

and readily accepted an inhalation induction of anesthesia. The other patients (60%), however, became agitated during induction. Patients in the control group who were agitated prior to the instillation of nose drops remained agitated during induction, but otherwise no pattern predicting which children were likely to be agitated during induction was apparent. Some children were temporarily distressed by the instillation of either the midazolam or normal saline, but all patients rapidly settled down again in the presence of their parents.

There was no evidence of delayed recovery in those patients receiving midazolam. Because narcotic usage and duration of anesthesia were not controlled, further studies will be required to determine more precisely the degree of postoperative sedation following short procedures.

Midazolam administered by intramuscular and rectal routes is an effective sedative in pediatric patients. Doses of 0.08–0.5 mg/kg produce adequate sedation within 30 min by the intramuscular route, but the onset times were not recorded.^{3–5} Following rectal administration 0.35 mg/kg, the apparent optimal dose, produces a demonstrable drug effect by 10 min, but reliable sedation requires 20–30 min.⁶

Intranasal administration of sufentanil produces anxiety and mild euphoria with similar onset time to midazolam, but there is some concern about decreased ventilatory compliance during induction of anesthesia, which may be exacerbated by the use of nitrous oxide.¹⁰ This was not seen with intranasal midazolam.

This present study demonstrates that intranasal midazolam produces anxiety and sedation in preschool

children with a rapid onset similar to that previously described for the same drug using the rectal route, and for a different drug (sufentanil) using the intranasal route. No additional benefit was seen from the higher dosage; thus, we recommend using the lower dose of 0.2 mg/kg midazolam.

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

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Prophylaxis against the development of stress ulcers and subsequent gastrointestinal bleeding is a major therapeutic challenge in intensive care medicine. Cimetidine

or ranitidine, both histamine H₂ antagonists, are commonly used, in an intravenous bolus form, to decrease gastric volume, increase gastric pH, and decrease the incidence of stress ulceration.^{1,2} The intravenous bolus injection of the imidazole, cimetidine, to stable intensive care unit (ICU) patients has been shown to cause a transient but significant reduction of mean arterial blood pressure (MAP) secondary to peripheral vasodilatation without a compensatory increase in cardiac output.³ More than 90% of the patients studied had a 10 mmHg decrease in MAP within 2 min of injection of cimetidine. In a similar study in stable ICU patients, we have recently shown

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TABLE 1. Hemodynamic Data after Cimetidine Administration* (Mean \pm SD)

Variable (Units)	Baseline	1 Min	2 Min	3 Min	5 Min	7 Min	12 Min
HR (beats/min)	100 \pm 13	101 \pm 14	103 \pm 14†	102 \pm 13†	101 \pm 14	100 \pm 14	101 \pm 13
MAP (mmHg)	88 \pm 12	80 \pm 14†	76 \pm 12‡	81 \pm 12‡	85 \pm 12†	88 \pm 12	91 \pm 9†
PCWP (mmHg)	12 \pm 5	12 \pm 5	11 \pm 5	12 \pm 5	12 \pm 5	12 \pm 5	13 \pm 5
Cardiac output (l/min)	7.42 \pm 2.4	*	*	7.46 \pm 2.3	7.44 \pm 2.0	7.62 \pm 2.3	7.50 \pm 2.1
SVR (dyne \cdot s ⁻¹ /cm ⁵)	933 \pm 375	*	*	842 \pm 347†	874 \pm 362†	890 \pm 350	917 \pm 307

* The drug was infused during the first 2 min of the study.
† $P < 0.05$.

‡ $P < 0.001$.

that ranitidine, a furan compound, does not cause significant hemodynamic sequelae or a decrease in MAP.⁴

With these two studies in mind, the present study was designed to compare the hemodynamic effects of cimetidine versus ranitidine in a cross-over study in hemodynamically stable ICU patients. This was done to eliminate the question of baseline variability in hemodynamic parameters and patient management that may have existed between the previous studies.

MATERIALS AND METHODS

Twenty critically ill adult medical, surgical, or neurosurgical patients in our Trauma and Life Support Center were studied. Twelve male and eight female patients ranging in age from 22 to 86 with a mean age of 54 were included. Patients studied had indwelling peripheral arterial and pulmonary arterial catheters and were receiving either cimetidine 300 mg iv q 8 h or ranitidine 50 mg iv q 12 h as ordered by their physicians. None of the patients had catheters inserted or either drug administered solely for the purpose of this investigation. To be eligible, patients had to be considered hemodynamically stable and not requiring vasopressors or inotropic agents for at least 12 h before evaluation. The study was approved by the Human Subjects Committee of the University of Wisconsin, and informed consent was obtained from each patient or guardian and the attending physician.

The study was performed prospectively in a double-blind manner, with cross-over. Treatments were ran-

domized with the assistance of the University of Wisconsin Hospital Pharmacy. Patients received both 20 ml of normal saline (NS) (control) and ranitidine 50 mg in 20 ml NS or cimetidine 300 mg in 20 ml NS 1 h apart. This sequence was repeated 12 h later with the other drug and NS again given randomly and separated by 1 h. Baseline hemodynamic data, including heart rate (HR), mean arterial pressure (MAP), pulmonary artery pressure (PAP), pulmonary capillary wedge pressure (PCWP), and cardiac output (\dot{Q}) via thermodilution, were obtained. Systemic vascular resistance (SVR) was calculated. Cimetidine, ranitidine, or NS was infused over 2 min at the completion of baseline measurements. The above parameters were measured at 1, 2, 3, 5, 7, and 12 min after baseline data were obtained.

All data were analyzed with the use of a repeated measures of analysis variance model to compare hemodynamic variables at different time points with baseline control, to compare the effect of each drug with a control saline infusion, and to compare the effect of each drug with the other drug.⁵⁻⁷ The change from baseline is used as the outcome variable to determine whether the change from baseline with cimetidine or ranitidine is greater than the change from baseline after NS. Both drugs were also compared with each other at the specified time points. Data were analyzed for a sequence effect to determine if the order of drug or saline administration caused an effect. A minimum alpha level of less than 0.05 was considered significant. In the study we defined clinical significance as a change of 10% or greater when compared with base-

TABLE 2. Hemodynamic Data after Ranitidine Administration* (Mean \pm SD)

Variable (Units)	Baseline	1 Min	2 Min	3 Min	5 Min	7 Min	12 Min
HR (beats/min)	102 \pm 17	101 \pm 17	100 \pm 17	99 \pm 16	99 \pm 16	98 \pm 16	97 \pm 16
MAP (mmHg)	90 \pm 17	89 \pm 18†	87 \pm 17†	90 \pm 18	91 \pm 18	92 \pm 20	91 \pm 17
PCWP (mmHg)	13 \pm 6	13 \pm 6	13 \pm 6	13 \pm 6	13 \pm 6	13 \pm 6	13 \pm 6
Cardiac output (L/min)	7.29 \pm 2.1	*	*	7.10 \pm 1.9	7.30 \pm 2.0	7.00 \pm 2.0	7.20 \pm 2.0
SVR (dyne \cdot s ⁻¹ /cm ⁵)	995 \pm 557	*	*	987 \pm 477	986 \pm 540	1054 \pm 586	1003 \pm 509

* The drug was infused during the first 2 min of the study.

† $P < 0.05$.

TABLE 3. Percentage Change in MAP—Comparison of Hemodynamic Changes after Ranitidine and Cimetidine Administration (Mean ± SD)

Time	1 Min	2 Min	3 Min	5 Min	7 Min	12 Min
Ranitidine	-4 ± 5	-4 ± 5	-1 ± 7	+1 ± 7	+2 ± 10	+2 ± 6
Cimetidine	-10 ± 11	-14 ± 10	-8 ± 6	-4 ± 4	-1 ± 5	+3 ± 6
P value	0.0001	0.0001	0.0001	0.003	NS	0.04

line. With the repeated measures of analysis of variance testing the power to detect a decrease of 10% from baseline is in excess of 99% for each parameter.

RESULTS

There was no sequence effect. In other words, it made no difference whether NS, cimetidine, or ranitidine was given first. There was also no clinically significant difference between hemodynamic parameters at the time points measured that were separated by 12 h. As expected, the infusion of NS did not produce a significant change from baseline for any of the variables measured. The data following infusion of cimetidine are summarized in table 1. There was a significant decrease in MAP at 1, 2, and 3 min that averaged 14% at 2 min ($P < 0.001$). The decrease in MAP ranged from 1 to 40 mmHg but was not associated with severe sequelae or ECG changes. The decrease in MAP resolved spontaneously within 7 min in our patient population. Associated with the decrease in MAP in cimetidine-treated patients was a significant decrease in calculated SVR at 3 and 5 min. This was not associated with a significant change in \dot{Q} .

The data after infusion of ranitidine are summarized in table 2. There were no clinically significant hemodynamic changes after infusion. Table 3 compares the effects of cimetidine versus ranitidine on MAP and reveals a significant difference in MAP at 1, 2, and 3 min.

DISCUSSION

This is the first study of which we are aware that compares the hemodynamic effects of intravenous infusions of both cimetidine and ranitidine in critically ill patients. The age and distribution of critically ill patients in this study is similar to that in previous studies examining the hemodynamic effects of these H_2 blockers. The change in hemodynamic variables after intravenous cimetidine in patients in the present study are similar to the changes reported by Iberti *et al.*⁹ Our study revealed an acute decrease in MAP of between 10 and 14% compared with a decrease of 10% in Iberti's patients. In the present study, all patients were considered hemodynamically stable with baseline parameters within or near the normal range and were not receiving inotropic or vasopressor support within 12 h of study. The hemodynamic effects after the injection of cimetidine were again observed 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. Kiowski and Frei found an average decrease of 14 mmHg in systolic arterial pressure in 75% of their 68 ICU patients. They also observed that the blood pressure decreased to a much greater extent in those ICU patients requiring vasoconstrictor drug support.⁸

Proposed mechanisms of cimetidine-induced hypotension include direct myocardial depression versus peripheral vasodilatation. Some investigators propose a mechanism related to blockade of myocardial and peripheral vessel H_2 receptors.⁹⁻¹¹ This blockade would blunt the positive inotropic and chronotropic responses of stimulation of these receptors. Our study supports a mechanism of peripheral vasodilatation. There was no significant decrease in \dot{Q} or increase in PCWP in these patients. Although SVR cannot be calculated during the initial 2 min of the study secondary to the drug infusion, it was significantly decreased even 3 and 5 min after cimetidine, further supporting the mechanism of peripheral vasodilatation. The circulatory effects of ranitidine in these patients are similar to these in our previous study and are not of clinical significance.⁴ The difference between the hemodynamic effects of cimetidine and ranitidine may be related to the difference in their structures. Both H_1 and H_2 receptors are present in the arterial smooth muscle cells. In previous animal studies, a histamine-induced decrease in blood pressure could be abolished only by combined H_1 and H_2 receptor blockade.⁹ It has been suggested that cimetidine may have a partial histaminergic activity that could lead to vasodilatation.⁹ In animal experiments, cimetidine has been demonstrated to interfere with alpha-adrenergic vasoconstriction.⁹ Kiowski and Frei used brachial artery infusions of cimetidine in normal volunteers to demonstrate arterial vasodilatation after the administration of cimetidine.⁸ In addition, these normal subjects had a greater decrease in forearm vascular resistance secondary to cimetidine when the forearm vessels were precontracted with norepinephrine or dopamine.

In earlier studies, bradycardia had also been a recognized side effect of therapy with cimetidine.¹² We did not observe a significant change in HR in this ICU population, however, the HR did not increase with the decrease in blood pressure, as might be anticipated. This could rep-

resent a relative negative chronotropic effect or a decrease in baroreceptor activity resulting from or independent of cimetidine.

In conclusion, a bolus injection of intravenous cimetidine in patients in an ICU was followed by moderate hypotension, whereas ranitidine was not. If relatively rapid bolus administrations of H₂ blockers are needed, ranitidine appears to be the more favorable of the two drugs, when the cost, drug interactions, and side effects of these agents are weighed carefully.

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Corneal Abrasion during Anesthesia and Surgery

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The occurrence of corneal abrasion during general anesthesia usually becomes apparent when the patient emerges from anesthesia and complains of symptoms in the eye. These eye injuries are painful, usually resolve over a period of days, and have a variety of causes. Prevention using eye ointment has been suggested. This study prospectively examines the frequency of such injury in a neurosurgical population and the effect of ointment on the occurrence of injury, and describes possible patterns of injury.

MATERIALS AND METHODS

Patients (n = 4652) undergoing elective neurosurgical procedures over a 13-month period under general anesthesia were studied with the approval of the Institutional Review Board. Patients usually received eye ointment if

the last digit of their registration number was odd and did not receive ointment if it was even. Some patients received ointment or not based on the routine of their anesthesiologist. All patients had their eyes taped closed after endotracheal intubation. The ointment group (n = 2439) was compared to the no-ointment group (n = 2213).

When corneal abrasion was suspected, an ophthalmology consultation was sought and the diagnosis confirmed by fluorescein staining. Treatment in all cases consisted of taping the eye closed until resolution of the injury. The record was reviewed and the anesthesiologist caring for the patient contacted to see if he had information regarding the suspected etiology.

RESULTS

The incidence of corneal abrasion in this patient population was 0.17%. Eight patients were suspected of having corneal abrasion based on their symptoms. All of them complained of eye symptoms in the recovery room and were found to have abrasions on fluorescein staining by ophthalmology. Four of the abrasions were in patients who received no ointment and four were in patients who received ointment.

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