



Effects of Cimetidine on Chronotropic Response to Cardiopulmonary Exercise Testing

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OBJECTIVE

To test the hypothesis that the administration of cimetidine will modify the chronotropic response to exercise testing through a random clinical trial.

METHODS

The study selected 24 eligible healthy subjects, ages between 20 and 68 years, not athletes, who agreed to undergo cardiopulmonary exercise testing after the administration of placebo and 400 mg of cimetidine twice a day for one week. The tests were performed on a treadmill using a ramp protocol and direct analysis of the expired gases. Peak, resting and anaerobic threshold heart rate were recorded.

RESULTS

The twenty subjects studied were equally distributed across sex with mean (\pm SD) age 43 ± 11 years. Tests on placebo and on cimetidine presented similar duration (578 ± 90 sec vs 603 ± 131 sec) and similar peak oxygen uptake (35 ± 8 ml/kg.min vs 35 ± 8 ml/kg.min). Cimetidine administration had no significant effect on resting heart rate (75 ± 10 bpm vs 74 ± 8 bpm), heart rate at peak exercise (176 ± 12 bpm vs 176 ± 11 bpm), and on the difference between the peak and the resting heart rates – delta HR (101 ± 14 bpm vs 101 ± 13 bpm).

CONCLUSION

The administration of cimetidine for 7 days has no significant effect on the chronotropic response to exercise testing.

KEY WORDS

Chronotropic response, cardiopulmonary exercise testing, cimetidine, H₁ and H₂ receptors, histamine.

The fact that the heart rate is a key element in ergometric exercise testing has been acknowledged in medical literature for over 40 years. One of the aims when beginning an exercise testing program is to reach the maximum predicted heart rate so that greater sensitivity in the detection of ischemia is achieved. The assessment of the chronotropic response to exercise testing also has prognostic implications^{1,2}.

Chronotropic incompetence (CI), the attenuated heart rate (HR) response to exercise, may be blamed for the loss of accuracy in non-invasive tests such as exercise testing and perfusion scintigraphy. CI is also considered to be a coronary disease marker with implications for prognosis. As some studies have demonstrated, the survival of individuals seems to be closely connected with their ability to reach their age-predicted heart rate, an important and independent mortality predictor^{1,2}. Therefore, it is clinically important to know which drugs used in medical practice may interfere with the heart rate during exercise testing.

Histamine has several effects on cardiac performance, mediated by H₁ and H₂ receptors^{3,4}. The latter are responsible for the positive chronotropic effect of histamine and are found mainly in the right atrium and around the sinus node⁵. H₂ receptor inhibitors such as ranitidine and cimetidine, widely used in medical practice since the 1970s, have been linked with cases of bradycardia and atrioventricular conduction disturbances⁶.

Preliminary data from a recent observation study⁷, where normal ergometric tests of 158 subjects not using any drugs and of 46 individuals who took ranitidine or cimetidine were reviewed, shows that the group taking no medication reached higher heart rates, with a mean (\pm standard deviation) of 98 ± 5 % of the maximum age-predicted heart rate when compared with 92 ± 12 % of the maximum age-predicted heart rate ($p < 0.05$) of the second group. In a study of 47 subjects taking no medication and 24 subjects on medication, paired according to sex, age and functional capacity, revealed that those who took no medication showed higher maximum heart rates (99 ± 4 % of the age-predicted value vs. 94 ± 6 % of the age-predicted value; $p < 0.05$). This observation study combined with data from experimental resting studies suggest that individuals who use H₂ blockers may show lower maximum heart rates during ergometric testing. Therefore, this randomized trial was conducted to test the hypothesis that the administration of cimetidine may modify the chronotropic response to exercise testing.

METHODS

The study selected 24 eligible healthy subjects, ages between 20 and 68 years, not athletes, who agreed to undergo cardiopulmonary exercise testing after the administration of placebo and 400 mg cimetidine twice

a day for one week. Prior to beginning, all were informed of the effects of this drug, the risks and the discomfort involved in the study and granted their written informed consent. The study was approved by the Committee of Ethics in Research of the Hospital de Clínicas de Porto Alegre. Exclusion criteria were: evidence of ischemic changes during the test, interruption in the use of the drug or use of any other drug which could affect the chronometric response during the tests.

A double-blind random cross-over study was carried out with 12 subjects, who were given a placebo in the first phase of the test while twelve others started with cimetidine. This was done to eliminate a potential source of confusion as the subjects could show a better performance in the second treadmill test because of the "learning effect". Each subject took either 400 mg cimetidine or a placebo pill twice a day for a week. There was a ten-day interval between the end of the first phase and the beginning of the second phase of the test. The main outcome of this study was the maximum HR reached expressed in absolute figures and as a percentage of the maximum age-predicted HR according to the formula: 220-age. The resting and anaerobic threshold HRs were also determined. The registers were considered of rest after a pause of at least 5 minutes, with stable heart frequency. An evaluator determined the heart frequency, considering the average of the registers in 6 seconds.

Twelve subjects underwent the two phases of the study at the Cardiopulmonary Laboratory of the Hospital de Clínicas de Porto Alegre and eight others at the Cardiometodo Laboratory of the Hospital Ernesto Dornelles under the supervision of the same physician in both tests. This physician was not aware of which drug the patients were taking. At the Hospital de Clínicas de Porto Alegre, the tests were run on a treadmill (Imbramed, TK10200, Porto Alegre, Brazil), and the 12-derivative ECG was permanently monitored using the Elite System (Micromed-Biotecnologia, Brasília, Brazil). At the Hospital Ernesto Dornelles, the same type of treadmill was used and the ECG was recorded using a Cardiax automated ECG system (Cardiax Systems, Budapest, Hungary). A ramp protocol was used according to the METS number predicted for each age⁸ and also taking into consideration the characteristics of each individual in relation to their routine physical activities. After that, initial speed and inclination were established and these were gradually increased in order to complete the protocol between 8 and 10 minutes. The same ramp program was repeated in the second phase of the study.

The expired gases were analyzed in the Teem 100 - VO 2000 system (Aerosport, Ann Arbor, USA), prevalidated by Novitsky et al⁹ and Wideman¹⁰. And periodically calibrated with volumes and gases of known concentrations. The readings were made after the stabilization of initial values, with an appropriate interval of rest and then every 20 seconds during the exercise. This

yielded derived calculations, graphs, tables and minute ventilation (V_E), carbon dioxide production (VCO_2), oxygen uptake (VO_2), heart rate (HR), ventilatory equivalent for oxygen (V_E/VO_2), ventilatory equivalent for carbon dioxide (V_E/VCO_2) and respiratory exchange ratio (R) curve. The peak VO_2 reached was used as the maximum oxygen uptake (VO_{2max}), using as a reference criterion R values above 1.1¹¹. The ventilatory anaerobic threshold and the compensation point were determined by a single observer after the criteria of Wassereman *et al*¹¹.

The variables represent the mean values and their corresponding standard deviations and are analyzed using the SPSS statistical software. The cardiopulmonary tests variables under the effect of the placebo and cimetidine were compared with the "t" test for paired samples. The initial sample size was to be 13 according to the observation study previously carried out to yield a statistical power of 80% and detect a difference in heart rates of at least 10% with a significance level of $p < 0.05$. The larger sample size was planned to compensate possible losses caused by technical difficulties.

RESULTS

Of the 24 subjects included in the study, 20 finished the two phases as planned and four had to be excluded: three were not able to complete the second phase of the study as arranged and one was not able to use the treadmill selected in the study. The 20 subjects then selected were equally distributed in two groups according to sex, with average age 43.4 ± 11 years, average height 169 ± 1 cm and average body mass index 24.5 ± 3 kg/m². Their ECG was normal at rest and during exercise. No arrhythmia or conduction disorders were recorded.

Table 1 shows the findings of cardiopulmonary tests under the effect of cimetidine and placebo for the 20 subjects studied. The exams were interrupted by fatigue and has similar length after fulfilling the criteria to be considered as maximum tests. The peak VO_2 was similar in the placebo and cimetidine test. The group was characterized by satisfactory physical condition, and peak VO_2 peak fell within 96% of the predicted value, on average. The $ATVO_2$ was similar in both tests.

Table 2 presents the findings of heart rate at rest and during cardiopulmonary tests under the effect of placebo and cimetidine. There was no significant difference in resting heart rate, anaerobic threshold intensity, peak exercise, nor in the difference between peak and resting heart rate. Similarly, the peak arterial blood pressure was similar in both conditions.

DISCUSSION

The assessment of the chronotropic response during exercise testing, through conventional ergometry or cardiopulmonary tests has implications to the diagnostic

Table 1 - Results of cardiopulmonary tests for 20 subjects under the effect of placebo or cimetidine

	Placebo	Cimetidine
Time (s)	578 \pm 90*	603 \pm 131
Peak VO_2 (ml/kg.min)	34.9 \pm 7.7*	35.2 \pm 7.6
Peak VCO_2 (l/min)	3.07 \pm 0.83*	2.99 \pm 0.91
Peak V_E (l/min)	71 \pm 18*	72 \pm 17
Peak R	1.23 \pm 0.13*	1.21 \pm 0.15
Anaerobic threshold VO_2 (% peak VO_2)	52 \pm 7*	50 \pm 9

*Mean values and standard deviation $p > 0.05$

Table 2 - Response of heart rate and arterial blood pressure to cardiopulmonary tests in 20 subjects under the effect of placebo or cimetidine

	Placebo	Cimetidine
Resting HR (bpm)	75 \pm 10*	74 \pm 8
Peak HR (bpm)	176 \pm 12*	176 \pm 11
Difference resting-peak HR (bpm)	101 \pm 14*	101 \pm 13
Anaerobic threshold HR (bpm)	121 \pm 12*	122 \pm 13
% maximum age-predicted HR	101 \pm 7*	101 \pm 6
Maximum systolic blood pressure (mm Hg)	174 \pm 12*	171 \pm 13

*Mean values and standard deviation $p > 0.05$

HR: heart rate

performance of exams. The arbitrary value of 85% of the maximum age-predicted heart rate has been used to validate the suitability of ergometric tests for the diagnosis of myocardial ischemia. In cardiopulmonary testing, the same percentage is used as a criterion of suitable exercise¹¹. More recently, the assessment of the chronotropic response to ergometric testing has shown great prognostic value. Lauer *et al*^{1,2} followed a cohort of low-risk patients for three years to establish the prognostic value of chronotropic response to exercise testing in contrast with the findings of myocardial scintigraphy. The survival rate of the group showing only perfusion defects in scintigraphy was similar to that of the group with unsuitable chronotropic response. In the multivariate analysis, chronotropic incompetence was identified as an important independent mortality predictor¹.

The response of heart rate to exercise testing depends on several factors and is modulated by the autonomic nervous system¹². During dynamic exercise with gradual load increase, the heart rate increases linearly through the removal of parasympathetic influence and the increased action of the sympathetic system on the sinus node¹³ and is influenced by several factors such as age, workload, physical conditioning, existing disease and commitment to the examination^{14,15}.

Histamine is a known vasodilator and in the sympathetic system it has a regulatory effect on noradrenaline release¹⁶. The inhibition seems to be mediated by H_2 receptors.

These receptors, which are most likely presynaptic, are also responsible for myocardial action⁶. Large amounts of histamine are stored in the heart tissue, particularly in the right atrium, around the sinus node, the atrioventricular node and the right ventricle. Receptors are distributed in different ways around different areas of the heart, with H₂ receptors prevalent in the right atrium, H₁ receptors in the left atrium and the right ventricle showing both¹⁷. The physiologic function of histamine in several tissues is not fully known but previous studies have shown that the heart responds to histamine by increasing atrial contractility and automaticity^{18, 19}.

H₂ inhibitors have been used for several years and were first developed to treat peptic disease²⁰⁻²². The cimetidine was the third H₂ receptor antagonist developed by Black and colleagues, with the first two drugs - burimamide and metiamide – being ineffective. Changes to the lateral chain achieved adequate oral absorption and suppression of gastric secretion for a period of 24 hours²³. Literature studies describe the effects of IV infusion of cimetidine on the cardiovascular system at rest. Perugini et al²⁴ in a random clinical trial demonstrated the effect of cimetidine on heart rate variation when compared to a placebo in the same group of subjects. The average resting heart rate in the groups under study was 71 ± 15 bpm. After administration of cimetidine, it fell to 63 ± 13 bpm. (p<0.001). The analysis of the cardiovascular effects of cimetidine in a resting individual suggests that this drug may also affect the heart rate during exercise. Patterson and Milne²⁵, in a case report, suggest that the use of H₂ inhibitors may increase the risk of atrioventricular block.

These experimental data, combined with our previous findings from an observation study⁷, suggested that the cimetidine would have a potential effect on the chronotropic response to exercise, which could alter the prognostic and diagnostic value of exercise testing. In the present study, it was observed that in normal subjects, with appropriate physical performance, there seems to be no difference in the hemodynamic response to exercise with the use of cimetidine in regular maintenance doses for a period of 7 days. The chronotropic response is unchanged after the administration of the drug, which possibly does not interfere on the exam results. These findings are in agreement with the study that assessed the effect of cimetidine on the response to exercise. Saltissi et al²⁶, in a double-blind study involving 19 subjects including cardiopaths with frequent ventricular arrhythmia who used drugs such as diuretics and dimenidrate,

assessed the effect of H₂ inhibitors on conventional ergometric testing. No significant difference was found in their maximum heart rate during exercise. However, the occurrence of ventricular extrasystoles in 15 of 19 subjects made assessment difficult. The assessment of heart rate, with its marked spontaneous oscillations, is adversely affected in the presence of ventricular arrhythmia.

The same way, Hughes et al compared, in a clinical assay, the effects of cimetidine, ranitidine and placebo in 19 individuals between the ages of 28 and 51 years old, with the purpose of evaluating the effects of H₂ receptor inhibitors over the cardiovascular system, considering that frequently it is difficult to do differential diagnose of peptic diseases and coronary disease. The study did not show any differences between the effects of the medicines when compared to each other and to the placebo, in the studied group. Daniel Hilleman et al evaluated the effects of the oral therapeutic, for 7 days, with cimetidine, famotidine and ranitidine, comparing those medicines to the placebo. The purpose was watching the action of the H₂ receptor inhibitors over the left ventricular function and over the exercise ability, in a group of 15 healthy men, at the average age of 26 ± 3 years old. The authors concluded that there were no meaningful differences in the ventricular function and in the aerobic exercise ability, between the tests made with medicines when compared to the placebo. It is important to stress that in none of these mentioned studies the main purpose was related to the analysis of the heart rate frequency, and that fact differs our experiment from the others.

The study presents limitations, because it was made on normal individuals, with proper body mass index and good physical performance, according to the American Heart Association (VO₂ max. of around 35 ml/Kg/min, for the average age of 43), without dyspepsia, obesity or any other co-morbid (like, for instance, cardiovascular disease or diabetes mellitus). On these people, the physiological adjustment mechanism, in the presence of an autonomic system without abnormality, could make the evaluation of minor effects over the block of the histamine action harder. New studies will be needed for proper enlightments, like, for instance, the effect over individuals with diabetes mellitus, in which there is a meaningful coincidence between autonomic system disorders and the presence of *Helicobacter pylori*²⁹.

In conclusion, the administration of cimetidine for seven days does not change the chronotropic response to exercise testing.

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