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HAEMODYNAMIC EFFECTS OF GUANFACINE

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1 The haemodynamic mechanism of action of guanfacine 4 mg intravenously was investigated in resting conditions and during exercise for up to 20 h after administration of the drug. Cardiac output and pulmonary arterial pressure were determined by the Swan-Ganz thermodilution method. Blood pressure was measured directly.

2 During and immediately after intravenous administration of guanfacine, blood pressure peripheral resistance and pulmonary arterial pressure increased (in keeping with an α-sympathomimetic effect of the compound), whereas heart rate and cardiac output decreased.

3 Subsequently blood pressure fell as a result of a decrease in cardiac output. From the third hour peripheral resistance decreased, whereas cardiac output increased again, sometimes exceeding the control value.

4 During exercise blood pressure was reduced from the third hour after administration, as in resting conditions, as a result of the reduction in peripheral resistance.

5 In resting conditions guanfacine reduced heart rate at the beginning and during the whole course of the investigation, whereas during exercise a reduction in heart rate was only demonstrable for 1 h after administration of the drug.

6 Side-effects noted included fatigue, drowsiness and bradycardia.

Introduction

A blood pressure lowering effect of guanfacine has been demonstrated in many clinical studies (Dubach, Huwyler, Radiolovic & Singeisen, 1977; Esch, 1976; Jäätelä, 1976*a*, 1976*b*; Kirch & Distler, 1978; Rockel, Sabel & Heidland, 1977, 1978; Turner, 1974). In our own study (Magometschnigg, Bonelli, Hitzenberger & Kaik, 1980) and in an unpublished study on the duration of action, we have shown that guanfacine lowers the blood pressure in a dose-dependent manner and that the effect of a single dose may persist for up to 72 hours. As an α-sympathomimetic compound, guanfacine, exerts a central and peripheral effect on the α-receptors and thus has opposing effects on blood pressure.

We have investigated the immediate and late haemodynamic effects of a single dose of guanfacine 4 mg intravenously. The effect was investigated both at rest and during physical exercise for a period of up to 20 h after the dose.

Methods

The patients included in the study had been admitted to the First Medical University Hospital for investigation of their hypertension. Patients were only included in the study if they were suffering from essential hypertension and had a diastolic blood pressure of at least 110 mm Hg. All patients were given a full explanation and gave their consent to participate in the trial procedure.

After thorough examination and diagnosis of essential hypertension, the pharmacodynamic study of guanfacine was undertaken in the cardiovascular laboratory of the Department of Clinical Pharmacology. With the patient supine, blood pressure was measured by means of a catheter inserted in the radial artery. Cardiac output, pulmonary arterial pressure and pulmonary wedge pressure were recorded by means of a Swan-Ganz thermodilution catheter which was passed into the pulmonary artery by way of the cubital vein. The ECG was monitored on an oscilloscope throughout the whole investigation.

The variables stroke volume and peripheral resistance were calculated.

All the haemodynamic variables were recorded first in the resting patient. The patients were then exercised on a bicycle ergometer in a supine position at a load of 40% of their theoretical effective capacity, calculated by the method of Bühlmann (1965). Haemodynamic measurements were made during the fifth minute. After a period of recovery of 1 h the resting values were again recorded. At this point

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Table 1 Diastolic blood pressure of the two non-responders

Non-responder number	*Control*	*Time after guanfacine 4 mg i.v. (h)*											
		1	*2*	*3*	*4*	*5*	*6*	*8*	*10*	*12*	*14*	*16*	*18*	*20*
		Diastolic blood pressure (mm Hg)												
1	96	100	88	96	100	96	100	88	92	104	96	92	92	92
2	100	100	106	98	106	94	102	108	102	102	102	95	99	99

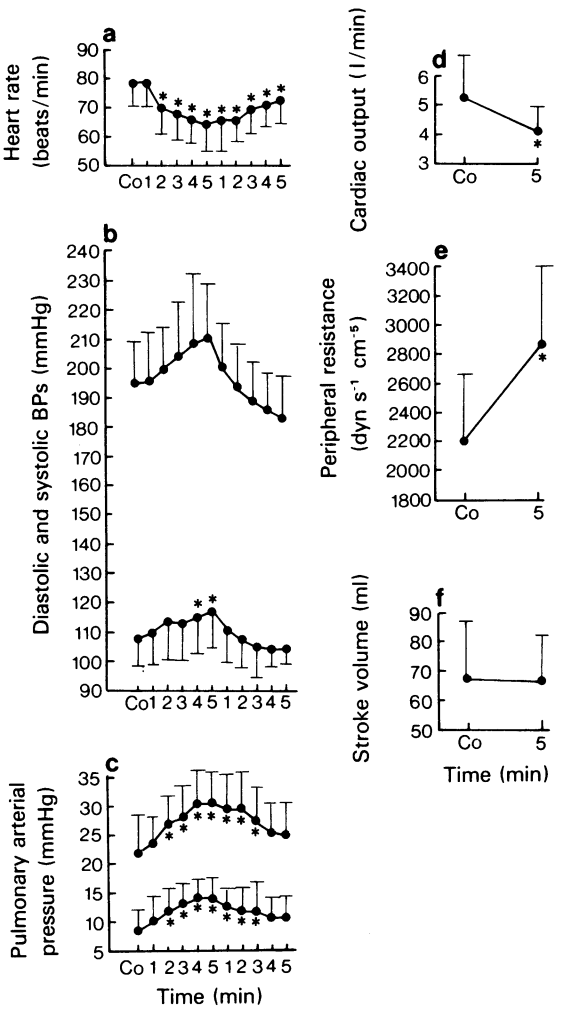

Figure 1 Haemodynamic effects during and immediately after intravenous infusion of guanfacine 4 mg (mean value ± s.d.). *a*, Hear rate; *b*, systolic and diastolic blood pressures; *c*, systolic and diastolic pulmonary blood pressure; *d*, cardiac output; *e*, peripheral resistance; *f*, stroke volume. $*P < 0.05$.

guanfacine 4 mg diluted with 50 ml normal saline was administered by intravenous infusion over 5 min using an infusion pump (Braun Melsungen). During infusion and for 5 min afterwards, blood pressure and pulmonary arterial pressure were recorded continuously. Before the drug was infused and in the fifth minute of the infusion, cardiac output was also recorded. In the subsequent period of the investigation the haemodynamic variables were recorded at hourly intervals up to the sixth hour and then at 2 hourly intervals up to the twentieth hour after administration of guanfacine.

Table 2 Haemodynamic effects (mean ± s.d.) for five patients during and immediately after intravenous infusion of guanfacine 4 mg

		Time during infusion (min)				*Time after infusion (min)*				
	Control	*1*	*2*	*3*	*4*	*5*	*1*	*2*	*3*	*4*	*5*
Heart rate (beats/min)											
Mean	78.6	78.9	76.0	74.1	72.5	70.6	70.2	69.7	69.7	70.0	70.3
s.d.	7.5	7.2	8.3	8.9	9.3	9.8	9.8	9.6	8.4	8.5	8.3
Systolic blood pressure (mm Hg)											
Mean	195.0	196.4	199.4	202.8	208.4	208.8	200.8	192.6	188.4	186.0	202.4
s.d.	13.3	15.1	14.0	20.0	22.0	23.6	14.2	14.7	13.5	11.9	54.9
Diastolic blood pressure (mm Hg)											
Mean	107.6	110.8	113.6	112.8	114.8	115.6	110.4	107.4	105.0	105.0	105.4
s.d.	9.8	11.6	12.7	12.5	12.2	12.0	10.1	7.8	9.5	6.6	3.6
Systolic pulmonary blood pressure (mm Hg)											
Mean	22.4	24.0	27.4	28.2	30.4	30.6	28.8	29.4	27.0	25.4	25.0
s.d.	5.6	4.0	4.2	4.9	5.4	5.9	6.1	6.7	5.7	4.7	5.7
Diastolic pulmonary blood pressure (mm Hg)											
Mean	8.8	9.8	12.0	12.6	14.0	14.0	12.6	12.2	12.4	10.8	10.8
s.d.	3.6	4.0	3.3	3.0	2.9	2.9	2.5	3.6	4.2	2.6	3.7

	Cardiac output (l/min)		*Stroke volume (ml)*		*Peripheral resistance (dyn s^{-1} cm^{-5})*	
	Control	*5 min*	*Control*	*5 min*	*Control*	*5 min*
Mean	5.2	4.1	67.0	66.2	2191	2918
s.d.	1.4	0.8	20.5	15.6	474	557

At 1, 3, 8 and 20 h after administration of the drug the ergometer exercise test was repeated as described above.

Evaluation

To describe the haemodynamic changes the results in five responders were used; those for two non-responders were not taken into account. A patient was considered a non-responder if there was no decrease in diastolic blood pressure during guanfacine treatment. Table 1 shows the diastolic blood pressure of the two non-responders.

Statistical evaluation was made using Student's *t*-test, $P<0.05$ being chosen as the limit for significance.

Results

A distinction was made between the immediate effects of intravenous guanfacine, that is, those occurring during infusion and immediately afterwards, and the effects which occur later.

Immediate effects

The intravenous infusion of guanfacine 4 mg (Figure 1) over 5 min induced an increase in blood pressure beginning after the second minute and varying from patient to patient (Table 2). The mean systolic blood pressure increased from 195 to 208 mm Hg and the mean diastolic blood pressure from 107.7 to 115 mm Hg. There were concomitant increases in pulmonary artery pressure and peripheral resistance, whereas cardiac output decreased because of a reduction in heart rate.

Stroke volume remained unchanged (Table 2).

After the infusion was terminated, blood pressure tended to decrease; and 5 min after termination it was on average lower than initially. Pulmonary arterial pressure had not yet returned to normal at that point, and heart rate remained reduced.

Side-effects such as paleness and tiredness occurred even while the drug was being infused.

Secondary (later) haemodynamic effects (Figure 2, Table 3)

During the hours following the infusion there was a statistically significant decrease in resting systolic and diastolic blood pressures (Figure 2). This decrease was still maximal after 20 h, the end of the observation period. There were individual differences (Table 3), but on average the mean arterial pressure fell from 138 ± 15.6 (control) to 103.4 ± 4.8 mm Hg at 20 h (mean ± s.d.).

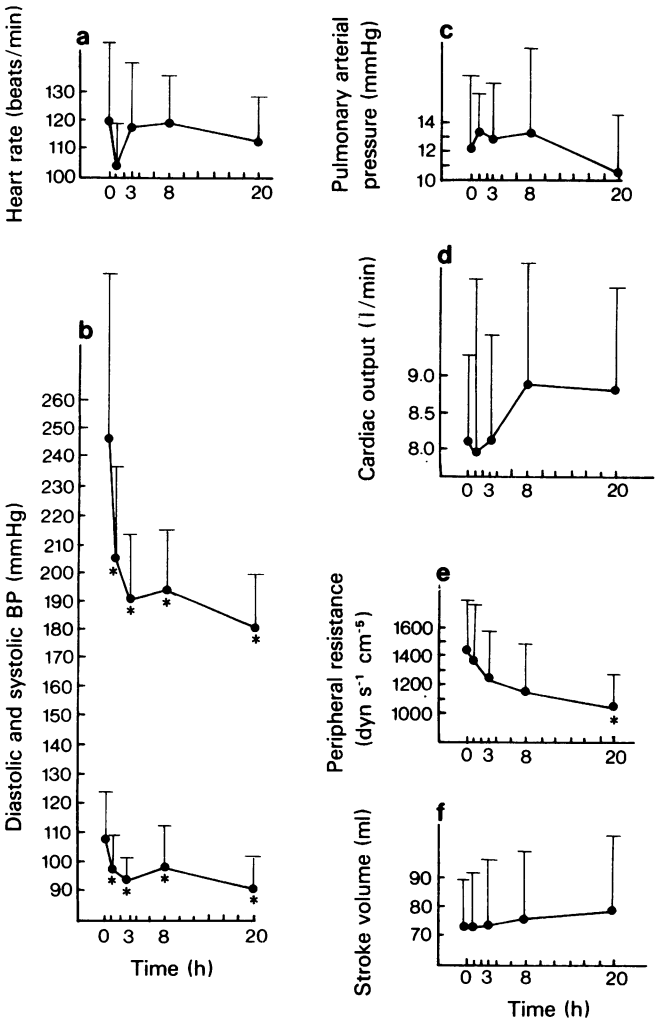

Figure 2 Secondary (later) haemodynamic effects after administration of guanfacine 4 mg intravenously (mean value ± s.d.). *a*, Heart rate; *b*, systolic and diastolic blood pressures; *c*, pulmonary wedge pressure; *d*, cardiac output; *e*, peripheral resistance; *f*, stroke volume. $*P < 0.05$.

The time course of peripheral resistance changes did not strictly parallel the blood pressure changes, as average peripheral resistance values started falling only after 3 h and reached their lowest point only after 20 h (Figure 2). Individual differences were observed in the intensity and time course of this effect (Table 3).

Large individual differences were observed with respect to cardiac output (Table 3), but at no time after drug administration was there a significant change in the cardiac output of the group as a whole.

Heart rate, stroke volume and pulmonary wedge pressure did not change significantly as compared with control values throughout the observation period (Figure 2, Table 3).

Exercise haemodynamics

Systolic and diastolic blood pressures were significantly lower than control values at all time intervals they were measured after guanfacine administration (Figure 3). The effect was still maximal at 20 hours. Peripheral resistance fell during the observation period and was significantly lower than control values at 20 h (Figure 3). Guanfacine

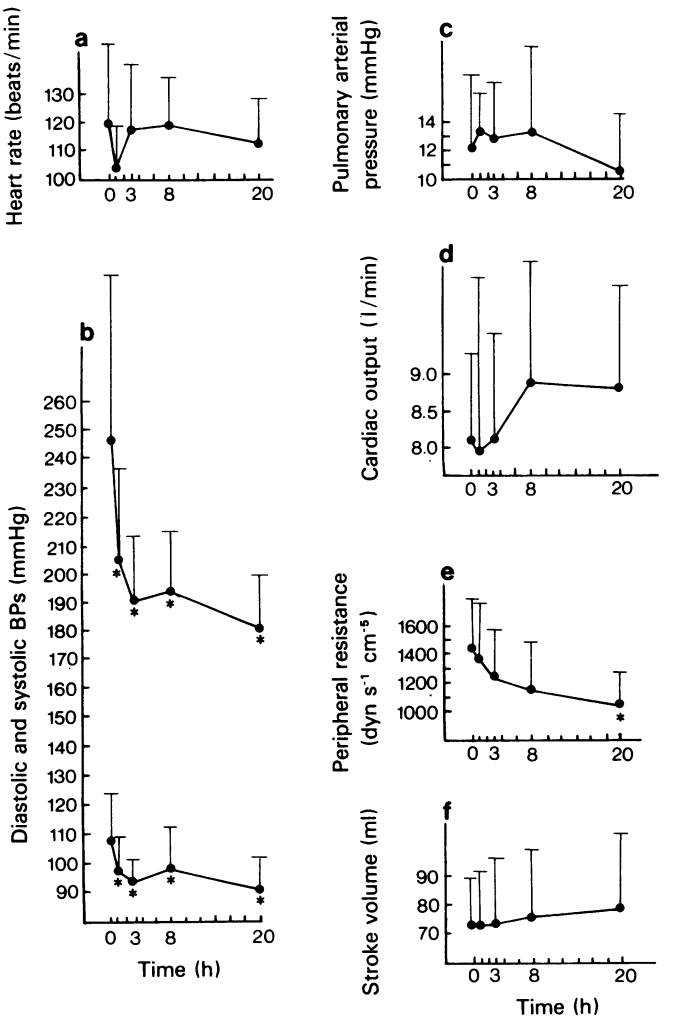

Figure 3 Haemodynamic changes during ergometer exercise after administration of guanfacine 4 mg intravenously (mean value ± s.d.) at 40% of the individual submaximal work capacity. *a*, Heart rate; *b*, systolic and diastolic blood pressures; *c*, pulmonary wedge pressure; *d*, cardiac output; *e*, peripheral resistance; *f*, stroke volume. $*P < 0.05$.

4 mg intravenously did not alter significantly cardiac output, exercise-induced tachycardia, stroke volume, pulmonary arterial pressure or pulmonary wedge pressure.

Non-responder

In a non-responder not taken into account in this report, an increase in pulmonary wedge pressure from 6 to 34 mm Hg was observed during exercise, 1 h and 3 h after guanfacine infusion. After 8 h it had returned to control values (Figure 4).

Discussion

During and after acute intravenous administration of guanfacine two phases could be distinguished:

Immediate effects

During and immediately after infusion of the drug an α-sympathomimetic effect on the peripheral vessels was evident. In response to stimulation of the α-receptors vasoconstriction occurred, thereby causing an increase in peripheral resistance. Blood pressure was increased but cardiac output was decreased.

In this primary phase a central antihypertensive

Table 3 Haemodynamic changes (mean ± s.d.) in five patients for up to 20 h after intravenous infusion of guanfacine 4 mg

	Time after guanfacine administration (h)												
	Control	*1*	*2*	*3*	*4*	*5*	*6*	*8*	*10*	*12*	*14*	*16*	*18*	*20*
Heart rate (beats/min)														
Mean	81.6	73.2	79.6	78.0	74.4	79.2	75.6	78.0	70.8	72.0	74.4	72.0	70.8	78.0
s.d.	13.2	11.5	11.0	12.0	12.4	13.0	12.4	17.0	13.0	12.0	6.8	12.7	9.9	9.5
Systolic blood pressure (mm Hg)														
Mean	197.6	174.0	162.8	155.6	158.4	154.0	157.6	142.4	142.0	143.2	140.4	137.6	137.2	141.2
s.d.	32.5	21.5	23.4	23.3	18.1	22.5	22.4	17.2	13.9	18.1	16.6	13.4	17.2	15.0
Diastolic blood pressure (mm Hg)														
Mean	109.6	104.8	95.6	92.8	88.8	89.6	90.4	85.2	82.8	86.4	86.4	83.6	81.2	85.6
s.d.	9.9	3.6	7.0	8.7	7.0	7.4	9.2	5.9	4.4	7.1	7.9	6.5	9.1	8.3
Pulmonary wedge pressure (mm Hg)														
Mean	6.9	10.6	8.1	6.4	7.0	7.6	8.6	6.6	5.8	5.8	5.7	7.7	5.9	8.5
s.d.	3.1	6.4	6.5	3.5	2.3	3.0	2.6	3.0	2.6	2.5	2.7	2.1	3.2	4.5
Cardiac output (l/min)														
Mean	4.6	4.2	3.9	4.2	4.3	4.3	4.3	4.0	4.2	4.2	4.8	4.3	4.3	4.8
s.d.	0.6	0.4	0.6	0.8	0.8	0.8	0.6	0.6	0.6	0.7	0.8	0.9	0.6	0.6
Peripheral resistance (dyn s^{-1} cm^{-5})														
Mean	2430	2464	2472	2306	2212	2217	2154	2129	2032	2103	1845	1973	1841	1702
s.d.	344	328	528	573	561	555	541	462	400	441	454	430	339	345
Stroke volume (ml)														
Mean	50.4	56.2	49.2	53.6	57.4	54.8	58.2	53.0	60.8	60.0	64.0	61.8	64.0	63.2
s.d.	11.7	4.9	5.5	5.7	8.3	7.1	10.6	11.0	16.2	18.9	16.0	18.6	15.3	14.8

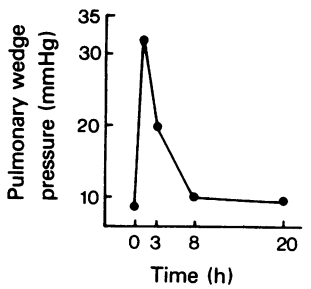

Figure 4 Pulmonary wedge pressure after administration of guanfacine 4 mg during exercise in a non-responder.

effect, if present at all, is masked by the peripheral effects. The fact that side-effects such as fatigue and drowsiness occur at this time is an indication that the drug is already beginning to exert a central effect.

Effects in the later stages

Under resting conditions: The blood pressure lowering effect in the first few hours after administration was mainly due to a reduction in cardiac output. Later, and clearly so from the third hour, there was a decrease in peripheral resistance. In the subsequent phase the hypotensive effect was solely due to a reduction in peripheral resistance. The cardiac output was initially reduced and later increased. This increase was mainly due to alteration of the stroke volume, as the heart rate was depressed throughout the whole period of the investigation.

During physical exercise: During exercise the cardiovascular pattern was similar to that in resting conditions. The initial peak effect on the blood pressure occurred after 3 hours. In the ergometric tests carried out 8 and 20 h after administration there was no further change in blood pressure, although the resting peripheral resistance had decreased still further.

During exercise, unlike the situation in resting conditions, heart rate was only markedly depressed 1 h after treatment. After 1 h the control values were attained or exceeded. From the third hour the increase in heart rate was not inhibited during exercise.

In the five patients described, there was no evidence of a negative inotropic effect. The pulmonary wedge pressure was not changed during exercise.

An exception to this was a non-responder, not included in this study, who showed an increase in pulmonary wedge pressure during effort for up to 3 h after administration of the drug.

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