Effect of cimetidine on augmented gastric blood flow in duodenal ulcer patients

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SUMMARY Blood flow in the human stomach was measured during operation with a $^{85}\text{Krypton}$ washout method which made simultaneous determinations of total blood flow and intramural flow distribution possible. The antrum and the corpus of the stomach could be investigated separately. Eleven patients with duodenal ulcer disease were studied during pentagastrin infusion and after the addition of cimetidine, 3 mg/kg bw, to evaluate the effect of the drug on augmented gastric blood flow. Eight recordings were made over the corpus of the stomach and three recordings over the antrum. Cimetidine caused a $66 \pm 5\%$ decrease (mean $\pm$ SE; range 56-86) in acid secretion and a $62 \pm 5\%$ decrease (range 44-91) in the corpus mucosal blood flow within 15 minutes. Changes were only seen in the acid secreting part of the stomach while the antral circulation remained unaltered. It is concluded that the decrease in pentagastrin induced vasodilatation in the stomach seen after giving cimetidine was secondary to an inhibition of acid secretion.

The pathophysiology of the duodenal ulcer disease is still a matter of research and considerable efforts are devoted to finding new methods for prevention and treatment. The introduction of the histamine H_2 -receptor antagonists initiated new investigations, not only in the treatment of the uncomplicated ulcer but the drugs were soon tested in the treatment of a serious complication of ulcer disease, acute bleeding. The results of these studies are in some respects contradictory but a pattern is emerging on which a rationale for treatment may be founded. It appears that the bleeding from an established peptic ulcer, especially if it is located in the distal stomach or the duodenum, is largely unresponsive to histamine H_2 -receptor antagonism,¹⁻³ while gastric ulcers and diffuse bleeding disorders in the gastric mucosa respond more favourably to this treatment.³⁻⁵

The importance of an altered gastric blood flow in the pathogenesis and treatment of the ulcer disease is not clear. Available information on the effect of histamine H_2 -receptor antagonism on augmented gastric mucosal blood flow suggest a marked decrease.^{6,7} A limitation of the studies reported, where a marker clearance method (neutral red) was

used, is that this method only reflects blood flow to the secreting part of the gastric mucosa, possibly only to the parietal cell mass, while the majority of peptic ulcer bleedings originate elsewhere in the stomach or duodenum.

Using an inert gas washout method, which provides information on total gastric blood flow as well as on its intramural distribution, we have earlier studied in a quantitative manner the gastric blood flow in normal subjects and duodenal ulcer patients. These studies showed that duodenal ulcer patients exhibited a different pattern of gastric blood flow from normal subjects, both in size and distribution.^{8,9} In the present study we investigated the effect of cimetidine on blood flow in the actively secreting human stomach. These studies were performed intraoperatively in duodenal ulcer patients. A few studies were also carried out in a series of experiments on the cat and these are also reported below.

Methods

The methods used in this study have been applied in human studies earlier for the determination of gastric small intestinal and colonic blood flow. They are described in detail previously.⁸⁻¹¹ The theoretical framework of the inert gas elimination

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methods has been outlined and discussed in detail by Kety,^{12 13} Zierler,¹⁴ and Bassingthwaite.^{15 16}

CAT EXPERIMENTS

The animal studies were performed on five cats anaesthetised with chloralose (50 mg/kg bw) after induction with ether. The cats breathed spontaneously *via* a tracheostomy. The gastric preparation for recording venous outflow (total gastric blood flow) was the same as described previously.⁸

⁸⁵Kr, dissolved in physiological saline, was injected into the coeliac artery *via* a catheter in the central end of the divided hepatic artery. Radioactivity was measured with a thalliumactivated NaI-crystal placed 3–5 cm from the surface of the stomach. The scintillation detector was coupled to a spectrometer and a linear ratemeter. Pulse corresponding to γ -energies above 70 keV were counted. Atropine was not administered. Cimetidine, 3–4 mg/kg bw was given as bolus injections intravenously.

HUMAN STUDIES

Measurements of gastric blood flow were carried out in 11 patients during surgery for duodenal ulcer disease. In three patients recordings were done over the antrum and in eight patients over the corpus of the stomach.

Droperidol-fentanyl, nitrous oxide, and oxygen were used for anaesthesia. Atropine was not included in the premedication of the patients. Respiration was controlled with an Engström respirator adjusted to maintain arterial pCO₂ within normal limits. Expired air and radioactive gases were evacuated *via* a safety system to avoid recirculation or accumulation in the operating room.

The study was approved by the Ethical and Isotope Committees at the University of Göteborg. The patients were informed about the purpose and purely scientific aim of the study and gave consent to participation.

Intra-arterial injection of ⁸⁵Kr

In all cases the stomach was prepared and the recording apparatus applied as described earlier.⁸ The radioactive isotope (1 mCi ⁸⁵Kr in one ml saline) was injected *via* a catheter (Portex, OD 1.02 mm) placed in the gastroepiploic artery. The arterial catheter was directed either towards the antrum or towards the corpus, to enable flow recordings in these two regions separately. The disappearance of the isotope, which emits both β - and γ -radiation, was monitored with a scintillation detector and a G-M tube.⁸

Determination of acid secretion

Acid secretion was determined preoperatively in all patients. In four patients routine studies were done, with determination of basal and peak acid output, using pentagastrin (Peptavlon^R, kindly supplied by ICI), six μ g/kg bw given subcutaneously as a secretory stimulant. In the remaining seven patients a modified secretion study was done. In this study, basal acid output was determined as usual. Peak acid output was determined during one hour of continuous pentagastrin infusion, 600 ng/kg $\times$ h. Cimetidine was then given as an intravenous bolus, 3 mg/kg bw, while the pentagastrin infusion was maintained. The effect of cimetidine on stimulated acid secretion was followed during three consecutive 15 minute periods.

STATISTICS

Blood flow (F) in the muscle layer tissue, as reflected by the disappearance of β -radiation, was calculated using Kety's equation^{12 13} for blood flow determination in homogenously perfused tissues:

$$F = \frac{\ln 2}{t_{\frac{1}{2}}} \times \lambda \times 100 \quad (1)$$

λ , the tissue-blood partition coefficient was set to 0.84 for ⁸⁵Kr.^{8 9} The washout curve was plotted semilogarithmically and blood flow calculated from the straight line obtained. The straightness of the line obtained after plotting served as a control of the experimental conditions, any change in its slope indicating an altered perfusion during the recording.

Total gastric blood flow was calculated from the linear plot of the λ -elimination curves, using the equation proposed by Zierler¹⁴ as modified by Bassingthwaite.^{15 16}

$$F = \frac{C_p - C_T}{\int_0^T C(t) dt} \times \lambda \times 100 \quad (2)$$

where C_p = peak value of recorded radioactivity; C_T = radioactivity at time T.

The relative weights of the wall layers of the stomach were determined in resected gastric specimens, from duodenal ulcer patients in the following manner: after fixation in formalin and staining with haematoxylin-eosin, slices 2 μ m thick were cut from the stomach wall. Specimens were photographed with a macro-lens (magnification, $\times 5$). The muscle and mucosa-submucosa layers, cut from the photographic paper were weighed (accuracy 1/1000 g) and the relative weights calculated. In 10 specimens from the antrum the relative muscle and mucosa-submucosa weights were $48 \pm 3\%$ and $52 \pm 3\%$ ($\bar{x} \pm SD$). In 11 corpus specimens the corresponding weights were $39 \pm 4\%$ and $61 \pm 4\%$.⁹

Knowing these weight ratios, mean blood flow in the mucosa-submucosa could be calculated from the measurements of total gastric blood flow (γ recording) and muscle layer blood flow (β recording).

Results

CAT STUDIES

The cat experiments were primarily performed to establish at which time, T , the recording of the elimination should be terminated. This question was studied in five animals (eight runs). Pentagastrin was infused throughout the experiments in doses ranging from 500 to 800 ng/kg $\times$ h. Blood flow recordings, using the ^{85}Kr washout and venous outflow techniques simultaneously, were done before and after the cat had been given cimetidine 3–4 mg/kg bw, as a bolus dose intravenously. Recordings of the elimination of ^{85}Kr were started 5–10 minutes after cimetidine had been given. Upon drug injection total gastric blood flow decreased moderately, at most about 30%. In order to reproduce the experimental situation in the human studies, no effort was made to await maximal effect of the injected drug (see Discussion). The curves, recorded by the scintillation detector, were plotted on a linear diagram and the flow calculated according to Bassingthwaite's modification of Zierler's original formula (equation 2). Blood flow was estimated from washout curves where the tail of the curves had been excluded at different times, T . The tracer concentration at T , C_T , was related to the peak radioactivity recorded, C_P , during each washout period. The ratio $C_T:C_P$ was varied between 0.20 and 0.60 as illustrated in Fig. 1 and the relationship between the estimated and measured flow was determined at each $C_T:C_P$ value. Figure 1 shows that a good agreement between the two methods was observed at a $C_T:C_P$ ratio around 0.5 before and 0.4 after giving cimetidine. These values were therefore used for calculating corpus blood flow before and after giving the drug. The 'resting' ratio of 0.20 was used when calculating blood flow in the antrum, under the same experimental conditions.^{8 9 17}

HUMAN STUDIES

Validation of the method

It was shown in an earlier study that human gastric blood flow was markedly increased during maximal gastric acid secretion evoked by pentagastrin.¹⁵ The vasodilatation was confined to the mucosal-submucosal layer to which about 95% of total gastric blood flow was distributed.¹⁵ Consequently, a monoexponential washout, probably reflecting

Fig 1 Ratio between estimated gastric blood flow in cat (determined from ^{85}Kr washout curves) and measured gastric blood flow (determined from recordings of total venous outflow) correlated to $C_T:C_P$ ratio during pentagastrin infusion before and after cimetidine. Bars denote SE.

blood flow in the mucosa, was observed in the initial part of the elimination curve recorded by the scintillation detector, as the small portion of radioactivity distributed to the muscle layer did not appreciably influence the initial shape of the curve. A comparison was therefore made between blood flow estimated from the initial slope (calculated according to Kety; equation 1) and the average blood flow estimated in the mucosa-submucosa (calculated according to Bassingthwaite *et al* as described in Methods). Figure 2 gives the results, when performing such an analysis on flow studies where total gastric blood flow exceeded 100 ml/min $\times$ 100 g in which muscle layer blood flow was 5% of total flow or less in all studied subjects except one. Observations made in this and previous studies⁹ were included in this Figure, showing a fairly good correlation between the two methods ($r=0.76$). As expected, average blood flow in the mucosa-submucosa was lower than that calculated from the initial slope, the latter reflecting mainly blood flow in the secretory portions of the mucosa.

Blood flow and flow distribution

A continuous infusion of pentagastrin, 600 ng/kg $\times$ h, was started in all patients once anaesthesia was induced. The first recording of pentagastrin stimulated blood flow, was performed 30–35 minutes later, immediately after which cimetidine was given as a bolus intravenously (3 mg/kg bw). The operative situation did not make it feasible to await maximal effect of the H_2 -receptor blockade

Fig 2 Correlation between mucosal-submucosal blood flow values estimated according to Bassingthwaite and from initial slope according to Kety. Line was constructed according to method of least squares. Dotted line indicates line of identity.

and the second injection of ^{85}Kr was therefore carried out five minutes after cimetidine was given. Each recording took 5–10 minutes. In three cases recordings were made over the antrum and in eight cases over the corpus of the stomach. The calculated values for total blood flow and flow distribution before and after cimetidine are given in the Table. There was a significant decrease in total gastric blood flow and in blood flow to mucosa-submucosa

layer tissue in all patients where the secretory part of the stomach was studied ($p < 0.05$; Wilcoxon's rank sum test). In the muscle layer tissue no significant changes were found. The results indicate that the decrease of corpus blood flow seen after cimetidine reflects a decrease of blood flow occurring only in the mucosa-submucosa. The flow determinations in the antrum revealed no changes, although the number of observations are too few to allow statistical analysis.

Blood flow and acid secretion

Gastric acid secretion was determined pre-operatively in seven patients, before and after giving cimetidine as described in Methods. Cimetidine decreased the pentagastrin induced secretion in all subjects studied. Within 15 minutes the peak acid secretion was reduced to $34 \pm 5\%$ (Mean $\pm$ SE) of that observed after pentagastrin. Between 30 and 45 minutes after the cimetidine bolus was given, the secretion rate had decreased further, to $19 \pm 4\%$ of maximum. Blood flow in the corpus mucosa-submucosa tissue layer, recorded five minutes after injection of cimetidine decreased as illustrated in Fig. 3, where flow is plotted *versus* acid secretion.

The response was remarkably similar in most studied subjects, even from a quantitative point of view. Figure 3 also shows that there was no apparent relationship in the antrum between blood flow in the mucosa-submucosa tissue layer and acid secretory capacity.

Table Blood flow and flow distribution in the actively secreting human stomach, before and after cimetidine

Patient (no)	Pentagastrin infusion, 600 ng/kg $\times$ h					Pentagastrin infusion, 600 ng/kg $\times$ h and cimetidine 3 mg/kg				
	Blood flow, ml/min $\times$ 100 g			Flow distribution %		Blood flow, ml/min $\times$ 100 g			Flow distribution %	
	Total	Mucosa-submucosa	Muscle-layer	Mucosa-submucosa	Muscle-layer	Total	Mucosa-submucosa	Muscle-layer	Mucosa-submucosa	Muscle-layer
Corpus										
1	95	149	12	95	5	41	57	16	85	15
2	139	222	10	97	3	76	118	9	95	5
3	77	119	10	95	5	29	41	10	87	13
4	66	104	7	96	4	34	51	8	91	9
5	48	75	4	96	4	21	31	6	89	11
6	106	162	18	93	7	33	45	14	83	17
7	88	135	7	97	3	11	12	9	68	32
8	98	153	6	98	2	54	85	5	96	4
Mean	90	140	9	96	4	37	55	10	87	13
SE	10	15	2	0.5	0.5	7	12	1	3	3
Antrum										
9	27	41	11	80	20	30	48	9	85	15
10	21	37	4	91	9	16	27	4	88	12
11	20	34	4	90	10	20	34	5	88	12
Mean	24.5	37	6	87	12	22	36	6	87	13
SE	2	2	2.5	3.5	3.5	4	6	2	1	1

Blood flow is expressed per 100 g of the respective tissue.

Fig 3 Mucosa-submucosa blood flow in the corpus and antrum in 11 duodenal ulcer patients during pentagastrin infusion, before and after the addition of cimetidine. Blood flow is correlated to peak acid output and acid output 15 minutes after cimetidine determined preoperatively.

Discussion

The importance of gastric blood flow for ulcer formation and bleeding disorders in the stomach duodenum is not clear. The effects on blood flow of various anti-ulcer drugs are insufficiently known, mainly for lack of a suitable measuring method, applicable in man. The methods available are mostly based on marker clearance¹⁸⁻²⁰ and, consequently, measure only blood flow in the secretory part of the gastric mucosa. Also, their validity in quantifying that particular flow is being questioned, especially for determination of resting blood flow.²¹⁻²² The qualitative analysis they allow, however, is in accordance with results obtained in animal experiments, using other techniques.²³⁻²⁴

An established concept is that an increase in acid secretion cannot occur without an increase in mucosal blood flow and that reduced acid secretion results in a decrease in flow under physiological conditions.²⁵ This has also been shown to be true for the human stomach using the present and other techniques.^{7-9 18-26} In consequence, drugs which reduce acid secretion have been tried in the treatment of upper gastrointestinal bleedings.^{1-5 27-28} Early clinical reports and experimental

evidence indicated that the histamine H₂-receptor antagonists cimetidine effectively reduced gastric mucosal blood flow and increased intragastric pH,^{2 6 29 30} albeit only in situations with active secretion and augmented flow.³¹ In a number of ensuing clinical reports on the effect of cimetidine in patients with gastroduodenal bleedings the results have been less impressive, both when the drug was used for treatment and for prophylaxis,^{1 3 26} making the whole issue unsettled.

To investigate what effect cimetidine might have on the size and distribution of augmented gastric blood flow we studied 11 duodenal ulcer patients intraoperatively. Application of a recently developed inert gas washout method, based on the β - and γ -emitting properties of the isotope ⁸⁵Kr, enabled simultaneous determination of total blood flow and blood flow distribution to the wall layers of the stomach. The method has earlier been applied to the study of colonic and small intestinal blood flow in man^{10 11} and the present modification allows measurement also of gastric blood flow in man.^{8 9} In animal studies and in human intestinal blood flow recordings the blood flow recordings can be validated with independent, simultaneously used techniques, for instance recording of venous outflow or isotope elimination after local injections in the various tissue layers studied.^{10 11} The local isotope injection technique was used also in the human stomach in an earlier study and a fairly good comparison could be shown between the flow values for gastric mucosa estimated from the elimination curves recorded after intra-arterial and local tissue injections.⁹ Moreover, the corresponding mucosal blood flow values found when using two different methods for the calculations serve to validate the method and the C_T:C_P ratio used (see Fig. 2).

The operative situation necessitated that the effect of cimetidine had to be measured starting five minutes after the drug was given – that is, before its full effect on acid secretion was reached. This probably implies that the effect of cimetidine on gastric blood flow was, if anything, underestimated.

Cimetidine evoked similar qualitative and quantitative changes in acid secretion and blood flow in all subjects studied (Table). We found that the induced change entirely reflected a decreased mucosa-submucosa blood flow in the corpus part of the stomach (Fig. 3), suggesting that observed flow effects of cimetidine reflected a change of the local chemical environment secondary to the decreased acid secretion.

In the muscle layer tissue of the corpus and in the whole of the antral wall virtually no change was seen nor did the blood flow in these parts of the stomach respond much to pentagastrin.⁹ This sheds some

doubt on the importance of histamine H₂-receptors in the direct regulation of gastric micro-circulation.^{6 32 33} Also, it provides a possible explanation as to why cimetidine fails to influence bleeding from the antral area, the source of bleeding here usually being from a peptic ulcer.

We have earlier studied the effect of pentagastrin on gastric blood flow in duodenal ulcer patients. In the corpus mucosa a 12-fold increase was found, compared with a five to six fold increase in the normal subjects. Our results from the present study indicate that half of this increase was abolished within 15 minutes after the injection of a therapeutic dose of cimetidine. We did not see any change in the relation between acid secretion and blood flow when either of these decreased in accordance with earlier observations.⁹ We therefore assume that the same dose of cimetidine is sufficient to bring blood flow down to a normal 'resting' level for duodenal ulcer patients, in accordance with results from the neutral red clearance studies.⁷

It has not yet been possible to study the blood flow in the duodenum with the ⁸⁵Kr-washout method. Considering the absence of parietal cells in the duodenal mucosa and the common arterial supply to the duodenum and the antrum it seems unlikely that cimetidine should have a different effect on the blood flow in the duodenum than on the antral circulation.

Thus, when using anti-secretory agents in attempts to control gastroduodenal bleeding the difference in effects on secretory and non-secretory parts of the mucosa must be considered. Cimetidine appears to have a profound influence on blood flow in the secretory gastric mucosa but the question if and when this effect is desirable in the clinical situation is not yet answered. Our findings support the observations that the drug may be effective in the temporary control of diffuse bleeding disorders from the corpus of the stomach. Recent experimental evidence indicates, however, that the prolonged use of cimetidine in this situation may indeed be harmful to the integrity of the gastric mucosa.³⁴

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