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Acute Effects of Alinidine on Heart Rate and Blood Pressure in Healthy Subjects and Patients with Hyperkinetic Heart Syndrome

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Summary. The effects of a single dose of alinidine (0.5 mg/kg i.v.), the N-allyl-derivative of clonidine, on heart rate and blood pressure were investigated in healthy volunteers and in patients with hyperkinetic heart syndrome, at rest and during bicycle exercise. In healthy volunteers plasma catecholamine levels were also determined. Alinidine did not change heart rate at rest in the healthy volunteers but it did significantly reduce exercise-induced tachycardia, whereas blood pressure and plasma catecholamine levels were not significantly affected by alinidine, either at rest or during exercise. In patients with hyperkinetic heart syndrome, alinidine reduced heart rate at rest and during exercise to a similar extent as propranolol (0.1 mg/kg i.v.). The blood pressure did not change with alinidine but it was significantly reduced by propranolol. The observation that an alinidine-induced reduction of heart rate occurs without a concomitant fall in blood pressure, and without a clonidine-like symphatho-inhibitory action, is in line with experimental findings suggesting a specific bradycardic action of alinidine under short-term conditions.

Key words: hyperkinetic heart syndrome, alinidine; bradycardia, blood pressure, sympatho-inhibition

Alinidine (ST 567) is a clonidine-like imidazoline derivative (Fig. 1). Its most prominent pharmacological action is bradycardia (Kobinger et al. 1979 a, b). Unlike clonidine, whose negative chronotropic effect is considered to be centrally mediated, and is usually associated with a fall in blood pressure, experimental data point towards a direct action of alinidine on the sinus node (Lillie et al. 1979). Preliminary clinical trials have suggested a bradycardic action of alinidine in man, too (Harron et al. 1981; Kaspar et al. 1981). The absence of β-receptor blocking activity, as well as the observation that bradycardia was not accompanied by a negative inotropic or negative dromotropic effect in low doses, clearly distinguish alinidine from all known bradycardic agents. In conjunction with the bradycardia a decrease in myocardial oxygen demand has been found (Traunecker and Walland 1980). Alinidine appeared, therefore, to be of therapeutic value in the treatment of ischaemic heart disease.

In order to obtain more information about the action of alinidine in man, its acute effects on exercise-induced changes in heart rate, blood pressure and plasma catecholamines were investigated in healthy subjects. And, the acute haemodynamic effects of alinidine and propranolol were compared in patients with hyperkinetic heart syndrome.

Patients and Methods

Part I of the study was performed at weekly intervals as a randomized, cross-over, double blind trial in 6 healthy males. Physical work consisted of bicycle

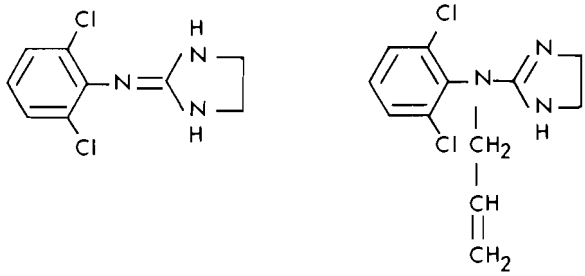

Fig. 1. Structure of alinidine (ST 567) 2-N-allyl-N-(2,6-dichlorophenyl)-amino-2-imidazoline (right), and clonidine (left)

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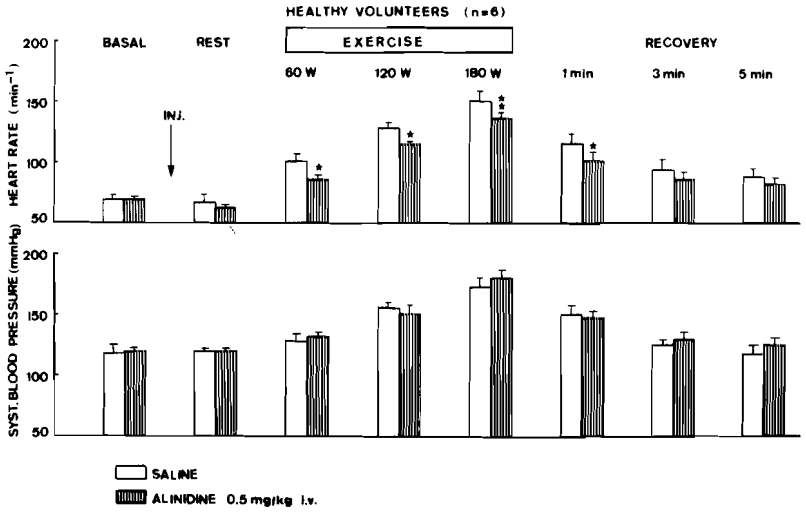

Fig. 2. Effect of a single i.v. injection of alinidine 0.5 mg/kg on heart rate and systolic blood pressure in 6 healthy volunteers at rest and during exercise

Table 1. Effects of alinidine 0.5 mg/kg i.v. or placebo (saline i.v.) on individual plasma norepinephrine (NE) levels and heart rate (HR) in 5 healthy volunteers

	Placebo Exercise						Alinidine Exercise					
	Basal	Rest	60 W	120 W	180 W	Recovery	Basal	Rest	60 W	120 W	180 W	Recovery
1 NE [pg/ml]	167	141	284	278	436	284	125	764	145	201	349	238
HR [min^{-1}]		75	110	134	180	115		64	77	124	155	98
2 NE [pg/ml]	621	437	568	602	626	284	408	364	418	557	618	268
HR [min^{-1}]		80	104	130	155	105		70	90	116	140	93
3 NE [pg/ml]	332	351	338	437	656	235	491	332	492	569	604	265
HR [min^{-1}]		66	112	142	155	98		55	93	113	138	86
4 NE [pg/ml]	189	195	220	356	577	282	273	297	2141	2386	680	303
HR [min^{-1}]		46	84	112	131	54		60	81	113	127	71
5 NE [pg/ml]	140	165	150	166	253	143	230	286	2872	266	432	175
HR [min^{-1}]		52	90	109	136	86		64	87	108	122	76
$n=5$ NE [pg/ml]	289,8	257,8			509,6	245,6	305,4	408,6			536,6	249,8
mean ± SEM	±89,2	±57,9			±74,4	±27,3	±64,9	±89,9			±58,8	±21,3

exercise in the supine position. In a pre-test maximal work load was determined by means of non-steady-state continuous exercise (Reiterer 1976), and was found to be similar in all 6 volunteers at 237.5 ± 5.6 (mean ± SEM, W). The work load used in the exercise test was 60, 120 and 180 W, which was 25%, 51% and 76% of the maximal work load, respectively. Each work load period lasted for 3 min.

A Venflon® catheter was inserted into the left antecubital vein, and after 45 min rest in the supine position, blood samples were taken for determination of basal catecholamine levels. Then, alinidine 0.5 mg/kg or an equivalent volume of saline was injected.

Fifteen min after injection the exercise test was started. Blood samples for the determination of catecholamines were taken immediately prior to work (= REST), during the third min of each work load (= EXERCISE) and 5 min after the end of exercise (= RECOVERY). Heart rate was derived from the ECG, systolic blood pressure was measured by cuff method. Plasma catecholamines were determined by a radioenzymatic method (Da Prada and Zürcher 1976).

Part II of the study was a comparison of the action of alinidine and propranolol in 8 patients with hyperkinetic heart syndrome, whose heart rate exceeded 110 beats/min when exercising at a zero W load. Maximal work load in these patients was determined in a pre-test as described above, and was about 86% of that of age-matched control subjects. The study was performed on different test days (weekly intervals) in a random order. Saline, alinidine (0.5 mg/kg

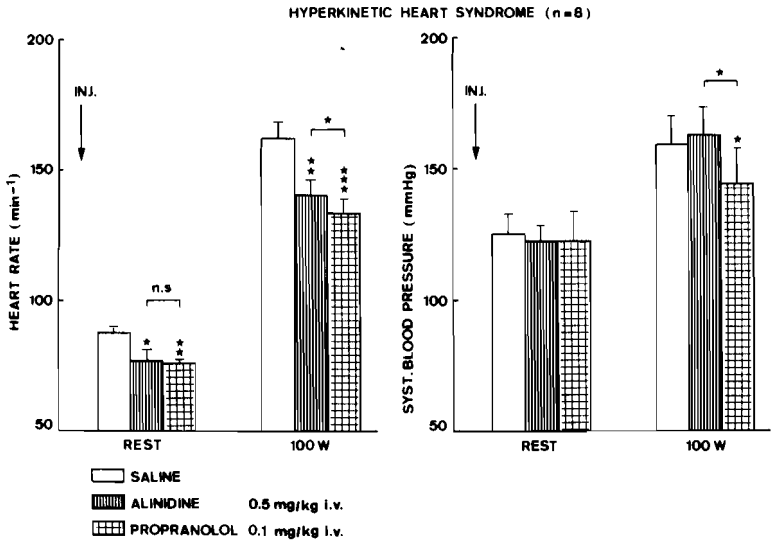

Fig. 3. Effects of a single i.v. injection of alinidine 0.5 mg/kg or propranolol 0.1 mg/kg on heart rate and systolic blood pressure in 8 patients with hyperkinetic heart syndrome at rest and during exercise

i.v.) or propranolol (0.1 mg/kg i.v.) were injected 10 min prior to the exercise test, which was performed at up to a 100 W load.

Statistical analysis used Student's *t*-test for paired data. Values are recorded as mean ± SEM.

For both studies written consent was given by each subject after complete explanation of the protocol and provison of information about possible risks.

Results

Part I: Healthy Volunteers

Effect of Alinidine (0.5 mg/kg i.v.) on Heart Rate and Systolic Blood Pressure (Fig. 2). Heart rate and systolic blood pressure at rest remained unchanged 15 min after the injection of alinidine. Alinidine did not significantly alter the rise in systolic blood pressure during exercise, whereas the exercise-induced increase in heart rate was significantly reduced by alinidine at each work load tested. This effect was not observed after 3 and 5 min of recovery.

Effect of Alinidine (0.5 mg/kg i.v.) on Plasma Norepinephrine (NE) Levels (Table 1). Plasma NE levels were determined in 5 subjects. Basal values of plasma NE were similar in the placebo and alinidine groups. Alinidine had no influence on plasma NE levels at rest.

With the first stage of exercise a marked increase in plasma NE was present in 2 of 5 subjects, which persisted in 1 during the next stage. Both subjects had normal basal NE levels and their plasma NE returned to levels comparable to the other subjects tested when exercise was continued at a 180 W load. Interestingly, both subjects had low pre-treatment heart rates and showed only minor changes in heart rate with alinidine when exercising at 60 and 120 W loads, respectively.

With submaximal exercise, the increases in plasma NE were not influenced by alinidine in any of the 5 subjects, nor were the decreases in plasma NE during recovery.

Part II: Patients with Hyperkinetic Heart Syndrome

Effect of Alinidine (0.5 mg/kg i.v.) or Propranolol (0.1 mg/kg i.v.) on Heart Rate and Systolic Blood Pressure (Fig. 3). In these patients, injection either of alinidine or propranolol significantly reduced resting heart rate by 10.0 ± 4.5 and 11.0 ± 3.0 beats/min, respectively, whereas resting systolic blood pressure remained unchanged. Alinidine reduced exercise-induced tachycardia by 22 ± 4.6 beats/min, which was comparable to the reduction achieved by propranolol (28 ± 4.8 beats/min). The exercise-induced increase in systolic blood pressure, was significantly reduced by propranolol but remained unchanged after alinidine.

Discussion

The bradycardic action of alinidine appears to depend on the pre-existing heart rate. Thus, alinidine (0.5 mg/kg i.v.) reduced exercise-induced tachycardia, but had no influence on resting heart rate in healthy subjects. In patients with hyperkinetic heart syndrome, alinidine reduced both resting heart rate and exercise-induced tachycardia. Similar effects of alinidine have been observed during sodium nitroprusside-induced reflex tachycardia in man (Zimpfer

et al. 1982), as well as in conscious dogs (Kobinger et al. 1979a, b).

The chemical relationship between alinidine and clonidine raises the question of a clonidine-like central cardiovascular action of alinidine, namely sympatho-inhibition. Basal catecholamine levels, which were in the range quoted in the literature (Lake et al. 1976), were not suppressed by alinidine in the present study, whereas catecholamine levels were found to be markedly reduced after a single oral dose of clonidine (Metz et al. 1978). The exercise-induced increase in plasma catecholamines under placebo conditions was comparable to that in previous studies (Christensen and Brandsborg 1973; Hansson and Hökfelt 1975). The same increase was observed with alinidine, indicating that it had no effect on exercise-induced reflex stimulation of the sympathetic nervous system.

Part II of the present study was performed in order to differentiate the haemodynamic effects of alinidine and a β-receptor antagonist, propranolol. At the dosages used, both alinidine and propranolol reduced exercise-induced tachycardia to a similar extent. However, there was a differential effect on the exercise-induced increase in systolic blood pressure, suggesting that the action of alinidine is not mediated by β-receptor blockade. Similar conclusions were drawn by Harron et al. (1981), who showed that alinidine attenuated exercise-induced tachycardia in healthy subjects but had no influence on isoprenaline tachycardia.

The present results support the concept that the acute bradycardic action of alinidine in man is due neither to clonidine-like central sympatho-inhibition nor to β-receptor blockade.

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