HAEMODYNAMIC RESPONSES TO INTRAVENOUS CIMETIDINE IN SUBJECTS WITH NORMAL LUNG FUNCTION AND IN SUBJECTS WITH CHRONIC AIRWAY OBSTRUCTION

P.K. LEE, C.L. LAI, A.S.F. LOK, T.F. TSE, K.N. LAI, S.F. CHOW & K.C. LAM

Department of Medicine, University of Hong Kong, Queen Mary Hospital, Hong Kong

1 The haemodynamic responses to a bolus intravenous injection of 400 mg cimetidine were studied in eight subjects with normal lung function and sixteen with chronic obstructive airway disease (COAD), under continuous systemic and pulmonary arterial monitoring. In all subjects there were significant immediate but transient (less than 10 min) drops in the systemic and pulmonary arterial pressures (both systolic and diastolic), the systemic vascular resistance and total pulmonary resistance. The percentage drops were significantly more marked in the COAD group in the following: systemic arterial pressures (systolic and diastolic), systemic vascular resistance and total pulmonary resistance. The cardiac output showed no significant change in the group with normal lung function but rose significantly in the COAD group. None of the subjects had any symptoms associated with the haemodynamic changes.

2 These results can be explained by a generalized vasodilatory effect of cimetidine, but the relationship to its H_2 -receptor blocking effect is undetermined. Hypoxia and/or hypercapnia may sensitize an individual to the vasodilatory effect of cimetidine.

Introduction

Certain cardiovascular effects of histamine have been proven to be mediated through H_2 -receptors in animals (Doyle & Strike, 1976; Flynn & Owen, 1974; Levi, Capurro & Lee 1975). However, reports on the exact nature of the cardiovascular effects of H_2 -receptor blockers in animal experiments are conflicting. In spite of the increasing acceptance of cimetidine (tagamet), a potent H_2 -receptor blocker, in clinical practice, there have only been a few isolated case reports on the haemodynamic effects of cimetidine (Jefferys & Vale, 1978; Mahon & Kolton, 1978; Reding, Devroede & Barbier, 1977). The aim of this study is to investigate the haemodynamic responses to intravenous cimetidine in subjects with normal lung function and subjects with chronic obstructive airways diseases (COAD). The latter group was chosen because of the higher incidence of gastrointestinal bleeding and the occurrence of hypotension and arrhythmia after intravenous cimetidine in isolated case reports among this population (Cohen, Weetman, Dargie & Krikler, 1978).

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Methods

Informed and written consents were obtained from eight subjects with normal lung function and sixteen

with COAD. The risks of the procedures were carefully explained to all subjects.

Lung function tests including forced vital capacity (FVC), forced expiratory volume in the first second (FEV_1), carbon monoxide transfer factor (Dco), together with arterial oxygen and carbon dioxide partial pressures were performed for all subjects. Basal electrocardiograms were normal in all subjects.

Systemic arterial pressure was monitored by percutaneous brachial artery puncture with angio-catheter with patients in supine position. Pulmonary arterial and pulmonary capillary wedge pressures were monitored via triple lumen Swan-ganz catheter positioned under fluoroscopy screening. Both catheters were introduced under local anaesthesia with no pre-medication.

Intravenous cimetidine (400 mg) from Smith, Kline & French Ltd (the base of which is water) was diluted in 40 ml of normal saline. The pH of the diluted solution was 6. The 40 ml of diluted cimetidine was injected as a single bolus over 15 s into the central venous line after the basal pressures were steady for 10 min and without the subjects' knowledge. The systemic and pulmonary arterial pressures were recorded continuously for 30 min on a Hewlett Packard 7753 C system together with the patient's electrocardiogram (standard lead II). The pulmonary wedge pressure was recorded at 2 min intervals throughout the study.

Blood samples were obtained from the pulmonary and brachial arterial lines at zero time and every 2 min after the injection of cimetidine for 20 min. Cardiac output at basal level and at the time of maximum changes of pressures were calculated by direct Fick principle. The systemic vascular resistance and total pulmonary resistance were also calculated at basal level and at the time of maximal changes of pressures. The changes in the various parameters were compared with Student's paired *t*-test within the same group of subjects and with Student's unpaired *t*-test between the two groups of subjects.

Results

1. Comparison of basal parameters in normal subjects and in COAD subjects (Table 1)

The healthy normal subjects had a median age of 45 years with two over the age of 60 years. The COAD group had a median age of 63 with eleven over the age of 60 years.

Compared with the eight normal subjects, all the sixteen subjects with COAD had significant impairment of lung function in the parameters measured. The basal systemic arterial pressures were comparable in the two groups, but the COAD subjects had significantly higher pulmonary arterial pressures and total pulmonary resistance.

2. Response to intravenous cimetidine

Figures 1 and 2 show the typical responses in systemic

arterial pressure, pulmonary arterial pressure and pulse rate on injection of a bolus of 400 mg cimetidine intravenously in a subject with normal lung function and with COAD respectively.

Figure 1 Typical changes in systemic and pulmonary arterial pressures (systolic and diastolic) and pulse rate after an intravenous bolus injection of 400 mg cimetidine in a subject with normal lung function.

Table 1 Various basal parameters (mean $\pm$ s.d.) of the subjects with normal lung function and the subjects with COAD

	<i>Eight subjects with normal lung function</i>	<i>Sixteen subjects with COAD</i>
Median age (years) (range)	45 (25–64)	63 (33–80)
Mean pO_2 (mm Hg)	95.6 ± 2.6	61.8 ± 14.0
Mean pCO_2 (mm Hg)	40.1 ± 1.4	50.9 ± 5.8
FEV ₁ (% predicted)	85.4 ± 6.8	31.7 ± 13.6
FVC (% predicted)	89.1 ± 7.4	52.3 ± 24.3
FEV ₁ /FVC (%)	76.1 ± 4.5	50.0 ± 16.8
Dco (% predicted)	88.2 ± 7.9	57.4 ± 12.6
Systemic arterial pressure (mm Hg)		
Systolic	123.8 ± 10.3	135.3 ± 27.8
Diastolic	71.9 ± 8.0	70.7 ± 11.9
Pulmonary venous pressure (mm Hg)		
Systolic	22.0 ± 2.2	37.6 ± 20.0
Diastolic	10.0 ± 1.4	19.1 ± 10.1
Total pulmonary resistance (mm Hg/l min ⁻¹)	1.3 ± 0.6	3.2 ± 0.7

Figure 2 Typical changes in systemic and pulmonary arterial pressures (systolic and diastolic) and pulse rate after an intravenous bolus injection of 400 mg cimetidine in a subject with chronic obstructive airway disease (COAD).

A transient but significant drop in the systemic and pulmonary arterial pressures were recorded in all subjects of both groups within 1–2 min after the bolus dose of 400 mg cimetidine. The maximum fall occurred within the first 5 min. All rose back to basal levels within 10 min. There was an accompanying increase in pulse rate with the fall in pressure, but no arrhythmia or conduction defects were recorded on the electrocardiogram. The pulmonary wedge pressures remained unchanged.

The changes in pressure are much more marked in subjects with COAD compared with the subjects with normal lung function irrespective of the age of the subjects. None of the patients complained of any symptoms during the fall in blood pressures.

Tables 2 and 3 summarize the changes in systemic arterial pressures, pulmonary arterial pressures, systemic vascular resistance, total pulmonary resistance and cardiac output in the two groups of subjects. The percentage drop in the various parameters in the two groups are compared in Figure 3.

Discussion

We have demonstrated a consistent fall in both systemic and pulmonary arterial pressures in response to intravenous cimetidine in all our tested subjects. The fact that these changes have not been reported before is probably due to the short duration of the effects.

It is unlikely that the blood pressure changes could be accounted for by the base of intravenous cimetidine (i.e. water), the saline, the pH of the solution, or

Table 2 Changes (mean $\pm$ s.d.) in various parameters in eight subjects with normal lung function after intravenous bolus injection of 400 mg cimetidine

	Basal level	Level at maximum change	% Drop	
Systemic pressure				
Systolic (mm Hg)	123.8 $\pm$ 10.3	107.5 $\pm$ 6.6	12.9 $\pm$ 4.6	$P = 0.0006$
Diastolic (mm Hg)	71.9 $\pm$ 8.0	63.8 $\pm$ 9.9	14.5 $\pm$ 12.6	$P = 0.0231$
Pulmonary pressure				
Systolic (mm Hg)	22.0 $\pm$ 2.2	19.4 $\pm$ 3.1	12.1 $\pm$ 8.3	$P = 0.0044$
Diastolic (mm Hg)	10.0 $\pm$ 1.4	8.6 $\pm$ 1.8	9.1 $\pm$ 11.0	$P = 0.0528$
Systemic vascular resistance (mm Hg/l min ⁻¹)	12.5 $\pm$ 4.8	10.4 $\pm$ 3.9	16.2 $\pm$ 8.5	$P = 0.0133$
Total pulmonary resistance (mm Hg/l min ⁻¹)	1.3 $\pm$ 0.6	1.1 $\pm$ 0.5	13.7 $\pm$ 2.6	$P = 0.0118$
Cardiac output (l/min)	7.2 $\pm$ 2.2	7.5 $\pm$ 2.3		NS

the method of injection. As the injections of intravenous cimetidine were made after the basal measurements had remained steady for 10 min and were given into established venous lines without the subjects' knowledge, it is also unlikely that anxiety reactions play any part in the changes. The most likely cause of the changes is cimetidine itself. The

falls in systemic and pulmonary arterial pressures were attributable to the drop in systemic vascular resistance and total pulmonary resistance signifying a generalized vasodilation. The cardiac output, on the other hand, showed a slight trend to rise, the rise being significant in the COAD group. It has been demonstrated in guinea pig experiments that both the

Table 3 Changes (mean $\pm$ s.d.) in various parameters in sixteen subjects with COAD after intravenous bolus injection of 400 mg cimetidine

	Basal level	Level at maximum change	% Drop	
Systemic pressure				
Systolic (mm Hg)	135.3 $\pm$ 27.8	95.7 $\pm$ 26.4	29.7 $\pm$ 8.0	$P < 0.00001$
Diastolic (mm Hg)	70.7 $\pm$ 11.9	52.1 $\pm$ 11.9	27.0 $\pm$ 10.7	$P < 0.00001$
Pulmonary pressure				
Systolic (mm Hg)	37.6 $\pm$ 20.1	33.1 $\pm$ 19.2	14.0 $\pm$ 9.1	$P = 0.0007$
Diastolic (mm Hg)	19.1 $\pm$ 10.1	16.5 $\pm$ 8.3	31.0 $\pm$ 51.7	$P = 0.0064$
Systemic vascular resistance (mm Hg/l min ⁻¹)	20.2 $\pm$ 4.5	14.1 $\pm$ 4.1	30.8 $\pm$ 10.3	$P = 0.0001$
Total pulmonary resistance (mm Hg/l min ⁻¹)	3.2 $\pm$ 0.7	2.7 $\pm$ 0.6	17.4 $\pm$ 1.7	$P = 0.001$
Cardiac output (l/min)	3.5 $\pm$ 0.8	3.8 $\pm$ 0.9		$P = 0.0042$

Figure 3 Comparison of percentage drop in systemic and pulmonary arterial pressures (systolic and diastolic), systemic vascular resistance and total pulmonary resistance after intravenous bolus injection of 400 mg cimetidine in eight subjects with normal lung function ($\square$) and in sixteen subjects with chronic obstructive airway disease (COAD) ($\blacksquare$).

H₁ and H₂-receptors contribute towards the fall in blood pressure in response to intravenous histamine (Callingham, 1978; Doyle & Strike, 1976). But so far the vasomotor effects of H₂-receptors in human beings have not been clearly defined. The vasodilatory effect of intravenous cimetidine that we have demonstrated may be related to its H₂-receptor blockade effect or a direct action on the blood vessels.

The vasodilatory effect of intravenous cimetidine was also shown to be significantly more marked in patients with COAD. Hypotension developing after intravenous cimetidine had been reported in one patient with late-onset asthma requiring steroid therapy (Cohen *et al.*, 1978).

The median age in the two groups of subjects studied were different. However, the percentage changes in pressures were the same for all ages within

the same group of subjects. The significantly more marked vasodilation in the COAD group is unrelated to the age difference. It is possible that hypoxia and/or hypercapnia sensitize an individual to the vasodilatory effect of intravenous cimetidine.

In conclusion, an intravenous bolus injection of cimetidine has been shown to cause immediate and transient falls in pressures in the systemic and pulmonary circulations as a result of vasodilation. These effects are far more pronounced among patients with COAD. No subjective symptoms occur during the fall in blood pressures. It would be worthwhile to look for any changes in blood pressures in patients on long-term oral cimetidine.

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