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Cimetidine and ulcers

At its peak incidence duodenal ulceration affects up to 10% of men and 4% of women. Furthermore, it is important not only because of the illness and pain but also because of the economic costs of its effects on the nation's work force. Beyond doubt histamine H_2 antagonists can dramatically suppress gastric acid secretion to a level which permits peptic ulcers to heal. Their degree of efficacy, their suitability for widespread use, the amount of supervision needed in their administration, the best dosage schedules, and their safety all need to be determined. A conference held in London recently has answered some of these questions for the drug cimetidine, but not all; and the remainder will require more exploration.

Cimetidine (marketed this month in Britain as Tagamet) will reduce the gastric secretion of acid to about 20% within an hour of oral administration, and it makes little difference whether the drug is taken before or after food. The effect is mainly on the volume of secretion.[1-3] In the patient eating normally and taking four doses daily gastric pH nevertheless remains below 2 for much of the time, but the acid secretion is sufficiently reduced to allow healing of the ulcer. Duodenal ulcers have a 70-80% likelihood of disappearing in four weeks, compared with a healing rate of about 45% treated with placebo,[4-6] but the drug has not been compared with anticholinergics. Healing of gastric ulcers is less certain; cimetidine is probably better than placebo, but so far comparisons with carbenoxolone have not resolved their relative merits. Anticholinergic drugs do not augment the effects of H_2 antagonists on acid secretion, so that there seems no good reason to use them conjointly.

There are other circumstances where cimetidine has potential value, though our information is scantier. Though the Zollinger-Ellison syndrome (multiple peptic ulcers due to gastric hypersecretion from excessive circulating gastrin) is rare, the doctor may have to act urgently to avoid life-threatening complications. Treatment with cimetidine has induced dramatic remissions in many patients (as did its predecessor metiamide[7-10]), though in some it has failed and others have ultimately escaped from control; but valuable time can usually be bought. Cimetidine is equally effective in arresting bleeding from gastric erosions. Its place in managing bleeding from chronic ulcers and the like remains uncertain, and no good evidence has been presented about its role in reflux oesophagitis.

Is it possible that these benefits—some definite, some merely hoped for—are being obtained at the price of other unwanted and hazardous actions? The drug appears safe enough over long periods in rats, mice, dogs, and cats. So far rashes, diarrhoea, and muscle pains have troubled only a few patients treated with the drug, though the serum creatinine concentration has risen in others[3 6] (but not progressively and without other evidence of renal deterioration). No haematological abnormalities have been seen. Hepatotoxicity remains in question. Rises in transaminase concentrations have been as common in controls as in patients taking cimetidine, but in two of the latter liver biopsy specimens showed centrilobular necrosis. A few men (mostly on high-dose regimens) have noticed uncomfortable breast soreness and enlargement after several months' treatment, but without evident hormonal or other sexual changes. Very few, however, have yet taken the drug for longer than six months, and scrupulous observations will have to continue. It appears that intrinsic factor secretion is preserved, if diminished—though not so far that iatrogenic pernicious anaemia is likely—and the rise in serum gastrin concentrations produced by prolonged low gastric acid concentrations seems not to cause problems or "rebound" hypersecretion on stopping the drug. Permanent adverse changes in the gastric mucosa have not been described.

The practising doctor will now ask how he is to use this entirely novel drug: for use it he will want to, as the huge consumption of relatively ineffective antacids and other agents prescribed for peptic ulceration bears witness. The drug must not be regarded as a panacea for all dyspepsia, a ready-made omnibus cure for all discomfort from xiphisternum to pubis. A huge catalogue of disorders produce abdominal discomfort, relatively few of them caused by acid, and many having no structural basis at all. Will doctors exert the restraint required to restrict the use of cimetidine initially to patients proved (by radiology or, preferably, endoscopy) to have a peptic ulcer? They should, for the hazards of indiscriminate use are considerable. The drug might gain an undeserved ill repute when it seems to "fail" or produces unwanted side effects in patients to whom it should not have been given. All too often cancer mimics peptic ulcer dyspepsia, and if it is inadvertently treated by an empirical course of cimetidine valuable time may be lost before the true diagnosis is discovered. And the NHS drug bill, for which doctors are already under attack, might rise notably higher.

A patient having pain from a proved duodenal ulcer deserves a course of cimetidine (200 mg thrice daily plus 400 mg at night) to try to heal it. This course should last two months and

then be stopped. The serum creatinine concentrations should be measured each month during the treatment. If an early relapse occurs the patient will need another course, but after that the choices are to give a single 400-mg dose every night to prevent further relapse; to stop the drug and wait; or to recommend surgery. With our present knowledge it seems better to choose surgery for the young, fit patient whose ulcer relapses often, for a lifetime of taking a drug whose hazards remain unknown is undesirable. For the old and unfit, on the other hand, the best options are recurrent courses for the patient who relapses occasionally and regular night-time dosage for the frequent sufferer. When an ulcer recurs after vagotomy there is an obvious potential for cimetidine, though reports are so far lacking. It is likely to be valuable in cases in which further surgery is undesirable or impossible.

Gastric ulcers present more difficult problems. As now, they should all be examined by endoscopy with cytology and biopsy to ensure that they are benign before any treatment is undertaken. If benign, the same policy as for duodenal ulcers applies, for, though the superiority of cimetidine over carbenoxolone has not been established, it seems likely at least to be as good, and (so far) less hazardous than the liquorice-based drug with its aldosterone-like effects on sodium and potassium balances. Cimetidine will also be called on as a temporary measure in anyone suffering from the Zollinger-Ellison syndrome, but so far it does not seem justified as an emergency aid in the management of upper gastrointestinal bleeding, except when the source is known to be erosions in a patient who is very ill.

All in all, cimetidine is a powerful new addition to the therapeutic armament that doctors deploy. Now that it has been released for routine clinical use by the Medicines Commission we need to think carefully about the ways it may be put to the service of our patients.

[1] Burland, W L, *et al*, *British Journal of Clinical Pharmacology*, 1975, **2**, 481.
[2] Henn, R M, *et al*, *New England Journal of Medicine*, 1975, **293**, 371.
[3] Pounder, R E, *et al*, *Gut*, 1976, **17**, 161.
[4] Blackwood, W S, *et al*, *Lancet*, 1976, **2**, 174.
[5] Bodemar, G, and Walan, A, *Lancet*, 1976, **2**, 161.
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[8] Richardson, C T, and Fordtran, J S, *Gastroenterology*, 1975, **68**, 973.
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Safe paediatric prescribing

Given that the adult dose of a drug is known, rules have been devised for calculating the dose required for an infant or child from the age, weight, and surface area. These rules have so many exceptions that they are best avoided, and it is far better to learn the correct dose of each drug in each age group. While the prescriber may rely on memory for familiar drugs he also needs a more comprehensive source of drug dosage than the *British National Formulary* or *MIMS* for safe paediatric prescription. Two sources may be recommended: the comprehensive and familiar *Paediatric Vade Mecum* edited by Wood and colleagues from Birmingham, now in its eighth edition,[1] and the modest *Alder Hey Book of Children's Doses* from Liverpool.[2] Both list over 160 drugs with doses related to age and weight. No doctor should feel inhibited from consulting such a reference source in prescribing for children.

Having the correct drug reference does not avert all prescribing tragedies. In spite of metrication and decimalisation being almost universal, disasters still occur because minims are prescribed and interpreted as millilitres[3] or the decimal point has been misplaced.[4] Great care is needed and calculations must be checked and rechecked, particularly with the many potent drugs now available. Incomplete or illegible prescriptions are an additional hazard which may make it less possible for a pharmacist to spot a mistake. One practice particularly to be deprecated is that of ordering a drug dosage by volume without designating the content by weight. This applies not only to intravenous agents such as potassium chloride but to well-tried drugs such as the oral hypnotic chloral hydrate. A prescription of 5 ml of chloral hydrate would give 200 mg of chloral hydrate to the patient if chloral elixir paediatric *BNF* were dispensed, but there are 1000 mg of chloral hydrate in chloral syrup *BPC*. The difference could have a disastrous effect if repeated doses were given.

[1] *A Paediatric Vade Mecum*, 8th edn, ed Ben Wood. London, Lloyd-Luke, 1974.
[2] *Alder Hey Book of Children's Doses*, 2nd edn. Liverpool, Liverpool Area Health Authority (Teaching), 1976.
[3] *Medical Defence Union Annual Report*, p 37. London, Medical Defence Union, 1975.
[4] *Medical Protection Society Annual Report and Accounts for 1973*. London, Medical Protection Society, 1974.

Edinburgh and medicine

The St Andrew's Day Symposium of the Royal College of Physicians of Edinburgh this year is the last of the events linked to the 250th Anniversary Celebrations of the Faculty of Medicine. In 1726, under the influence of Leiden and of the two Edinburgh royal colleges, was initiated the first faculty of medicine in Britain to provide a full medical course with appropriate examinations. In part this resulted from the farsightedness of Lord Provost George Drummond, who, dismayed by the falling fortunes of the City of Edinburgh after the Act of Union in 1707, saw that a medical school, attracting students from far and wide, would strengthen the city's influence in world affairs. Simultaneously, the ambition of John Monro, Deacon of Surgeons, for his son, Alexander, led to the latter's being trained for a professorship, to which he was appointed by the city council in 1720. Six years later the city's college had its faculty of medicine, and the Royal Infirmary followed soon after.

The influence on world medicine of medical students who trained in Edinburgh has been immense. They can be numbered among the founders of the University of London, University College Medical School, the Middlesex Hospital Medical School, the modern St Bartholomew's Hospital Medical School, and the Royal Society of Medicine. In America Edinburgh graduates founded Philadelphia Medical School and King's College Medical School (Columbia), and influenced the medical schools in South Carolina, Maryland, and Virginia—not to mention McGill, Dalhousie, Sydney, and Otago. Indeed, had not James Lind (who graduated in Edinburgh) shown how to prevent scurvy at sea, it is doubtful whether Captain Arthur Phillip, convinced by the experience of Captain Cook, would have reached Australia or whether it would have become a British possession.

Not surprisingly, then, the Royal Scottish Museum, which is in close proximity to the University's Old College, chose this year to arrange for the first time an ambitious exhibition of nearly 600 medical treasures. Displayed to the public under the title of "Edinburgh and Medicine," the exhibits range from