Dynamics of β -adrenoceptor blockade with cetamolol

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1 Cetamolol is a new β -adrenoceptor blocking agent shown in animals to have moderate β_1 -adrenoceptor selectivity and partial agonist activity.

2 In healthy normal volunteers, β_1 -adrenoceptor blockade was measured as the reduction of exercise-induced tachycardia, systolic blood pressure, and double product at 2, 8, and 24 h after a single oral dose of 10, 25, and 50 mg cetamolol.

3 β_1 -adrenoceptor blockade was significantly linearly related to log serum cetamolol level, was maximal at 2 h, and was still clinically significant at 24 h.

4 A crossover study of single 0, 10, and 25 mg doses confirmed these findings.

Keywords cetamolol dynamics β -adrenoceptor blockade

Introduction

Cetamolol (AI-27,303, ICI-72,222, Betacor®, Ayerst Laboratories), chemically described as 2-[2-[3-(1, 1-dimethylethyl) amino-2-hydroxypropoxy] phenoxy]-*N*-methyl-acetamide hydrochloride with a molecular weight of 346.5, is a new synthetic β -adrenoceptor blocking agent with intrinsic sympathomimetic activity (ISA) and moderate β_1 -adrenoceptor selectivity in animal studies (Grimes *et al.*, 1982).

This paper reports clinical pharmacological data obtained from two studies conducted on healthy human male volunteers. The data describe the interrelationship between serum cetamolol levels and the duration and extent of β -adrenoceptor blockade.

Methods

Subjects

A total of 56 normal male volunteers between the ages of 18 and 40 years participated in these studies. All volunteers were housed in a supervised environment throughout the study. Cetamolol and placebo were given as matched capsules, before breakfast. The studies were

approved by an independent human studies committee, and written informed consent was obtained from all subjects.

Design of studies

Two studies are presented. Study I was double-blind and placebo-controlled. Four groups of eight subjects were studied in sequence of increasing dose, with single oral 5, 10, 25, and 50 mg doses. Within each group of eight, three subjects were randomized to placebo. Exercise tests were performed before, and 2, 8, and 24 h after dosing using a bicycle ergometer adjusted to elicit each individual's target heart rate at 4 min of exercise. Target heart rate was defined as 85% of the theoretical maximum for each subject's age and cardiorespiratory fitness (Fox *et al.*, 1971).

Venous blood samples, used to determine serum levels of cetamolol, were drawn pre-dosing, and 2 and 24 h after dosing. Cetamolol was measured by radioreceptor assay with a limit of detection of 1 ng/ml based on 2 ml serum (Stern, 1983).

Study II was a double-blind, multiple crossover (3×3 latin square), placebo-controlled

study. Twenty-four subjects were randomized to receive single oral doses of placebo, 10 mg and 25 mg of cetamolol in three different sequences, with a 1 week washout between dosings. Procedures and schedules were identical to those in Study I, except that venous blood samples for cetamolol serum level determinations were drawn at more frequent intervals in order to determine the elimination rate constant(s). Pharmacokinetic data will be reported separately in detail.

Variables for analysis and statistical methods

Variables used to evaluate β -adrenoceptor blockade were 4 min exercise heart rate, systolic blood pressure, and the double product (heart rate $\times$ systolic blood pressure). Serum levels of cetamolol are presented for Studies I and II to show their relationship to β -adrenoceptor blockade.

Two-way analysis of variance (ANOVA) was used to test for predosing comparability regarding demographic data, vital signs, and the Study I exercise-test variables, as well as changes from baseline in the vital signs and Study I exercise-test variables. ANOVA appropriate for a double-crossover Latin Square was used in Study II to test predosing comparability among the dose groups regarding vital signs and exercise tests, plus the differences in the dose groups' changes from baseline in these variables. Regression analysis was used to estimate the relationship between cetamolol serum levels and the degree of β -adrenoceptor blockade.

Results

Comparability

There were no significant differences between dose levels, drug groups, or sequence groups for any demographic variables at baseline in the two studies. The average age for all volunteers was 23 with a range of 18 to 40 years, average height was 177.3 cm with a range of 165 to 194, and average weight was 69.7 kg with a range of 55.1 to 83.3. Vital signs and exercise-test values were comparable at baseline among treatment groups. Responses to exercise at baseline, i.e. prior to any drug treatment, were clinically similar between both studies (Table 1).

β -adrenoceptor blockade

During exercise tests, decreases in heart rate of 10 beats/min or greater, in systolic blood pressure of 10 mm Hg or greater, and in the double

Table 1 Baseline values for exercise variables (Studies I and II) (mean $\pm$ s.e. mean)

	Study I	Study II
Heart rate (beats/min)	164 $\pm$ 2	162 $\pm$ 1
Systolic blood pressure (mm Hg)	189 $\pm$ 4	193 $\pm$ 3
Double product (Systolic BP $\times$ HR)	30928 $\pm$ 696	31138 $\pm$ 499

product of 3000 (beats/min $\times$ mm Hg) or greater were considered clinically significant. Decreases of at least this magnitude were present 24 h after doses of 10, 25, and 50 mg (Table 2, Figure 1).

In Study I, the mean heart rate was significantly reduced by cetamolol at the 2 h and 8 h, and 24 h time points ($P < 0.001$) compared with placebo. The mean exercise systolic blood pressure was significantly reduced by cetamolol at the 2 h ($P < 0.001$) and 8 h ($P < 0.01$) exercise tests compared with placebo, but not at 24 h. Significant reductions in the systolic blood pressure also occurred in Study II with both the 10 and 25 mg cetamolol dose levels at the 2 and 8 h exercise tests (Figure 1). Cardiac work, estimated by the double product, was proportionately reduced by the cetamolol doses compared with placebo in all exercise tests for both studies (Table 2, Figure 1). Double-product reductions were due primarily to the effect of cetamolol on exercise heart rate rather than on systolic blood pressure.

In Study II, at 2 h post dosing, 25 mg cetamolol reduced systolic blood pressure ($P < 0.01$) and the double product ($P < 0.001$) significantly more than 10 mg, and at 2, 8, and 24 h, the effect of the 25 mg dose was significantly greater than 10 mg for exercise heart rate attenuation ($P < 0.05$).

All blood pressure and heart rate changes with exercise testing were well tolerated.

Serum levels and β -adrenoceptor blockade

Serum cetamolol levels peaked at 1 to 2 h after dosing, in proportion to dose. The average elimination half-life of cetamolol was 6.4 h.

For two subjects in the 5 mg group (Study I) and four in the 10 mg group (Study II), cetamolol was not detected in blood samples at 24 h after a single oral dose and the arbitrary value of 0.5 ng/ml was assigned to these samples in order to permit logarithmic transformation.

Data for mean serum level per dose level and the corresponding mean heart rate and double product changes at 2, 8, and 24 h after dosing are shown in Table 3. As dose levels increased, serum levels of cetamolol increased, and reductions in heart rate and double product increased.

Table 2 β_1 -adrenoceptor blockade effect of cetamolol with 4 min exercise testing (Study I)

Variables	Drug	Mean changes from baseline $\pm$ s.e. mean		
		2 h	8 h	24 h
Heart rate (beats/min)	Cetamolol (mg)			
	5	-24 ± 2	-14 ± 3	-6 ± 2
	10	-30 ± 2	-22 ± 3	-10 ± 2
	25	-35 ± 4	-26 ± 2	-18 ± 3
	50	-43 ± 2	-36 ± 2	-24 ± 3
	All levels ^a	$-33 \pm 2^\dagger$	$-25 \pm 2^\dagger$	$-14 \pm 2^\dagger$
	Placebo ^b	4 ± 1	1 ± 2	-1 ± 1
Double product (HR $\times$ Systolic BP)	Cetamolol (mg)			
	5	-5792 ± 683	-4996 ± 944	-540 ± 1100
	10	-10000 ± 920	-6452 ± 1484	-4272 ± 957
	25	-12552 ± 825	-8068 ± 1560	-5352 ± 1602
	50	-10144 ± 842	-8224 ± 1492	-4856 ± 892
	All levels ^a	$-9622 \pm 674^\dagger$	$-6935 \pm 707^\dagger$	$-3755 \pm 691^*$
	Placebo ^b	1037 ± 686	982 ± 457	-993 ± 528

^aAll levels = mean value for all cetamolol dose levels combined

^bMean pooled placebo values

Cetamolol compared with placebo: $^*P < 0.01$, $^\dagger P < 0.001$

Figure 1 Study II. β -adrenoceptor blockade effect (heart rate, systolic blood pressure, double product) of cetamolol (■ 10 mg, ▲ 25 mg) with 4 min exercise testing. Mean reductions $\pm$ s.e. mean are plotted for 2, 8, and 24 h post-dosing. Significance of cetamolol compared with placebo (●) = $^*P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$.

Table 3 Cetamol serum levels at 2, 8, and 24 h after dosing in relation to exercise heart rate and double product*

	Cetamolol dose (mg)	2 h post-dosing Serum levels (ng/ml)	Change in heart rate (beats/min)	Change in double product
Study I	5	10.2 ± 1.2	-24 ± 2	-5792 ± 683
	10	26.0 ± 5.3	-30 ± 2	-10000 ± 920
	25	139.0 ± 11.6	-35 ± 4	-12552 ± 825
	50	229.6 ± 33.8	-43 ± 2	-10144 ± 842
Study II	10	24.7 ± 2.4	-27 ± 2	-7778 ± 550
	25	66.2 ± 5.7	-39 ± 2	-10944 ± 472
8 h post-dosing ^a				
Study II	10	9.8 ± 0.7	-21 ± 1	-5080 ± 507
	25	25.7 ± 1.7	-31 ± 2	-7295 ± 588
24 h post-dosing				
Study I	5	1.1 ± 0.3	-6 ± 2	-540 ± 1100
	10 ^b	1.5 ± 0.2	-10 ± 2	-4272 ± 957
	25	6.8 ± 1.8	-18 ± 3	-5352 ± 1602
	50	11.4 ± 0.9	-24 ± 3	-4856 ± 892
Study II	10 ^b	1.8 ± 0.2	-9 ± 2	-2888 ± 676
	25	4.3 ± 0.3	-17 ± 2	-3897 ± 637

*Values are expressed as means ± s.e. mean

^aBlood for serum level determination was not drawn at 8 h for Study I.

^bThe limit for detection of cetamolol was 1 ng/ml. Cetamolol was not readily detected at 24 h in two subjects in Study I and four subjects in Study II, therefore a value of 0.5 ng/ml was assigned for the estimation of mean values.

There was good internal consistency in Study II between serum levels and β -adrenoceptor blockade. The mean 8 h serum value of 25.7 ng/ml for the 25 mg dose of cetamolol was similar to the 2 h level of 24.7 ng/ml for the 10 mg dose; corresponding similar heart rate reductions of 31 and 27 beats/min were recorded. These results were also consistent with Study I, where a 26.0 ng/ml mean serum level was associated with a 30 beats/min reduction in exercise heart rate (Table 3).

Heart rate and double product were each significantly linearly related ($P < 0.0001$) to log serum cetamolol levels in both studies (Figure 2). With each unit increase in the natural logarithm of mean cetamolol serum levels, the 4 min exercise heart rate decreased by 6.1 beats/min in Study I and by 7.4 beats/min in Study II ($P = 0.0001$ for both studies); the double product decreased by 1883.7 in Study I and by 1964.8 in Study II ($P = 0.0005$ for both studies).

The resting pre-exercise vital signs were relatively unaffected by cetamolol (Table 4). All doses were well tolerated by the subjects.

Discussion

The results of these studies in normal human volunteers confirm that cetamolol is a potent, relatively long-acting β_1 -adrenoceptor blocking

agent. β_1 -adrenoceptor blockade with cetamolol was evident in exercise tests performed at 2 h post dosing, the time of peak drug serum levels (to be published), at 8 h, and again at 24 h when the drug's serum concentration was at its minimal level.

At 24 h, a reduction of at least 10 beats/min was noted in all subjects after a single oral dose of 25 mg. The average exercise heart rate reduction 24 h after a 25 mg dose was 17–18 beats/min in both studies (Table 3). With propranolol, a reduction of this magnitude was noted after a 160 mg daily dose (Mullane *et al.*, 1982) giving an approximate potency of $\times 6$ for cetamolol relative to propranolol. A more precise definition of the potency ratio will require a direct comparison of the two drugs in the same subjects.

β -adrenoceptor blockers without ISA cause a greater reduction in resting heart rate than do those with ISA (Svensden, 1983; Svensden *et al.*, 1981). Cetamolol produced only minimal changes in the resting supine heart rate. The heart rate in the standing position was slightly reduced. These changes are consistent with animal studies indicating that cetamolol possesses ISA, and with a study of intravenous cetamolol (identified as 'BMMP') in humans which showed a smaller decrease in heart rate and cardiac output relative to β -adrenoceptor blockers without ISA (Svensden *et al.*, 1981).

In conclusion, cetamolol is a potent β -

Figure 2 Relationship of β -adrenoceptor blockade (a) Inhibition of 4 min exercise-induced tachycardia; (b) 4 min exercise double product reduction) to the natural logarithm of the mean serum cetamolol concentration (ng/ml). Serum values for the regression lines and for the depicted points were derived by averaging all values falling within the following ng/ml serum level intervals (sample size per interval): 0–1 (4), 1.1–5 (8), 5.1–10 (6), 10.1–15 (8), 15.1–40 (4), 40.1–150 (5), 150.1 or more (5).

adrenoceptor blocker with a duration of action probably suited for once-daily dosing in the treatment of hypertension, angina pectoris, and arrhythmias. A more precise definition of its β_1 -adrenoceptor selectivity and ISA must await further studies.

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Table 4 Positional heart rate and blood pressure changes at rest after cetamolol administration (Study II).^a

Variable	Drug (mg)	Baseline		2 h		8 h		24 h	
		Supine	Standing	Supine	Standing	Supine	Standing	Supine	Standing
Heart rate (beats/min)	Cetamolol 10	64 $\pm$ 2	81 $\pm$ 2	8 $\pm$ 2	4 $\pm$ 2	6 $\pm$ 2	1 $\pm$ 2	1 $\pm$ 2	0 $\pm$ 3
	Placebo 25	65 $\pm$ 2	86 $\pm$ 3	6 $\pm$ 2	-4 $\pm$ 3*	4 $\pm$ 2	-1 $\pm$ 1	-1 $\pm$ 1	-7 $\pm$ 2
Systolic blood pressure (mm Hg)	Cetamolol 10	66 $\pm$ 2	83 $\pm$ 2	10 $\pm$ 2	10 $\pm$ 3	5 $\pm$ 2	-3 $\pm$ 3	1 $\pm$ 2	-3 $\pm$ 4
	Placebo 25	112 $\pm$ 3	117 $\pm$ 3	2 $\pm$ 2	-2 $\pm$ 3	8 $\pm$ 3	0 $\pm$ 3	2 $\pm$ 3	-5 $\pm$ 3
Diastolic blood pressure (mm Hg)	Cetamolol 10	111 $\pm$ 2	113 $\pm$ 2	3 $\pm$ 2	-1 $\pm$ 2	6 $\pm$ 2	6 $\pm$ 3	2 $\pm$ 3	0 $\pm$ 3
	Placebo 25	113 $\pm$ 3	115 $\pm$ 3	6 $\pm$ 2	4 $\pm$ 3	9 $\pm$ 3	6 $\pm$ 2	2 $\pm$ 2	-2 $\pm$ 2
	Cetamolol 10	72 $\pm$ 2	81 $\pm$ 2	-4 $\pm$ 3	-5 $\pm$ 2	4 $\pm$ 3	-1 $\pm$ 3	2 $\pm$ 2	-3 $\pm$ 2
	Placebo 25	73 $\pm$ 2	79 $\pm$ 2	-5 $\pm$ 2	-4 $\pm$ 2	2 $\pm$ 2	4 $\pm$ 3	1 $\pm$ 3	0 $\pm$ 3
	Cetamolol 10	72 $\pm$ 2	77 $\pm$ 2	-1 $\pm$ 2	-1 $\pm$ 2	4 $\pm$ 3	4 $\pm$ 2	1 $\pm$ 2	2 $\pm$ 2
	Placebo 25	72 $\pm$ 2	77 $\pm$ 2	-1 $\pm$ 2	-1 $\pm$ 2	4 $\pm$ 3	4 $\pm$ 2	1 $\pm$ 2	2 $\pm$ 2

^aOnly supine vital signs were measured in Study I

* $P < 0.05$, cetamolol 25 mg vs 10 mg

† $P < 0.001$, cetamolol 25 mg vs placebo

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