THE EFFECTS OF CHRONIC ORAL CIMETIDINE THERAPY ON THE CARDIOVASCULAR SYSTEM IN MAN

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1 The demonstration of histamine (H_2) receptors in the cardiovascular system in man and the widespread use of the specific H_2 receptor antagonist cimetidine for the treatment of peptic ulcer has necessitated assessment of the cardiovascular effects of this drug during oral therapy in man.

2 Consequently, nineteen patients with a history of peptic ulcer but in symptomatic remission underwent a double-blind crossover trial of oral cimetidine v placebo, each treatment period lasting 4 weeks. No significant difference in various cardiac parameters at rest (heart rate, blood pressure, ECG) or following a maximal treadmill exercise test (time-into-protocol, maximum heart rate and blood pressure) was found between the groups. Similarly, cimetidine produced no change in the incidence of ventricular ectopics or in heart rate on 24 h ambulatory monitoring and had no effect on left ventricular volume or contractility as measured by echocardiography.

3 Thus oral administration of cimetidine in a dose of 400 mg four times daily was associated with no demonstrable cardiovascular changes. In addition, since this dose is thought compatible with cardiovascular H_2 receptor blockade this study favours the lack of a physiological role for these receptors in man.

Introduction

Histamine receptors, both H_1 (Ash & Schild, 1966) and H_2 (Black, Duncan, Durant, Ganellin & Parsons, 1972) have been demonstrated in the cardiovascular system of many animal species (Owen, 1977). In the majority, H_2 receptor stimulation has resulted in increased heart rate (positive chronotropism) and contractility (positive inotropism) and enhanced automaticity (Levi, Allan & Zavecz, 1976). The existence of cardiac histamine H_2 receptors in man has recently been demonstrated both *in vitro* (Levi, 1978; Wolleman & Papp, 1979) and *in vivo* (Watkins, Dargie, Brown & Dollery, 1979) but their role, if any, in physiological and pathological situations remains to be defined.

The introduction of the specific H_2 receptor antagonist cimetidine (Brogden, Heel, Speight & Avery, 1978) has resulted in its widespread use for the treatment of peptic ulcer. In view of this, we felt it necessary to investigate non-invasively the cardiovascular actions of oral cimetidine in a recommended dosage and in particular its effects on heart rate, incidence of arrhythmias, left ventricular function and exercise tolerance. In the light of these findings, recent case reports documenting cardiovascular changes associated with its use (Table 1) can be placed in perspective.

Methods

Approval for the study was obtained from St Thomas' Hospital Ethics Committee. Twenty-four ambulatory outpatients who had attended the gastroenterology clinic and who were in symptomatic remission commenced the trial. Patients with hepatic or renal impairment were excluded. Of these 24 patients, 19 completed the trial, the remaining 5 withdrawing for personal reasons unrelated to the drug therapy.

The existence of mild to moderate cardiovascular disease did not constitute an exclusion criterion. Consequently, one patient with known ischaemic heart disease (previous myocardial infarction) and seven others who complained of intermittent palpitations either spontaneously or on direct question were included.

The study protocol consisted of a double-blind crossover trial of placebo v cimetidine 400 mg four times a day orally. Each treatment period lasted 4 weeks and a 'washout' period of 2 days was allowed to elapse between treatments. The dose used approached the maximum recommended by the manufacturers.

Each patient was initially interviewed, clinical examination performed and informed consent

Table 1 Reports documenting cardiovascular changes in man on cimetidine therapy

Source	Number of patients	Route oral (O) or intra-venous (i.v.)	Cardiovascular changes during cimetidine therapy	Indication and associated conditions
Reding <i>et al.</i> (1977)	1	O	Atrio-ventricular dissociation idioventricular rhythm	Gastro-intestinal bleeding
Jeffreys & Vale (1978)	2	O	a) sinus bradycardia b) sinus bradycardia	Gastric ulcer Aspirin-induced bleeding
Bournerais <i>et al.</i> (1978)	1	O	Sinus bradycardia, large, inverted T waves, QT prolongation. Multiple ventricular ectopics. Fatal ventricular fibrillation	Polycystic kidneys, renal failure. septicaemia, hypokalaemia, duodenal ulcer
Luciano <i>et al.</i> (1978)	1	O	Nodal bradycardia	Gastric ulcer
Stimmesse <i>et al.</i> (1978)	1	i.v.	Sinus bradycardia-reversed by haemo-dialysis	Duodenal ulcer, acute renal failure
Ligumsky <i>et al.</i> (1978)	1	Not stated	Sinus bradycardia and suppression of ectopics. Reversal on stopping cimetidine and return on rechallenge	CVA, IHD, marked supraventricular and ventricular ectopy. Bleeding gastric ulcer
Cohen <i>et al.</i> (1979)	2	O and i.v. i.v.	a) Hypotension Fatal cardiac asystole b) Sinus arrest, atrial extrasystoles. Cardiac asystole.	Polyarteritis nodosa Antral ulcer Septicaemia, cardiac asystole prior to cimetidine. Prophylaxis of gastro-intestinal bleeding.

obtained. Where possible all regular drug therapy was suspended. However, one patient continued regular diuretic therapy (amiloride 5 mg, hydrochlorothiazide 50 mg, Moduretic®); another received dimenhydrinate 50 mg (Dramamine®) for acute vertigo lasting approximately 1 week which developed near the beginning of the cimetidine period and several patients took occasional antacids or simple analgesics.

During the last 2 days of each 4 week period, patients underwent the following non-invasive investigations whilst still taking the prescribed drug:

(a) Clinical history and examination to elicit the onset of new symptoms or signs. Blood pressure was recorded in the upright posture.

(b) M-mode echocardiography using a Smith-Kline Ekoline 20 ultrasonoscope with a 2.25 MHz focused transducer. Recordings were made on photographic paper at speeds of 25–100 mm/s. The left ventricular internal diameter was measured during both systole (at the peak inward motion of the posterior wall—LVIDs) and during diastole (at the electrocardiographic Q wave—LVIDd). Stroke volume was calculated as $LVIDd^3 - LVIDs^3$ (ml). The fractional

shortening percent (FS%) and the mean velocity of circumferential fibre shortening (V_{CF}) were derived as follows:

$$FS\% = \frac{LVIDd - LVIDs}{LVIDd} \times 100$$

and

$$V_{CF} = \frac{LVIDd - LVIDs}{LVIDd \times Et}$$

where Et is the ejection time in seconds (interval between echocardiographic aortic valve opening and closure).

(c) Resting 12 lead electrocardiography.

(d) Maximal exercise stress testing—on an Avionics E16 programmable treadmill using the standard Bruce protocol (Bruce & Hornsten, 1969). The ECG was continuously monitored and 9 lead print-out (the 6 limb leads and V4-6) obtained towards the end of each stage. Exercise capability was assessed by total exercise time (time-into-protocol), maximal oxygen consumption (VO_2 max) (Bruce, Kusumi & Hosmer,

1973), maximum heart rate (max HR) achieved and maximum systolic blood pressure (max SBP) recorded.

(e) 24 h ambulatory ECG monitoring, using an Oxford Medilog recorder with the indifferent lead on the manubrium and the active lead at V5: Analysis of recorded data was performed using a Pathfinder high-speed ECG analyser (Reynolds Medical Electronics Ltd), and included hourly heart rates, hourly ventricular ectopic count and the incidence and type of other arrhythmias.

Statistics

Most analyses involved the Student's *t*-test. However, treatment of the data in this way is inadequate when analysing the incidence of arrhythmias and particularly of ventricular ectopics since it does not take into account the effect of mutual interaction between different factors. The incidence of ventricular ectopics may be markedly influenced by several factors including inter-patient variability (Morganroth, Michelson, Horowitz, Josephson, Pearlman & Dunkman, 1978), spontaneous variation from hour to hour (Winkle, 1978) and heart rate changes. It may thus be very difficult to establish any further effect due to an intervention. One solution to this problem is to apply standard analysis of variance (Snedcor & Cochran, 1967) which we did by means of a 'generalised linear model' fitting programme (GLIM). With this programme, the log of the number of ventricular ectopics was used as the response variable and a model incorporating inter-patient variability, effect of heart rate and type of treatment (placebo or cimetidine) was created. An estimate of the fit between this model and the actual data was provided by the deviance. Each factor in the model was then excluded in turn and any worsening in the fit between the remaining model and the data evaluated by the difference in their deviances. The independent effect of each individual factor was thus assessed having allowed for the effect of the other two factors.

Results

(1) Clinical

No new cardiovascular symptoms or signs appeared

during cimetidine therapy though one patient developed acute vertigo probably unrelated to drug therapy.

(2) Resting parameters

No significant difference ($P > 0.1$) in resting heart rate, systolic or diastolic blood pressure was found between cimetidine and placebo periods (Table 2).

The resting 12 lead electrocardiograph (ECG) was normal in 17 of the 19 patients on placebo and did not change following cimetidine treatment. Two patients had abnormal ECGs at rest, one showing an old anterior myocardial infarction and the other mild non-specific ST/T changes in inferior leads. In neither case did the administration of cimetidine produce any further changes.

(3) Exercise parameters

Cimetidine produced no significant change ($P > 0.1$) in any of the maximal exercise parameters (Table 3) when compared with placebo. In particular, time-interval-protocol (mean $\pm$ s.e.mean) was unchanged (11.3 ± 0.5 min v 11.0 ± 0.5 min; $P > 0.1$).

In 14 of the 19 patients, the ECG on exercise was normal during both treatment periods; in one patient (with a normal resting ECG) changes indicative of ischaemia (> 1 mm downsloping ST depression) appeared in at least one lead during exercise on both placebo and cimetidine; in two patients unifocal ventricular ectopic beats (VEs) occurred on exercise in the placebo period only; and in a further two patients VEs appeared in the cimetidine period alone (multifocal in the case of the patient with a previous anterior myocardial infarction). Overall, cimetidine thus produced little, if any, effect on the exercise ECG.

(4) M-mode echocardiography

Cimetidine therapy produced no significant change in systolic or diastolic left ventricular (LV) dimensions, stroke volume, or in parameters of LV contractile function (EF, FS%, V_{CF}) (Table 4). Thus cimetidine had no negative inotropic effect in the patients studied.

Table 2 Haemodynamic parameters at rest on cimetidine and placebo (mean $\pm$ s.e.mean)

	Placebo	Cimetidine	t	P
Heart rate (beats/min)	83.6 $\pm$ 2.9	85.7 $\pm$ 4.2	0.79	>0.1
Systolic blood pressure (mmHg)	134.2 $\pm$ 3.8	136.1 $\pm$ 3.5	0.64	>0.1
Diastolic blood pressure (mm Hg)	81.0 $\pm$ 2.1	78.2 $\pm$ 2.2	2.10	>0.05

Table 3 Exercise-derived parameters on cimetidine and placebo (mean $\pm$ s.e.mean)

	Placebo	Cimetidine	t	P
Maximum heart rate (beats/min)	170.4 $\pm$ 5.0	166.8 $\pm$ 4.8	1.3	>0.1
Maximum systolic blood pressure (mmHg)	200.4 $\pm$ 7.2	199.4 $\pm$ 7.8	0.6	>0.1
VO ₂ max (ml min ⁻¹ m ⁻²)	1.6 $\pm$ 0.06	1.6 $\pm$ 0.06	1.4	>0.1
Time-into-protocol (min)	11.3 $\pm$ 0.54	11.0 $\pm$ 0.5	1.4	>0.1

(5) 24 h ambulatory ECG monitoring

Interpretable ambulatory data for 24 h on both placebo and cimetidine was available in 18 of the 19 patients. This enabled more detailed analysis of heart rate changes and assessment of the incidence of arrhythmias during cimetidine therapy. In the following section, means $\pm$ s.e. mean are quoted:

(i) Heart rate—the mean hourly heart rate on cimetidine was 80.7 $\pm$ 1.9 beats/min (range 64–91 beats/min) which was not significantly different ($P > 0.1$) from that on placebo (mean 80.7 $\pm$ 2.3 beats/min; range 66–102 beats/min). Similarly, cimetidine produced no change ($P > 0.1$) in mean maximum hourly heart rate (92.3 $\pm$ 2.5 beats/min *v* 93.7 $\pm$ 4.0 beats/mean) nor in mean minimum hourly heart rate (70.9 $\pm$ 2.0 beats/min *v* 72.9 $\pm$ 2.7 beats/min).

(ii) Arrhythmias—the only arrhythmias recorded in any of the 36 ambulatory tapes consisted of VEs and the number of hours in which these totalled more than 10 was similar on both placebo and cimetidine (Table 5). Considerable variation existed in the number of VEs/hour within either treatment period both between individuals and from one hour to another in the same patient. Analysis of variance showed that the inter-patient variability in hourly VE rate was highly significant ($P > 0.001$) but no significant effect ($P > 0.1$) due to heart rate changes was

found. Allowing for both of these factors, no significant differences ($P > 0.1$) in the incidence of VEs was found between the cimetidine and placebo treatment periods.

Discussion

The existence of cardiac H₂ receptors in many animal species has been established (Owen, 1977) and their actions characterised (Levi *et al.*, 1976) (Table 6). Few studies have been conducted in humans, but *in vitro* histamine (10⁻⁹ to 10⁻⁴ M) has been shown to enhance atrial automaticity in a preparation of right atrial fibres (Levi, 1978). In addition, Wollemann & Papp (1979) used hearts from apparently healthy human embryos and fetuses (6–18 weeks) obtained at legal abortion and found a significant age and concentration-dependent increase in spontaneous atrial rate and contractility of paced ventricles. The above effects were readily antagonised by cimetidine indicating the involvement of H₂ receptors. *In vivo* evidence consistent with the existence of cardiovascular H₂ receptors has been provided by the use of impromidine, a new specific H₂ receptor agonist (Boyce, Balusubramanian & Wareham, 1980), chlorpheniramine (an H₁ receptor antagonist) and

Table 4 Echocardiographic parameters on cimetidine and placebo (mean $\pm$ s.e.mean)

	Placebo	Cimetidine	t	P
LVIDd (cm)	5.1 $\pm$ 0.1	5.0 $\pm$ 0.1	2.0	>0.05
LVIDs (cm)	3.2 $\pm$ 0.1	3.2 $\pm$ 0.1	0.4	>0.1
EF	0.74 $\pm$ 0.01	0.73 $\pm$ 0.01	1.2	>0.1
FS%	36.4 $\pm$ 1.1	35.4 $\pm$ 1.3	1.5	>0.1
Stroke volume (ml)	98.6 $\pm$ 5.6	93.5 $\pm$ 6.5	1.7	>0.1
V _{CF} (circ/s)	1.5 $\pm$ 0.1	1.5 $\pm$ 0.1	0.9	>0.1

LVIDd left ventricular internal diameter during diastole

LVIDs left ventricular internal diameter during systolic

EF Ejection fraction

FS% fractional shortening %

V_{CF} mean velocity of circumferential fibre shortening

Table 5 Ambulatory ECG data on cimetidine and placebo

Patient number	Hourly mean HR (beats/min)	Placebo			Cimetidine	
		Total Number of VEs	Number of hours with >10/h	Hourly mean HR (beats/min)	Total number of VEs	Number of hours with >10/h
1	66	1	0	74	0	0
2	86	12	0	89	6	0
4	88	9	0	88	9	0
*† 5	66	268	10	69	234	8
6	65	4	0	64	12	0
* 7	78	0	0	81	0	0
8	68	6	0	78	233	12
*10	76	20	0	84	12	0
*11	92	6	0	88	14	0
*12	84	8	0	68	5	0
15	87	6	0	84	7	0
*16	85	0	0	84	0	0
17	80	0	0	91	0	0
19	109	8	0	—	—	—
20	102	15	3	84	25	4
21	85	3731	24	86	519	18
22	82	4	0	81	2	0
*24	85	2	0	84	3	0
25	78	0	0	75	2	0

† Patient had known ischaemic heart disease (previous myocardial infarct).

* Patient complained of palpitations spontaneously or on direct questioning.

cimetidine in healthy volunteers (Boyce, Owen & Wareham, 1980).

In the light of these studies, evaluation of the clinical importance of such cardiac H_2 receptors has become necessary and this need has been highlighted by the widespread therapeutic application of cimetidine (a specific H_2 receptor antagonist) for peptic ulcer. In the present study, an oral dose of 400 mg four times a day of cimetidine was used. No direct evidence exists that this dosage given orally is appropriate for the blockade of cardiovascular H_2 receptors in man. However, a divided daily dose of 1.6 g has been shown to reduce 24 h mean H^+ activity by 67% in patients with duodenal ulcers, a decrease of intra-gastric acidity resulting from gastric H_2 receptor blockade which is compatible with successful medical treatment of duodenal

ulceration (Pounder, Williams, Milton-Thompson & Misiewicz, 1976). By analogy, the same dosage is likely to produce substantial cardiovascular H_2 receptor antagonism. In addition, 400 mg of cimetidine orally has been found to produce mean blood concentrations in fasted subjects of 9.0–11.6 μM (Broden *et al.*, 1978), levels which are very similar to those shown by Wollemann & Papp (1979) to block cardiac H_2 receptors in human foetal hearts *in vitro*. These workers found that cimetidine in a concentration of $10^{-5} M$ antagonised all the studied effects of histamine and caused a shift to the right of the histamine dose-response curves corresponding to about 2–3 log units. It thus seems likely that the cimetidine dosage used in this study is compatible with cardiac H_2 receptor blockade in man.

Table 6 Cardiac effects of histamine in animals and the involved receptor type

Receptor type	Parameter	Effect
H_1	Atrial contractility	Increase
	A-V conduction time	Increase
H_2	Ventricular contractility	Increase
	Sinus rate	Increase
	Atrial automaticity	Increase
	Ventricular automaticity	Increase
Combined H_1 and H_2	Coronary sinus flow	Increase

Using this dosage, we were unable to demonstrate any negative chronotropic effect either at rest, following maximal treadmill exercise or in mean hourly heart rates during ambulatory monitoring. Cimetidine also exhibited no negative inotropic effect on LV function as measured by echocardiographic parameters (Table 4), exercise tolerance (Table 3) and resting blood pressure (Table 2). Further, no alterations in the 12 lead resting ECG nor in the 9 lead exercise ECG were found between the cimetidine and placebo treated groups.

Assessment of the effects of H₂ receptor blockade on cardiac automaticity as reflected in the incidence of VEs on 24 h ambulatory recordings was more difficult. Winkle (1978) has shown that in patients with frequent VEs individuals showed a marked spontaneous variability from one 0.5 h to the next in the total number of ectopic beats (−99% to +1000%) and in the occurrence of pairs of salvoes. Such spontaneous changes could easily mimic either drug suppression or drug-induced exacerbation. In addition, Morganroth *et al.* (1978) have documented similar marked spontaneous variability in ectopic frequency not only between individuals but also from hour to hour and day to day in the same patients during continuous 72 h monitoring. Consequently, we have assessed our results by an analysis of variance approach. We thus found a highly significant inter-patient variation in VE count ($P < 0.001$). When allowance was made for this and for the effect of heart rate, treatment with cimetidine resulted in no significant change in incidence of VEs.

The cardiovascular actions of chronic oral cimetidine therapy have not been previously reported. The results of the present study show that cimetidine in doses thought likely to block cardiac H₂ receptors does not significantly alter heart rate, LV contractility or ventricular automaticity. These results are in accord with the findings of Warburton, Opie, Kennelly & Müller (1979) that oral cimetidine for 3 days does not alter the heart rate or blood pressure response to treadmill exercise. In addition by the intravenous route cimetidine has been found to pro-

duce no alteration in systolic time intervals, heart rate or blood pressure (Gianrossi, Azzolini, Livi & Nizzo, 1979), nor in heart rate, sinus node recovery time or sinoatrial conduction time (parameters of sinus node function (Engel & Luck, 1979).

The lack of cardiovascular effects produced by cimetidine found in this study does not deny the existence of human cardiac H₂ receptors, but providing receptor blockade has occurred at this dosage it implies that under physiological conditions (rest or exercise) such receptor pathways do not represent important cardiovascular control mechanisms. The situation may however be entirely different in pathological situations. Histamine is known to be stored in large amounts in cardiac tissue (Vugman & Rocha e Silva, 1966) particularly around the sino-atrial and atrio-ventricular (Engel & Luck, 1979) nodes and there is evidence that mobilisation of histamine from its storage sites can be provoked by a variety of stimuli including anaphylaxis, cardio-pulmonary bypass and drugs e.g. digitalis (Levi, Zavec, Lee & Allan, 1978). Of interest, in this regard, is the observation that the three reported cardiac fatalities (Bournerias, Ganeval & Danan, 1978; Cohen, Weetman, Dargie & Krikler, 1979) occurred in gravely ill patients with co-existent disease processes and in whom concurrent administration of other drugs took place, situations in which it may be hypothesised that histamine release and H₂ receptor function could be important.

Thus the present study has demonstrated the lack of cardiovascular changes on oral treatment with cimetidine for four weeks at a dose thought compatible with H₂ receptor blockade. This finding favours the absence of a physiological role for cardiovascular H₂ receptors in man.

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