Adimolol, a long acting β -adrenoceptor blocker in man

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1 A comparative study in eight healthy normotensive males of the effects on blood pressure, heart rate and β -adrenoceptor function following single oral doses of adimolol (600 mg), propranolol (240 mg) and placebo.

2 Both active treatments produced small but significant reductions in blood pressure and heart rate, supine and erect. These effects persisted for up to 7 days after adimolol.

3 The heart rate increases following both dynamic exercise and intravenous isoprenaline were attenuated by both propranolol and adimolol. With adimolol evidence of functional β -adrenoceptor antagonism was sustained for up to 7 days.

4 Lymphocyte β -adrenoceptor binding studies showed that both adimolol and propranolol significantly reduced affinity for β -adrenoceptors. In addition, adimolol significantly reduced receptor number and even by 3 days after dosing $B_{\max}$ had only returned to half the control value.

5 In a small sub-group of subjects there was no evidence to suggest that adimolol had additional α -adrenoceptor antagonist properties.

6 Adimolol was detected in plasma for up to 3 days after dosing. The mean terminal elimination half-life was 14 h, compared to 3 h for propranolol.

7 This study confirms that adimolol has prolonged β -adrenoceptor antagonist activity with effects persisting for up to 7 days after a single dose. The reduction in β -adrenoceptor number following adimolol suggests that this prolonged effect may not be solely due to competitive antagonism but may additionally depend upon non-competitive antagonism at β -adrenoceptors.

Keywords adimolol prolonged β -adrenoceptor antagonism
in vivo and *in vitro* studies

Introduction

Adimolol (MEN 935; 1-3-3 [3-(1-naphthoxy)-2-hydroxypropyl-amino -3,3-dimethyl-propyl -2-benzimidazolinone hydrochloride; Boehringer Ingelheim KG) has been shown in animals and in preliminary studies in man to have marked and prolonged β -adrenoceptor antagonist activity with inhibition of exercise-induced tachycardia for up to 72 h after a single dose (Riddell *et al.*, 1985). It has been claimed also to possess weak α -adrenoceptor antagonist activity in animals

(Hoefke *et al.*, 1984) but a recent study in man failed to show any significant effect at α_1 -adrenoceptors (Riddell *et al.*, 1985).

This study was designed to investigate further the nature and duration of the cardiovascular effects of single doses of adimolol and its effects on the responses modulated by actions on α - and β -adrenoceptors. The plasma concentrations and pharmacokinetics of adimolol were also determined. In addition parallel *in vitro*

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studies of the effects of adimolol on α - and β -adrenoceptors on platelets and lymphocytes were undertaken.

Methods

The study population comprised eight normotensive males, aged 21–26 years, weight 68–84 kg with no significant abnormality on pre-study clinical examinations and laboratory investigation. The protocol was approved by the Research and Ethical Committee of the Northern District of the Greater Glasgow Health Board and all subjects gave written informed consent.

Three subjects undertook a preliminary single-blind phase in which 600 mg of adimolol was compared with placebo to assess safety, general tolerability and the approximate duration of the β -adrenoceptor antagonist effects. α -adrenoceptor activity, at both α_1 - and α_2 -adrenoceptors, was also evaluated in this pilot phase.

The main study was a double-blind, randomised crossover comparison of single doses of 600 mg adimolol, 240 mg propranolol and placebo. Observations were made frequently over an 8 h study day and continued for 7 days after each treatment. There was a further period of 7 days between each treatment period.

Subjects reported at 08.30 h on each study day having abstained from alcohol, nicotine and caffeine since 22.00 h on the previous evening. For the duration of the whole study, and for 1 week beforehand, no other medication was taken, particularly and specifically excluding salicylates and related drugs.

After a period of recumbency of not less than 30 min following the insertion of a cannula into a forearm vein, active drug and placebo were orally administered.

Blood pressure and heart rate

Blood pressure and heart rate were measured supine, after not less than 10 min recumbency, and erect, after 2 and 5 min standing by semi-automated sphygmomanometer (Sentron: Bard Medical) at frequent predetermined intervals up to 8 h after drug administration and thereafter at 24 h, 3 days and 7 days.

β -adrenoceptor responses in vivo

The heart rate responses to dynamic exercise (5 min at 75% of the individually pre-determined maximal workload on a bicycle ergometer) and to an incremental intravenous infusion of isoprenaline (with not less than four dose levels,

each of 7 min duration) were determined between 5–6 h after each treatment and repeated at 24 h, 3 and 7 days. The order of these tests was randomly allocated but kept constant for each individual throughout the study. The chronotropic responses to isoprenaline were assessed by fitting all data points from each individual infusion study to a quadratic function (Sumner *et al.*, 1982).

α -adrenoceptor responses in vivo

In the pilot study (three subjects) the pressor responses to incremental infusions of phenylephrine (selective α_1 -adrenoceptor agonist) and α -methylnoradrenaline (preferential α_2 -adrenoceptor agonist) were assessed between 5 and 6 h after dosing. Pressor dose-response curves were fitted to a quadratic function, as for the isoprenaline responses (Sumner *et al.*, 1982).

Drug concentrations and pharmacokinetics

Both adimolol (Weidmann, 1983) and propranolol (Girault & Fourtillan, 1981) were measured by h.p.l.c. with fluorescence detection. The detection limits were respectively 1 ng ml⁻¹ and 2.5 ng ml⁻¹ and the coefficients of variations were respectively 6.8 and 5.4%.

The plasma concentration data for adimolol were most appropriately fitted to a two compartment model and for propranolol to a one compartment model. The appropriateness of those fits was determined by application of the general linear test (Boxenbaum *et al.*, 1974).

In vitro studies

Venous blood samples were obtained prior to drug administration (time 0: control) and thereafter at 4 and 24 h and at 3 and 7 days during each treatment phase.

Platelet α_2 -adrenoceptor studies were performed only in a small subgroup of subjects ($n = 3$) in the preliminary study and the main study ($n = 8$) investigated lymphocyte and platelet β_2 -adrenoceptors.

(a) *Platelet studies* Aggregometry was performed by the standard turbidometric method of Born (1962) in a Payton dual channel aggregometer.

(1) *Adrenaline induced α_2 -adrenoceptor mediated platelet aggregation* The rate of primary adrenaline induced aggregation was measured in terms of change in light transmittance units per min at the steepest initial part

of the curve. Parameter values were obtained for $E_{\max}$, the maximum rate of primary platelet aggregation ($E_{\max}$: Δ OD/min) and C_{50} the concentration of adrenaline required to produce 50% maximum aggregation (C_{50} : nM) and γ the slope of the dose-response relationship:

$$\text{Effect} = \frac{E_{\max} \times (C/C_{50})}{1 + (C/C_{50})}$$

(2) *α -adrenoceptor binding* Platelet preparations with incubated with [3 H]-yohimbine (Amersham 92 Ci/mmol). Bound radioactivity was determined by liquid scintillation counting at an efficiency of 36% and the non specific binding was determined in the presence of 1 μ M phentolamine. Saturation binding isotherms were analysed by plotting free/bound radioactivity vs free using least squares fitting to obtain values for $B_{\max}$ (fmol/ 10^9 platelets) and K_D (nM). In this laboratory the α -adrenoceptor binding assay has an intra assay coefficient variation of 4.8%.

(3) *Isoprenaline β_2 -adrenoceptor mediated inhibition of platelet aggregation* Platelet β -adrenoceptor mediated responses were measured according to the method of Kerry & Scrutton (1983) using isoprenaline to inhibit the response to 8-arginine vasopressin. Responses were measured as a percentage inhibition of the control AVP response in the absence of isoprenaline.

(b) *Lymphocyte studies* Lymphocytes were isolated according to the method of Boyum (1968) and ultimately a broken cell lysate prepared according to a modification of the method of Aarons *et al.* (1980).

(1) *Lymphocyte β -adrenoceptor binding assay* β -adrenoceptor binding studies were performed according to the method of Brodde *et al.* (1981) using [125 I]-iodocyanopindolol (ICYP Amersham UK 2000 Ci/mmol) 5–15 pM in the presence and absence of 1 μ M (–)-propranolol (ICI UK, Macclesfield, Cheshire).

Non specific binding of ICYP was defined as radioactivity bound to membranes which was not displaced by 1 μ M (–)-propranolol. Specific binding was defined as total radioactivity minus non specific binding and amounted to 50–60% of total binding at 80 pM ICYP. The equilibrium binding constant K_D (pM) and maximum number of binding sites $B_{\max}$ (fmol/mg protein) were calculated from plots of free/bound vs free ICYP by least squares fitting of the regression analysis, r values were greater than 0.9 for all plots.

Protein concentration was measured by the method of Lowry *et al.* (1951).

Statistical analysis

Statistical evaluation of the repeated measurements was by analysis of variance. Where appropriate for individual time points. Student's paired t -test with Bonferroni correction has been applied.

Results throughout are expressed as mean $\pm$ s.d.

Results

Both active drugs were generally well tolerated apart from feelings of tiredness and fatiguability, particularly during the first 24–48 h. Neither the subjects nor the investigators were able to distinguish adimolol from propranolol in terms of this side effect. There were no changes in routine haematological or biochemical variables.

Blood pressure and heart rate

Compared with placebo, there were significant reductions in supine systolic blood pressure after adimolol and propranolol, particularly 4–8 h after dosing. Additionally, adimolol caused a significant reduction in supine systolic blood pressure at 1, 3 and 7 days compared with both placebo and propranolol, but from 24 h onwards propranolol was not significantly different from placebo. A statistical difference for supine diastolic pressure was also observed at 1, 3 and 7 days after adimolol compared with placebo. These results are shown in Figures 1 and 2 and are summarised in Table 1.

A comparable pattern was observed for standing blood pressure after adimolol. There was no evidence of an orthostatic component to the blood pressure reduction (Table 1).

The supine heart rate showed no significant differences throughout the 0–8 h period although there was a rank order for heart rate reduction of adimolol > propranolol > placebo. From 6 h after dosing until the seventh day, a significant reduction in supine heart rate was observed with adimolol. The erect heart rates showed a similar response with a significant reduction due to adimolol from 4 h onwards. The heart rates are also shown in Figures 1 and 2 and are summarised in Table 1.

β -adrenoceptor responses in vivo

Dynamic exercise Both adimolol and propranolol caused a marked and significant reduction

Figure 1 Supine systolic and diastolic blood pressures and heart rates during the first 8 h after administration of adimolol (●), propranolol (▲) and placebo (○).

in exercise heart rate at 6 h (Figure 3). This effect was sustained until 24 h with adimolol and thereafter there was a gradual return towards placebo although even after 7 days the chronotropic responses to exercise remained significantly different from placebo. With propranolol, evidence of β -adrenoceptor antagonism was still apparent at 24 h but at 3 and 7 days it was not significantly different from placebo.

Isoprenaline chronotropic response With adimolol, particularly at 6 and 24 h after drug administration, there were profound shifts to the right in the dose-response curves. The slopes of these curves, in five of the eight subjects, were not consistent with parallelism when compared with the corresponding individual placebo curves. For comparative purposes and the calculation of a dose ratio, however, a parallel shift has been assumed in these individuals. At the same early times in the remaining three subjects and in all subjects at 3 days and 7 days after adimolol, it was found that the slopes of the dose-response

curves were not inconsistent with parallel rightward shifts. After 24 h there was a progressive decline in the extent of the antagonism attributable to adimolol but a statistically significant shift was still present at 7 days (Figure 4). With propranolol significant parallel shifts were obtained at 6 and 24 h but not thereafter. These data are summarised in Table 2.

α -adrenoceptor responses in vivo

In the pilot group in whom α -adrenoceptor antagonism was examined there was no evidence of significant alterations to the pressor dose-response relationships mediated via either α_1 - or α_2 -adrenoceptors as the pressor effects of phenylephrine and α -methyl noradrenaline were not altered (Figure 5).

Pharmacokinetics

The pharmacokinetic parameters for adimolol were obtained by fitting the plasma concentration

Figure 2 Erect (5 min) systolic and diastolic blood pressures and heart rates during the first 8 h after administration of adimolol (●), propranolol (▲) and placebo (○).

Table 1 Summary of average blood pressures and heart rates (mean $\pm$ s.d.)

	Adimolol (mm Hg) (beats min ⁻¹)		Propranolol (mm Hg) (beats min ⁻¹)		Placebo (mm Hg) (beats min ⁻¹)	
<i>Supine</i>						
0 h	125/66 $\pm$ 9/8	64 $\pm$ 12	123/65 $\pm$ 9/7	64 $\pm$ 12	118/65 $\pm$ 9/7	63 $\pm$ 9
4 h	108/60 $\pm$ 10/9	56 $\pm$ 10	107/61 $\pm$ 5/10	57 $\pm$ 8	116/61 $\pm$ 6/10	60 $\pm$ 10
8 h	112/57 $\pm$ 10/10	63 $\pm$ 9	113/57 $\pm$ 11/7	58 $\pm$ 17	124/62 $\pm$ 4/7	71 $\pm$ 13
24 h	111/60 $\pm$ 7/7	54 $\pm$ 10	117/59 $\pm$ 7/9	58 $\pm$ 8	119/60 $\pm$ 7/6	65 $\pm$ 8
3 days	113/56 $\pm$ 6/6	61 $\pm$ 9	115/60 $\pm$ 12/6	66 $\pm$ 10	121/66 $\pm$ 7/7	64 $\pm$ 9
7 days	114/57 $\pm$ 5/5	60 $\pm$ 7	120/62 $\pm$ 4/8	65 $\pm$ 7	122/65 $\pm$ 9/7	65 $\pm$ 8
<i>Erect</i>						
0 h	125/72 $\pm$ 7/5	77 $\pm$ 8	122/72 $\pm$ 4/7	79 $\pm$ 10	122/73 $\pm$ 10/5	77 $\pm$ 10
4 h	107/67 $\pm$ 8/9	69 $\pm$ 12	111/65 $\pm$ 6/10	67 $\pm$ 9	118/71 $\pm$ 9/8	82 $\pm$ 10
8 h	105/61 $\pm$ 11/9	80 $\pm$ 10	108/64 $\pm$ 9/12	78 $\pm$ 6	121/68 $\pm$ 11/11	96 $\pm$ 11
24 h	107/64 $\pm$ 12/8	67 $\pm$ 9	116/68 $\pm$ 8/8	73 $\pm$ 8	123/74 $\pm$ 10/6	77 $\pm$ 7
3 days	113/62 $\pm$ 6/6	70 $\pm$ 8	115/71 $\pm$ 8/8	78 $\pm$ 9	125/74 $\pm$ 4/7	76 $\pm$ 7
7 days	122/65 $\pm$ 7/6	74 $\pm$ 7	125/70 $\pm$ 5/7	78 $\pm$ 8	124/73 $\pm$ 5/5	78 $\pm$ 6

data to a two compartment model. Representative plasma concentration-time profiles for both adimolol and propranolol are shown in Figure 6. There was fairly wide interindividual variation

in the derived parameters with the terminal elimination half-lives ($t_{1/2,z}$) for adimolol ranging from 7.3 to 23.9 h with a mean value (s.d.) of 14.1 ± 4.7 h. Clearance/ F ranged from 351 to

Figure 3 Exercise heart rates at 6 and 24 h, 3 and 7 days following administration of adimolol (●), propranolol (▲) and placebo (○).

Figure 4 Isoprenaline chronotropic dose-response curves in a representative subject: (a) adimolol; (b) propranolol.

Table 2 Summary of isoprenaline chronotropic responses ($\mu\text{g kg}^{-1} \text{min}^{-1}$, mean $\pm$ s.d.)

	Adimolol		Propranolol		Placebo
	CD_{20}	Dose ratio	CD_{20}	Dose ratio	CD_{20}
6 h	$12.1^* \pm 12.5$	466	1.77 ± 1.41	64	0.028 ± 0.006
24 h	$8.3^* \pm 4.1$	328	$0.08^* \pm 0.02$	3	0.025 ± 0.004
3 days	$0.32^* \pm 0.12$	14	0.027 ± 0.01	0.9	0.029 ± 0.012
7 days	$0.051^* \pm 0.01$	1.6	0.029 ± 0.017	0.9	0.031 ± 0.007

* $P < 0.05$ compared with placebo.

Figure 5 Pressor dose-response curves for phenylephrine and α -methylnoradrenaline in the pilot study ($n = 3$). ● adimolol, ○ placebo.

1033 ml min^{-1} with a mean ($\pm$ s.d.) of $800 \pm 358 \text{ ml min}^{-1}$). The pharmacokinetic parameters for propranolol were obtained from fitting the plasma concentration data to a one compartment model and the interindividual variation in the derived pharmacokinetic parameters was similar to that observed for adimolol. The elimination half-life ($t_{1/2,z}$) ranged from 2.10 to 4.08 h with a mean ($\pm$ s.d.) value of $3.11 \pm 0.57 \text{ h}$. Clearance/ F ranged from 1282 to 5080 ml min^{-1} with a mean of $2615 \pm 1272 \text{ ml min}^{-1}$.

In vitro studies

(a) α_2 -adrenoceptors (1) Platelet aggregation. No significant change was seen in C_{50} , the concentration of adrenaline required to induce 50% maximal aggregation, although for the maximum aggregatory response (OD/min) there was an apparent reduction (Table 3). This trend was maximal at 4 h.

(2) Platelet α_2 -adrenoceptor binding. No alteration of platelet α_2 -adrenoceptor number was seen during the study and similarly there were no changes in affinity (Table 3).

In this small study, following the *in vivo* dosing with adimolol, no evidence was obtained *in vitro* for significant α_2 -adrenoceptor antagonist activity.

(b) β_2 -adrenoceptors (1) Lymphocyte receptor binding studies. These results are summarised in Table 4.

Adimolol caused a considerable reduction in the number of lymphocyte β -adrenoceptors. The fall was marked at 4 h and even by 3 days had only returned to half the pretreatment (control) values. Adimolol also increased K_D and thus lowered affinity.

After the single dose of propranolol there was no change in β -adrenoceptor number although the affinity of ICYP binding was reduced and K_D increased at 4 and 24 h.

(2) Isoprenaline-mediated inhibition of platelet aggregation. The inhibition of the aggregatory response to 8-arginine vasopressin which is induced by isoprenaline and mediated by β -adrenoceptors on platelets was prevented by both propranolol and adimolol (Figure 7). The effect of adimolol appeared to be long lasting and had not fully recovered even by 7 days.

Discussion

This study was designed to examine the cardiovascular effects and pharmacokinetics of adimolol

Figure 6 Representative plasma concentration-time profiles for adimolol and propranolol.

Table 3 Platelet α_2 -adrenoceptor responses and ligand binding after adimolol 600 mg orally ($n = 3$) (mean $\pm$ s.d.)

	Before treatment	4 h	24 h	3 days	7 days
<i>Adrenaline aggregation</i>					
C_{50} (nM)	0.06 ± 0.02	0.08 ± 0.07	0.08 ± 0.03	0.08 ± 0.03	0.07 ± 0.03
$\Delta OD/min$	64 ± 21	44 ± 20	53 ± 22	59 ± 29	65 ± 22
<i>[³H]-yohimbine ligand binding</i>					
Receptor number (fmol/ 10^9 platelets)	25 ± 2.8	27 ± 1	26 ± 4	23 ± 3	28 ± 3
αK_D (nM)	2.24 ± 0.19	3.08 ± 0.35	2.54 ± 0.74	2.25 ± 0.79	3.76 ± 0.63

Table 4 Lymphocyte β -adrenoceptor binding to [125 I]-iodocyanopindolol after propranolol 240 mg and adimolol 600 mg ($n = 8$) (mean $\pm$ s.d.)

	Control (Duplicate)	Adimolol	Propranolol
(a) $B_{\max}$ (fmol mg $^{-1}$ protein)			
4 h	11 $\pm$ 3	1 $\pm$ 2	11 $\pm$ 3
24 h	11 $\pm$ 3	4 $\pm$ 3	11 $\pm$ 3
3 days	11 $\pm$ 3	5 $\pm$ 4	11 $\pm$ 5
7 days	11 $\pm$ 3	11 $\pm$ 5	10 $\pm$ 2
(b) K_D (pM)			
4 h	35 $\pm$ 18	98 $\pm$ 8	68 $\pm$ 21
24 h	35 $\pm$ 18	90 $\pm$ 57	62 $\pm$ 7
3 days	35 $\pm$ 18	52 $\pm$ 21	32 $\pm$ 17
7 days	35 $\pm$ 18	33 $\pm$ 14	37 $\pm$ 16

in man and to investigate the *in vitro* effects on α - and β -adrenoceptors. In addition to long-lasting β -adrenoceptor antagonism there had been previous suggestions of another possible anti-hypertensive mechanism mediated via α -adrenoceptors (Hoefke *et al.*, 1984). The pilot phase of this study provided no evidence of either α_1 - or α_2 -adrenoceptor antagonist activity *in vivo* and in addition there were no effects *in vitro* on platelet α_2 -adrenoceptor number or function.

On the basis of these preliminary findings, in conjunction with evidence from a similar study (Riddell *et al.*, 1985), the main study concentrated on an examination of the duration and intensity

of the effects of β -adrenoceptors. Adimolol 600 mg orally caused a significant and long lasting reduction in blood pressure for up to 7 days. There was marked cardiac β -adrenoceptor blockade *in vivo*, in response to both exercise and isoprenaline, which also persisted for up to 7 days. The effects of adimolol were more marked and significantly longer lasting than propranolol 240 mg orally. A feature of the displacement of the dose-response curves with adimolol, at 6 and 24 h, was the lack of parallel shifts in five of the eight subjects. A parallel shift in the dose-response curve is characteristic of a competitive antagonist and accordingly the lack of a parallel shift with adimolol raises the possibility that the drug is not a conventional receptor antagonist.

It is well recognised with propranolol that the time course of effect and plasma concentration kinetics are out of phase (McDevitt & Shand, 1975) but, although adimolol had a long plasma half-life (14 h compared to 3 h for propranolol) and was detectable in plasma for up to 72 h, it seems unlikely that this alone can account for its prolonged duration of action. The inter-relationships between pharmacological effects, drug concentrations and receptor binding characteristics are complex (as recently described by Wellstein *et al.*, 1985a,b) but it is difficult to explain the time course of effect solely on the basis of the time required for drug-receptor binding. For example, during the period 24–72 h in the *in vivo* study, when there was approximately a 10-fold fall in plasma levels of adimolol, there was only a modest recovery of exercise-induced tachycardia.

Figure 7 Effects of adimolol and propranolol on isoprenaline-mediated inhibition of platelet aggregation.

The additional information from the *in vitro* study also suggests that adimolol is not a simple, competitive β -adrenoceptor antagonist. There was confirmatory evidence of long lasting β -adrenoceptor blockade after a single dose of adimolol but in addition a marked fall in lymphocyte β -adrenoceptor number was observed with slow recovery over 7 days. Chronic β -adrenoceptor antagonism usually results in an increase in β -adrenoceptors by the process of receptor upregulation (Aarons *et al.*, 1980; Molinoff & Aarons, 1983). In contrast, a reduction in β -adrenoceptor number and down regulation has been reported for β -adrenoceptor antagonists with marked partial agonist activity (Molinoff *et al.*, 1982; Giudicelli *et al.*, 1984). However, for adimolol there is no previous report of significant partial agonist activity and, from the clinical study, the reduction in resting heart rate also suggests that adimolol does not possess this property.

An alternative explanation for the reduction in lymphocyte β -adrenoceptor number, and the clinical evidence of prolonged β -adrenoceptor blockade, is non-competitive or irreversible β -adrenoceptor antagonism. Similar trends were seen in the time courses of recovery for both platelet β -adrenoceptor function and lymphocyte β -adrenoceptor number, and also for the chronotropic responsiveness to isoprenaline *in vivo*. This is consistent with the hypothesis that propranolol is a competitive β -adrenoceptor

antagonist whereas adimolol may have additional non-competitive antagonist properties with the reduction in β -adrenoceptor number due to receptor inactivation by irreversible β -adrenoceptor blockade and the recovery thereafter perhaps due to 'new receptor synthesis'.

It might be suggested that residual β -adrenoceptor blocker, persisting in plasma or non-specifically bound to cells, was the underlying cause. This is unlikely since similar changes were not seen after propranolol and the experimental procedure involved extensive washing of lymphocytes. Furthermore, although propranolol, at 4 and 24 h, reduced β -adrenoceptor affinity it had no effect on β -adrenoceptor number at any time.

These studies show that adimolol given as a single dose of 600 mg can cause long lasting β -adrenoceptor blockade and reduction of blood pressure. In this comparative single dose study the side effects of single doses of the two active agents were not distinguishable; however, both drugs were relatively well tolerated. Clinical investigations with adimolol given once or twice weekly in angina or hypertension appear to be justified. Further studies are indicated to clarify the nature of the antagonist effect of adimolol at β -adrenoceptors but it seems likely that clinically useful drug activity might be achieved during chronic therapy with lower doses than those used in this study.

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