Graefe's Arch Clin Exp Ophthalmol (1995)
233:131–134

CLINICAL INVESTIGATION

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Plasma kinetics and antagonist activity of topical ocular timolol in elderly patients

Received: 31 December 1993
Revised version received:
12 September 1994
Accepted: 16 September 1994

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Abstract ● Background: Systemic adverse effects of ocular timolol therapy are due to absorption of the drug from the eye into the systemic circulation. Elderly patients are frequently more susceptible to side effects than younger patients. This study was conducted to evaluate the plasma kinetics and antagonist activity of ocular timolol in elderly patients. ● Methods: Plasma kinetics and antagonist activity of timolol were studied in 12 patients scheduled for extracapsular cataract extraction and intraocular lens implantation. The patients received 40 µl of 0.25% timolol into the lower cul-de-sacs of each eye. Blood samples were collected over a period of 12 h and plasma concentrations of timolol were analyzed using a radioreceptor assay. The corresponding ex vivo β_1- and β_2-receptor occupancies were calculated using radioligand binding techniques. ● Results: Timolol was absorbed rapidly into the systemic circulation and occupied on average up to 68% of β_1-receptors and up to 87% of β_2-receptors. The β_1- and β_2-receptor occupancy decreased slowly and was on average 38% and 64%, respectively, 12 h after the single dose. The calculated mean area under concentration-time curve of timolol in plasma was 10.28 ng/ml per hour and the mean half-life was 4.8 h. Both values were about twice as high as those found in healthy young volunteers following an intravenous 0.25-mg dose of timolol. ● Conclusions: In elderly patients the β-receptor antagonist effect of ocular timolol after a single dose is strong and long-lasting. This finding may explain the frequent reported systemic side effects of ophthalmic timolol.

Introduction

Timolol, a non-selective beta-adrenergic antagonist [14], is widely used to lower intraocular pressure. Systemic side effects, such as bradycardia and pulmonary reactions associated with therapy of timolol eyedrops [6, 8], appear rapidly after drug instillation because the drug is readily absorbed from the eye into the systemic circulation [3].

β-Receptor antagonists produce their effects by binding to the β-receptors in the place of endogenous catecholamines. The percentage of receptor occupancy shows the proportion of receptors occupied by the drug. For example, a drug with low affinity to β-receptors may produce high tissue concentrations but does not significantly occupy receptors. On the other hand, at 100% receptor occupancy by a drug the effects of endogenous catecholamines are completely blocked.

Because the systemic effects of ocular timolol therapy are obviously due to absorption of the drug from the eye into the systemic circulation, we conducted a study to evaluate plasma kinetics and the antagonist activity of topical timolol in elderly cataract surgery patients and

compare the findings with previous data on healthy young volunteers [5].

Materials and methods

Twelve patients scheduled for extracapsular cataract extraction (ECCE) and intraocular lens (IOL) implantation were included in the study. Cataract patients were selected in the study because timolol has been shown to be effective in preventing postoperative intraocular pressure increase [10]. Their mean age (±SD) was 74.9±9.9 years and their mean weight (±SD) was 72.4± 13.1 kg. Written informed consent was obtained, and the study protocol was approved by the Ethics Committee of Turku University and University Hospital. The study was conducted according to the Helsinki declaration. Patients taking β-blocking medication or having any contraindications for β-blocking agents such as manifest congestive heart failure, atrioventricular block or bronchial asthma were excluded from the study. Immediately before the cataract operation, the patients received 40 µl of 0.25% timolol maleate (Oftan-Timolol, Leiras, Finland) (200 µg) into the lower cul-de-sacs of each eye. The dose was administered with a micropipette (Finnpipette, Labsystems, Finland).

Blood samples of 8 ml were collected in EDTA tubes immediately before and 5, 10, 15, and 30 min and 1, 2, 3, 4, 8, and 12 h after instillation of the drug. All patients underwent uneventful ECCE with posterior chamber lens implantation.

Timolol concentrations in plasma were determined using a radioreceptor assay (RRA) [2]. The sensitivity of RRA is 30 pg/ml for timolol. The rat reticulocyte β_2-receptor occupancy in plasma samples was measured using the assay described earlier by Wellstein et al. [11]. The β_1-receptor occupancy was determined by replacing the rat submandibular gland membrane in the original assay [11] with the rabbit lung membrane containing 200 nM ICI 118,551. The apparent equilibrium binding constant (*Ki* value) of timolol was determined by displacing 2.0 nM (−)-H3-CGP-12177 from the β_1- and β_2-receptor sites in the rabbit lung membrane or rat reticulocyte membrane solution. The best fits for the Ki values were calculated using the Ligand program.

Timolol displaced concentration dependently (−)-H3-CGP-12177 from the β_1-receptors of rabbit lung and from the β_2-receptors of rat reticulocytes in assay buffer and plasma. The affinities (*Ki* values) of timolol for the β_1-receptor site and for the β_2-receptor site (mean±SD) were 1.4±0.2 nM and 0.6±0.1 nM, respectively.

The percentage receptor occupancy was calculated using the following equation:

$$\text{Receptor occupancy } \% = 100 \times (i/Ki)/(i/Ki) + 1$$

The drug concentration *i* in the sample was divided by its *Ki* value for estimating the receptor occupancy in the circulating plasma. The equation based on the receptor theory was presented by Williams and Lefkowitz [13] for competitive radioligand binding assays.

Kinetic analysis

The pharmacokinetic characteristics of ocular timolol were calculated using the Siphar program (Simed, Poitiers, France). The mean $AUC_{0-\infty}$ (area under concentration-time curve) was calculated using the trapezoidal rule. The terminal elimination half-lives ($T^1/_2$) were estimated by using two-compartmental model of elimination. The total plasma clearance (Cl) was calculated from the relationship Cl = dose/AUC and the total apparent volume of distribution from the relationship $V_\beta = Cl/k_e$. The elimination rate constant (k_e) was calculated from the relationship $k_e = T^1/_2/\ln 2$. The pharmacokinetic characteristics are presented in Table 1.

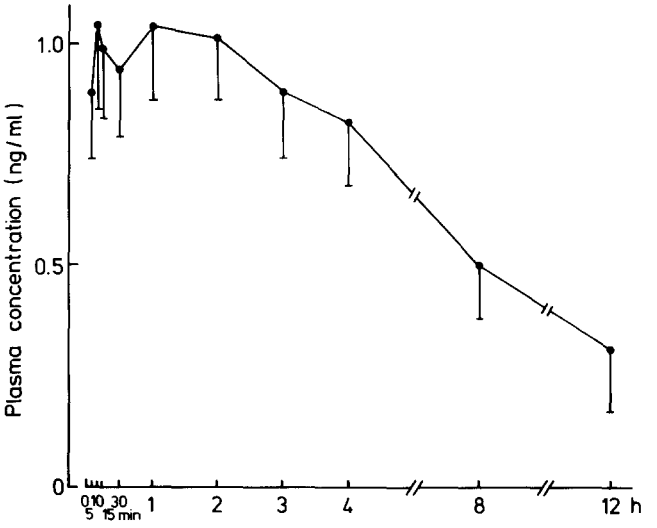

Fig. 1 The concentration of timolol (ng/ml, mean±SEM) in plasma up to 12 h after ocular administration

Statistical analysis

Timolol concentrations are given in ng/ml as mean±standard deviation (SD). In Figs. 1 and 2 plasma timolol concentrations (ng/ml) and β-receptor occupancies (%) are shown as mean±SEM. The data were analyzed using Systat 5.02 software.

Results

Timolol was absorbed rapidly from the eye into the systemic circulation. The highest average timolol concentrations (1.04±0.66 ng/ml) were found only 10 min after drug administration. Timolol plasma levels decreased slowly, so that the mean concentration was 0.29±0.31 ng/ml, ranging from 0.07 to 1.2 ng/ml, after 12 h. The mean peak concentration (C_{max}) was 1.34±0.56 ng/ml, and the mean time to peak value (T_{max}) was 78±65 minutes. The average plasma concentrations of timolol are shown in Fig. 1. The calculated $T^1/_2$ for the elimination phase was 4.8±0.8 h. The mean $AUC_{0-\infty}$ was 10.28±7.32 ng/ml per hour. The individual pharmacokinetic characteristics are presented in Table 1.

Figure 2 presents the time course of the rabbit lung β_1- and rat reticulocyte β_2-receptor occupancy of timolol in the circulating plasma up to 12 h after ocular instillation. Timolol occupied up to 68% of β_1-receptors and 87% of β_2-receptors on average following drug administration. Some 38% (range 15–76%) of β_1-receptors and 64% (range 37–91%) of β_2-receptors were still occupied 12 h after the dose.

Table 1 Pharmacokinetic characteristics of ocular timolol in 12 elderly patients

Patient no.	Age (years)	Weight (kg)	C_{max} (ng/ml)	C_{min} (ng/ml)	$AUC_{0-12\,h}$ (ng/ml per hour)	$AUC_{0-\infty}$ (ng/ml per hour)	Cl (ml/min per kilogram)	V_{β} (l/kg)	T1/2el (h)
1	69	97	0.59	0.18	4.68	6.22	7.34	0.015	5.6
2	58	84	0.86	0.13	6.67	8.37	5.95	0.015	4.7
3	69	70	0.86	0.15	5.41	6.29	8.80	0.025	4.1
4	73	68	1.00	0.16	4.74	6.03	10.34	0.021	5.6
5	85	70	2.20	0.26	11.68	12.99	4.08	0.013	3.5
6	75	54	1.90	0.44	13.38	16.32	4.61	0.012	4.6
7	61	55	1.50	0.11	5.53	6.12	10.96	0.033	3.8
8	87	85	0.91	0.37	8.91	12.82	4.40	0.010	5.3
9	87	58	2.20	1.20	20.31	30.21	2.83	0.006	5.7
10	85	69	1.70	0.19	7.32	8.49	6.60	0.018	4.3
11	79	81	1.40	0.07	2.57	3.15	16.01	0.032	5.8
12	71	78	0.93	0.18	5.18	6.32	8.25	0.022	4.4
Mean	74.9	72.4	1.34	0.29	8.03	10.28	7.51	0.019	4.8
SD	9.9	13.1	0.56	0.31	4.940	7.32	3.69	0.008	0.8

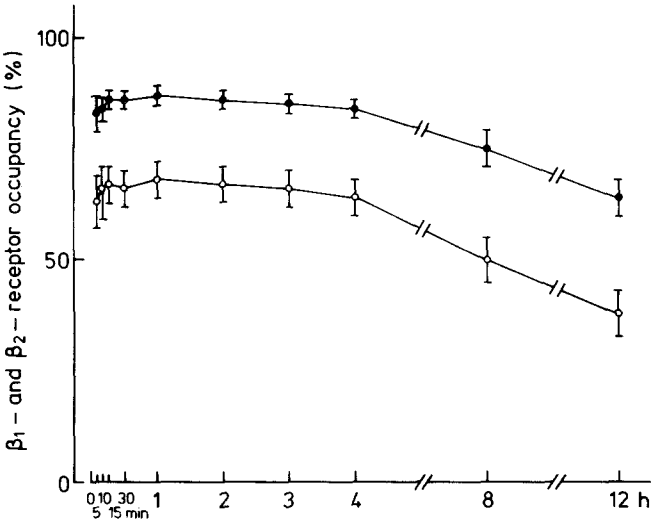

Fig. 2 The β_1- and β_2-receptor occupancy (%, mean ± SEM) of timolol in plasma up to 12 h after ocular administration

Discussion

In the present study we measured timolol plasma kinetics [2] and β-receptor binding activity [5] for 12 h after administration in elderly patients awaiting cataract surgery, using a sensitive RRA method. In previous studies timolol concentrations have been measured up to 4 h after a single administration [1, 2]. In the study by Passo et al. [7] the mean plasma concentration 12 h after drug instillation was 0.34 ± 0.3 ng/ml after chronic treatment with 0.5% timolol twice daily into both eyes. In our study the corresponding mean plasma concentration was 0.31 ± 0.31 ng/ml. Thus the drug concentrations after ocular drug instillation were very similar.

The $T^1/_2$ for timolol in plasma was 2.6 ± 0.9 h in healthy young volunteers following a 0.25-mg intravenous dose of timolol, similar to the amount of timolol in one 0.5% eyedrop [5]. In the present study $T^1/_2$ was 4.8 ± 0.8 h, almost twice as long as the value found in healthy young volunteers. Thus in elderly patients the elimination of timolol during cataract surgery appears to be much slower than in young volunteers. Consequently, the mean $AUC_{0-\infty}$ in the elderly patients after an ocular 0.2-mg dose of timolol was also higher (10.28 ng/ml per hour) than that after a 0.25-mg intravenous dose in healthy young volunteers (4.10 ng/ml per hour) [5].

The ability of β-adrenergic antagonists to occupy β-receptors is the molecular basis of their β-adrenoceptor blocking effects [12]. Therefore, the extent and time course of receptor occupancy is more important than plasma concentrations in explaining drug effects in man because it includes the affinity of the drug for the receptor [11]. The extent to which timolol occupies rabbit lung β_1- and rat reticulocyte β_2-receptors in the circulation predicts the degree to which timolol blocks the actions of isoprenaline in healthy volunteers [5]. The extent of β-receptor occupancy up to 12 h after ocular instillation of timolol has not, to our knowledge, been reported previously.

The mean β_1-receptor occupancy by timolol in plasma was 67 ± 12%, and the mean β_2-receptor occupancy 87 ± 7%, as soon as 15 min after administration of the drug. The mean β_1-receptor occupancy was 38 ± 17% and the mean β_2-receptor occupancy 64 ± 15% 12 h after the dose. Timolol β-receptor occupancy decreased more rapidly after intravenous infusion in healthy young volunteers, and on average 37 ± 13% of β_1-receptors and 75 ± 11% of β_2-receptors were occupied 5 h after administration of the drug [5]. Thus the β-receptor occupancy appears to decline more slowly in elderly

patients than in young healthy volunteers. As the dosage interval for ocular timolol has been recommended to be 12 h, at least in some patients timolol may produce considerable systemic β-blockade during ocular drug treatment.

The systemic β-adrenoceptor blocking effects of timolol can be detected at drug plasma concentrations beginning from 0.17 ng/ml, corresponding to β_1- and β_2-receptor occupancy of 10% and 24%, respectively [4]. In this study, the mean concentration of timolol (0.31 ng/ml), and the corresponding β_1- and β_2-receptor occupancies (38% and 64%, respectively) in elderly patients were higher than the limit for the β-blockade to occur as long as 12 h after a single dose.

The systemic β-blockade after administration of ocular β-adrenergic antagonists depends primarily on the extent to which these drugs occupy β-receptors outside the eye. Some side effects, especially the respiratory ones, are produced by the antagonism of pulmonary β_2-receptors. Our study shows that the β-receptor antagonist activity of ocular timolol is strong and long-lasting in elderly patients in association with cataract surgery. This finding may explain the frequent reported systemic side effects of ophthalmic timolol.

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