	24
30	26	32	26	10	22	14	18
19	15	18	16	18	26	14	14
18	14	20	17	17	26	14	18
18	16	20	18	17	32	16	18
18	26	17	20	16	18	20	24
19	23	23	17	18	14	21	24
23	25	20	16	22	17	19	24
16	15	16	28	17	32	28	14
14	16	14	30	24	28	29	14
16	17	14	28	18	32	26	18
n = 72.00				72.00			
ε = 1540.00				1473.00			
m = 21.38				20.46			
s = 6.05				5.61			
v = 36.09				31.00			
SE (M ₁ -M ₂) = 0.98				SE (M ₁ -M ₂) = 0.89			
t = 0.94				t = 0.42			
p = NS				p = NS			

In the comparisons made so far 'cross-over' effects have been avoided by considering only 'double-placebo' pressures. Pressures on placebo while the other eye was on pindolol have not yet been presented. Such pressures, which may conveniently be called 'single-saline' or 'single-placebo' pressures, can be compared with 'double-saline' pressures in the same eyes.

The results are set out in Table 9. It can be seen that in all the right eyes the mean of the double-saline pressures was 21.38 and the single-saline was 20.46, a

Table 10 Pulse rates (24 patients)

All pulses while on saline (includes pretrial pulse and pulse during SS period)		All pulses on pindolol	
Observations (n)	= 96.00		144.00
ϵ	= 7215.00		10774.00
m	= 75.16	[D = 0.34]	74.82
SD	= 13.69		9.42
var	= 185.60		88.07
SEM	= 1.40		0.79
SE (M ₁ -M ₂)	= 1.61		
t	= 0.21		
p	= NS		

difference of 0.92 favouring a possible slight cross-over effect. However, with this number of observations the difference is not statistically significant. A smaller difference but in the same direction occurs in the left eyes, the figure being 0.37. This is also not statistically significant. Thus although the figures are in favour of a small cross-over effect the point is not proved.

PULSE RATE

Table 10 shows that the mean of the pulse rates of all patients when not taking pindolol, that is, on 4 occasions, once in the pretrial examination and 3 times during the double saline period, was 75.16. The mean pulse rate during the pindolol periods, that is, on 6 occasions for each patient, was 74.82, a negligible difference of 0.34 beats per minute.

BLOOD PRESSURES

On each of the 24 patients the blood pressure was taken 4 times when no pindolol was in use, that is, at the pretrial examination and at each of the examinations during the double-saline period. The blood pressure was taken on 6 occasions while pindolol was in use, 3 times when in use in one eye and a further 3 times when it was in use in the other eye. Thus there were 96 readings taken with the patient off pindolol and 144 on pindolol (Table 11).

Table 11 Diastolic blood pressure

On saline		On pindolol	
n	= 96.00		144.00
ϵ	= 8423.00		12783.00
m	= 87.73	[D = -1.04]	88.77
SD	= 10.91		9.33
var	= 117.94		84.377
SEM	= 1.12		0.78
SE (M ₁ -M ₂)		= 1.86	
t		= 0.56	
p		= NS	

The means of the diastolic pressures 87.73 mmHg off pindolol and 88.77 mmHg on pindolol. The difference of -1.04 mmHg is not statistically significant.

SIDE EFFECTS

One patient complained of headaches lasting one week, but this was later found to have occurred during the double-placebo period. Another had a short period of conjunctival injection in the right eye after one week of pindolol, but the effect did not persist when the drug was continued. No other side effects were noted.

Discussion

In a previous study³ timolol was shown to lower intra-ocular pressure when added to existing medication. As in the present study the degree of lowering calculated by comparing pretrial pressure with pressure on timolol was greater than the in-trial comparison of the pressure when on saline compared with the pressure when on timolol.

Such a difference could be due either to a so-called placebo effect producing a lower in-trial saline pressure or to a cross-over effect from the contralateral eye on timolol. It was not feasible to disentangle the 2 possible effects in that study, so that the validity of the various comparisons made was weakened to some degree.

In the present study, however, the introduction of a double-placebo period has enabled us to identify with much more accuracy possible placebo effects, follow-on effects, and cross-over effects. As will have been seen in the account of the results, a placebo effect of 3.79 was found (Table 1). There is no possibility of this being influenced by cross-over from the other eye, as the in-trial saline readings are all 'double saline' pressures. The existence of such a large placebo effect is of some interest and indicates the need for caution in assessing results in trials of this nature. Without the filtering out of the placebo effect (which we have achieved by ignoring pretrial readings) we would have been led into the trap of assuming a pindolol effect of 6.52 mmHg (Table 1), more than half of which would in fact have been spurious.

The exact reasons for the placebo effect are not easy to determine. One possibility in this particular type of trial is that the pretrial pressure was taken at what the patient would have regarded as a routine visit, whereas later in-trial readings would be taken at what the patient would regard as a special visit. Under such conditions he or she might be more likely to have used their other prescribed treatment more conscientiously; in other words a clinical trial improves patient compliance.

Placebo effects having been obviated, tests for follow-on effects having shown a negative result (Table 8), and cross-over effects having been avoided by comparing only double-saline pressures with pindolol, we are left with the result that pindolol undoubtedly lowered the pressure on average 2.79 mmHg when added to existing treatment.

Slowing of the pulse, effects on diastolic blood pressure, and other side effects were all negligible, so that it now seems justifiable to make further clinical trials of this drug.

Our thanks are due to Messrs Sandoz for supplies of pindolol for this trial.

References

- 1 Bonomi I, Steindler P. Effect of pindolol on intraocular pressure. *Br J Ophthalmol* 1975; **59**: 301-3.
- 2 Smith S E, Smith S A, Reynolds F, Whitmarsh VB. Ocular and cardiovascular effects of local and systemic pindolol. *Br J Ophthalmol* 1979; **63**: 63-6.
- 3 Smith RJH, Nagasubramanian S, Watkins R, Poinoosawmy D. Addition of timolol maleate to routine medical therapy: a clinical trial. *Br J Ophthalmol* 1980; **64**: 779-81.