Our studies showed that serum potassium concentration fell in proportion to the fall in plasma glucose concentration. The fall in serum potassium concentration occurred irrespective of whether the fall in plasma glucose concentration was caused by inhibition of glucose output by the liver or by stimulation of peripheral glucose uptake. This suggests that insulin may affect potassium transport into cells independently of changes in glucose transport. This concept is not new—insulin increases potassium uptake into the isolated liver in a glucose-free medium,^{23 24} and small doses of insulin cause potassium uptake but no glucose uptake in the human forearm.²⁵ The changes in serum potassium concentration that we found differ from those reported by Schade and Eaton²⁶ in dexamethasone-pretreated diabetics. In their patients the plasma potassium concentration had not changed after one hour of infusion of insulin at 0.01 and 0.1 U/kg/h.

Our findings that concentrations of ketone bodies and free fatty acids are reduced by the low- and high-dose infusions of insulin suggest that these metabolic pathways are highly sensitive and that the plasma insulin concentration achieved with the low-dose infusion is sufficient to inhibit free fatty acid release and ketogenesis. Schade and Eaton²⁶ also reported that ketone bodies and free fatty acids were maximally reduced by an insulin infusion of 0.1 U/kg/h. Low-dose insulin regimens will probably be effective in correcting the ketonaemia and acidaemia in uncontrolled diabetes and also cause less profound changes in serum potassium concentration.

The dose-dependent effect of insulin on the liver and peripheral tissues that we have shown in man emphasises the importance of steady-state plasma insulin concentrations in experiments designed to investigate the mechanism of action of insulin. Our results also emphasise the importance of the effect of insulin on glucose production in diabetes, which has been largely ignored.

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Cimetidine for recurrent ulcer after vagotomy or gastrectomy: a randomised controlled trial

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Summary and conclusions

In a randomised controlled trial cimetidine 1 g daily for six weeks was compared with placebo in the treatment of recurrent ulcers after gastrectomy or vagotomy for duodenal ulcer. Healing, assessed endoscopically, was seen in seven out of 12 patients given cimetidine and in five out of 12 controls. Four of the controls whose ulcers did not heal were subsequently treated with cimetidine, and in two the ulcers healed after six weeks. Pain recorded

by the patient and consumption of alkalis were each slightly but not significantly less in the cimetidine-treated patients.

When cimetidine is to be used for recurrent ulceration probably the dosage and duration of treatment should be increased.

Introduction

Cimetidine reduces gastric acidity and promotes healing of duodenal and gastric ulcers. When ulceration recurs after gastrectomy or vagotomy the usual cause is inadequate reduction of acidity; thus cimetidine might also be expected to promote healing of these ulcers. Delle Fave *et al*¹ found healing at two months in nine out of 10 patients with recurrent ulcer after gastrectomy; Hoare *et al*² were successful at six weeks in 17 out of 20 patients; and Wastell *et al*³ found healing in four out of eight patients at the end of six weeks.

All these were open trials without controls. We have con-

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ducted a randomised controlled trial of cimetidine for recurrent ulceration after operations for duodenal ulcer.

Patients and methods

Patients were admitted to the trial only if an active ulcer, recurring after gastric surgery, had been seen endoscopically within seven days of entry. Patients were randomly allocated to two groups, each taking one tablet three times daily with main meals and two tablets at bedtime. The tablets contained either cimetidine 200 mg or placebo. A simple antacid containing calcium carbonate, magnesium carbonate, and magnesium hydroxide was also supplied. Patients were permitted to take these tablets without restriction for the relief of pain but were asked to take no other anti-ulcer drugs. The trial was conducted in outpatients in all cases. Patients were reviewed at two-weekly intervals and endoscopy was repeated after six weeks, within two days of the end of treatment. With two exceptions endoscopy was performed by the same observer, who was unaware of which tablets the patient had been taking. If the ulcer was unhealed the code was broken and patients who had received placebo were given six weeks' treatment with cimetidine 1 g daily on an open basis followed by further endoscopy.

Each patient kept a diary card recording episodes of day or night pain and their severity. Use of antacid was also recorded and was checked at each visit by a tablet count. The consumption of cimetidine or placebo tablets was similarly checked.

Twenty-five patients entered the trial during 15 months. One failed to co-operate in taking tablets and attending for review and is excluded from the analysis. Of the remainder, 12 received cimetidine and 12 placebo. Two patients in the placebo group were withdrawn during the fourth week because of intolerable pain and were treated surgically.

Table I shows the primary operations performed in the two groups and the numbers of patients whose ulcers remained unhealed after six weeks' treatment with cimetidine or placebo. The sites of the recurrent ulcers are given in table II. There was no difference in the distribution of treatments in either respect. There were three women in the trial, all of whom received placebo.

Results

After six weeks, healing was seen in seven of the cimetidine-treated and five of the placebo-treated patients (table I). The two patients withdrawn from the placebo group because of intolerable pain were regarded as treatment failures. At operation their ulcers were found to be unhealed.

TABLE I—Primary operations performed in the two treatment groups (patients whose ulcers remained unhealed at six weeks are given in parentheses)

	Gastrectomy	Vagotomy and pyloroplasty	Vagotomy and gastro-jejunostomy	Proximal gastric vagotomy	Total
Cimetidine	1	3 (1)	3 (1)	5 (3)	12 (5)
Placebo	2 (1)	3 (1)	4 (3)	3 (2)	12 (7*)

*Includes two patients who were withdrawn.

TABLE II—Sites of recurrent ulcers in the two treatment groups (patients whose ulcers remained unhealed at six weeks are given in parentheses)

	Duodenum		Stomach		Jejunum	
	Cimetidine	Placebo	Cimetidine	Placebo	Cimetidine	Placebo
No of patients	5 (3)	4 (3)	3 (1)	4 (2)	4 (1)	4 (2)

Of the 10 patients who completed the trial but whose ulcers remained unhealed, three in the cimetidine group and one in the placebo group were thought to have had a reduction in the size of their ulcers. In one patient in the placebo group the ulcer was judged to be larger. Mucosal inflammatory changes—for example, jejunitis or duodenitis—were thought to be less severe in two of the cimetidine-treated and one of the placebo-treated patients whose ulcers were unhealed.

TABLE III—Occurrence of pain and use of antacids recorded by patients in the two treatment groups. (Expressed as percentage of days in each fortnight on which pain occurred and average number of tablets used per patient per fortnight)

	Days 1–14		Days 15–28		Days 29–42	
	Pain (% of days)	Antacid (tablets/patient)	Pain (% of days)	Antacid (tablets/patient)	Pain (% of days)	Antacid (tablets/patient)
Cimetidine	37.5	15.4	32.5	18.0	25.0	15.6
Placebo	46.0	23.1	46.0	25.0	30.0	22.7

Four patients in the placebo group whose ulcers had not healed were subsequently given cimetidine. Healing was achieved in six weeks in two; in the third the ulcer was unchanged, and in the fourth a duodenal ulcer was smaller, so he was given a further four weeks of cimetidine. That ulcer healed, but the patient was found to have developed a new gastric ulcer, which was treated by re-vagotomy and antrectomy.

Six patients, four of whom were in the cimetidine group, had no pain at any stage of the trial, nor did they have pain in the week preceding the trial. Bleeding was the presenting symptom in three of these patients. In each observation period less pain and less antacid consumption were recorded in the cimetidine group, but the differences were not statistically significant (table III).

Discussion

Though there was a trend favouring cimetidine in terms of healing, ulcer pain, and consumption of antacids, there were no significant differences. We had originally intended to include larger numbers in the trial but it had become almost impossible to find patients who had not been treated with cimetidine before referral to us. It seems unlikely that doubling the numbers would have altered our conclusions.

Our results are disappointing when compared with the experiences of Delle Fave *et al*¹ and Hoare *et al*,² but their trials were both open. Delle Fave *et al* treated 10 patients with recurrent ulcers after gastrectomy; six were unhealed at the end of the first month, though nine were healed after two months. Their patients received 1.6 g cimetidine daily, so perhaps we gave our patients too low a dose for too short a time. In the experience of Hoare *et al*, 17 out of 20 ulcers healed in six weeks and two more were healed by the twelfth week. The dosage in their trial was the same as our own. The varied nature of the primary operations and the inclusion of seven patients with gastric ulcers in our trial could be criticised, but they were evenly distributed between the treatment groups. Duodenal recurrences, with six out of nine ulcers failing to heal, had the worst record, for reasons that we cannot explain.

We conclude that if cimetidine is to be used for recurrent ulcer it should be given in larger dosage and for longer, perhaps 1.6 g daily for two months. The maintenance treatment required will need to be determined. Most surgeons would be reluctant to keep patients with healed ulcers taking cimetidine indefinitely. Possibly cimetidine should be reserved for the poor-risk patient and preparing others for reoperation. Of the 24 patients in our series, nine have already come to definitive operation.

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