MEDICAL PRACTICE

*Medical Controversies***Cimetidine and duodenal ulcer***British Medical Journal*, 1979, 1, 169-173

Dr J H Baron was asked by the *BMJ* to present a case for medical treatment for duodenal ulcer. His article, published below, was then sent to a surgeon and a physician and all three met to discuss the topic with one of the *BMJ* medical editors, Dr Tony Smith, acting as chairman.

Working paper

Effective rational treatment of duodenal ulcer disease, a life-long diathesis with bouts and remissions, is based on ill-understood pathophysiology: excessive acid enters the duodenum with peptic digestion and ulceration.

Most ulcers heal over a period of weeks, but the natural healing rate can be improved by increasing mucosal resistance with drugs such as carbenoxolone or by decreasing gastric secretion with drugs such as the H_2 receptor antagonist cimetidine. Patients with clinically intractable or chronic recurrent duodenal ulcers used to be advised operation. In the early 1900s gastroenterostomy diverted gastric juice away from the bulb and allowed almost every duodenal ulcer to heal. This operation was abandoned because ulceration occurred in the jejunum receiving the diverted stream of acid pepsin. Vagotomy and/or antrectomy or partial gastrectomy reduce peak acid output by 60% to 80% and prevent ulcer recurrence in about 90%. In my model (fig 1) there is a threshold peak acid output

FIG 1—Parietal cell mass, peak acid output, and the secretory situation in peptic ulcer. From Baron¹ by permission of Butterworths.

(and parietal cell mass) below which duodenal ulcer disease is uncommon. Operative success in preventing relapse is proportional to the acid-lowering effect of the operation as well as the skill of the operator, so that nearly all, or merely most, or only some patients have their gastric secretion reduced by operation to safe levels.²

Are drugs a satisfactory alternative? Walan³ gave the anticholinergic 1-hyoscyamine in an optimum effective dose twice daily for two years to 28 patients and their course was significantly better than that of 28 patients on dummy tablets. Those who kept well had definite reductions of basal and maximal histamine-stimulated acid, whereas others could not tolerate an adequately acid-inhibitory dose because of side effects.

Royal Postgraduate Medical School and Hammersmith Hospital,
London W12 0HS

J H BARON, DM, FRCP, senior lecturer and consultant

General Hospital, Birmingham B4 6NH

J ALEXANDER-WILLIAMS, CHM, FRCS, consultant surgeon

Gastrointestinal Unit, Hull Royal Infirmary, Hull HU3 2JZ

J R BENNETT, MD, FRCP, consultant physician

Maintenance trials of cimetidine in duodenal ulcer

	Cimetidine dose and duration	n	Recurrence	Assessment
Bodemar and Walan ⁴	400 mg bd 1 year	19	3 16%	Endoscopy
	0	23	18 78%	
Blackwood <i>et al</i> ⁵	800 mg nocte 6 months	21	5 24%	Endoscopy
	0	24	21 88%	
Gudmand-Høyer <i>et al</i> ⁶	400 mg bd 1 year	26	3 12%	Radiological/clinical
	0	25	20 80%	
Gray <i>et al</i> ⁷	400 mg nocte 1 year	26	9 35%	Endoscopy
	0	30	25 83%	
Hetzel <i>et al</i> ⁸	400 mg bd 9 months	45	4 9%	Endoscopy
	0	48	32 75%	

Cimetidine does not have dose-related side effects, and in maintenance trials (see table) about 65% to 85% of patients kept free of relapse for 12 months, compared with recurrence rates of about 80% with placebo. Side effects were slight, and patients who relapsed on maintenance dosage of either cimetidine or placebo usually rehealed with a further course of cimetidine in full dosage. When maintenance treatment was stopped at the end of a year, the high relapse rate was the same as when full-dose cimetidine was stopped after initial healing of a duodenal ulcer (fig 2). These results suggest that maintenance cimetidine treatment for patients with chronic continuous symptoms might have to be for ever, a course most doctors are reluctant to embark upon because of the unknown risks of permanent H₂ blockade.

An alternative method of treatment is to stop cimetidine

after full dosage has healed an ulcer. Periodic relapses are treated by further full-dosage courses and so on intermittently.

We need long-term controlled trials of maintenance treatment versus operations. The anticholinergic inhibitor benzilium has been compared in a controlled trial with selective proximal vagotomy.⁹ After one year peak acid output was reduced by 49% in patients taking the drug and by 66% in the vagotomised; the 24 vagotomised patients had none (19) or minimal (six) symptoms, but only 10 of the 23 medically treated were symptom free, 10 having occasional eructations and three more severe symptoms, two of whom had relapsed when they defaulted from tablet taking.

It will be years before results are available for the more potent inhibitor cimetidine as compared with operation. Until then clinicians will have to make up their own minds whether they use maintenance cimetidine semi-permanently, or advise elective operation.

FIG 2—Life-table analysis showing estimated percentage probability (± 2 SE) of continued remission during and after cimetidine treatment for one year (solid line) and during placebo treatment for one year (broken line). From Gudmand-Høyer *et al*.⁶

Conclusion

Maintenance treatment with a potent inhibitor of gastric secretion such as cimetidine can appreciably reduce the known high recurrence rate of duodenal ulceration. Only controlled trials will allow a clear view of the relative merits for drug and operation in terms of acute and chronic safety, efficacy, acceptability, and cost.

References

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Discussion

CHAIRMAN: Could I start by asking each of you how he treats his patients with duodenal ulcers?

Dr J H BARON: I treat all endoscopic duodenal ulcers with cimetidine in full dosage. Nearly all heal as assessed endoscopically after four weeks and the rest after eight weeks' treatment. If they have a chronic history of recurrent ulceration which in previous years would have warranted an operation I then put them on maintenance treatment, 400 mg at night, for a year and then stop. If they relapse I reheal their ulcer with a further course of cimetidine and advise them to have an elective operation. Most patients refuse my advice. Some patients with periodic remissions and relapses prefer to repeat short courses in full dosage for each relapse, and others with chronic con-

tinuous symptoms wish to continue with maintenance cimetidine indefinitely even though I point out to them the unknown problems of efficacy and safety.

Mr J ALEXANDER-WILLIAMS: I treat my patients as I would wish to be treated; if I had a duodenal ulcer I would treat myself with cimetidine. At last we have a relatively non-toxic drug that can reduce acid secretion just as effectively as can a surgeon. The rate of referral for surgical treatment of duodenal ulcers has fallen to only half that of two or three years ago. Surgeons are all waiting for the backlash, but it has not yet happened.

Cimetidine is a perfect drug for treating the patient who has periodic exacerbations of duodenal ulceration—the man who is

seriously incapacitated three or four times a year for a week or two at a time. The drug is as effective as vagotomy in reducing acid secretion and it is much more convenient to take tablets for a week or so two or three times a year than it is to have the major upset to life of having an operation. However, surgical treatment is needed for the patient who is constantly relapsing. The patient who has a course of cimetidine, goes into remission, and as soon as the cimetidine is stopped has fresh symptoms: he will need an operation.

"I treat my patients as I would wish to be treated; if I had a duodenal ulcer I would treat myself with cimetidine"—Mr John Alexander-Williams.

Dr J R BENNETT: I quibble with the form of the question. I don't treat patients with duodenal ulcers: I treat their symptoms and deal with the complications as they occur. I'm not yet persuaded that we're in a position to alter the course of duodenal ulcer disease or prevent its complications. My methods are very close to those of John Williams: I use cimetidine to treat painful exacerbations, but if a patient quickly relapses and does this several times then I believe he's a candidate for surgical treatment. We know a great deal about what an operation does on both sides of the balance sheet. I'm not sure that we know so much about cimetidine.

Natural history

CHAIRMAN: How much do we know about the natural history of duodenal ulcer? If someone has got an abnormal gastric acid output now and proved duodenal ulcer, can we say that his gastric acidity is going to remain abnormal for the next 10, 20, or 30 years? If we can then perhaps one operation that will put him back closer to normal might be a reasonable option.

DR BARON: So far as we know the hypersecretion associated with duodenal disease is life-long. Similarly, in clinical experience patients who have troublesome duodenal ulcers giving frequent episodes of pain go on doing this year in and year out. I don't see patients whose condition burns itself out. A patient who has been having only one or two episodes a year can be controlled with cimetidine. For the patient having constant frequent pain my advice is an acid-lowering operation.

CHAIRMAN: Rather than take continuous cimetidine?

DR BARON: Most—I think I would say all—of my patients who have duodenal ulcer are given cimetidine and after a course of either four or eight weeks these have healed and are very satisfied. If the patient has had recurrent episodes I am prepared to put him on maintenance treatment with two tablets at night for a year. But what do you then do at the end of a year? I advise the patients to stop; and many relapse. I then advise them to have an operation. Almost without exception they refuse. They say if they can have one year completely symptom free by taking two tablets per night why can't they go on taking them indefinitely.

CHAIRMAN: Professor C G Clark at University College Hospital has raised the point (*BMJ*, 1978, 2, 123) that if we accept that perhaps 80% of patients who have cimetidine for a year stay free of symptoms the cumulative relapse rate over about five years could be expected to be 50% or more. Aren't we, says he, just putting off operation in these patients?

DR BARON: We used to talk about gastric ulcer in that way. The Americans said that at the end of 10 years half of all patients with gastric ulcers would have had a recurrence needing operation so they should all have had operations to start with.

The British said that at the end of 10 years half of patients with gastric ulcers did not have recurrences needing operation so that they should all be treated medically to begin with. The same data, different interpretations. When my patient says I don't want an operation, I want to go on with cimetidine, I am prepared to agree and go on prescribing cimetidine 400 milligrams nightly.

Another practolol?

DR BENNETT: Whereas I am not—and I'm not enthusiastic even on giving it for a year. I am cautious about all drugs and I have a dread that cimetidine could be another practolol.

MR ALEXANDER-WILLIAMS: At least cimetidine is specific in its action of reducing acid secretion. Whereas the least disturbing surgery—proximal gastric vagotomy or highly selective vagotomy—is still blunderbuss treatment. Vagotomy not only reduces acid secretion: it divides all the afferent nerve fibres from the body of the stomach; it produces accelerated gastric emptying of liquids; and it leads to a whole set of symptoms of its own that cimetidine does not. Having spent my last 20 years studying the bad effects of operations, I'm very pleased to find that now there is a drug that is absolutely specific and will stop acid secretion.

DR BARON: Yes and no. Cimetidine is a H_2 receptor antagonist and is specific—but the trouble is that there are (though we couldn't have known until cimetidine came along) H_2 receptors in the heart and elsewhere in the circulation, so that there is ample scope for potential major side effects by chronic maintenance use of cimetidine.

MR ALEXANDER-WILLIAMS: You haven't measured the effects of any of these?

DR BARON: Not yet.

DR BENNETT: And some of them are immeasurable. I've no doubt that outside hospital cimetidine is being used in large doses over long periods. In my conservative apprehensive way this concerns me even more than your practice of a small dose for a year—because there are some people who seem to be taking full dosage for a period of months.

DR BARON: Some doctors consider that they should take the responsibility and not allow their patients to have maintenance treatment because of the unknown effects. I take the opposite view. The patient should be able to ask questions and be given answers. Two questions they always ask about cimetidine are whether they might "get used to" the drug and what are the long-term side effects. I tell them that so far as we know tolerance has not developed to cimetidine and we can reasonably predict that it will go on inhibiting acid; but that we cannot know yet about long-term side effects—so that some unknown risks have to be taken by patients who want the drug. And if patients do

"I am cautious about all drugs and I have a dread that cimetidine could be another practolol"—Dr J R Bennett.

wish to take it I am prepared to allow them to take maintenance cimetidine.

CHAIRMAN: What about the hazards of stopping treatment—rebound perforations, for example?

DR BARON: There have been suggestions that by giving cimetidine and suppressing acid we are interfering with a normal system and that prolonged treatment may lead to hyperplasia of the parietal cells, so that when cimetidine is withdrawn the patient has an excess number of cells secreting

acid and rebound hypersecretion. I don't think that this happens. Even so, when a patient who has been on cimetidine stops the drug the acid secretion returns to what it was beforehand; and possibly the sudden reintroduction of acid secretion on to a duodenum that was healed might allow sudden reulceration of the duodenum and perforation.

MR ALEXANDER-WILLIAMS: There must be thousands of patients who have stopped taking cimetidine. Everybody who has ever taken it has stopped except those who are still on it. Set against that, the number of reported cases of rebound perforation must be very small.

Asymptomatic ulcers

DR BENNETT: I should like to ask Hugh Baron about the treatment of ulcers seen endoscopically—for example, in patients whose symptoms are confined to gastrointestinal bleeding. Do you treat these asymptomatic ulcers with cimetidine?

DR BARON: Yes, I do. I don't believe anybody should be left with a duodenal ulcer.

DR BENNETT: I regard that as too extreme. For hundreds of years tens of thousands of people have been walking around

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with untreated ulcers. I can see no reason at all for giving the drug to the patient who's bled from a duodenal ulcer and sits up in bed the next day having stopped bleeding and says he feels fine.

CHAIRMAN: Supposing you have a patient who's got diabetes and refuses to produce any symptoms. Do you treat him?

DR BARON: Certainly.

DR BENNETT: I don't think the conditions are comparable. The diabetic will develop progressive ill health and complications.

DR BARON: Hypertensives don't have symptoms, but the analogy is sound. 1952 was the year when ganglion-blocking drugs came in and I well remember the arguments. "You are not seriously suggesting that patients should take a drug two or three times a day for the rest of their lives to keep their blood pressure down, why shouldn't they have an operation, such as sympathectomy, which will do it for good?" There was the same concern about committing patients to potential life-long side effects. Now we know that everything we were taught in 1952 was wrong.

"Failed cimetidine"

MR ALEXANDER-WILLIAMS: I am now being referred for operation patients who have been diagnosed as having duodenal ulcer and whose symptoms are not controlled adequately by cimetidine. I think this is very dangerous since the pain is almost certain to be due to something other than the duodenal ulcer. Or if it is due to the duodenal ulcer the cause of the ulcer is something that cannot be relieved by vagotomy. I do not know whether anyone has performed an analysis of the success rate of duodenal ulcer surgery in so-called "failed cimetidine" patients, but I would suspect it would be low.

We have studied a group of people with "the phantom ulcer syndrome"—patients who've had surgery for ulcers diagnosed

on radiological evidence in whom there was little or no evidence of ulcer at operation. They fare badly after operation. I think that in the cimetidine era surgeons will need to be wary of patients who have failed medical treatment. The patients I welcome are those who have had cimetidine with very good relief but who have relapsed quickly and make the decision that rather than go on like that for the next 15 years they'd prefer an operation. Patients who cannot remember to take tablets, whose life is very irregular—these are patients that I will operate on with a clear conscience.

DR BARON: Cimetidine is a very good therapeutic test for surgery: if the patient has had a good result with the drug I think it highly likely he will do well after an operation. If, on the other hand, somebody has not responded to eight weeks of cimetidine in standard dosage (and this is very rare) then there is something drastically wrong with his secretory mechanism. He needs a full investigation.

DR BENNETT: You say it's rare, and I would have said it was rare too—and yet all the controlled trials have a failure rate at four weeks. You quoted a success rate at four weeks of 80%. What happened to the other 20%?

DR BARON: You can't expect every duodenum to heal in four weeks. There must be some biological variation. I go on for another four weeks and sometimes I double the dose.

CHAIRMAN: What about that other difficult problem—the treatment of patients whose symptoms recur after vagotomy? Is cimetidine effective for recurrent ulceration?

MR ALEXANDER-WILLIAMS: In the short term the response of recurrent ulcers to cimetidine is quite dramatic. But I have attended a number of meetings, particularly in the United States, at which surgeons have voted very much against the idea of treating recurrent ulcers with cimetidine. I think the great advantage of cimetidine is that even if it only controls the ulcer temporarily (and the symptoms return rapidly once the drug is stopped) at least I am in a position to operate without encountering a very acute oedematous inflammatory process around the ulcer. It makes surgery a great deal safer to operate after cimetidine.

What we do now is to heal the recurrent ulcer; then we titrate the patient against cimetidine and see how we can keep him in symptomatic remission. If we can do that at a dose of, say, two tablets at night then I think I would go on treating such patients indefinitely.

DR BARON: I agree. The patient should have a choice. We reckon that 10% of all patients who have stomach operations, whether it's vagotomy or whatever, have some recurrent ulceration—and I think it's fair to tell the patient of that possibility before they agree to surgery. Some patients say they couldn't possibly go on taking tablets for the rest of their lives; others are only too willing to do so.

MR ALEXANDER-WILLIAMS: To me as a surgeon who used to deal with many recurrent ulcers this has been the greatest boon of cimetidine.

DR BENNETT: Even so, the morbidity and mortality of second operations are greater than for first operations?

MR ALEXANDER-WILLIAMS: Yes they are, though the statistics are a little biased. Primary operations are performed by surgeons at various levels of training. Recurrent ulceration tends to be referred to experienced specialist surgeons and therefore the mortality rate may be less. My unit's series of recurrent ulceration is about 80 patients without mortality. However, overall the reported mortality rate for re-operation for recurrent ulcer is about 5%. If cimetidine is given to produce complete ulcer remission and then there is an elective re-operation, I think the risk could be reduced to the same 0.5% as that of the primary operation.

DR BARON: Which is why cimetidine comes in much more solidly for recurrent ulceration. I press the patient less firmly to accept re-operation.

MR ALEXANDER-WILLIAMS: We should remember that the natural history of recurrent ulcer is rather more aggressive than a primary ulcer. In the days before cimetidine surgeons

used to write in their textbooks that recurrent ulcers never respond to drugs. Now you have to weigh up the balance sheet very carefully.

Side effects

CHAIRMAN: Is there in fact adequate machinery for collecting and measuring side effects of a drug which, like cimetidine, comes into general use very quickly? There have been large numbers of series published on patients followed for 12 months. Are there enough series in hand at the moment of patients who are being followed for a longer period than that?

DR BENNETT: I think there are. As we know the Committee on Safety of Medicines is considering monitored release of new drugs and I'm certain that will be a change that will prove

crucial for the patients' benefit. The companies themselves are going to see such a change in their own interest because the reaction today of any patient who has any suspected adverse effect is to slap a writ on the company. But I think that Smith Kline and French are very actively collecting all the information there is and long-term trials are being done.

CHAIRMAN: So that within a year or two we should be able to say to patients that just as we can measure the long-term risks as well as the immediate risks of vagotomy we can do the same thing with cimetidine.

DR BARON: Data from double-blind trials of cimetidine over one year so far suggest it is reasonably safe. So far I have been happy to provide it for a year. I'm not confident in prescribing it for more than a year—but I am willing to do so because I'm a physician and if I don't prescribe new drugs for periods longer than that for which there are data, who will?

For Debate . . .

Fats and atheroma: an inquest

Sir JOHN McMICHAEL

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Summary and conclusions

All well-controlled trials of cholesterol-reducing diets and drugs have failed to reduce coronary (CHD) mortality and morbidity. Nevertheless, commercial, professional, and even government-sponsored propaganda continues. Experimentally some vegetable oils and hardened fats can be more damaging to arteries than butter. There are other hazards to heart muscle from vegetable oils.

Israelis consume a high polyunsaturated fat diet equal to that recommended for prevention of CHD in USA but their CHD incidence is very high. Urban Bedouins are also affected. The primary clofibrate prevention trial underlines unacceptable risks which could apply also to diets. Official medical endorsement of these cholesterol reducing measures should be withdrawn.

Introduction

Because cholesterol deposition is an important feature in the anatomy of atheromatous plaques, though in only 50% of them,¹ and since cholesterol can move from the blood in and out of the plaque, it has been assumed that raised concentrations of cholesterol in the blood increase the severity of the lesion and may be a factor in its development. This has been the basis of many reports by national committees and epidemiologists who have correlated the incidence of coronary heart attacks and

deaths from coronary heart disease with a high fat intake in more prosperous populations. Recommendations have been made to lower the cholesterol content of the blood,² and indeed many trials have been organised to test if this might be beneficial. The best-conducted dietary trials under the auspices of the MRC's statistical control have given convincingly negative results. In survivors who have had coronary manifestations, and are thus at special risk, low-fat³ and soy-bean oil diets,⁴ which can lower the blood cholesterol concentration, have been entirely ineffective in slowing the progress of the disease towards recurrences or death. Drugs that reduce the blood cholesterol concentration also failed to influence⁵ outcome when tried on large numbers of similarly affected patients whose disorder was liable to deteriorate.

In addition to the carefully conducted British trials evidence had accumulated to suggest that raised cholesterol concentration had little to do with atheroma. Anitschkow, who first produced patchy fatty lesions in the arteries by feeding large amounts of cholesterol to rabbits, said that the blood cholesterol concentrations were raised to a degree that is never seen in man and he did not believe that this was the cause of atheroma.⁶ Substantial rises in cholesterol concentration after thyroidectomy in the treatment of heart disease before the war equally did not produce an excess of coronary atheroma in man.⁷ Diets with a high and low fat content that were consumed by different monastic orders did not alter the incidence of coronary disease.⁸

Polyunsaturated fats

Nevertheless, many committees who have recommended taking hopeful attitudes to potential benefits from cholesterol reduction continue to make their assertions, and the propaganda is now being endorsed by political and government organisations. Senator McGovern's Committee in the USA⁹ recommended reduction of fat intake by substituting polyunsaturated

London NW11 7AA

Sir JOHN McMICHAEL, FRCP, FRCS