Title: THE HEMODYNAMIC SEQUELAE OF INTRAVENOUS CIMETIDINE VS. RANITIDINE IN ICU PATIENTS: A DOUBLE-BLIND, PROSPECTIVE CROSSOVER STUDY

Authors: DB Coursin, M.D., C Farin-Rusk, R.N., SR Springman, M.D., SL Goelzer, M.D.

Affiliation: Departments of Anesthesiology and Internal Medicine, University of Wisconsin Clinical Science Center, Madison, Wisconsin 53792

INTRODUCTION: Cimetidine or ranitidine, both histamine H2 antagonists, are commonly used to decrease gastric volume, increase gastric pH, and decrease the incidence of stress ulceration in the critically ill. The present study was designed to compare the hemodynamic effects of cimetidine vs. ranitidine in a crossover study in hemodynamically stable ICU patients to eliminate the question of baseline variability in hemodynamic parameters and patient management that may have existed between previous studies with these drugs (1,2).

METHODS: Twenty critically ill adult patients were studied. Twelve male and eight females patients ranging in age from 22-86 with a mean of 54 were included. Individuals studied had indwelling peripheral arterial and pulmonary arterial catheters and were receiving either cimetidine 300mg i.v. q 8 hours or ranitidine 50mg i.v. q 12 hours as ordered by their physicians. To be eligible patients had to be considered hemodynamically stable off vasopressors and inotropes for at least 12 hours prior to evaluation. The study was approved by the institutional Human Subjects Committee. The study was performed prospectively in a double-blind manner, with crossover. Patients received both 20cc of normal saline (NS) (control) and ranitidine 50mg in 20 cc NS or cimetidine 300mg in 20cc NS one hour apart. This sequence was repeated twelve hours later with the other drug and NS again given randomly and separated by one hour. Baseline hemodynamic data including heart rate(HR), mean arterial pressure(MAP), pulmonary artery pressure(PAP), pulmonary capillary wedge pressure(PCWP), and cardiac output(Q) via thermodilution were obtained. Systemic vascular resistance(SVR) was calculated. Cimetidine, ranitidine, or normal saline was infused over two minutes at the completion of baseline measurements. The above parameters were serially measured at 1,2,3,5,7, and 12 minutes after baseline data was obtained. All data was analyzed using a repeated measures of analysis of variance model to compare hemodynamic variables. A minimum alpha level of <0.05 was considered significant. Clinical significance was defined as a change of ten percent or greater when compared to baseline.

RESULTS: As expected, the infusion of normal saline did not produce a significant change in comparison to baseline in any of the variables measured. The data after infusion of cimetidine is summarized in table 1. The major area of interest is the significant decrease in MAP (range of 1-40 mm Hg) at 1,2,and 3 minutes that averaged 14% at two minutes with a $p<0.0001$ compared to control. The decrease was not associated with severe sequelae or ECG changes and resolved spontaneously or responded promptly to fluid infusion or change in patient position. Calculated systemic vascular resistance was decreased at 3 and 5 minutes with no significant change in cardiac output. Infusion of ranitidine resulted in no clinically significant hemodynamic alterations. Table 2 summarizes the effects of cimetidine vs. ranitidine on MAP. These are remarkable for the significant difference in MAP at 1,2, and 3 minutes with $p<0.0001$.

DISCUSSION: This is the first study to compare the hemodynamic effects of iv infusions of cimetidine and ranitidine in critically ill patients. The age, distribution of patients, and change in hemodynamic variables after intravenous cimetidine in patients in the present study are similar to the changes reported by Iberti, et al. (1). The hemodynamic effects were again noted to be rapid in onset. Although they did not cause major clinical repercussions, it is important to remember that this study was performed in a preselected critically ill patient group that was hemodynamically stable. We can only speculate about the potential circulatory effects of cimetidine bolus infusion in a patient(s) that had a more tenuous clinical status. Proposed mechanisms of cimetidine induced hypotension include direct myocardial depression versus peripheral vasodilatation. Our study supported a mechanism of peripheral vasodilatation. Although SVR cannot be calculated during the initial two minutes of the study secondary to the drug infusion, it was still significantly decreased even at the 3 and 5 minute time points. The difference between the hemodynamic effects of cimetidine and ranitidine may be related to their structures. In conclusion, bolus intravenous cimetidine, as administered in this study, has significant hemodynamic effect while ranitidine does not. If relatively rapid bolus administrations of H2 blockers are to be used, ranitidine appears to be the more favorable of the two drugs weighing carefully the cost, drug interactions and side effects of these agents.

Table 1 Hemodynamic data for cimetidine* (mean±SD)

Variable (Units)	Baseline	1 min	2 min	3 min	5 min	7 min
HR (beats/min)	100±13	101±14	103±14‡	102±13‡	101±14	100±14
MAP (mmHg)	88±12	80±14†	76±12†	81±12†	85±12‡	88±12
PCWP (mmHg)	12±5	12±5	11±5	12±5	12±5	12±5
Cardiac Output (L/min)	7.42±2.4	•	•	7.46±2.3	7.44±2.0	7.62±2.3
SVR (dyne·sec/cm5)	933±375	•	•	842±347‡	874±362‡	890±350

†p<0.001 ‡p<0.05
*The drug was infused during the first 2 minutes of the study

Table 2
% Change in MAP - Comparison of Ranitidine and Cimetidine (mean ± SD)

Time	1 min	2 min	3 min	5 min	7 min
Ranitidine	-4 ±5	-4 ±5	-1 ±7	+1 ±7	+2 ±10
Cimetidine	-10 ±11	-14 ±10	-8 ±6	-4 ±4	-1 ±5
p value	0.0001	0.0001	0.0001	0.003	NS

References:

1. Iberti TJ, et al: The hemodynamic effects of intravenous cimetidine in intensive care unit patients: A double-blind, prospective crossover study. Anesthesiology 64:87-90, 1986.
2. Golezer SL, et al. Ranitidine produces minimal hemodynamic depression in stable intensive care units patients: A double- blind prospective study. Crit Care Med 16:8-10, 1988.