Improved Delivery Through Biological Membranes. LVI. Pharmacological Evaluation of Alprenoxime—A New Potential Antiglaucoma Agent[1]

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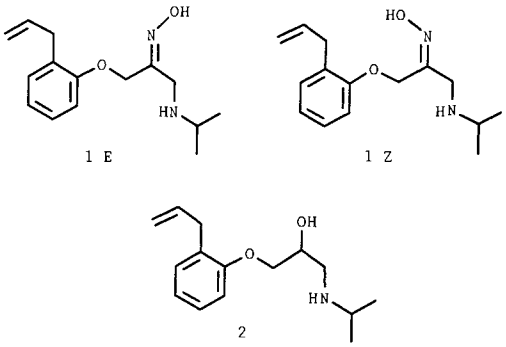
A new site-specific chemical delivery system (CDS) for alprenolol was designed and investigated as a potential novel antiglaucoma agent. The effect of this compound, alprenoxime (AO), on the intraocular pressure (IOP) of rabbits was evaluated after its uni- and bilateral administration. AO produced significant reduction of the IOP starting at 30 min and lasting for more than 6 hr after its topical administration. Both in rats and in rabbits the i.v. bolus injection of AO (6 mg/kg) led to insignificant transient bradycardia, while no activity was found after oral or topical administration. Alprenolol (ALP) in a similar dose produced a sustained and significant bradycardia for more than 30 min. When the beta-adrenergic blocking activity was assessed against isoprenaline-tachycardia, the same results were obtained, i.e., AO led to a transient brief activity, whereas ALP produced a significant long-lasting beta blockade. These results support the potent ocular hypotensive action and the weak systemic beta-adrenergic blocking and cardiovascular activity of AO: a significant improvement in the therapeutic index. This finding recommends alprenoxime as a potent site-specific antiglaucoma agent with minimal systemic side effects.

KEY WORDS: site-specific chemical delivery systems; beta-adrenergic blockers; antiglaucoma agents; alprenoxime.

INTRODUCTION

We have previously reported the ocular site-specific action of novel ketoxime analogues of known beta-adrenergic antagonists (1). These ketoximes displayed a remarkable ocular hypotensive activity, apparently via a hydrolysis-reduction bioactivation sequence to the active forms, in the iris-ciliary body. Results of a qualitative structure–activity study suggested a possible correlation between the lipid solubility of these ketoximes and their ocular hypotensive activity, as well as their ease of biotransformation to a parent β-blockers in the ocular tissues. Based on these studies, the ketoxime precursor (AO) of alprenolol (2) (Scheme I) was selected as the one with the higher lipid solubility and a more potent ocular hypotensive activity-reduced systemic toxicity than the previously studied analogue (oximes derived from propranolol, timolol, carteolol, etc.). The synthesis of this compound was described in a previous report (2). The present work continues the evaluation of some pharmacological properties of this compound in experimental animals.



Scheme I

Its effect on the intraocular pressure (IOP) of rabbits was studied following uni- and bilateral topical administration. Its intrinsic beta-adrenergic antagonistic activity is also assessed in rats and rabbits in comparison with the parent drug, alprenolol, following their topical, oral, and parenteral administration. As 1 can exist as both the E and the Z isomers (2,3), the studies were extended to the pure isomers and their mixture.

MATERIALS AND METHODS

Effect on the Intraocular Pressure (IOP) of Rabbits

Adult male New Zealand albino rabbits weighing 2.5–3.5 kg were used. Animals were kept in individual cages with free access to food and water and were adjusted to the laboratory environment by measuring their normal IOP for 2–3 days before carrying out the main experiment. Intraocular pressure was measured in a quiet room with the light left on for the entire duration of the experiment using a Digilab Model 30R Pneumatonometer. The tonometer readings were checked at least twice a day using the Digilab calibration verifier. All measurements were obtained from unrestrained unanesthetized rabbits. One drop of 0.5% proparacaine (Ophthetic-Allergan Pharmaceuticals, Inc.) diluted 1:2 with saline was instilled in each eye immediately prior to IOP measurement. One hundred microliters of a phosphate buffer solution (pH 7.4) was instilled in both eyes of a group of four to six rabbits. IOP was recorded after 30 and 60 min and then after 2, 3, 4, 5, and 6 hr following the vehicle administration. On the next day the drugs were administered at the same time of the day (8:30 AM ± 30 min) as 1% solution in both eyes of each rabbit and the IOP was recorded at the same time intervals.

Effect of AO was also studied after its unilateral administration. The compound was administered as a 1% solution in one eye, whereas phosphate buffer (pH 7.4) was instilled in the control eye.

In another experiment the effect of the two isomers (Z and E) of AO and their mixture on the IOP was determined. The same group of 20 rabbits was used on three different studies: the first time the E form of the drug, 1 week later, the Z form was tested, and after 1 more week, the E and Z mixture was examined. All IOP measurements were carried out by the same operator using the same tonometer. Values are given as the mean ± standard error of the mean (M ± SE). Significance of the difference between the effect of the

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vehicle and the effect of the drugs under investigation on the IOP was determined using Student's t test.

Effect on the Resting Heart Rate

In Rats

Groups of at least seven male Sprague–Dawley rats weighing 150–250 g were used. Each animal was anesthetized with sodium pentobarbital (50 mg/kg, i.p.). The heart rate of each animal was monitored using a physiograph (Projector Model, Type PMP-4B, Narco Biosystems, Inc.). Thirty minutes was allowed as an equilibration period before any drugs were given. Drugs were dissolved in normal saline as 0.3% solution and were administered either as an intravenous bolus injection or as an intravenous slow infusion at a rate of 0.2 ml/min. The resting heart rate was then recorded after 1, 3, 5, 10, 15, and 30 min following administration. The control group received saline intravenously and was studied in the same manner as the drug-treated group.

In Rabbits

Groups of at least five New Zealand albino rabbits weighing 1.0–1.1 kg were used. Animals were treated exactly in the same manner as above described in the preceding paragraph. Drugs were dissolved in normal saline as 1.2% solution and were administered into the marginal ear vein as an intravenous bolus injection.

Effect on the Isoproterenol-Induced Tachycardia

In Rats

Groups of at least seven male Sprague–Dawley rats weighing 150–250 g were used. Animals were anesthetized with an i.p. injection of 50 mg/kg of pentobarbital sodium. The heart rate of each animal was monitored as above described. Thirty minutes were allowed as an equilibration period before any drugs were given. Drugs were dissolved in normal saline as 0.3% solution and were administered as an i.v. bolus or slow infusion at a rate of 0.2 ml/min. After the appropriate time intervals (directly, 10 min, or 30 min), following the i.v. administration of the drug, a s.c. injection of isoproterenol (50 μg/kg) was administered and the heart rate was measured for 1, 3, 5, 15, 30, 45, and 60 min after administration. A control group (n = 7) received saline solution intravenously and was studied in the same manner as the drug-treated group.

In another set of experiments the effect of the orally administered alprenoxime and alprenolol (50 mg/kg) on the isoproterenol (50 μg/kg)-induced tachycardia was evaluated. Drugs were administered to groups of seven rats using a stomach tube. After 1 hr isoproterenol was administered subcutaneously and the heart rate was recorded after 0, 1, 3, 5, 15, 30, 45, and 60 min following isoproterenol administration. A control group of seven rats received saline solution only.

In Rabbits

Groups of at least five male New Zealand albino rabbits weighing 1.0–1.1 kg were used. Animals were treated as described above. Drugs were dissolved in normal saline as 1.2% solution and were administered into the marginal ear vein as i.v. bolus or i.v. slow infusion at a rate of 1.2 ml/min. For testing the oral activity, drugs were administered at a dose of 50 mg/kg using a stomach tube.

In another set of experiments the effect of the topical administration of alprenolol and alprenoxime at a dose of 25 mg/kg on isoproterenol-induced tachycardia was evaluated. Drugs were administered topically to the eye as a 5% solution. Fifty microliters of each drug was instilled into each eye every 5 min for five time periods (total of 500 μl of a 5% solution). Then pentobarbital (50 mg/kg, i.v.) was administered. After 30 min isoproterenol was subcutaneously administered at a dose of 50 μg/kg and the heart rate was recorded after 0, 1, 3, 5, 15, 30, 45, and 60 min following isoproterenol administration. A control group of seven animals was treated exactly in the same manner after topical administration of the appropriate volume of distilled water.

Results of all the above sets of experiments are expressed as the mean ± standard error of the mean. Significance of the difference between the effect of saline solution (or distilled water) and that of the drugs under investigation on the resting heart rate and isoproterenol-induced tachycardia was analyzed using Student's t test under two levels of significance ($P < 0.05$ and $P < 0.01$).

RESULTS

Effect on the IOP of Rabbits

Results of this set of experiments are summarized in Tables I, II, and III. As shown in Table I, the bilateral administration of AO (1% solution) led to a remarkable decrease in the IOP of rabbits which started at 30 min and was still observed 6 hr following topical administration. Compared to the action of timolol maleate and timolone oxime oxalate as described in our previous work (1), the action of AO was much more pronounced and prolonged than that of either of these two compounds.

Following its unilateral administration at the same con-

Table I. Effect of the Bilateral Topical Administration of Alprenoxime (AO) (1% Solution) on the IOP of Rabbits

Time after administration	IOP (mm Hg)[a]		% change after treatment
	Control[b]	Treated	
0 min	17.3 ± 0.5	16.7 ± 0.9	0.0
30 min	17.6 ± 0.3	13.4 ± 0.7	19.5*
60 min	16.7 ± 0.4	10.9 ± 0.6	34.5*
2 hr	16.3 ± 0.3	8.5 ± 0.5	49.0*
3 hr	16.5 ± 0.2	10.8 ± 0.5	35.5*
4 hr	17.3 ± 0.4	10.8 ± 0.7	35.5*
5 hr	17.3 ± 0.3	10.7 ± 0.6	36.0*
6 hr	19.3 ± 0.4	12.8 ± 0.7	23.5*

[a] Figures represent the mean ± standard error of the mean of four to six rabbits.

[b] Figures represent readings taken from both eyes of rabbits after bilateral administration of buffer solutions 24 hr (±30 min) before bilateral administration of the investigated drug.

* Highly significant change, $P < 0.01$.

Table II. Effect of the Unilateral Topical Administration of Alprenoxime (1% Solution) on the IOP of Rabbits

Time after administration	IOP (mm Hg)[a]		% change after treatment
	Control[b]	Treated[c]	
0 min	16.6 ± 1.2	16.4 ± 0.8	0.0
30 min	16.4 ± 1.3	14.0 ± 1.1	14.6**
60 min	14.8 ± 1.0	12.6 ± 0.8	23.2**
2 hr	16.0 ± 1.0	13.0 ± 0.8	20.7**
3 hr	16.0 ± 1.1	13.6 ± 0.6	17.1**
4 hr	15.6 ± 1.0	14.2 ± 0.8	13.4**
5 hr	16.6 ± 1.0	15.2 ± 0.8	7.3*
6 hr	16.6 ± 1.1	15.8 ± 1.0	3.7

[a] Figures represent the mean ± standard error of the mean of six rabbits.
[b] Figures represent readings from separate eyes of rabbits after unilateral treatment with buffer solution.
[c] Figures represent readings from the other eyes of the same rabbits after unilateral treatment with the investigated drug.
* Significant change, $P < 0.05$.
** Highly significant change, $P < 0.01$.

centration, AO (1) has also displayed a significant reduction of the IOP of rabbits (Table II). The reduction in the IOP was less than that observed after the bilateral administration of AO.

In another experiment, the possible difference between the two isomeric forms (E and Z) of AO was evaluated in rabbits after their unilateral administration. As shown in Table III, no statistically significant difference in the lowering of IOP was observed in the treated eyes. The onset and duration of the IOP reduction were also similar after administration of the two isomers.

Effect on the Resting Heart Rate

In rats the i.v. injection of 6 mg/kg of alprenolol produced a significant and sustained decrease in the heart rate (Table IV). A similar dose of AO caused a small and transient bradycardia. Doubling the dose of AO (to 12 mg/kg) did not lead to prolongation of its negative chronotropic action. However, the i.v. infusion of AO produced a significant and sustained bradycardia, which was, however, much less than that produced by the same dose of alprenolol.

In rabbits, the i.v. bolus injection of alprenolol (6 mg/kg) caused a sustained and significant bradycardia, whereas the same dose of AO did not produce any change in the heart rate of animals (Table V).

Effect on Isoproterenol-Induced Tachycardia

After i.v. Bolus Injection

In rats, both alprenolol and AO (6 mg/kg) administered immediately before isoproterenol produced a significant antagonism of tachycardia. However, alprenolol was much more effective in this respect. The action of AO at this dose level was almost similar in potency to alprenolol administered at a dose of 2 mg/kg (Fig. 1A). Administration of AO at doses of 6 and 12 mg/kg 10 min and at a dose of 6 mg/kg 30 min before isoproterenol did not produce any significant antagonism of the tachycardia (Figs. 1B and C).

Similar results were obtained in rabbits (Fig. 2A and 2B). Alprenolol (6 mg/kg) administered immediately prior to

Table III. Effect of the Unilateral Administration of the Two Isomers (E and Z) of AO and Their Mixture (1% Solution) on the IOP of Rabbits

Time after administration	IOP (mm Hg)[a]					
	E		Z		E and Z	
	Control[b]	Treated[c]	Control[b]	Treated[c]	Control[b]	Treated[c]
0 min	16.4 ± 1.3	16.6 ± 1.4	17.3 ± 0.6	17.0 ± 0.9	16.8 ± 1.2	16.6 ± 0.9
% change	0.0	0.0	0.0	0.0	0.0	0.0
30 min	16.2 ± 0.9	14.3 ± 1.1	17.0 ± 0.7	14.6 ± 1.2	16.5 ± 1.3	14.1 ± 1.0
% change	−1.2	−13.9**	−1.7	−14.1**	−1.8	−15.1**
60 min	16.0 ± 1.0	12.8 ± 0.9	17.0 ± 0.9	13.4 ± 1.0	15.9 ± 0.8	12.9 ± 1.1
% change	−2.4	−22.9**	−1.7	−21.2**	−5.4	−22.0**
2 hr	15.8 ± 1.3	13.0 ± 1.2	18.2 ± 0.5	13.3 ± 0.6	16.9 ± 0.9	13.4 ± 0.8
% change	−3.7	−21.9**	+5.2	−21.5**	+0.6	−19.3**
3 hr	17.0 ± 1.3	14.0 ± 1.1	17.2 ± 0.7	14.1 ± 0.9	16.3 ± 1.1	13.9 ± 0.9
% change	+3.7	−15.7**	−0.6	−17.0**	−3.0	16.3**
4 hr	16.0 ± 1.0	14.2 ± 1.0	17.5 ± 0.6	14.7 ± 0.8	16.2 ± 1.2	14.0 ± 1.0
% change	−2.4	−14.5**	+1.2	−13.5**	−3.6	−15.7**
5 hr	16.6 ± 1.1	15.3 ± 1.2	17.0 ± 0.8	15.6 ± 1.0	16.6 ± 1.0	15.4 ± 1.1
% change	+1.2	−7.8*	−1.7	−8.2*	−1.2	−7.2*
6 hr	16.8 ± 1.2	16.6 ± 1.1	17.5 ± 0.7	16.7 ± 1.1	16.8 ± 1.4	16.9 ± 1.0
% change	+2.4	0.0	+1.2	1.7	0.0	+1.8

[a] Figures represent the mean ± standard error of the mean of 20 rabbits.
[b] Figures represent readings from separate eyes of rabbits after unilateral treatment with buffer solution.
[c] Figures represent readings from the other eyes of the same rabbits after unilateral treatment with the investigated drug.
* Significant change, $P < 0.05$.
** Highly significant change, $P < 0.01$.

Table IV. Effect of Parenteral Administration of Alprenolol and Alprenoxime on the Heart Rate of Rats

Treatment	% decrease in heart rate ± SE at time after administration (min)					
	1	3	5	10	15	30
Alprenolol (6 mg/kg, i.v. bolus)	25.6* ± 1.5	21.3* ± 2.0	19.8* ± 1.9	19.4* ± 1.1	20.4* ± 1.1	22.8* ± 1.0
Alprenoxime (6 mg/kg, i.v. bolus)	16.8* ± 1.5	14.1* ± 0.9	12.0* ± 1.0	10.1* ± 1.2	13.3 ± 2.7	14.8 ± 3.6
Alprenoxime (12 mg/kg, i.v. bolus)	27.5* ± 2.5	25.6* ± 1.7	20.7* ± 1.7	15.6* ± 2.4	13.9 ± 1.8	16.1 ± 1.9
Alprenolol (6 mg/kg, i.v. infusion)	28.8* ± 1.7	31.4* ± 0.4	31.4* ± 1.7	31.4* ± 1.7	31.4* ± 2.4	33.9* ± 0.8
Alprenoxime (6 mg/kg, i.v. infusion)	22.4* ± 2.0	17.5* ± 1.4	13.9* ± 0.7	15.0* ± 0.9	16.9* ± 1.0	24.2* ± 1.0
Control (saline)	0.0 ± 0.0	2.5 ± 0.7	4.7 ± 0.6	6.3 ± 0.6	11.2 ± 1.0	16.3 ± 1.2

* Highly significant decrease, $P < 0.01$.

isoproterenol produced a complete blockade of the tachycardia, whereas AO caused only a transient slight blockade. When the two drugs were injected 30 min prior to isoproterenol challenge, only alprenolol produced a significant antagonism of the tachycardia (Fig. 2B).

After i.v. Infusion

In rats, when alprenolol (6 mg/kg) was administered immediately before isoproterenol, a significant reversal of the tachycardia was recorded. A shorter duration of action was observed when alprenolol was given 30 min prior to isoproterenol. When AO was administered directly or 30 min before isoproterenol, no blockade of the tachycardia was observed. On the other hand, at certain time intervals following i.v. infusion of AO, the action of isoproterenol was more enhanced the AO-treated than in the control untreated animals (Figs. 1D and E).

In rabbits, this potentiation of isoproterenol action by AO was not observed. Thus, whereas alprenolol led to complete reversal of isoproterenol tachycardia for 60 min, AO produced a significant decrease in the intensity of isoproterenol action only for the first 5 min following its administration (Fig. 2C).

After Oral Administration

Both in rats and in rabbits, alprenolol (50 mg/kg) caused a complete blockade of isoproterenol-induced tachycardia 60 min following its oral administration. AO administered under the same conditions did not produce any significant antagonism of the action of isoproterenol (Figs. 1F and 2D).

After Topical (Ocular) Administration

Alprenolol, topically administered to the rabbit's eye at a dose of 25 mg/kg, produced a significant blockade of isoproterenol tachycardia. AO administered at the same dose level did not produce any significant antagonism of isoproterenol action (Fig. 2E).

DISCUSSION

Beta-adrenergic blockers are widely used for the treatment of glaucoma, although a number of serious systemic adverse reaction secondary to their topical use have been reported (4–8). This has tempted us first to design novel antiglaucoma drugs that could be delivered to the ocular compartments in a sustained and controlled manner with the least systemic absorption and/or no systemic side-effects (9,10). These "soft β-blockers" are remarkably successful in separating the desired and the unwanted effects. An entirely different approach reported here involves the design of drugs with site (eye)-specific activation. In our previous studies (1,11) we have described the design, synthesis, and pharmacological properties of the ketoxime precursors of some of the known beta-adrenergic antagonists. In the present work we extended our experiments to investigate the pharmacodynamic activity of the selected novel ketoxime precursor of the beta-adrenergic blocker, alprenolol. This compound was

Table V. Effect of the i.v. Injection of 6 mg/kg of Alprenolol and Alprenoxime on the Heart Rate of Rabbits

Treatment	% decrease in heart rate ± SE at time after administration (min)					
	1	3	5	10	15	30
Alprenolol	9.5** ± 0.3	9.1** ± 0.4	10.0** ± 0.9	10.1* ± 0.9	12.8* ± 1.0	14.6 ± 1.3
Alprenoxime	1.7 ± 1.1	4.3 ± 1.3	6.1 ± 1.1	9.5 ± 1.0	9.5 ± 1.3	13.8 ± 0.8
Control	0.5 ± 0.5	2.0 ± 0.8	4.2 ± 1.0	6.0 ± 1.3	8.2 ± 1.4	11.9 ± 1.7

* Significant decrease ($P < 0.05$).
** Highly significant decrease ($P < 0.01$).

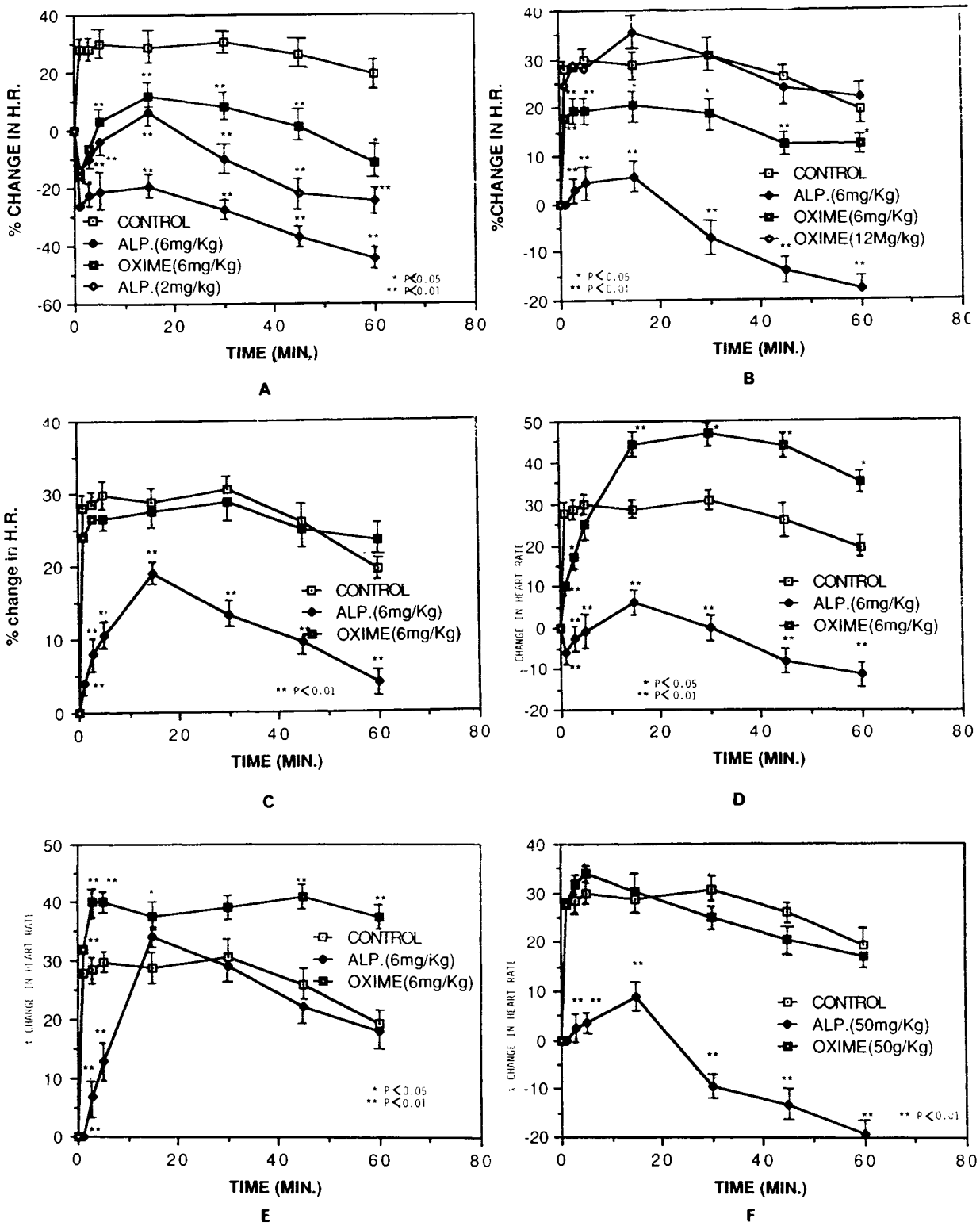

Fig. 1. Effect of alprenolol and alprenoxime on the isoprenaline-induced tachycardia in rats. (A) Compounds intravenously injected directly before isoprenaline; (B) compounds intravenously injected 10 min before isoprenaline; (C) compounds intravenously injected 30 min before isoprenaline; (D) compounds administered as intravenous infusion directly before isoprenaline; (E) compounds administered as intravenous infusion 30 min before isoprenaline; (F) compounds administered orally 1 hr before isoprenaline.

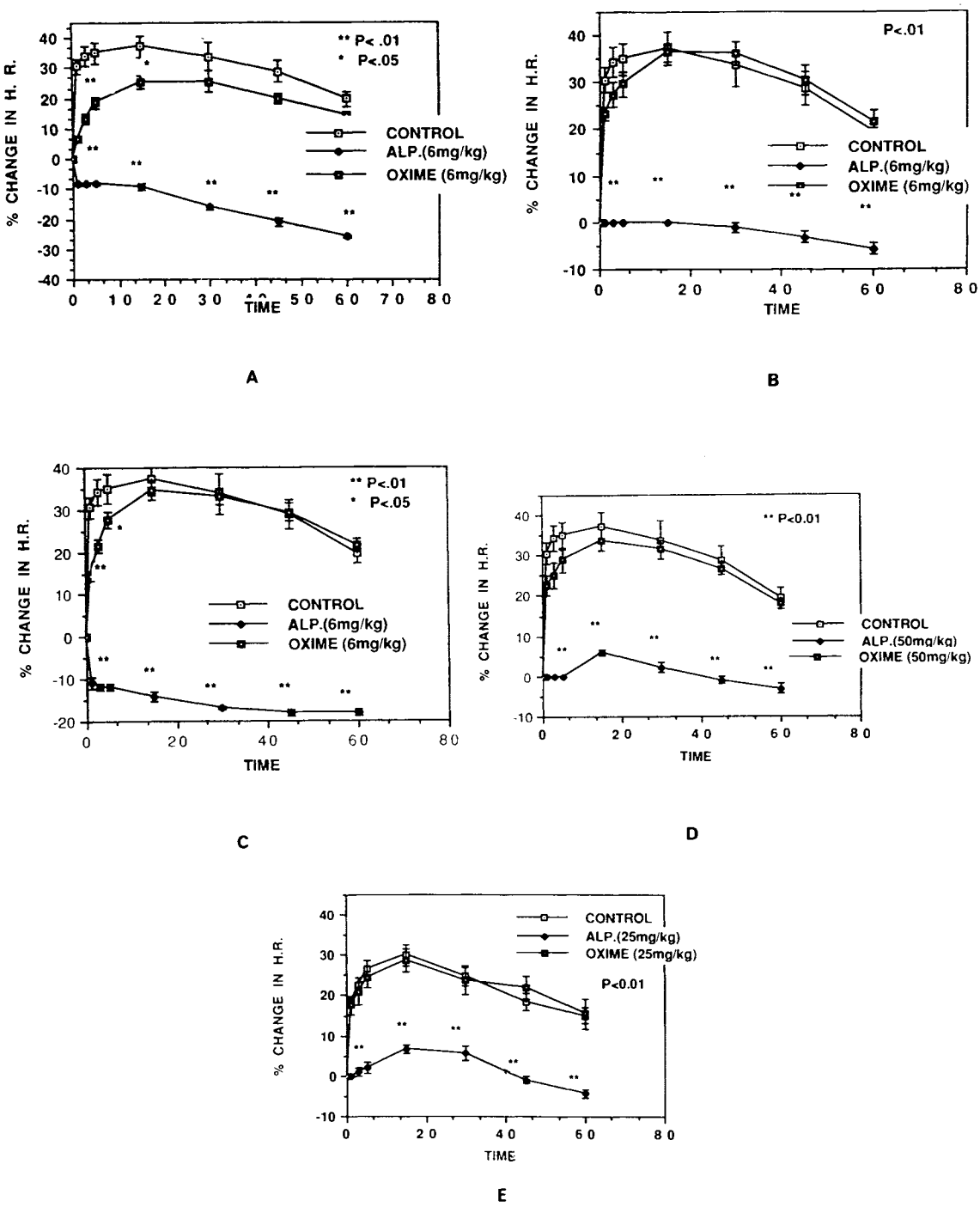

Fig. 2. Effect of alprenolol and alprenoxime on the isoprenaline-induced tachycardia in rabbits. (A) Compounds intravenously injected directly before isoprenaline; (B) compounds intravenously injected 30 min before isoprenaline; (C) compounds administered as an i.v. infusion directly before isoprenaline; (D) compounds orally administered 1 hr before isoprenaline; (E) compounds topically administered 1 hr before isoprenaline. Numbers below the abscissa represent time in minutes after isoprenaline administration.

selected, as its lipophilic properties apparently make it a better substrate for the enzymes involved in its rapid conversion to alprenolol in the iris/ciliary body (3) and lead to enhanced ocular hypotensive activity. Results of the IOP studies support this concept. Thus, following both its uni- and its bilateral administration, AO appeared to exert a remarkable hypotensive effect on the IOP of rabbits. In our previous work (1) both timolol and the other ketoximes of the different β-blockers produced less extensive reduction of the IOP than AO did in this study.

We have previously reported that the oxime 1 exists in two interconvertible isomeric forms designated as Z and E isomers (3). The ratio of these isomers depends on the synthetic conditions and on the temperature and the pH of the

solution in which they are dissolved. It was necessary, therefore, to investigate any potential differences in the ocular hypotensive activity of these two isomers. Results of this experiment indicate that there were no statistically significant differences in the intensity, onset, or duration of action of the two isomers or their isomeric mixture. This means that either both isomers are good substrates for the oxime hydrolase enzyme or the E ⇄ Z interconversion takes place very rapidly in the eye tissue.

The next sets of experiments were designed to evaluate some of the systemic cardiovascular and beta-adrenergic actions of the ketoxime (**1**) after its administration by different routes. The parent beta-antagonist, alprenolol (**2**), was used as a reference compound. Two commonly used parameters were used for this purpose: the negative chronotropic effect and the ability to antagonize the positive chronotropic effect of the beta-adrenergic stimulant isoproterenol. Similar results were obtained, independent of the route of administration of the two compounds (parenteral, oral, or topical). Thus, alprenolol was able to induce a significant negative chronotropic action and to antagonize or reverse the beta-adrenergic stimulation caused by isoproterenol injection. On the other hand, AO either produced a weak and transient action or failed to produce such activity even after increasing its dose to double that of alprenolol. Further, in certain cases and, in particular, when the ketoxime was administered by i.v. infusion to rats, a potentiation of isoproterenol action was obtained. This finding might be tentatively attributed to a possible intrinsic sympathomimetic activity of this compound. However, this activity was not observed in rabbits treated under the same conditions.

In general, the results obtained after parenteral or oral administration of this novel ketoxime revealed that this compound exerts a very weak beta antagonistic activity with a much shorter duration of action in the systemic circulation than the parent drug alprenolol. This finding supports the idea that **1** is not converted to **2** to any significant extent in the systemic circulation. When **1** was given as an i.v. bolus injection directly before isoproterenol administration, it exerted some weak beta antagonistic activity which completely disappeared when it was given 10 or 30 min before isoproterenol. These results are consistent with a minimal **1** → **2** conversion or some weak intrinsic activity **1**. The short duration is consistent with the previously observed (1,11) very fast disappearance of a structurally similar analogue, propranolone oxime, in the blood, but without detecting any of the parent β-blocker propranolol. Furthermore, when AO was administered by i.v. infusion, either it led to a transient antagonistic activity (in rabbits) or it failed to produce such an effect or even enhanced isoproterenol action (in rats).

The most significant finding from this study was, however, the results obtained following the topical administration of the two drugs to the rabbit's eyes. Alprenolol under these conditions displayed significant systemic beta antagonistic activity. AO, however, did not show any systemic cardiovascular activity when topically administered at a dose equivalent to 25 mg/kg, whereas the anticipated maximum daily dose in humans is about 0.04 mg/kg.

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