Topics in Therapeutics

Edited by D.W. Vere

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EDITOR'S PREFACE

The aim of this book is to present the advancing front of medical treatment, using examples. There is no attempt at a comprehensive account. The examples include both successes, which tend to be recognised, and disaster areas which are often overlooked and where progress is impeded by that if for no other reason. These aspects are further broken down into sections – new drugs, new ways to use old drugs, new forms of patient care or planned treatment schedules, and a new look at certain problems and adverse effects.

Clinical pharmacology is the relevant applied scientific basis for drug therapy. This book is, in a sense, also a shop window for clinical pharmacology in the main street of general medicine. Some will say that it is 'just' a part of general medicine. It is true that it is an organic part of the body of general medicine, but it is an increasingly specialised part, with knowledge, attitudes and skills which are recognisably its own, and which makes an indispensable contribution to the whole organism of medicine. From its own standpoint, the science of clinical pharmacology changes the practice of medicine. But general medicine points the way and provides relevant problems for clinical pharmacology. The present series of contributions illustrates this relationship between medicinal therapy and clinical pharmacology.

It is a pleasant duty to thank those who have helped so much to produce this book. A fine team of contributors, the staff of Pitman Medical and the smoothly effective team at the Royal College of Physicians may not "make drudgery divine", but at least they transform the exercise into something pleasant, amusing and quite fascinating. Seldom can so much useful information have been brought so quickly to so many by so few.

CONTRIBUTORS

P M Brown MB, BS, MRCP	Research Fellow, St Thomas's Hospital, London
P W Brunt MD, FRCP	Consultant Physician/Gastroenterologist, Clinical Senior Lecturer in Medicine, Aberdeen University, Aberdeen
M Caplin FRCP	Consultant Physician, London Chest Hospital, London
R D Cohen MD, FRCP	Professor of Metabolic Medicine, The London Hospital, London
D M Davies FRCP	Senior Lecturer in Clinical Toxicology, University of Newcastle upon Tyne, and Consultant Physician, Newcastle AHA(T) and Shotley Bridge General Hospital, Co. Durham
M Davis MD, MRCP	Consultant Physician, Liver Unit, King's College Hospital, London
Susannah J Eykyn MBBS, MRCPath	Senior Lecturer in Microbiology, St Thomas's Hospital, London
A M Geddes FRCP(Ed), MRCP	Department of Communicable and Tropical Diseases, East Birmingham Hospital, Birmingham
F J Goodwin MB, FRCP	Consultant Physician, The London Hospital, London
J P Keet MB, BS, MRCP	Consultant Physician, Croydon Area Geriatric Services, Queen's Hospital, Croydon
A F Lant PhD, FRCP	Professor of Clinical Pharmacology and Therapeutics, Westminster Hospital, London
T Leung FIM, FIMLS	Chief Technician, Department of Medical Microbiology, The London Hospital Medical College, London
J S Malpas MB, BSc, DPhil, FRCP	Director, Imperial Cancer Research Fund, Medical Oncology Unit, St Bartholomew's Hospital, London
T W Meade BM, MRCP, FSCM	Director, MRC/DHSS Epidemiology and Medical Care Unit, Northwick Park Hospital, Harrow, Middlesex
D D Munro MD, FRCP	St Bartholomew's Hospital, London and Edgware General Hospital, Middlesex
Margaret Rehahn FIS	Statistician to the National Heart and Chest Hospitals, London
C M Saunders OBE, FRCP	Medical Director, St Christopher's Hospice, London

J H B Saunders MB, MRCP	Department of Therapeutics, University of Dundee, Dundee
P H Sönksen MD, FRCP	Reader in Medicine, St Thomas's Hospital Medical School, London
L A Turnberg MD, FRCP	Professor of Medicine, University of Manchester, Hope Hospital, Salford
R Twycross MA, DM, FRCP	Consultant Physician, Churchill Hospital, Oxford
D W Vere MD, FRCP	Professor of Therapeutics, The London Hospital Medical College, London
J D Williams BSc, MD, MRCPath, DCP	Professor, Department of Medical Microbiology, The London Hospital Medical College, London
K G Wormsley DSc, MD, FRCP	Department of Therapeutics, University of Dundee, Dundee

CONTENTS

CIMETIDINE

J H B Saunders and K G Wormsley

Pharmacology

In 1966, Ash and Schild (1) wrote that the pharmacological actions of histamine could best be explained by postulating the existence of two types of cellular receptor for histamine. The first type of receptor (H_1) mediates the actions of histamine on the smooth muscle of gut and bronchi. These actions are competitively blocked by small amounts of the 'conventional' antihistaminic drugs such as mepyramine, which are therefore H_1-receptor blockers. The histamine H_1 antagonists do not, however, block the stimulant actions of histamine on heart rate and uterine contraction in the rat and, particularly in the context of the present topic, do not block the action of histamine on the gastric secretion of acid. Ash and Schild therefore proposed that these actions were mediated by H_2 receptors for histamine. In 1972, as a result of a superb set of studies by J W Black and his colleagues(2), antagonists for the H_2 receptors were described. The two which have been clinically studied are metiamide and cimetidine.

The pharmacological bases of the differences between H_1 and H_2 blockade have not been entirely defined. At first, it was suggested that the difference depended on the spatial configuration of the side chain of the histamine molecule. In its maximally extended position, a distance of 5.1 Å separates the N atom of the side chain and the N_1 atom of the imidazole ring of histamine(3). Since this is the approximate inter-nitrogen distance in the molecule of some conventional antihistaminics, it has been proposed that H_1 receptors, or pharmacophores, were appropriately sized to accommodate this type of molecule, while the H_2 receptors responded to derivatives of histamine with a folded type of side chain, with an inter-nitrogen distance of about 3.6 Å (4).

Subsequently, it was suggested that the conformation of the side chain was not the principal determinant of the difference between H_1 and H_2 receptors. Instead, it was proposed that molecules with a high degree of antagonism to H_1 receptors needed the charged ammonium, or similar group, of the side chain of

histamine, attached to a nucleus or groups with a high degree of lipid solubility, unlike the imidazole nucleus of histamine, which is hydrophilic. Conversely, H_2 receptor antagonists required the water-soluble imidazole group attached to an uncharged side chain (although the latter had to be electrophilic) (5).

The pharmacological action of the H_2 antagonists which is of interest to us is the effect on gastric secretion. These drugs were invented – the word is used advisedly – to counteract the stimulant effect of histamine on gastric secretion of acid, and they do so by a mechanism compatible with competitive inhibition (6,7). However, in addition to blocking the actions of histamine on the stomach, the H_2 antagonists also block the stimulant action of gastrin and of vagal activity on gastric secretion. Thus, it was shown that both metiamide and cimetidine (with identical actions on the stomach) inhibited basal (8) and nocturnal (9,10) gastric secretion, as well as the gastric secretory response to food (8,11,12), intravenous pentagastrin (13), insulin (14) and caffeine (15). The mechanisms by which the H_2 antagonists inhibit the gastric response to such a wide range of stimulants is not known. It has been suggested that the inhibition indicates the involvement of histamine in the gastric response to all these stimulants, perhaps because histamine is the 'final mediator' of the gastric stimulatory effects of these agents (16) or, alternatively, because H_2 receptors in some way tonically influence the receptors to other stimulants of gastric secretion, like gastrin and acetyl choline (17). However, recent studies on isolated gastric mucosa have shown that the inhibition of gastric secretion in response to histamine and to gastrin occurs at different functional levels of cellular activity(18). In man, pentagastrin-stimulated gastric secretion of acid is inhibited in a non-competitive manner by H_2 antagonists (19) compared with the competitive inhibition of histamine-stimulated secretion.

Whatever the mechanisms of the inhibition of gastric secretion by the H_2 antagonists, the degree of gastric inhibition is such as to point to the possibility of successful therapeutic application in peptic ulceration, on the basis that vagotomy permits ulcers to heal by reducing gastric secretion in response to all stimulants by an average of greater than 60 per cent. The H_2 antagonists reduce the gastric acid-secretory response to pentagastrin by an average of about 75 per cent (13) and a similar degree of inhibition of food-stimulated secretion has also been reported(11), although pepsin secretion is not inhibited quite as much (20,13,19).

While burimamide (the first H_2 antagonist used in human studies) was found to be relatively ineffective when given orally, the gastric inhibitory actions of metiamide and cimetidine were shown to be equally effective whether given intravenously or intraduodenally(20,13). The stage was thus set for therapeutic trials in diseases presumed to be causally related to the gastric secretion of acid and pepsin. Metiamide was used first, but a number of patients developed neutropenia, presumably because metiamide had a thiourea group in the side chain. Change from the thiourea group of metiamide to the cyanoguanidine group of cimetidine abolished the bone marrow toxicity (21) without altering the gastric

inhibitory properties, so that cimetidine is now the H_2 antagonist in clinical use.

Duodenal Ulcer

The 'peptic' disease most appropriately treated with the H_2 antagonists is duodenal ulceration. In all published UK series, the effect of cimetidine has been to permit healing of between 70 and 80 per cent of duodenal ulcers within four weeks, compared with healing of between 20 and 30 per cent of the placebo-treated controls. Perhaps even more dramatic is the relief of pain, which disappears within two days, so that cimetidine produces very grateful patients. Such statistically and clinically impressive therapeutic success led investigators to ask why some of the duodenal ulcers did not heal so easily, or at all. The definitive answer is not yet available, but there is evidence which points to some possible causes. In the first place, we noted that, occasionally, duodenal ulcers in patients with associated intra-abdominal disease such as Crohn's disease did not respond to H_2 antagonists. We do not know the reason, but we have learnt that in patients with duodenal ulcer who suffer from abdominal pain, the pain is not necessarily caused by the duodenal ulcer. Some studies which we undertook with metiamide seemed to indicate that the greater the acid-secretory capacity of the stomach, as measured by the response to pentagastrin, the greater the amount of metiamide needed to inhibit gastric secretion(19). This type of study has not been carried out with cimetidine but in the clinical trials with this drug no obvious relationship has been noted between acid-secretory capacity and the healing of duodenal ulcers. Nevertheless increasing the dose of cimetidine, or prolonging the course of treatment for two or three months, does heal some of the ulcers which have not healed with standard courses of therapy.

The possibility that standard doses of cimetidine may, on occasion, fail to inhibit gastric secretion sufficiently for therapeutic purposes is also illustrated by the effects of H_2 antagonists on nocturnal gastric secretion, particularly since we assume that acid and pepsin in the duodenal bulb for long periods at night is related to the pathogenesis of the duodenal ulceration. Early studies with metiamide showed that nocturnal gastric secretion was not always inhibited sufficiently to bring nocturnal acid output within the normal range(20) and studies with cimetidine have shown that despite high doses at night, the contents of the stomach (and therefore probably of the duodenum) may remain acid at night (22,9,10). We found that anticholinergic drugs increased and prolonged the degree of gastric inhibition produced by the H_2 antagonists(19,10) and have therefore used combinations of cimetidine and long-acting anticholinergics such as poldine in some patients who did not respond to cimetidine alone. Other studies have, however, failed to show any additional inhibitory effects of anticholinergic drugs on the gastric secretion of cimetidine-treated patients.

During the therapeutic trials with cimetidine, very few adverse reactions were noted. A few cases of gynaecomastia have been recorded(23,24,25) and although the cause is not known, increased blood concentrations of prolactin have been

noted in some of these patients. A few individuals have developed erythematous eruptions which have necessitated discontinuing therapy.

Early studies with H_2 antagonists showed that the inhibition of gastric acid secretion was attributable partly to inhibition of the rate of secretion of gastric juice and partly to decrease in the concentration of acid in the secreted juice (20,13). The latter phenomenon sometimes indicates the development of gastric mucosal damage. It is always necessary to make sure that gastric secretory inhibitors do not damage the gastric mucosa, since gastritis is a precursor of malignant change (26) and because therapeutic gastric inhibition may be required for long periods of a patient's life. In the event, studies of gastric mucosal 'barrier function' showed that this very important index of gastric mucosal integrity was not affected by H_2 antagonists (27–29).

Prolonged use

Since cimetidine has been shown to relieve the pain of duodenal ulceration very effectively and to heal the duodenal ulcers (30–33), the outstanding therapeutic problem now is how to keep the ulcers healed – that is, how to cure the ulcer disease. Short term treatment with cimetidine, for periods up to four or six weeks, is almost invariably followed by relapse of the duodenal ulceration, often quite rapidly. It is not yet known whether the tendency to relapse after cimetidine is greater and more rapid than for ulcers which have healed spontaneously. As a result of the tendency of duodenal ulcers to relapse, a number of centres are studying regimes for continuing treatment of duodenal ulcers with cimetidine after the ulcers have healed. The Committee on Safety of Medicines has issued a product licence only for short term use of cimetidine. Unfortunately, only preliminary information is available in published reports, so that the following analysis is taken from our ongoing study of more than 100 patients with duodenal ulcer who have been, or are being, treated with cimetidine at present.

We have used full doses of cimetidine (1 g per day, or more) continuously for periods up to 12 months. Nine of 19 patients treated for three months with continuous full dose cometidine and six of 15 patients who have beentreated continuously for six months have remained healed for at least six months after cessation of treatment, as have 5 of 11 patients treated for nine months and 2 of the 5 patients who have so far completed 12 months' continuous treatment with cimetidine. Nine patients, of the 50 who have so far completed their full course of therapy, have relapsed during treatment. Five had symptoms and 4 had clinically silent, active duodenal ulceration on routine endoscopy. Following cessation of full-dose therapy, 42 per cent of our patients have developed recurrences within six months, of whom the majority (28%) recurred within three months of stopping the cimetidine. In our patients, the tendency to 'break through' during treatment and to relapse after a course of treatment have correlated with the capacity to secrete acid and pepsin of the individual patients.

The results of our studies with cimetidine support the findings of our earlier

long-term studies with metiamide (34) that treatment with full doses of H_2 antagonists for up to one year is not sufficient to prevent relapse of duodenal ulceration. We have also had to face the problem of management of patients with clinically silent relapses of their duodenal ulcers. This problem has been emphasised by the many recent studies with ulcer-healing drugs, but unfortunately no information is yet available about the incidence of complications in these patients, so that medical, ethical and medico-legal problems remain to be resolved.

Nocturnal maintenance therapy

As an alternative to full-dose therapy, many centres are studying the effects of the long-term administration of cimetidine at night on the rate of relapse of healed duodenal ulcers. With metiamide, we found no difference in the relapse compared with placebo in patients treated up to one year (34). The results of nocturnal maintenance treatment with cimetidine are not yet available, since in published reports cimetidine has only been used for up to six months (35,36,37). During these relative short periods of study, six to 30 per cent of duodenal ulcers treated with nocturnal cimetidine relapsed, compared with from 30 to 100 per cent of patients treated with nocturnal placebo. The rate of relapse after stopping nocturnal treatment with cimetidine has not been recorded.

Intermittent treatment

In a number of centres, treatment with cimetidine has been used to control, rather than prevent, relapses by giving discrete, limited courses of full-dose treatment for symptomatic recurrences of duodenal ulceration. Not enough data are available for an accurate assessment of the efficacy of repeated courses of treatment but it seems possible that during second and subsequent recurrences, the rates of relief of pain and healing of the ulcers are less rapid than during the initial courses of treatment, while relapses of the ulceration tend to occur more rapidly than after the initial course of treatment (34). However, preliminary data from other centres seem to show that the results of second courses of treatment are as good as first courses, so that the efficacy of repeated, discrete, courses of full-dose treatment is not yet clear.

In summary, the most satisfactory treatment regime for the long-term management of duodenal ulcer with cimetidine has not yet been defined so that, at present the choice of maintenance treatment with cimetidine must be left to individual physicians.

Gastric ulcer

Cimetidine has also been used in the treatment of gastric ulceration. Rates of healing between 70 and 100 per cent have been reported, together with rapid relief of pain (38,39,40), although the associated chronic gastritis does not improve. It has been reported that gastric ulcers tend to relapse quite rapidly after stopping treatment with cimetidine (39), but this report has not been confirmed so that the role of cimetidine in the treatment of gastric ulceration is not yet clear. In addition

TABLE I.

DRUG	ACTION	COUNTRY OF TRIAL	DU HEALING AT 4 WEEKS DRUG	PLACEBO	SYMPTOM RELIEF DRUG v PLACEBO	REFERENCE
Cimetidine	H_2 Blocker (Gastric Inhibitor)	UK Norway	72% 85%	29% 60%	65% v 30% = sign. 94% v 84% = n.s.	(48)
Anisotropine Methyl Bromide	Anti-Cholinergic (+ inhibitor)	USA	81%	57%		(49)
Trimipramine (Surmontil)	Anti-Depressant (+ inhibitor)	Norway	75%	46%	70% v 25% = sign.	(50)
Gastrozepin	Tricyclic + inhibitor	Germany	94%	55%		(51)
Carbenoxolone (Duogastrone)	Mucus Stimulant (?)	UK	69%	22%	72% v 54% = n.s.	(52)
Glyptide	Anti-Pepsin	USA	81%*	60%*		–
Denol	Ulcer Coating (?)	UK	74%	21%	78% v 58% = n.s.	(53)
Aluminium Hydroxide	Antacid	USA	76%	40%	89% v 87% = n.s.	(54)
15S–15Me PGE_2	Prostaglandin	Poland	75%**	42%**		(55)

* 6 weeks treatment ** 2 weeks treatment

to healing chronic gastric ulcers, H_2 antagonists have also been claimed to be very effective in the treatment of haemorrhage from acute gastritis and erosions (41,42, 43,44) although cimetidine is less effective if the bleeding is attributable to a focal lesion (43,45).

Oesophagitis

Cimetidine has been used in the treatment of oesophagitis and although considerable symptomatic improvement is often reported (46), the endoscopic and histological improvement is not always commensurate. The long-term effects of treatment of oesophagitis with cimetidine have not yet been reported.

Pancreatic enzyme replacement therapy

One further clinical application of cimetidine which requires mention is the use of this drug in the treatment of the steatorrhoea caused by pancreatic insufficiency. The treatment of pancreatic steatorrhoea requires replacement of endogenous pancreatic enzymes by the pancreatic enzymes in commercially available pancreatic extracts. Replacement therapy has hitherto been unsatisfactory because the pancreatic enzymes in the pancreatic extracts have been rapidly and irreversibly destroyed by gastric acid and pepsin, both during gastric transit and because the contents of the duodenum and upper small intestine are often acid in these patients. We have shown that an H_2 antagonist must be used to inhibit gastric secretion before satisfactory replacement of pancreatic enzymes can be assured (47).

Comparison with other drugs

Before leaving the topic of cimetidine, it is necessary to emphasise the therapeutic revolution which has been triggered by the H_2 antagonists. The table shows that there are now at least nine drugs for which rates of healing of 70 to 80 per cent of duodenal ulcers have been claimed. In our opinion, only cimetidine has been investigated satisfactorily, in sufficient numbers of patients and under sufficiently stringent conditions in a large number of centres. It does look, however, as if patients with duodenal ulcer are going to be saved from the knife of the surgeon in the not too distant future.

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