Anesthesiology
64:87–89, 1986

The Hemodynamic Effects of Intravenous Cimetidine in Intensive Care Unit Patients: A Double-blind, Prospective Study

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The histamine H2 receptor antagonist cimetidine frequently is used in the intensive care unit (ICU) patient to reduce the acidity of gastric acid secretions. Adverse reactions often are reported, but the overall incidence and severity of reactions is considered to be low.[1,2]

Cardiovascular toxicity associated with iv cimetidine is rarely reported. A study of normal human volunteers receiving 200 mg iv cimetidine over 1 min[3] and a study of ventilated ICU patients who were receiving iv bolus cimetidine[4] both demonstrated no significant hemodynamic changes. In a recent study of patients receiving iv cimetidine as a rapid bolus (200 mg over 5–10 s), however, a significant decrease in blood pressure was noted.[5] Several case reports have also suggested the possibility of cimetidine-related cardiovascular toxicity.[6–8]

The manufacturers of cimetidine (Smith, Kline, and French Laboratories, Philadelphia, Pennsylvania), citing these rare reports of hypotension associated with rapid bolus iv administration, recommend that the drug be given by infusion over a period of not less than 2 min. Despite this, routine observation of ICU patients receiving cimetidine demonstrated the possibility that cimetidine might have adverse hemodynamic effects. We therefore undertook a double-blinded, prospective study of ICU patients receiving cimetidine to determine the hemodynamic effects of this agent.

METHODS

Patients. Twenty-four postoperative ICU patients, 13 female patients and 11 male patients, were studied. The age range was 54–89 yr, with a mean of 74 yr. To be eligible for the study, the patient was required to have an arterial line and pulmonary artery catheter in place and to be receiving 300 mg iv cimetidine as ordered by the patient's physician. No patients had catheters inserted or cimetidine instituted solely for the purpose of the study. All patients were hemodynamically stable for 12 h before the study. The study was approved by the Mount Sinai Research Review Committee, and consent was obtained from both the patient and the attending physician.

Study Design. The study was double blinded. Syringes labeled A and B contained either 300 mg of cimetidine diluted in 20 ml of normal saline, or 20 ml of saline alone. After baseline data were recorded, the patient received the contents of syringe A infused over 2 min. Hemodynamic measurements including heart rate (HR), mean arterial pressure (MAP), and mean pulmonary artery pressure (MPAP) were continuously recorded using a six-channel recorder, and pulmonary artery wedge pressures (WP) and cardiac outputs (CO) using the thermodilution technique were obtained at 1, 3, 5, and 10 min after completion of the infusion. Systemic vascular resistance (SVR) was calculated using the formula $SVR = MAP - CVP/CO \times 80$.

One hour after the injection of the contents of syringe A, the contents of syringe B were administered and the above protocol repeated.

Statistical Analysis. We employed nonparametric statistical analysis, and each treatment measurement was compared with baseline control values. The Wilcoxon sign rank test was computed for each of these comparisons, and a two-tailed test of significance was assumed throughout the analyses at a minimum alpha level of 0.05.

RESULTS

Normal saline infusion (control) did not exhibit a significant change in any hemodynamic variable with respect to baseline over the 12-min observation period.

The hemodynamic effects of cimetidine are summarized in table 1. The most significant effect was upon MAP. Twenty-two of the 24 patients (92%) demonstrated a decrease in MAP of greater than 10 mmHg. MAP was maximally decreased immediately following the infusion ($P < 0.0001$) and returned to baseline ($P > 0.05$) by the

Received from the Departments of Surgery and Anesthesiology, Mount Sinai Medical Center, City University of New York, One Gustave L. Levy Place, New York, New York 10029. Accepted for publication August 2, 1985. Presented at the Fourteenth Annual Symposium of the Society of Critical Care Meeting, Chicago, Illinois, May 21–25, 1985.

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Key Words: Histamine: cimetidine. Pharmacology: cimetidine.

TABLE 1. Hemodynamic Data—Cimetidine

	Baseline	1 Min	2 Min	3 Min	5 Min	7 Min	12 Min
HR	95.8 ± 13	97.3 ± 14*	100.1 ± 16†	99.5 ± 16*	100.0 ± 16*	97.9 ± 16	98.3 ± 16
MAP	100.7 ± 23	88.1 ± 23†	78.6 ± 24‡	82.4 ± 24‡	91.3 ± 25†	95.8 ± 25*	99.0 ± 16
MPAP	23.7 ± 10	23.1 ± 9	21.7 ± 9†	22.2 ± 9*	23.5 ± 9	24.7 ± 9	25.6 ± 10*
WP	12.4 ± 8	11.3 ± 7*	10.3 ± 7†	10.6 ± 6*	11.4 ± 7	12.0 ± 7	12.9 ± 8
CO	5.8 ± 2	—	—	5.9 ± 2	6.2 ± 2*	6.3 ± 2†	6.3 ± 2*
SVR	1,412.0 ± 541	—	—	1082.0 ± 422†	1190.0 ± 479†	1,221.0 ± 487‡	1,263.0 ± 522†

HR = heart rate; MAP = mean arterial pressure (mmHg); MPAP = mean pulmonary artery pressure (mmHg); WP = pulmonary capillary wedge pressure (mmHg); CO = cardiac output (l/min); SVR = systemic vascular resistance (dyn · s · cm $^{-5}$).

* Values are significantly ($P < 0.05$) different from baseline.
† Values are significantly ($P < 0.005$) different from baseline.
‡ Values are significantly ($P < 0.0001$) different from baseline.

final measurement (fig. 1). SVR was significantly decreased for the duration of the study. HR was increased for the first 5 min, returning to baseline by 7 min.

No patients experienced symptoms as a result of the transient decrease in MAP. One patient had a decrease in MAP from 80 to 36 mmHg and required volume therapy to restore MAP. There was no evidence of ECG changes in any patient after the study was completed.

DISCUSSION

This study demonstrates that the administration of iv cimetidine is followed by a significant decrease in MAP in most ICU patients. Significant vasodilation, as evidenced by a decreased SVR, accounts for the decrease in MAP.

Previous investigations that have studied the effects of iv cimetidine in healthy volunteers have not demonstrated significant hemodynamic changes.[3,9] In a study by Mangiameli *et al.*,** 25 healthy male medical students who were given iv cimetidine had cardiac function evaluated by noninvasive studies. There were no changes noted in the ejection fraction or blood pressure. Results of similar studies done by the manufacturer of cimetidine have shown that cimetidine has an insignificant effect upon cardiac function in healthy patients.[3,9]

By contrast, the present study demonstrated a significant decrease in blood pressure and vascular resistance associated with the iv infusion of cimetidine in ICU patients. These effects occurred rapidly within the first 3 min following the administration of the drug. In all patients the effects were transient, with the maximal effects seen in the first 2 min following the infusion. This finding may explain why a previous study of ICU patients receiving iv cimetidine demonstrated no significant hemodynamic changes.[10] In that study the first measurements were made 5 min after the infusion was completed and therefore may not have recorded the early hemodynamic effects observed in our study. Our results are consistent with the findings of Heining *et al.*,[5] who investigated the effects of cimetidine given as a rapid bolus over 5–10 s to patients on coronary artery bypass. Arterial pressure was significantly decreased ($P < 0.001$) and the maximal effect was observed at 1.5 min after the infusion.

Our results demonstrate only slight changes in other hemodynamic values. As in a previous study in healthy volunteers,[9] CO and HR were modestly increased by cimetidine. The sharp decrease in MAP and SVR did not produce the dramatic increases in CO and HR that usually accompany acute vasodilation. There have been reports of cimetidine-induced bradycardia,[11,12] and cimetidine may act to prevent a marked increase in HR in ICU patients. Studies of isolated human heart muscle have demonstrated the presence of H2 receptors, which are responsible for a positive inotropic and chronotropic response when stimulated by histamine, and that these hemodynamic changes can be partially antagonized by cimetidine.[13]

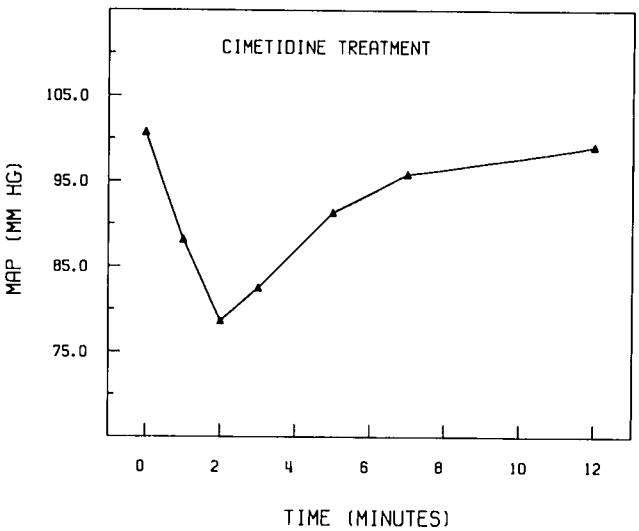

FIG. 1. Effects of iv bolus cimetidine upon mean arterial pressure (MAP). Refer to Table 1 for statistical significance and variability.

** Mangiameli A, Condorelli G, Dato A, Monaco S: Cardiovascular response to the acute intravenous administration of the H2-receptor antagonists ranitidine and cimetidine. Current Therapeutic Research 36:13–17, 1984.

Hemodynamic changes as noted in our study could potentially produce deleterious effects in the critically ill. Although the present study group had no obvious adverse effects from the decrease in SVR and MAP, large fluctuations in these values could be dangerous in select groups of patients, such as those with coronary artery disease, carotid stenosis, or renal vascular disease. Further, hemodynamically unstable patients (who were excluded from this study) might be at high risk for complications.[2,5,6-8] It should be noted that the present study involved an elderly population and that the changes observed might be age related.

In summary, we have shown that iv cimetidine given as a slow infusion over 2 min produces a transient but significant decrease in MAP. The mechanism for this effect appears to be direct vasodilation. Cimetidine administration should be included in the differential diagnosis of unexplained hypotension in the ICU or anesthetized patient. Further studies are warranted to identify which patients are at greatest risk for such a reaction and the pharmacologic mechanism of action.

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Anesthesiology
64:89–90

An Unusual Cause of Patient Movement during Anesthesia

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Surgery involving the use of the microscope requires that the patient remain motionless. We describe an episode of intraoperative patient movement resulting from unusual cause.

Report of a Case

An 18-year-old man weighing 65 kg was to have emergency surgical removal of a bullet fragment that had penetrated the cornea of his right eye and lodged behind the lens. The patient was in excellent health; was taking no medications; had no history of any significant disease, allergies, or prior operations; and had no family history of anesthetic difficulties. His arterial blood pressure was 120/80 mmHg with a heart rate of 88 beats/min, and no premedication was given.

After breathing 100% oxygen, thiamylal 350 mg and pancuronium 6 mg were given iv, after which his trachea was intubated without evidence of moving or coughing. Anesthesia was maintained with 40% oxygen and 60% nitrous oxide, to which 2% enflurane was added. Ventilation was controlled with a tidal volume of 700 ml and a rate of 12 times per minute. The rectal temperature remained at 36.4° C, although arterial blood pressure did not change but heart rate gradually increased to 120 beats/min over the next hour. At this point, the surgeon noted that the patient appeared to be bucking. Close observation revealed that the patient was in fact moving in a reciprocating manner in a cephalad–caudad direction at a rate of approximately 2.0 Hz. The movement was very slight and probably would not have been noticed if the microscope had not been in use at the time. Although the peripheral nerve stimulator indicated about a 75% depression in twitch height, 6 mg of *d*-tubocurarine was administered with resultant elimination of muscular response to electrical stimulation, but the patient continued to move.

It was then noted that the patient's heart rate was exactly the same rate at which the movements were occurring. When propranolol 0.5 mg was administered iv[1] for the purpose of decreasing heart rate, it decreased to 110 beats/min and the movements stopped. The patient remained immobile for the remaining 1½ h of the operation. When the enflurane and nitrous oxide were discontinued and the patient

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Received from the Department of Anesthesiology, School of Medicine, State University of New York at Buffalo, 462 Grider Street, Buffalo, New York 14215. Accepted for publication August 6, 1985.

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Key words: Complications: movement. Surgery: ophthalmology.