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Esmolol, an ultrashort-acting, sèlective β_1-adrenoceptor antagonist: pharmacodynamic and pharmacokinetic properties

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Abstract. The effects of esmolol at different rates of infusion (100, 250 and 500 $\mu g \cdot kg^{-1}$ BW $\cdot min^{-1}$) were compared with β-adrenoceptor occupancy (β_1 and β_2, estimated by a subtype selective radioreceptor assay) and plasma concentrations of esmolol and its acid metabolite were measured by HPLC. Up to a rate of infusion of esmolol of 500 $\mu g \cdot kg^{-1}$ BW $\cdot min^{-1}$ there was a maximal β_1-receptor occupancy of 84.7 % while β_2-receptor occupancy was below the detection limit; confirming the β_1 selectivity of esmolol. Exercise-induced increases in heart rate and systolic blood pressure were reduced by esmolol in a dose-dependent manner. The estimated EC_{50} values of rate of infusion for the reduction in heart rate and systolic blood pressure during exercise were 113 and 134 $\mu g \cdot kg^{-1}$ BW $\cdot min^{-1}$, respectively. Additionally, heart rate and systolic blood pressure were reduced moderately at rest. Because of the short elimination half-life of esmolol caused by the rapid hydrolysis to its acid metabolite, 45 min after end of infusion high plasma concentrations of the metabolite (maximally 80 $\mu g \cdot ml^{-1}$) but no esmolol were detectable. Since no in vivo effects have been observed, despite the presence of high plasma concentrations of the metabolite, the metabolite did not participate in the observed effects up to an infusion rate of esmolol of 500 $\mu g \cdot kg^{-1}$ BW $\cdot min^{-1}$. The plasma concentrations of antagonist detected by radioreceptor assay and plasma concentrations of esmolol detected by HPLC showed a good correlation ($r = 0.97$). Since the cardiovascular effects, determined before and 45 min after termination of infusion of esmolol were similar, it can be concluded that the observed effects on heart rate and systolic blood pressure are exclusively mediated by esmolol.

Key words: Esmolol, β_1-Adrenoceptor antagonist; tricresylphosphate, pharmacokinetics, effect kinetics

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Esmolol (methyl 3-[4-[2-hydroxy-3-(isopropylamino) propoxy] phenyl]propionate hydrochloride) is an ultrashort-acting β-adrenoceptor antagonist with an elimination half-life of about 9 min [1–4]. Based on experiments in isolated organs it has been concluded that esmolol has a higher affinity for β_1- than for β_2-adrenoceptors. It is rapidly hydrolyzed by esterases present in the cytosol of erythrocytes to its major metabolite (3-[4-[2-hydroxy-3-(isopropylamino)propoxyl] phenyl]propionic acid) and methanol [5, 6]. The metabolite, which has an elimination half-life of 3.72 h [3, 7], has weak β-adrenoceptor blocking activity [7–10]. Therefore esmolol is a titratable β-adrenoceptor antagonist with rapidly initiated and reversed effects.

Esmolol has been shown to be of benefit in the treatment of patients with acute myocardial infarction because of the possibility for rapid reversal of its β-adrenoceptor blocking action if congestive heart failure or bronchospasm supervene [2, 11, 12]. Esmolol is also well suited for acute antiarrhythmic interventions (i. e. supraventricular tachyarrhythmias) and for preventing intraoperative stress, which should be very intensive but often brief in duration [13–17].

Although esmolol is of clinical interest and its beta-blocking potency and "cardioselectivity" have been evaluated using standard procedures both in vitro and in vivo [3, 18]; radioligand binding studies have revealed the 30- to 40-fold higher affinity of esmolol for β_1-adrenoceptors than for β_2-adrenoceptors [19]. The acid metabolite of esmolol had a 400-fold lower affinity than the parent compound.

The aim of the present investigation was to correlate the in vivo effects caused by infusion of esmolol with β_1- and β_2-adrenoceptor occupancy and with plasma concentrations of esmolol and its metabolite. Esmolol was infused at three diffent rates of infusion to healthy volunteers. Effects on heart rate and blood pressure were measured at rest and during bicycle ergometer exercise. The in vivo receptor occupancy in plasma esmolol was deduced from the results obtained by an in vitro radioreceptor assay (separately for β_1- and β_2-receptors; for review,

see Wellstein et al. [20]) of plasma samples. Since the radioreceptor assay cannot distinguish between the parent drug and the active metabolite, the concentrations of esmolol and the metabolite present in the plasma samples were determined separately by HPLC.

Subjects and methods

Radioligand binding experiments

β-Adrenoceptor-containing membranes were prepared from salivary glands (β_1) and rat reticulocytes (β_2) [20]. For saturation and competition experiments membranes were resuspended in 310 mosm $\cdot l^{-1}$ of sodium phosphate buffer (pH 7.4 at 25 °C). The incubation volume of 300 µl contained 50 µl of the membrane suspension (30–180 µg protein), 30 µl of the radioligand (−)-^{3}H-CGP 12177 (Amersham Buchler, Braunschweig, Germany; 43–53 Ci $\cdot$ mmol^{-1}, 0.6–0.8 nmol $\cdot l^{-1}$), 20 µl of competing ligand or buffer and 200 µl of native human plasma from the drug-free or verum phase. The human plasma contained 0.1 mol $\cdot l^{-1}$ tricresylphosphate (diluted with ethanol 1:1 v/v), a potent inhibitor of esmolol-metabolising carboxyesterase [19]. The incubation was terminated after 2 h (at 25 °C) by rapid filtration through a Whatman GF-C Filter (Dunn-Lab; Ansbach, Germany). Filters were washed with 10 ml of ice-cold buffer and were suspended in 6 ml of scintillant (Quicksafe A; Zinsser Analytic, Germany) and counted for retained radioactivity in a Tricarb 2660 scintillation counter with external standardisation (Packard Instruments, Frankfurt, Germany).

HPLC assay of drug concentration in plasma

In parallel with the radioreceptor assay, the concentrations of esmolol and its metabolite were determined in the plasma samples by an HPLC method, using ultraviolet detection at 229 nm. The detection method employs a precolumn and reversed-phase HPLC. Esmolol and the metabolite were detected in a nonchiral manner. The method was modified according to Sum et al. and Achari et al. [7, 21]. The limit of detection was 0.025 µg $\cdot$ ml^{-1} esmolol and 1 µg $\cdot$ ml^{-1} metabolite [19]. Esmolol and its acid metabolite were gifts from DuPont Pharma (Bad Homburg v. d. H., Germany).

Studies in volunteers

The study design was approved by the ethical committee of the University Hospital, Frankfurt am Main. The volunteers gave fully informed written consent before participating in the study. The study was carried out in eight healthy, non-smoking, male volunteers after a clinical and laboratory check-up. The demographic data were: age 23–31 ($\bar{x}$ = 27.7) years; body weight 67–87 ($\bar{x}$ = 73.7) kg; height 1.72 to 2.00 ($\bar{x}$ = 1.82) m. The individual loading intervals on bicycle ergometer in supine position up to a heart rate of 150 beats $\cdot$ min^{-1} were determined. The ergometry in the study was performed over 10 min with five (individual) loading intervals (25-W steps) every 2 min. All subjects were instructed to abstain from alcohol for 1 day before the beginning of each study day. To avoid drug interactions, no additional medication was allowed 6 days before and during the entire study.

Study design

The study was a randomized, single-blind, crossover trial. It was performed at the Kerckhoff-Klinik (Bad Nauheim, Germany). On three different days, at least 7 days apart, each volunteer received esmolol (Brevibloc) in a running saline infusion over 70 min at rates of either 100 µg $\cdot$ kg^{-1} bodyweight (BW) $\cdot$ min^{-1} (A), 250 µg $\cdot$ kg^{-1} BW $\cdot$ min^{-1} (B) or 500 µg $\cdot$ kg^{-1} BW $\cdot$ min^{-1} (C). To reach steady state conditions within the first 30 min, a bolus of 600 µg $\cdot$ kg^{-1} BW (A), 1.50 mg $\cdot$ kg^{-1} BW (B) and 3.0 mg $\cdot$ kg^{-1} BW (C) was given before esmolol infusion was started.

Protocol of the study day

Two hours after a standardised breakfast (07.30 h) the volunteers received two separate indwelling cannulas (Braunüle; Braun, Melsungen, Germany). The one on the left arm was used for esmolol infusion and that on the right arm to draw blood samples. The volunteers rested for 45 min in a supine position with an i.v. infusion of 0.9% saline (284 ml $\cdot$ h^{-1}) before baseline registrations of blood pressure and heart rate were taken. Heart rate was obtained from an ECG running at 25 mm $\cdot$ s^{-1}. Blood pressure was measured with a cuff mercury manometer. Afterwards the first exercise on a bicycle ergometer was performed (exercise 1). It was followed by a resting period of 45 min before the esmolol bolus was given, followed by esmolol infusion over a period of 70 min. During the last 10 min of esmolol infusion the second exercise on a bicycle ergometer was performed (exercise 2). At the end of exercise 2 the infusion was terminated. After an additional resting period of 45 min (without esmolol infusion) the third bicycle ergometric exercise was performed (exercise 3).

In parallel with effect measurements, heparinised blood samples conditioned with 0.05 mol $\cdot l^{-1}$ tricresylphosphate, in order to prevent further metabolism of esmolol, were drawn and plasma was separated by centrifugation and stored frozen at −70 °C until use.

Data evaluation

Estimation of parameters was performed by the Giessen Iteration Program for nonlinear, least-squares curve-fitting using the following equation for competitive antagonists [22–24]:

$$B = B_{max} \times L/[L + K_d \times (1 + i/k_i)] + nsb \times L \quad (1)$$

where B is bound radioligand at the respective concentration L, with a maximal binding capacity B_{max}, an equilibrium dissociation constant K_d, and nonspecific binding nsb. The concentration of inhibitory (nonlabelled) ligand is i, if present, with the respective equilibrium dissociation constant k_i.

Values for i/k_i calculated from Eq. 1 were used to estimate percentage receptor occupancy in vitro according to the equation:

$$\% \text{ receptor occupancy} = \frac{i/k_i}{1 + i/k_i} \times 100 \quad (2)$$

It is possible to estimate the receptor occupancy in vivo by the receptor occupancy in vitro if there is an equilibrium between the central and the effect compartment [20].

To calculate antagonist concentrations present in unknown plasma samples, the equation was solved for i. From the respective amount of radioligand bound (B) together with L and the parameters B_{max}, K_d, nsb, and k_i, the concentration of the antagonist (i) was determined. The detection limit in general is 0.1- to 0.2-fold of k_i of the respective antagonist [24].

Plasma concentrations of drug obtained from the radioreceptor assay are given in multiples of the respective k_i values (i.e. i/k_i) of the antagonist(s) present in plasma. The k_i values of esmolol and metabolite were calculated from competition isotherms covering several log units of drug concentrations above and below the k_i value [20].

The steady-state concentration of esmolol present in plasma was calculated by averaging the concentrations measured between 25 and 65 min of infusion. The presented data are given as mean values with (SEM) of eight volunteers. Statistical significance of in vivo effects was tested with Student's t-test.

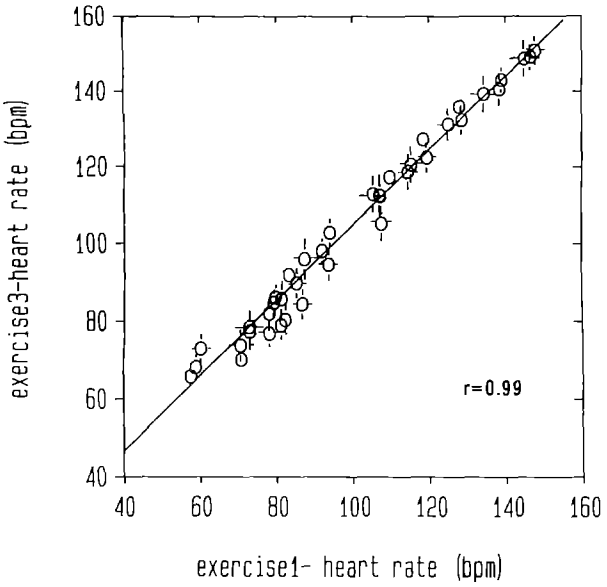

Fig. 1. Correlation between effects of esmolol infusion on heart rate during bicycle ergometry before (*abscissa:* exercise 1) and 45 min after termination (*ordinate:* exercise 3) of infusion. Given are mean values with SEM; $n = 8$. Rates of infusion: 100–500 $\mu g \cdot kg^{-1}$ $BW \cdot min^{-1}$

The IC_{50} values of plasma concentrations and rates of infusion of esmolol for the reduction of exercise-induced increase in heart rate and systolic blood pressure were calculated using the Hill equation.

Results

In vivo investigations

At rest, esmolol infusion for 60 min decreased heart rate moderately but significantly in all three regimens [100 $\mu g \cdot kg^{-1}$ $BW \cdot min^{-1}$ (A), 250 $\mu g \cdot kg^{-1}$ $BW \cdot min^{-1}$ (B) and 500 $\mu g \cdot kg^{-1}$ $BW \cdot min^{-1}$ (C)]. This effect was not dose-dependent ($P < 0.05$). The maximal reduction was 8.8 (1) beats $\cdot min^{-1}$ (A), 4.9 (2) beats $\cdot min^{-1}$ (B) and 3.9 (1) beats $\cdot min^{-1}$ (C). While no effect of esmolol on diastolic blood pressure was observed, systolic blood pressure was reduced significantly in regimen B [8.2 (1.5) mm Hg] and C [14.2 (2) mm Hg] ($P < 0.05$; not shown).

The data for heart rate and blood pressure obtained during exercise 1 and exercise 3 (before and after infusion of esmolol) were almost identical. The good correlation for heart rate (Fig. 1) and systolic blood pressure (not shown) during exercise before and after esmolol infusion with correlation coefficients of 0.99 and 0.98, respectively, indicate that the metabolite of esmolol, despite pronounced accumulation (see Fig. 4 b), did not influence the in vivo parameters. The mean baseline values of heart rate and systolic blood pressure were 64 (2) beats $\cdot min^{-1}$ and 109 (1) mm Hg. Bicycle ergometer exercise caused an increase of 84 (2) beats $\cdot min^{-1}$ and 80 (1) mm Hg, respectively (Fig. 2).

Esmolol infusion caused significant reductions in heart rate and systolic blood pressure increase during bicycle ergometric exercise. The maximal exercise-induced increases in heart rate were 75 (4) beats $\cdot min^{-1}$ (A), 61 (3) beats $\cdot min^{-1}$ (B) and 52 (3) beats $\cdot min^{-1}$ (C) in comparison to 84 (2) beats $\cdot min^{-1}$ without esmolol. The maximal increase in systolic blood pressure during exercise was 52 (7) mm Hg (A), 37 (7) mm Hg (B) and 34 (8) mm Hg (C) in comparison to 80 (1) mm Hg without esmolol.

One volunteer ended bicycle ergometry at maximal work loading during esmolol infusion of 250 $\mu g \cdot kg^{-1}$ $BW \cdot min^{-1}$ and three volunteers stopped bicycle ergometric exercise during esmolol infusion of 500 $\mu g \cdot kg^{-1}$ $BW \cdot min^{-1}$.

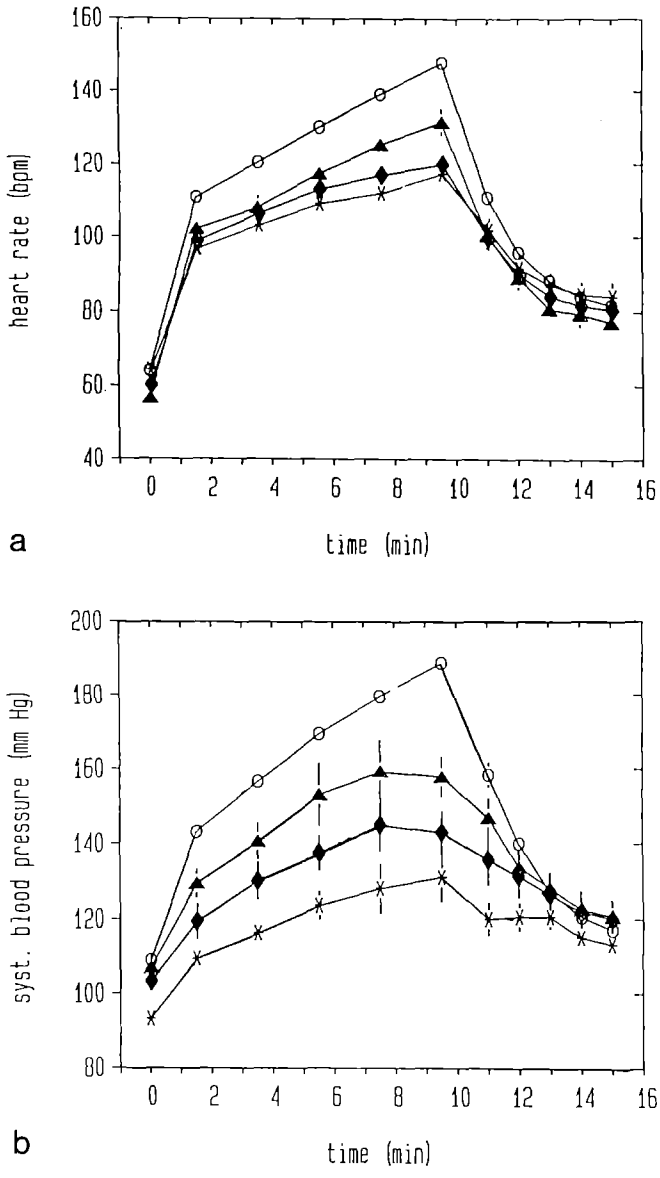

Fig. 2 a, b. Effects of infusion of esmolol on heart rate (**a**) and systolic blood pressure (**b**) during bicycle ergometry. Given are mean values with SEM; $n = 8$. SEMs for control measurements were smaller than the symbols. Rates of infusion ($\mu g \cdot kg^{-1}$ $BW \cdot min^{-1}$): Δ 100, ◆ 250, * 500. The respective resting heart rates before infusion of esmolol were 66 (1), 64 (2) and 67 (2) beats $\cdot min^{-1}$. The systolic blood pressure values were 106 (3), 111 (5) and 107 (1) mm Hg

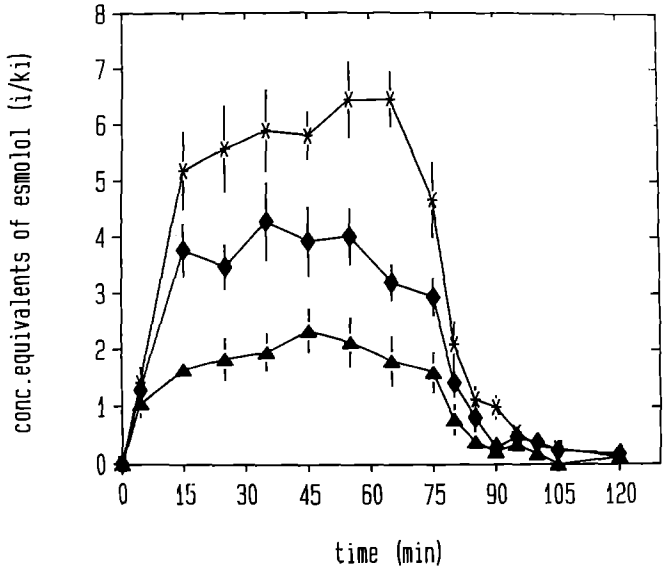

Fig. 3. Time course of esmolol equivalents, expressed as multifolds of i_i *(i/k_i)*; for details, see experimental design), during and after bolus and infusion respectively of esmolol over 70 min as detected from radioreceptor assay. Given are mean values with SEM; $n = 8$. Rates of infusion ($\mu g \cdot kg^{-1}\,BW \cdot min^{-1}$): Δ 100, ◆ 250, * 500

In vitro investigations

The plasma concentrations of antagonist detected by radioreceptor assay (RRA), expressed in multiples of the k_i-value *(i/k_i)* and in receptor occupancy (%) were calculated from the inhibition of receptor binding of radioligand (Eq. 2). Esmolol infusion of 100 (A), 250 (B) and 500 $\mu g \cdot kg^{-1}\,BW \cdot min^{-1}$ (C) caused relative steady-state plasma concentrations of 1.7 (0.02) × k_i (A), 3.6 (0.3) × k_i (B) and 5.8 (0.7) × k_i (C). The respective β_1-adrenoceptor occupancies were 59 (3) (A), 77 (2) (B) and 85 (2) % (C) (Fig. 3). Esmolol infusion of 500 $\mu g \cdot kg^{-1}\,BW \cdot min^{-1}$ caused a β_2-adrenoceptor occupancy of below 15 %.

Since the RRA cannot distinguish between the parent drug and active metabolites, the concentrations of esmolol and the metabolite were determined separately by HPLC. The steady state concentrations of esmolol were 0.5 (0.1) $\mu g \cdot ml^{-1}$ (A), 1.1 (0.1) $\mu g \cdot ml^{-1}$ (B) and 2.4 (0.3) $\mu g \cdot ml^{-1}$ (C). The maximal concentrations of metabolite observed after the end of infusion were 19.4 (4.4) $\mu g \cdot ml^{-1}$ (A), 41.7 (7) $\mu g \cdot ml^{-1}$ (B) and 80.3 (14.7) $\mu g \cdot ml^{-1}$ (C) (Fig. 4). About 25 min after termination of infusion, esmolol concentrations were beyond the limit of detection. As shown in Fig. 5 there is a linear correlation between rate of infusion and plasma concentration detected by RRA and HPLC. The good correlation of plasma concentration determined by the two methods ($r = 0.975$) indicates again that the metabolite, despite the high maximal concentration of 80 $\mu g \cdot ml^{-1}$, caused no detectable β_1-adrenoceptor occupancy and apparently did not interfere with the antagonistic effects of esmolol on β_1-adrenoceptors.

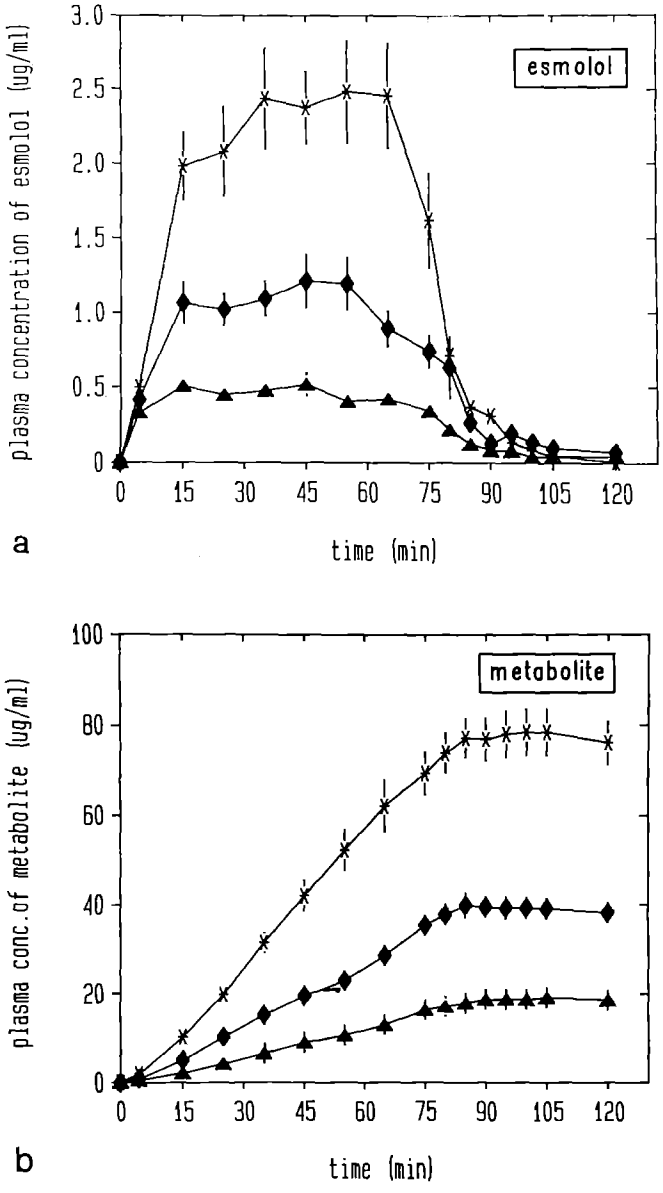

Fig. 4a, b. Time course of plasma concentrations of esmolol (**a**) and its metabolite (**b**) during and after bolus and infusion of esmolol concentrations over 70 min as detected by HPLC. Note the rapid decline of esmolol after termination of infusion whereas the high metabolite concentrations are still increasing. Given are mean values with SEM; $n = 8$. Rates of infusion ($\mu g \cdot kg^{-1}\,BW \cdot min^{-1}$): Δ 100, ◆ 250, * 500

Discussion

As reported recently [19], in in vitro radioligand binding studies esmolol showed a 34-fold higher affinity for β_1- than for β_2-adrenoceptors. It is, therefore, conceivable that esmolol is also highly β_1-selective in vivo. This was confirmed in the present investigation. In view of the affinity profile of esmolol i/k_i-values of 6–7, corresponding to a β_1-adrenoceptor occupancy of 85 %, this should cause a maximal β_2-adrenoceptor occupancy of 10 %.

In radioligand binding investigations in vitro the acid metabolite of esmolol had a 400-fold lower affinity for β_1-adrenoceptors than the parent drug [19]. Therefore it has been predicted that the acid metabolite will not occupy β-

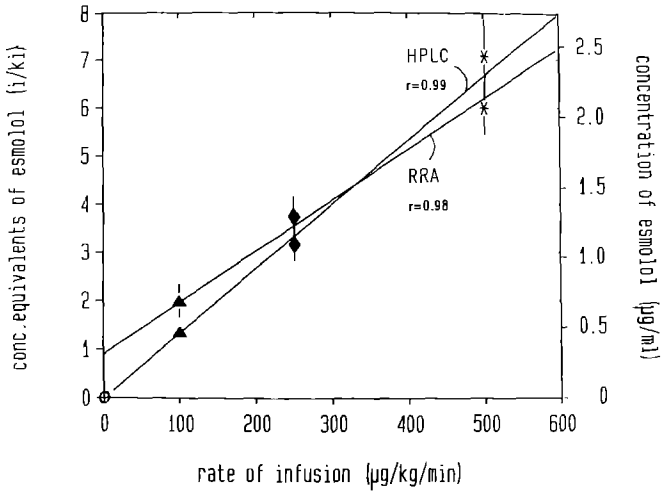

Fig. 5. Correlations between rates of infusion of esmolol and the resulting plasma concentrations as detected by radioreceptor assay (concentration equivalents in i/k_i-values on the left ordinate) and HPLC (concentrations in µg/ml on the right ordinate). Given are mean values with SEM; $n = 8$. Rates of infusion ($\mu g \cdot kg^{-1}$ BW·min^{-1}): Δ 100, ◆ 250, * 500

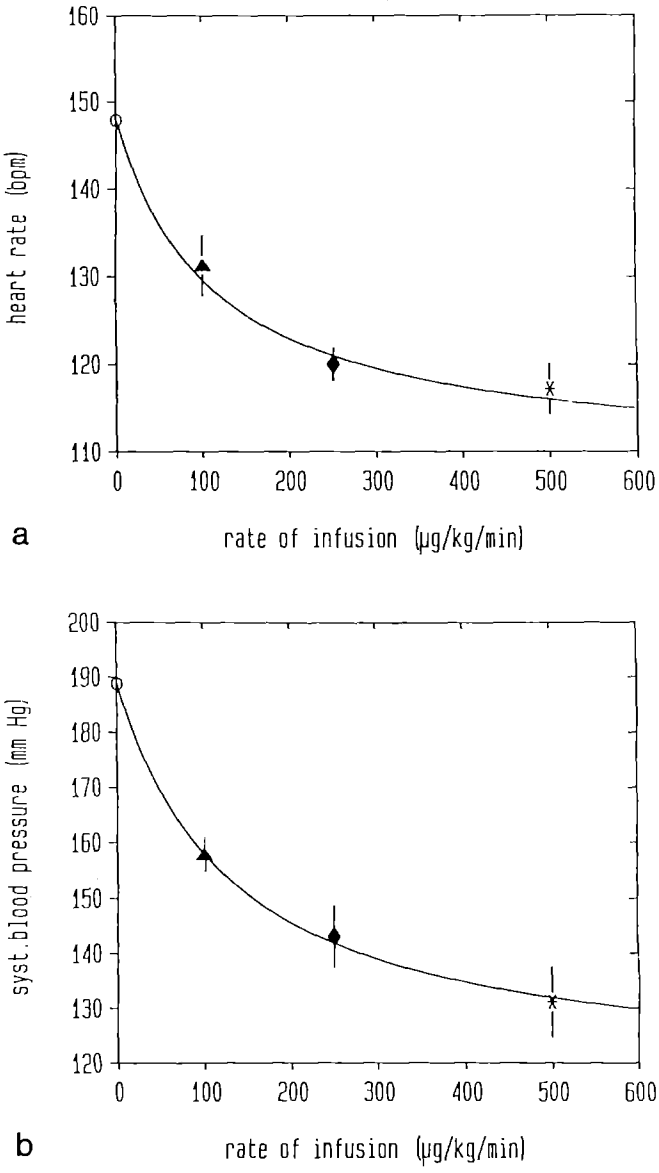

Fig. 6a, b. Cardiovascular effects (**a** heart rate, **b** systolic blood pressure) of esmolol during bicycle ergometric exercise dependent on the rates of infusion. The hyperbolic "dose"-effect relationships represent the best fit according to the Hill equation. The respective IC_{50} values for the rates of infusion were 113.5 $\mu g \cdot kg^{-1}$ BW·min^{-1} for heart rate and 134.3 $\mu g \cdot kg^{-1}$ BW·min^{-1} for systolic blood pressure. Given are mean values with SEM; $n = 8$. Rates of infusion ($\mu g \cdot kg^{-1}$ BW·min^{-1}): Δ 100, ◆ 250, * 500

adrenoceptors at plasma concentrations which can be expected to occur during esmolol infusion in man. It is clear from our results that there is a direct correlation between the rates of infusion of esmolol and the corresponding plasma concentrations as detected either by the RRA or the HPLC method. The observed plasma concentrations of esmolol and its acid metabolite are in the range of those observed by other authors [1, 7, 8, 25]. If the accumulation of the acid metabolite during and after infusion of esmolol interfered with the β_1-adrenoceptor occupancy of esmolol, the concentrations of esmolol detected by HPLC would be below the concentrations calculated by the radioligand binding. However, we observed a good correlation between the results obtained from both methods ($r = 0.98$). Hence, up to 80 $\mu g \cdot ml^{-1}$ the metabolite did not interfere with β_1-adrenoceptor occupancy by esmolol. There was also no interference of the metabolite with β_1-adrenoceptor-mediated effects: exercise-induced rise in heart rate and systolic blood pressure were identical before and 45 min after termination of esmolol infusion, i.e. when esmolol concentrations in plasma were undetectable and metabolite concentrations were as high as 80 µg·ml. This obvious lack of effect of the acid metabolite is in accordance with results obtained by other authors using different methods [8–10].

From the dose-response curves depicted in Fig. 6 the IC_{50} values for the rates of infusion can be estimated: increase in heart rate and systolic blood pressure are inhibited half maximally by infusion rates of 114 and 134 $\mu g \cdot kg^{-1}$ BW·min^{-1}. The corresponding IC_{50} values for plasma concentrations of esmolol were 0.54 and 0.62 $\mu g \cdot ml^{-1}$, respectively. These results are in agreement with those obtained by Sum et al. [7]. These authors determined IC_{50} values of esmolol, according to its isoprenaline-antagonistic effects, of 0.3 $\mu g \cdot ml^{-1}$ for heart rate and 0.6 $\mu g \cdot ml^{-1}$ for systolic blood pressure increase.

It should be noted that the above-mentioned half-maximally effective plasma concentration equivalents correspond to i/k_i values of 2.5 and 3.2, respectively. This can be explained by the presence of agonists at the receptor site: due to the enhanced sympathetic tone during bicycle ergometry, the β-adrenoceptor antagonist has to compete with high noradrenaline concentrations for the β_1-adrenoceptor, whereas under in vitro conditions the k_i value of esmolol is obtained in the absence of agonists. Similar results, i.e. i/k_i values of around 3 have also been obtained by Wellstein et al. [20] under similar experimental conditions in man after application of propranolol.

Resting heart rate was reduced significantly during all three infusion rates while the systolic blood pressure was reduced only during esmolol infusion of 250 and 500 $\mu g \cdot kg^{-1}$ BW $\cdot min^{-1}$ by at most 14 mm Hg ($P = 0.05$). Some authors have reported an immediate reduction of blood pressure on infusion of esmolol [1, 25]. Flaherty et al. [8] have underlined the propensity of esmolol to cause hypotensive reactions. This effect was also noted by Reilly et al. [26], who compared the β-adrenoceptor antagonistic effects of esmolol and propranolol. These authors showed that esmolol had greater potency to lower systolic than diastolic blood pressure, which is in line with our results. These pronounced hypotensive effects of esmolol may explain the withdrawal of four volunteers during exercise.

In conclusion, from the results of the in vitro RRA esmolol is a highly selective β_1-adrenoceptor antagonist. Its cardiovascular effects after i. v. infusion up to 500 $\mu g \cdot kg^{-1}$ BW $\cdot min^{-1}$, which are directly correlated to the rate of infusion, are solely due to the parent compound and not to its acid metabolite. Furthermore, from such in vitro measurements rates of infusion of esmolol and plasma concentrations can be evaluated which lead to a well-defined β_1-adrenoceptor occupancy and also to the corresponding cardiovascular effects in vivo. Such results can otherwise be obtained only by more invasive methods such as gradual infusion of isoprenaline to imitate an enhanced sympathetic tone.

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References

1. Benfield P, Sorkin EM (1987) Esmolol: a preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy. Drugs 33: 392–412
2. Viray R, Turlapaty P, Laddu A (1988) Esmolol: a short-acting titratable beta-blocker in acute moycardial ischemia. Int J Clin Pharmacol Ther Toxicol 26: 153–161
3. Lowenthal DT, Porter RS, Saris SD, Bies CM, Slegowski MB, Staudacher A (1985) Clinical pharmacology, pharmacodynamics and interactions with esmolol. Am J Cardiol 56: 14F–18F
4. Gorczynski RJ (1985) Basic pharmacology of esmolol. Am J Cardiol 56: 3F–13F
5. Erhardt PW, Woo CM, Gorczynski RJ (1982) Ultra-short acting beta-adrenergic blocking agents: Aryloxypropanol-amines containing esters in the nitrogen substituent. J Med Chem 25: 1402–1407
6. Erhardt PW, Woo CM, Anderson WG (1982) Ultra-short acting beta-adrenergic blocking agents. 2. (Aryloxy)propanolamines containing esters on the aryl function. J Med Chem 25: 1408–1412
7. Sum CY, Yacobi A, Kartzinel R, Stampfli H, Davis CS, Lai CM (1983) Kinetics of esmolol, an ultra-short-acting beta blocker, and of its major metabolite. Clin Pharmacol Ther 34: 427–434
8. Flaherty JF, Wong B, La Follette G, Warnock DG, Hulse JD, Gambertoglio JG (1989) Pharmacokinetics of esmolol and ASL-8123 in renal failure. Clin Pharmacol Ther 45: 321–327
9. Shaffer JE, Quon CY, Gorczynski RJ (1988) Beta-adrenoceptor antagonist potency and pharmacodynamics of ASL-8123, the primary acid metabolite of esmolol. J Cardiovasc Pharmacol 11: 187–192
10. Turlapaty P, Laddu A, Murthy VS, Singh B, Lee R (1987) Esmolol: a titratable short-acting intravenous beta blocker for acute critical care settings. Am Heart J 114: 866–885
11. Iskandrian AS, Hakki A, Laddu A (1985) Effects of esmolol on cardiac function: evaluation by noninvasive techniques. Am J Cardiol 56: 27F–32F
12. Koner RA, Kirshenbaum J, Lange R, Antman EM, Braunwald E (1985) Experimental and clinical observations on the efficacy of esmolol in myocardial ischemia. Am J Cardiol 56: 40F–48F
13. Greenspan AM, Spielman SR, Horowitz LN, Senior S, Steck J, Laddu A (1985) Electrophysiology of esmolol. Am J Cardiol 56: 19F–24F
14. Reves JG, Flezzani P (1985) Perioperative use of esmolol. Am J Cardiol 56: 57F–62F
15. Morganroth J, Horowitz LN, Anderson J, Turlapaty P, Esmolol Research Group (1985) Comparative efficacy and tolerance of esmolol to propranolol for control of supraventricular tachyarrhythmia. Am J Cardiol 56: 33F–39F
16. Ellenbogen KA, McCarthy EA, Pritchett ELC (1987) Effects of bolus injection of esmolol in healthy, exercising subjects. Clin Pharmacol Ther 41: 455–459
17. Covinsky JO (1987) Esmolol: a novel cardioselective, titratable, intravenous beta-blocker with ultrashort half-life. Drug Intell Clin Pharm 21: 316–321
18. Zaroslinski J, Borgman RJ, O'Donnell JP (1982) Ultra-short acting beta-blockers: a proposal for the treatment of the critically ill patient. Life Sci 31: 899–907
19. Jahn P, Volz-Zang C, Eckrich B, Schneidrowski B, Schulte B, Palm D (1992) Cardiovascular effects of esmolol in man – influence of rate of infusion, plasma concentration and occupancy of β1-adrenoceptors. Naunyn Schmiedeberg's Arch Pharmacol 345 [Suppl]: R9
20. Wellstein A, Palm D, Belz GG, Pitschner HF (1985) Receptor binding of propranolol is the missing link between plasma concentration kinetics and effect time course in man. Eur J Clin Pharmacol 29: 131–147
21. Achari R, Drissel D, Hulse JD (1986) Liquid-chromatographic analysis for esmolol and its major metabolite in urine. Clin Chem 32: 374–376
22. Wellstein A (1989) Radioreceptor assay of β-blockers. In: Marco V (Ed) Determination of beta-blockers in biological materials. Elsevier Amsterdam, pp 264–278
23. Wellstein A, Palm D, Belz GG (1986) Affinity and selectivity of β-adrenoceptor antagonists in vitro. J Cardiovasc Pharmacol 8 [Suppl 11]: S 36–40
24. Wellstein A, Belz GG, Palm D (1988) Beta adrenoceptor subtype binding activity in plasma and beta blockade by propranolol and beta-1-selective bisoprolol in humans. Evaluation with Schild plots. J Pharmacol Exp Ther 241: 328–337
25. Lowenthal DT, Porter S, Achari R, Turlapaty P, Laddu AR, Matier WL (1987) Esmolol-digoxin drug interaction. J Clin Pharmacol 27: 561–566
26. Reilly CS, Wood M, Koshakji RP, Wood AJJ (1985) Ultrashort-acting beta-blockade: a comparison with conventional beta-blockade. Clin Pharmacol Ther 38: 579–585