

Comparative Evaluation of the Hemodynamic Effects of Oral Cimetidine, Ranitidine, and Famotidine as Determined by Echocardiography

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Study Objective. To evaluate the influence of cimetidine, ranitidine, famotidine, and placebo on cardiac performance as determined by echocardiography.

Design. Randomized, four-way crossover trial.

Setting. Echocardiography laboratory at a university hospital.

Participants. Twelve healthy volunteers.

Interventions. Volunteers received oral treatment with placebo, cimetidine 800 mg, ranitidine 300 mg, or famotidine 40 mg once/day for 7 days.

Measurements and Main Results. On the seventh day of each study phase, 2 hours after administration of the final dose, each subject underwent cardiac echocardiography and Doppler flow studies. No significant differences were detected in ejection fraction, peak flow velocity, or percentage fractional shortening among the treatment phases. A large degree of variability in ejection fraction was observed, with some subjects experiencing marked decreases.

Conclusion. The histamine-2 (H₂)-receptor antagonists had no effect on the hemodynamic variables as determined by echocardiography. The variability in the hemodynamic response may in part explain the conflicting results reported in the literature. It also raises the question as to whether certain individuals are more sensitive to the potential cardiac effects of H₂-receptor antagonists.

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Histamine-2 (H₂)-receptor antagonists are used to treat a variety of acid-peptic disorders, including

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gastric ulcer, duodenal ulcer, Zollinger-Ellison syndrome, and gastroesophageal reflux disease. Although these agents inhibit gastric acid secretion, they may also antagonize the effects of histamine on the myocardium.¹⁻³ Stimulation of H₁ and H₂ receptors on the myocardium results in a fine balance of inotropic effects, with H₁ receptors mediating a negative effect and H₂ receptors eliciting a positive effect.^{2,3} Under normal conditions, the positive inotropic effect mediated by the H₂ receptor usually predominates over the negative inotropism caused by stimulation of the H₁ receptors.³ In vitro studies indicate that cimetidine and ranitidine may inhibit histamine's positive inotropic effects, resulting in a negative inotropic effect on the myocardium.²⁻⁴

Studies assessing the impact of H₂-receptor antagonists on cardiac performance in humans have produced conflicting results.⁵⁻¹² In some

studies oral famotidine, but not cimetidine or ranitidine, exerted a negative inotropic effect on cardiac performance.⁵⁻⁷ Other investigators, however, were unable to substantiate these results,⁸⁻¹² and in fact one group demonstrated a positive inotropic effect with oral ranitidine.¹² The reasons for these discrepancies are not clear, but they may be due to the techniques used to determine cardiac function, the agents studied, the population examined, the route of administration, or the dosage of the H₂-receptor antagonist.

The purpose of this study was to determine the effects of the three most commonly prescribed H₂ antagonists, cimetidine, famotidine, and ranitidine, on left ventricular performance as assessed by a standard technique, echocardiography, which derives its measurements by direct visualization of the heart. Unlike previous studies,⁵⁻¹² this one employed once-daily dosing of each drug and assessed cardiac performance at steady state (day 7) using accepted echocardiographic techniques.

Methods

Subjects

The study was approved by the hospital's institutional review board. Twelve volunteers (6 men, 6 women) were enrolled in this randomized, single-blind, four-way, crossover trial and provided written informed consent. They were in good health as determined by medical history, physical examination, electrocardiogram, complete blood count, urine pregnancy test (if applicable), and serum chemistries. Persons with a history of renal, hepatic, or cardiovascular disease were excluded from participation, as were women who were pregnant or lactating. Also excluded were those who had received any drug known to inhibit or induce drug metabolism within 30 days of study entry.

All subjects were nonsmokers and within 20% of their ideal body weight (Metropolitan Life Insurance Co., 1983). They were drug free, including over-the-counter agents, 7 days before study initiation and throughout the study period. They were requested to refrain from xanthine-containing foods and beverages for 24 hours before each assessment of cardiac function.

Study Design

In a randomized, crossover manner, each subject received oral doses of cimetidine 800 mg, ranitidine 300 mg, famotidine 40 mg, or placebo (lactose tablet) once/day between 3 and 5 P.M. every day for 7 days. A 1-week washout period

separated each of the treatment phases. Compliance with the drug regimens was assessed by questioning the participants and by tablet counts. In addition, subjects were queried during each study phase as to whether or not they experienced any adverse events.

On the seventh day of each study phase, after a 6-hour fast, subjects returned to the hospital where they took the study drug with 240 ml of water and then underwent noninvasive cardiac studies.

Noninvasive Assessment of Cardiac Function

Blood pressure and heart rate were measured in triplicate using automated blood pressure devices before and 30, 60, and 90 minutes after drug administration. Two hours after drug administration, each subject underwent two-dimensional echocardiography and Doppler flow studies while lying in a left lateral position. These were performed by a technician who was blinded to the treatment schedule.

To facilitate the study, the studies were performed using three-phase array echocardiographic systems, the Interspec/Vingmed Color Flow Mapping System 700 (ATL/Interspec Cardiology, Ambler, PA), the Ultramark 9 Ultrasound System (Advanced Technology Laboratories, Bothell, WA), and the Acuson 128XP/E Computed Sonography System (Acuson Corp., Mountain View, CA). Three echocardiographic systems facilitated echocardiographic assessments of all 12 volunteers on a single study day. Although there were three separate echocardiographic systems and three independent technicians, the device and technician for a given patient remained constant throughout the study (e.g., different systems were used for different subjects). The echocardiograms were recorded onto videotape and read by two technicians who were blinded to the treatment schedule.

Standard two-dimensional echocardiographic measurements and Doppler flow velocities were obtained according to the guidelines prepared by the American Society of Echocardiography as outlined briefly.¹³ Simpson's rule was used to obtain left ventricular volume and ejection fraction. Specifically, the endocardial surface of the left ventricle was first traced at end diastole (upstroke of the R wave) to obtain the end-diastolic volume. The end-systolic volume was obtained by tracing the endocardial surface of the smallest left ventricular cavity. Left ventricular ejection fraction (EF) was estimated by subtracting the left ventricular volumes during systole (ESV) from left

ventricular volumes during diastole (EDV) divided by the left ventricular volume during diastole (EDV) ($EF = [EDV - ESV]/EDV$).¹⁴ The percentage fractional shortening (FS), which also measures left ventricular function (contractility), was calculated as end-diastolic diameter (EDD) minus end-systolic diameter (ESD) divided by the product of end-diastolic diameter (EDD) multiplied by 100 ($FS = [EDD - ESD]/[EDD * 100]$). Ascending aortic blood flow velocity (peak flow velocity) was obtained by Doppler measurements. Peak flow velocities were measured from the leading edge of the high-frequency opening sound to the leading edge of the closing sound of the aortic valve cusps.

Interobserver variability in EF was evaluated for each of the 48 echocardiograms that were read in duplicate (data set 1). The average interobserver coefficient of variation was $11.16 \pm 7.79\%$; however, the coefficient of variation ranged from 0–27.1% for the data pairs.

Since inspection of the EF data revealed that in 33% of the measurements the coefficient of variation exceeded 15%, the videotapes of these echocardiograms were reread by two technicians who were unaware of the treatment schedule. Thus, these echocardiograms had four readings. Subsequently, to minimize the variance, the high and low observations were discarded and the average was obtained for the remaining two readings (data set 2). The average interobserver coefficient of variation for data set 2 was $6.57 \pm 4.20\%$. In addition, due to the unexpected variability observed at our institution, all videotapes were evaluated in a blinded manner by an independent laboratory (data set 3).

For purposes of this analysis the parasternal short axis view of the left ventricle at or near the papillary muscle tips was used to obtain end-diastolic and end-systolic endocardial contours, and an apical four-chamber view to measure end-systolic and end-diastolic long axes. The bullet formula for measuring left ventricular volume was employed to obtain the volumes for the EF calculations. Interobserver variability at the independent laboratory yielded a coefficient of correlation of 0.78.

Statistical Analyses

Statistical analysis of heart rate and blood pressure among the four treatments over time was performed using a repeated measures analysis of variance. Comparisons among the four regimens for EF, percentage fractional shortening, and peak flow velocity obtained from data set 1 were

performed by three-way analysis of variance with treatment, subject, and period being the class variables. Differences among the treatment regimens in data sets 2 and 3 were evaluated by three-way analysis of variance. To evaluate whether there was an overall effect of H₂-receptor antagonists versus placebo on cardiac performance (EF, percentage fractional shortening, peak flow velocity), for each of the three data sets the mean effect obtained during treatment with the H₂-receptor antagonists (e.g., mean effect of the treatments) was compared with placebo using paired Student's *t* tests. A paired Student's *t* test was used to compare the ejection fractions determined in our laboratory with those obtained by the independent laboratory. A *p* value less than 0.05 was set as the critical level for statistical significance. The reported data are represented as mean and standard deviation unless otherwise specified.

Results

All 12 subjects completed all four phases of the investigation without any complications or adverse reactions. They were compliant with study drugs and procedures. They ranged in age from 20–43 years (27.3 ± 6.4 yrs), with a weight of 62.8 ± 13.2 kg (range 45–94 kg) and a height of 66.5 ± 4.5 inches.

Minor fluctuations in heart rate and blood pressure occurred across the 2-hour study; however, no significant differences were observed in systolic or diastolic blood pressure or heart rate among the treatment phases immediately before echocardiography (e.g., at 1.5 or 2.0 hrs).

Data Set 1

According to the initial data analysis, the mean EFs were $58.6 \pm 8.6\%$, $57.3 \pm 5.4\%$, $55.9 \pm 5.8\%$, and $55.1 \pm 6.3\%$ after placebo, cimetidine, ranitidine, and famotidine, respectively ($p > 0.05$). A large degree of variability in EF was observed among the individual subjects (Figure 1). Since one subject appeared to be an outlier, the data were reanalyzed without this subject's data; however this did not significantly alter the results (e.g., no significant differences among treatments). Therefore, the following are results from all 12 subjects.

Differences in EF during the placebo phase versus the treatment phases (EF placebo - EF treatment) for the individual subjects ranged from -12 to 16%, -12.5 to 8%, and -14.5 to 11% during cimetidine, ranitidine, and famotidine, respectively.

Table 1. Ejection Fraction (%)

Treatment	Data Set 1 ^{a, b}	Data Set 2 ^{a, c}	Data Set 3 ^{a, d}
Placebo	58.6 ± 8.6	59.9 ± 6.2	59.1 ± 5.9
Cimetidine	57.3 ± 5.4	57.4 ± 5.3	61.0 ± 3.1
Ranitidine	55.9 ± 5.8	56.4 ± 5.2	60.3 ± 4.1
Famotidine	55.1 ± 6.3	55.6 ± 6.2	60.9 ± 6.2

^aNo significant differences were detected among the treatment phases.

^bOriginal data set.

^cRevised data based on reevaluating the echocardiograms. The high and the low figures were subsequently discarded and the average was obtained for the remaining two readings.

^dResults based on echocardiograms being read by an independent blinded laboratory.

The mean differences during the placebo phase versus those during cimetidine, ranitidine, and famotidine phases were $1.29 \pm 6.53\%$, $-2.75 \pm 8.91\%$, and $3.54 \pm 8.76\%$, respectively. Decreases in EF compared with placebo occurred in nine, seven, and seven subjects after the three agents, respectively. The mean peak flow velocity was 1.11 ± 0.17 , 1.06 ± 0.16 , 1.10 ± 0.18 , and 1.07 ± 0.16 cm/second after placebo, cimetidine, ranitidine, and famotidine, respectively ($p > 0.05$). The mean percentages fractional shortening were 35.3 ± 6.4 , 34.0 ± 7.3 ,

34.1 ± 2.9 , and 33.6 ± 3.7 , respectively ($p > 0.05$).

Data Sets 2 and 3

Due to the large degree of interobserver variability, the echocardiographic videotapes were reevaluated both at our institution (data set 2) and by an independent laboratory (data set 3). Analyses of the EFs derived from the two data sets revealed no significant differences among the treatment regimens ($p > 0.05$) (Table 1). Using data set 2, decreases in EF compared with placebo were observed in eight, eight, and nine subjects after cimetidine, ranitidine, and famotidine, respectively. In contrast, with data set 3, decreases occurred in only five, three, and two subjects after cimetidine, ranitidine, and famotidine, respectively. Although, the EFs reported by the independent laboratory tended to be higher than those reported by our laboratory, the difference between them was not significant.

Independent of the data set examined, no significant differences were detected between the overall effect of H₂-receptor antagonists (e.g., mean effect of the 3 treatments) and placebo.

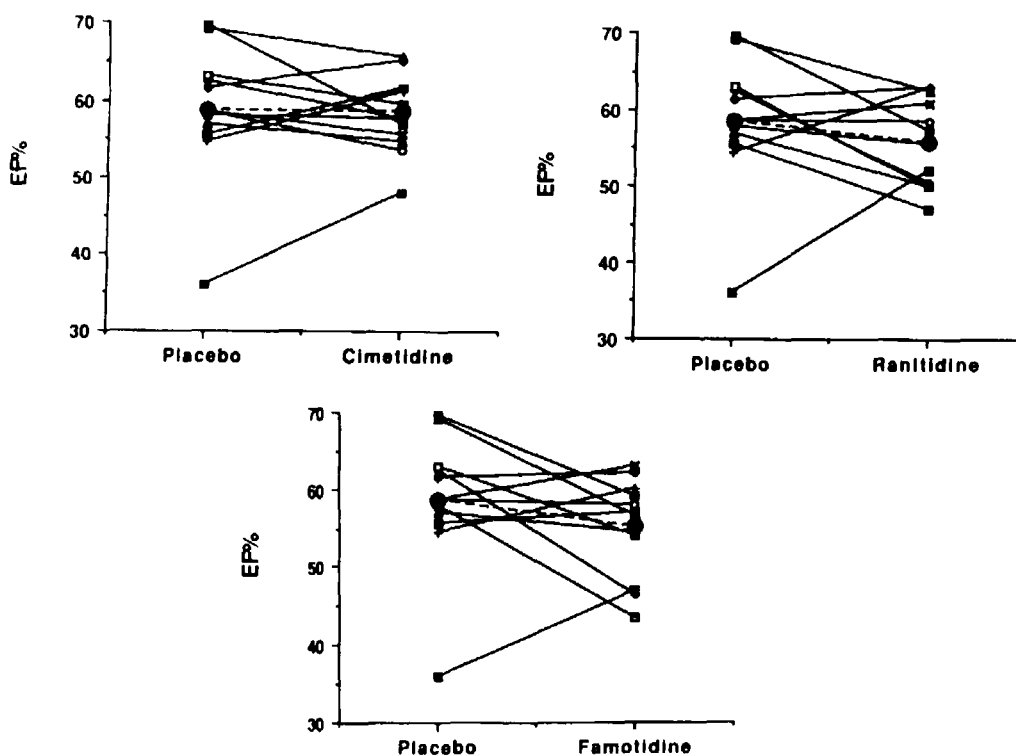


Figure 1. Ejection fraction (EF%) for each subject during each treatment phase compared with placebo. The symbols refer to individual patients; ● = mean.

Discussion

The H₂-receptor antagonists are generally regarded as safe, as evidenced by their low frequency of serious adverse reactions.¹⁵ Nevertheless, concern exists regarding the potential for these agents to cause undesirable cardiovascular side effects. In vitro and animal studies suggest that they may oppose the action of histamine on the myocardium, resulting in negative inotropic action.²⁻⁴ In 1989, oral famotidine, but not cimetidine or ranitidine, was reported to have negative inotropic effects in healthy volunteers.⁵ Although these investigators confirmed their findings in two subsequent studies,^{6,7} independent laboratories failed to support the results.⁸⁻¹² Potential reasons for the conflicting data include differences in the methods of assessing cardiac performance, agents studied, dosage regimens, duration of drug therapy, time of cardiac assessment in relationship to drug administration, and/or populations studied. Our study intentionally employed a design similar to that used by Kirch et al,⁵⁻⁷ except that cardiac performance was assessed by echocardiography rather than impedance cardiography.

Our results indicate that 7 days of therapy with cimetidine 800 mg, ranitidine 300 mg, or famotidine 40 mg is not associated with any significant alteration in cardiac performance in healthy individuals as determined by two-dimensional echocardiography and Doppler flow studies. Using duplex ultrasonography⁸ and exercise echocardiography,⁹ other investigators similarly demonstrated that famotidine 40 mg/day had no deleterious effect on cardiac function.

The apparent most likely explanation for the disparate results between these investigations^{8,9} and the others⁵⁻⁷ appears to be the methods by which cardiac function was assessed. Kirch et al⁵⁻⁷ used impedance cardiography, which is based on impedance changes in the thorax that result from pulsatile flow in the thoracic aorta.¹⁶ Although impedance cardiography correlates with invasive measurements of cardiac output, it correlates poorly with radionuclide ventriculography.^{17,18} Echocardiography is commonly performed to evaluate myocardial function in the United States. The ability to identify changes in myocardial function secondary to drug effects with both two-dimensional echocardiography and Doppler echocardiography is well established.^{14,19}

It is important to point out that we observed a large degree of variability in cardiac response to the three agents. This may be explained in part by the

higher than expected interobserver variability in the assessment of EF. The mean interobserver coefficient of variation in ejection fraction was 11.16% and is higher than that normally reported for our laboratory or for other laboratories.¹⁴ It is probably due to the range restriction in our EFs. In contrast to the wide range normally seen by an echocardiography laboratory, all of our EFs were essentially within normal limits.

In addition to interobserver variability, one may question whether certain individuals may be more sensitive than others to the cardiac effects of these agents. Decreases in EF occurred during each of the treatment phases. The maximum decreases were -12%, -12.5%, and -14.5% for cimetidine, ranitidine, and famotidine, respectively. Since our study was conducted in healthy volunteers, it is difficult to ascertain whether these changes would represent clinically significant alterations in cardiac function in patients with heart failure.

Alternatively, the variability may be related in part to the range of doses (mg/kg) of H₂ antagonists. Although they were therapeutic doses, based on subjects' weight, there is a 2-fold variation in them when normalized to milligrams/kilogram. However, similar doses of famotidine exerted a negative inotropic effect on cardiac performance in healthy volunteers.^{5,6}

Another explanation for the changes may relate to the variability in the interpretation of the echocardiograms rather than changes related to a specific H₂ antagonist. This can be indirectly inferred by comparing the echocardiography results from data sets 1 and 3. The EFs measured by the independent laboratory tended to be higher than those in our laboratory, which can be explained by differences in how the EFs were calculated. Those calculated by the bullet method tend to be higher than those determined using Simpson's rule.¹³ Basing assessment strictly on the results from data set 1, one might conclude that a slight decrease in EF during therapy might occur with these three drugs ($p > 0.05$). Conversely, basing conclusions strictly on the results from data set 3, one might conclude a slight increase in EF is associated with the agents ($p > 0.05$). Clearly, the magnitude of change in each case is extremely small, is highly dependent on the method used to calculate the EF, and was not statistically significant regardless of data set employed. This may suggest that such changes are the result of the variability in the methodology and not the result of a specific drug.

With the variance observed, this study had a power of 80% to detect a 10% difference in EF

means among the treatments. The mean differences actually seen during the three treatment phases were less than 4%, and thus a type II error may have occurred. However, it is important to recognize that such small changes in EF (< 4%) are probably of little or no clinical significance.

Based on previous conflicting results regarding the impact of H₂ antagonists on cardiac performance in healthy volunteers, we believed that it was important to rectify the discrepancy and evaluate this population. However, given the results of our study in conjunction with others,⁸⁻¹¹ we now firmly believe that cimetidine, ranitidine, and famotidine do not significantly impair cardiac performance in healthy volunteers as determined by echocardiography. Our results cannot be directly extrapolated to critically ill patients or those with a history of heart disease, or to intravenous H₂ antagonists. Although, we believe that our variability in response is secondary to inherent variability in methodology, we cannot rule out the possibility that certain subjects may be at greater risk for cardiovascular adverse effects with these drugs. Therefore, it may be prudent to assess the potential impact of these H₂-receptor antagonists on cardiac performance in patients who are at risk for suffering deleterious consequences from small changes in EF. Specifically, those with heart failure may theoretically be more sensitive to drug-induced changes in cardiac function and may also not be able to compensate for such changes.

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