Negative chronotropic effects of nizatidine

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Abstract

Twelve healthy volunteers were given one week's oral treatment with each of 300 mg nizatidine, 40 mg famotidine, and placebo once daily in a randomised, placebo controlled, double blind study. Three hours after administration, nizatidine led to a significant reduction in the mean (SD) resting heart rate compared with placebo (63.6 (6.4) beats/minute on placebo to 55.9 (7.2) beats/minute on nizatidine ($p < 0.05$)), whereas famotidine did not influence the heart rate significantly. Both drugs, however, increased significantly the pre-ejection period and the ratio of pre-ejection period to left ventricular ejection time on mechanocardiography and led to a significant decrease in cardiac output on impedance cardiography. The exercise heart rate on nizatidine as well as the resting heart rate on concurrent administration of nizatidine and the β receptor blocking agent atenolol were subsequently investigated in the same volunteers. Nizatidine slightly inhibited exercise tachycardia by 4.4% ($p < 0.05$). When compared with placebo, the mean resting heart rate was decreased on atenolol alone by a mean of 10.6 beats/minute ($p < 0.01$) and fell further on co-administration with nizatidine to a total of 16.1 beats/minute ($p < 0.05$ versus atenolol alone). In conclusion, the effect of nizatidine in reducing the heart rate needs careful evaluation in elderly patients with heart failure or those also taking β blockers. In contrast to famotidine, long term treatment with 300 mg nizatidine a day has mainly negative chronotropic effects.

In addition to inducing increased gastric secretion, histamine also exerts positive inotropic and chronotropic effects on the heart, mainly via H_2 receptors.^{1,2} It is therefore possible that H_2 receptor blocking drugs have cardiodepressant properties in vivo.³ While the well established H_2 receptor blocking agents cimetidine and ranitidine do not seem to have negative influences on cardiac performance,^{4,7} a recent study indicated that a more potent and longer acting H_2 blocker such as famotidine may have these.⁸

Nizatidine is a new treatment for peptic ulcer disease. Its effectiveness when administered once daily (300 mg at night)^{9,10} suggests that it is a potent H_2 receptor blocker. The aim of this study was to compare its effects with those of famotidine on non-invasively measured haemodynamic parameters. Additional studies were subsequently conducted to examine the haemodynamic effects of nizatidine when coadministered with the β adrenergic blocking agent atenolol and after submaximal ergometric bicycle exercise.

Methods

Twelve healthy volunteers (six men, six women; mean (SD) age 25.0 (2.0) years; body weight 60.3 (8.0) kg) were included in an initial placebo controlled, randomised, double blind, cross over investigation. Each participant was assigned to receive one oral dose of either placebo, 40 mg famotidine, or 300 mg nizatidine once daily for seven days. Subjects were then crossed over to the two subsequent seven day treatment periods after two week, therapy free intervals.

Haemodynamic parameters were measured non-invasively using mechanocardiography (systolic time intervals) and impedance cardiography. Blood pressure (Riva-Rocci method) was also determined. Subjects were tested on the first and seventh treatment days before and at 90 minutes and three, six, and 12 hours after administration of the test substances, thereby permitting determination of haemodynamic effects after single and repeated dosing of these drugs.

The results of the preceding study prompted us to perform additional investigations. Firstly, the effects of nizatidine on non-invasively measured haemodynamic parameters were studied when combined with the β adrenergic blocking agent atenolol. This was a placebo controlled, randomised, double blind, cross over study wherein the same 12 healthy volunteers were each treated for one week periods with either placebo, 100 mg atenolol (plus one tablet placebo), or 300 mg nizatidine combined with 100 mg atenolol taken once daily; cross over was again separated by two week, wash out periods. All drugs were prepared as identically looking capsules. Impedance- and mechanocardiographic parameters were measured on the seventh treatment day before and at 90 minutes and three, six, and 12 hours after administration of the drugs.

Secondly, changes in heart rate after submaximal ergometric bicycle exercise were also determined. Testing of the same 12 subjects was carried out in a double blind fashion after treatment for one week on placebo and after one week on oral nizatidine 300 mg once daily. Exercise testing was performed three hours after dosing with subjects in the sitting position. Starting at 100 W, workload was increased in a stepwise manner every two minutes by 25 W until subjects achieved a heart rate of at least 165 beats/minute on placebo. Two weeks later, the same procedure and workload were used after nizatidine. Heart rate was measured by electrocardiogram. The test was performed at a room temperature ranging from 18°C to 22°C and at a relative humidity of 70%.

All subjects had given their written consent after a full explanation of the nature and purpose of the investigations. The study protocol was

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Figure 1: Mean (SEM) heart rate and cardiac output in 12 healthy subjects after one week of oral treatment with placebo (●—●) or 300 mg nizatidine (○—○) once daily with determinations made before, and 1.5, 3, 6, and 12 hours after dosing.

approved by the ethics committee of the Schleswig-Holstein Regional Medical Board.

MECHANOCARDIOGRAPHY

Mechanocardiography, a non-invasive method for assessing left ventricular function, was carried out by simultaneous recording of the electrocardiogram, phonocardiogram, and carotid pulse tracing in the supine position after a 15 minute rest period. Measurements were made from five consecutive heart beats¹¹ at a paper speed of 100 mm/second, repeated three times, with the results then averaged. Total QS₂ (electromechanical systole) was measured from the beginning of the QRS complex in the ECG to the beginning of the high frequency vibrations of the second heart sound in the phonocardiogram. The left ventricular ejection time (LVET) was measured from the beginning of the carotid pulse tracing upstroke to its dicrotic notch. The pre-ejection period (PEP) was calculated from the difference between QS₂ and LVET (PEP = QS₂ - LVET). The ratio of PEP to LVET was also determined. Heart rate was calculated

from 20 R to R intervals in the electrocardiogram at 50 mm/second. Heart rate corrections (QS₂₀ and LVET₂₀) were made according to Weissler *et al.*¹² The pre-ejection period is presented with and without heart rate correction in order to discriminate heart rate effects from other influences on this parameter. Measurements were performed under standardised conditions.^{8, 13, 14} Subjects observed detailed restriction concerning food, fluid, and activities on the days of measurements.

IMPEDANCE CARDIOGRAPHY

Impedance cardiography was performed by the simultaneous registration of an electrocardiogram, a phonocardiogram, and the changes in transthoracic electrical impedance. The latter were detected by a Kardio-Dynagraph (Diefenbach GmbH, Frankfurt/Main, FRG). Four bands of self adhesive electrodes were placed around the patient's body: two around the neck, the third at the level of the xiphisternum, and the fourth at 5 to 10 cm below the xiphisternum. The two outer electrodes transmitted a constant

TABLE I Mean (SD) heart rate, stroke volume, cardiac output, and Heather index before and 1.5, 3, 6, and 12 hours after one week's administration of placebo, 40 mg famotidine, or 300 mg nizatidine

Haemodynamic parameter	Treatment	Time after administration (hr)				
		Before	1.5	3	6	12
Heart rate (beats/min)	Placebo	64.9 (6.3)	64.3 (6.5)	63.6 (6.4)	65.6 (6.6)	65.0 (6.3)
	Famotidine	63.8 (5.4)	62.1 (5.9)	61.7 (5.9)	63.2 (7.6)	61.2 (6.2)
	Nizatidine	64.4 (5.0)	55.9 (6.2)*	55.9 (7.2)*	62.5 (7.6)	64.2 (5.4)
Stroke volume (ml)	Placebo	105.4 (12.7)	107.5 (12.5)	107.4 (12.2)	102.7 (12.5)	107.1 (12.3)
	Famotidine	106.8 (13.7)	95.5 (13.4)†	96.3 (12.6)†	101.0 (14.4)	106.3 (13.4)
	Nizatidine	103.3 (15.1)	102.9 (15.1)	101.2 (17.2)	102.8 (15.1)	104.2 (13.9)
Cardiac output (l/min)	Placebo	6.5 (1.1)	6.4 (1.1)	6.4 (1.2)	6.5 (1.3)	6.6 (1.0)
	Famotidine	6.7 (1.0)	5.6 (0.8)†	5.7 (1.0)*	6.3 (1.0)	6.5 (1.0)
	Nizatidine	6.6 (0.9)	5.7 (0.9)*	5.6 (1.0)*	6.3 (1.1)	6.7 (0.9)
Heather index (Ωsec ⁻²)	Placebo	24.1 (4.4)	24.2 (4.4)	24.6 (6.0)	24.4 (4.6)	23.9 (4.6)
	Famotidine	23.8 (4.7)	21.1 (3.4)†	21.1 (3.9)†	22.6 (3.1)	24.3 (4.7)
	Nizatidine	24.1 (4.8)	22.0 (4.8)*	22.9 (5.4)	23.6 (4.9)	24.0 (4.8)

*p<0.05 compared with placebo; †p<0.01 compared with placebo.

Figure 2: Exercise heart rate in the 12 subjects (single values and mean (SEM)) after one week of oral treatment with placebo or 300 mg nizatidine once daily. Determinations were made 3 hours after dosing.

sinusoidal alternating current (40 kHz) through the thorax, and the changes in thoracic impedance were detected by the two inner electrodes. Measurements were carried out with the patient in the supine position and holding his or her breath at end expiration.

Stroke volume was calculated using the equation described by Kubicek *et al.*¹⁵

$$\Delta V = p(L^2/Z_o^2) \cdot (dz/dt)_{\max} \cdot t.$$

In this equation, ΔV is the stroke volume in ml; p represents the resistivity of the blood which can, according to Quail and Traugott,¹⁶ be assumed to be a constant with a value of $135\Omega\text{-cm}$ (in the subjects investigated, haematocrit values measured on the first and seventh treatment day immediately after the determination of impedance cardiography remained unchanged); L is the average distance between the inner electrodes in cm; Z_o is the mean thoracic impedance between these same electrodes in ohms; $(dz/dt)_{\max}$ is the maximum amplitude of the dz/dt curve; and t (in seconds) is the time interval between the

zero crossing of the dz/dt curve just before the maximal peak and the beginning of the second heart sound. Cardiac output (CO) was calculated as $\text{CO} = \Delta V \times \text{heart rate}/1000$.

Another impedance cardiographic parameter used in the present study was the Heather index. This index is considered as a measure of cardiac performance which correlates with the PEP/LVET ratio, stroke volume, and cardiac output.¹⁷ As its calculation need not take into account the distance between the electrodes – the main source of error in determining stroke volume and cardiac output – the Heather index seems to be the most reliable parameter of impedance cardiography.¹⁸

The Heather index (Ωsec^{-2}) was evaluated as $\text{HI} = (dz/dt)_{\max}/\text{RZ}$. In this equation, RZ is the time interval between the 'R' deflection in the electrocardiogram and the maximum amplitude of the dz/dt curve.

Statistical analysis of the haemodynamic data obtained was performed using the Friedman and Wilcoxon-Wilcox tests.¹⁹

Results

HAEMODYNAMIC EFFECTS OF NIZATIDINE AND FAMOTIDINE

Haemodynamic effects of both H_2 blockers are presented for the seventh treatment day only. These values did not differ significantly from the single dose results and are of greater clinical relevance (chronic treatment). At 90 minutes and three hours after dosing, nizatidine led to significant reductions in resting heart rate compared with placebo and baseline values, whereas famotidine had no noticeable impact on heart rate (Fig 1). Famotidine significantly decreased the stroke volume, cardiac output, and the Heather index in impedance cardiography up to three hours after its administration (Table I).

Mechanocardiography showed that both drugs significantly increased the pre-ejection period and PEP/LVET ratio up to three hours after administration (Table II). As famotidine but not nizatidine resulted in raised PEP_c value (heart rate corrected) three hours after intake, the effects of nizatidine on these parameters of cardiac performance were predominantly a result of its negative chronotropism. Neither famotidine nor nizatidine led to any clinically relevant

TABLE II Mean (SD) pre-ejection period, heart rate corrected pre-ejection period, and the ratio of the pre-ejection period to the left ventricular ejection time before and 1.5, 3, 6, and 12 hours after one week's administration of placebo, 40 mg famotidine, or 300 mg nizatidine

Haemodynamic parameter	Treatment	Time after administration (hr)				
		Before	1.5	3	6	12
PEP (ms)	Placebo	105.7 (4.8)	106.3 (4.0)	106.5 (4.5)	104.1 (3.9)	105.1 (4.2)
	Famotidine	106.2 (4.2)	115.7 (3.9)†	117.5 (5.4)†	107.5 (5.0)	106.4 (3.9)
	Nizatidine	104.4 (4.4)	113.6 (3.9)*	113.2 (5.5)*	105.0 (6.1)	104.9 (4.4)
PEP _c (ms)	Placebo	130.4 (4.4)	130.2 (4.3)	130.1 (4.3)	129.8 (3.5)	129.8 (4.0)
	Famotidine	131.7 (3.9)	140.6 (4.3)†	142.2 (4.4)†	132.4 (3.6)	130.9 (3.7)
	Nizatidine	130.3 (4.5)	136.8 (6.1)*	135.5 (4.5)	130.8 (5.9)	130.6 (4.0)
PEP/LVET	Placebo	0.341 (0.02)	0.339 (0.02)	0.338 (0.01)	0.342 (0.01)	0.341 (0.01)
	Famotidine	0.342 (0.02)	0.367 (0.02)†	0.375 (0.02)†	0.353 (0.02)*	0.340 (0.01)
	Nizatidine	0.338 (0.02)	0.357 (0.0)*	0.358 (0.0)*	0.346 (0.02)	0.336 (0.02)

* $p < 0.05$ compared with placebo; † $p < 0.01$ compared with placebo.

PEP=pre-ejection period; PEP_c=heart rate corrected pre-ejection period; PEP/LVET=ratio of the pre-ejection period to the left ventricular ejection time.

Figure 3: Resting heart rate in the 12 subjects investigated after one week of oral treatment with placebo, 100 mg atenolol, or 100 mg atenolol and 300 mg nizatidine once daily with determinations made 1.5 and 3 hours after dosing.

or statistically significant changes in blood pressure in the subjects investigated.

EXERCISE TACHYCARDIA ON NIZATIDINE

Nizatidine slightly but significantly reduced heart rate after ergometric bicycle exercise by 4.4%. The mean (SD) maximum heart rate, 168.9 (2.7) beats/minute three hours after placebo, averaged 161.4 (3.3) beats/minute on 300 mg nizatidine ($p < 0.05$; Fig 2).

COADMINISTRATION OF NIZATIDINE AND ATENOLOL

When compared with placebo, administration of atenolol alone led to a significant fall in the resting heart rate up to six hours after drug intake. The maximum mean reduction in heart rate from the placebo value (63.7 (6.4) beats/minute) occurred three hours after dosing when the heart rate fell by an average of 10.6 beats/minute to 53.1 (6.8) beats/minute ($p < 0.01$). A further significant drop in the heart rate to 47.6 (6.0) beats/minute was observed when atenolol was taken with nizatidine ($p < 0.05$ versus atenolol three hours after dosing) indicating that nizatidine distinctly enhanced the negative chronotropic effect of atenolol. This action of the H_2 blocker was observed at 90 minutes and three hours after concurrent administration (Fig 3),

but could no longer be detected by the sixth and 12th hours. Blood pressure in the healthy volunteers was slightly decreased by atenolol alone or when combined with nizatidine. When measured by impedance cardiography, cardiac output and stroke volume were decreased significantly by atenolol alone, and further reduced when atenolol was taken with nizatidine.

Discussion

Results of the present study clearly indicate that nizatidine exerts negative chronotropic effects. Resting and exercise heart rate were decreased by this H_2 receptor blocking agent. In addition, the heart rate reducing effect of the β receptor blocker atenolol was further enhanced when it was taken at the same time as nizatidine. The bradycardic influence of nizatidine has not been reported previously.

Sinus bradycardia between 44 and 48 beats/minute after oral administration of other H_2 blockers such as cimetidine or ranitidine has been described very rarely,²⁰⁻²³ though somewhat more frequently after intravenous injection.²⁴⁻²⁸ These previous observations were all based on single case reports, some of which concerned patients with underlying coronary disease. In the present study, however, the negative chronotropic effect after administration of 300 mg nizatidine was consistently observed in all the volunteers investigated, with comparable degrees of heart rate reduction noted in all subjects.

When considering histamine's known positive inotropic and chronotropic properties, mainly mediated via H_2 receptors,¹² nizatidine's influence on heart rate is not surprising. Furthermore, the negative chronotropic properties of this H_2 blocker may also be caused by a cholinergic mechanism since adverse effects such as lacrimation, salivation, emesis, miosis, and diarrhoea have been reported to occur with nizatidine in animal experiments.

Negative effects on cardiac performance have also been reported for famotidine, although these were not the result of a reduction in heart rate.⁸ In this study, both nizatidine and famotidine decreased cardiac output in impedance cardiography, thereby increasing both the pre-ejection period and the PEP/LVET ratio in mechanocardiography – effects that indicate negative influences on cardiac performance. The extent of these changes was more pronounced with famotidine, clearly confirming previously reported data^{7,8} and indicating that it seems to exert direct influences on myocardial contractility. By contrast, nizatidine reduced cardiac output mainly because of its negative chronotropic properties, as a result of which we would even have expected to see an increase in stroke volume. Nevertheless, stroke volume on nizatidine remained unchanged or even reduced indicating that this H_2 blocker may exert a slight negative inotropic effect which was certainly less pronounced than that of famotidine.

In conclusion, the results of this study could be of clinical importance, as the reductions in heart rate after 300 mg of nizatidine were not just observed in single individuals but consistently

found in all subjects investigated. Since these were noted in healthy subjects, the relevance of these findings to the treatment of elderly patients with heart failure and those who are also taking β blocker or verapamil therapy need careful evaluation. Finally, these results confirm previous data on the negative effects of famotidine on cardiac performance^{17,8}; effects which are not the result of the heart rate reducing properties of this H₂ blocker.

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