Review Article

H_2 receptor antagonists and anaesthesia

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Histamine-2 (H_2) receptor antagonists are drugs which inhibit gastric acid secretion by competitive antagonism of the action of histamine on H_2 receptors. H_2 receptors are present in gastric parietal cells, heart, uterus, and blood vessels. H_1 receptors, blocked by classical antihistamines, are present in the smooth muscle of blood vessels also, and in that of the gut and bronchus.

Cimetidine was introduced in 1976 as the first H_2 receptor antagonist for clinical use.[1] Further drugs of this type have been synthesized; ranitidine is now available,[2] and further drugs such as tiotidine and oxmetidine are undergoing clinical trials.

The principal clinical use of these drugs is in the treatment of peptic ulceration and other gastric acid related disorders.[3]

The main interests of anaesthetists in these drugs are, firstly, the actions and side-effects of such drugs, and any likely interactions with anaesthetic agents, and secondly, the use of H_2 receptor antagonists as premedicants to reduce the risk of acid aspiration pneumonia associated with anaesthesia. An additional possibility is the combined use of H_1 and H_2 receptor antagonists, which may be of value in premedication of patients with allergic problems.

Clinical Pharmacology

Cimetidine is a weak imidazole base, which, given orally, achieves peak blood levels 45–60 minutes after administration. Plasma half life is about two hours in normal patients, and following the normal 300 mg dose, effective blood concentrations are maintained for four hours. Intramuscular or intravenous administration gives higher peak levels, but an identical length of effective action.[5] The drug is excreted renally within 24 hours, 25–50 per cent being metabolised in the liver, the rest unchanged.

Ranitidine (a substituted amino-alkyl furan derivative) is more potent than cimetidine, and has a longer duration of action. A 100 or 150 mg oral dose produces peak blood levels in 60–90 minutes, and therapeutically effective blood concentrations for over eight hours. It is mostly excreted renally.[8]

Both drugs are reversible, competitive, H_2 receptor antagonists. Effective blood levels produce marked inhibition of basal gastric acid secretion and of secretion in response to gastrin or food. Gastric juice secretion and the hydrogen ion concentration are both markedly reduced. Anticholinergic agents such as atropine suppress acid secretion by a different mechanism, but may have a synergistic effect when given in combination with H_2 receptor antagonists.[6]

Concurrent administration of oral antacids may reduce bioavailability of oral cimetidine by 22–35 per cent, and oral ranitidine by 33 per cent.[7]

Side effects

Cimetidine is generally well tolerated, with a low incidence of side effects. Less than 2 per cent of patients on short-term therapy complain of effects such as headache, fatigue, skin rashes, constipation, or diarrhoea.[4,9–11]

Elevation of serum transaminase concentration has been reported, always returning to normal during continued treatment or after cessation. Elevation of serum creatinine has occurred, usually transient, and only rarely exceeding the normal

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range. Very rarely, interstitial nephritis has occurred.

Mental confusion has been reported, typically in elderly patients with renal impairment receiving high doses.[11] An anti-androgenic effect, producing gynaecomastia in men and galactorrhoea in women, can occur on long term therapy. Bone marrow suppression occurs occasionally, with an estimated incidence of 1/100,000 for neutropenia, and 3/1,000,000 for agranulocytosis and thrombocytopenia.[12] Cimetidine reduces the threshold dose of histamine to produce bronchoconstriction, and should be used with caution in asthmatic patients. Intravenous bolus administration of cimetidine has been associated with bradycardia, hypotension and asystole.[15] Although the pregnant uterus contains H_2 receptors, and cimetidine readily crosses the placenta,[13] no adverse effects of cimetidine have been reported on the progress of labour or on the foetus or neonate.[14]

Cimetidine significantly inhibits hepatic oxidative drug metabolism, probably due to binding of the imidazole ring in the cimetidine molecule onto microsomal cytochrome P450.[16] Cimetidine has been shown to inhibit metabolism of anticoagulants, barbiturates, benzodiazepines, propranolol and theophylline,[17–19] and has been reported as causing postoperative somnolence with diazepam.[20] Cimetidine may also interfere with lidocaine clearance, and with the metabolism of narcotic analgesics. Ranitidine, which does not contain an imidazole ring, was reported initially to have no effect on drug metabolism.[21] However, more recent reports suggest some effects on drug metabolism[22] and hepatic blood flow.[23,24] Further information is required. In addition there has been a single case report[25] on bradycardia following ranitidine administration but this has not been supported by a more recent and larger study.[26] Clinical experience so far suggests that ranitidine is free of other major side effects.

Other new H_2 receptor antagonists all seem to be free of any effect on liver metabolism, but clinical experience regarding other side effects is limited.

H-2 receptor antagonists as prophylaxis against acid aspiration syndrome

Aspiration of acid gastric contents can occur as a complication of any general anaesthetic.[27] However, acid aspiration syndrome (Mendelson's syndrome) was described originally in obstetric patients,[28] and this group, together with the morbidly obese,[30] are regarded as being most at risk of this problem.[29]

Since the demonstration that lung damage is particularly associated with aspiration of 25 ml or more of gastric juice with a pH of 2.5 or less,[28,31,32] various methods have been advocated to reduce the proportion of patients at risk. The principal measure advocated has been oral administration of antacids, either regularly throughout labour, or as a single dose before anaesthesia.[33–37]

However, evidence has accumulated that antacid regimes may not be as reliable as was hoped in preventing the effects of acid aspiration.[38,40,43] It has been suggested that this may be due to a direct toxic effect on lung tissue of particulate antacids,[39,42] or to inadequate mixing of emulsion antacids with gastric contents.[41] This has led to the assessment of H_2 receptor antagonists as an alternative approach to the problem.

Several trials have assessed the effectiveness of cimetidine, and a few the newer drug ranitidine, as prophylaxis against acid aspiration syndrome. The results of these trials are summarised in Table I.

Discussion

Table I summarises trial results as the number and percentage of patients having gastric pH of 2.5 or less, and volumes of 25 ml or more. However, volume measurements of gastric contents by aspiration are not usually accurate, but may provide some indication of gross differences between groups.

In most trials using cimetidine, 80–90 per cent of patients have gastric pH of 2.5 or more. Although one trial, involving small numbers, suggested an advantage in giving an additional dose of cimetidine the evening before surgery, in order to reduce the acidity of resting gastric juice before the main dose is given,[49] the summated results of several trials do not support this view.[44–49,51–53]

The four trials using ranitidine show a slightly lower proportion of patients "at risk".[47,62,63*] In addition, ranitidine used orally shows a probable real advantage when given in an additional evening dose.[63] This advantage may be due to the longer duration of action of ranitidine allowing an evening dose to have a more prolonged effect.

*Williams J.G., Strunin L. Trial in progress.

TABLE I

N.	*n.*	*Route*	*Dose*	*pH < 2.5*	*Vol > 25 ml*	*pH < 2.5 + vol > 25 ml*	*Refs*
1 CIMETIDINE							
(a) Elective general surgery							
8	223	Oral	3–400 mg	28 (12.6%)	9/117 (7.7%)	3/117 (2.6%)	44–49, 52
3	61	Oral	3–400 mg +3–400 mg prev. night	13 (21.3%)	6/20 (30%)	4/20 (20%)	49, 51, 53
1	38	I/M	300 mg	5 (13.2%)	2 (5.3%)	2 (5.3%)	64
1	6	I/M	300 mg +300 mg oral prev. night	0 (0%)	—	0 (0%)	49
4	79	I/V	300 mg	5 (6.3%)	5/68 (7.4%)	2/79 (2.5%)	46, 47, 54, 55
(b) Emergency general surgery							
1	20	I/V	200 mg	4 (20%)	—	—	60
(c) Elective obstetrics							
2	95	Oral	400 mg	14 (14.7%)	0/31 (0%)	0/31 (0%)	56, 57
1	9	I/M	300 mg	2 (22.2%)	9 (100%)	2 (22.2%)	58
1	20	I/V	200 mg	3 (15%)	—	—	59
(d) Emergency obstetrics							
1	46	Oral	400 mg+ 200 mg 2 hrly	2 (4.3%)	(vol "usually high")		61
2 RANITIDINE							
Elective general surgery							
2	54	Oral	150 mg	6 (11.1%)	8 (14.8%)	5 (9.3%)	47, 62
2	48	Oral	150 mg+ 150 mg prev. night	1 (2.1%)	3 (6.3%)	0 (0%)	62, 63
1	65	I/M	50/100 mg	3 (4.6%)	6 (9.2%)	2 (3.1%)	64
1	48	I/V	50/100 mg	2 (4.2%)	2 (4.2%)	0 (0%)	47
3 MAGNESIUM TRISILICATE MIXTURE							
Elective obstetrics							
1	396	Oral	20 ml	2 (0.5%)	—	—	65

TABLE I (*concluded*)

N.	*n.*	*Route*	*Dose*	*pH < 2.5*	*Vol > 25 ml*	*pH < 2.5 + vol > 25 ml*	*Refs*
4 MAGNESIUM AND ALUMINIUM HYDROXIDE MIXTURE							
Elective obstetrics							
2	73	Oral	?	7 (9.5%)	15/25 (60%)	—	35, 44
5 0.3 M SODIUM CITRATE							
(a) Elective general surgery							
1	15	Oral	30 ml	2 (13%)	13 (87%)	2 (13%)	48
(b) Elective obstetrics							
1	26	Oral	30 ml	0 (0%)	(mean 26 ml)	0 (0%)	66

Table I represents a summary of published studies investigating the effect of (1) cimetidine and (2) ranitidine on gastric pH and volume at induction of anaesthesia. Representative studies of (3) magnesium trisilicate mixture, (4) magnesium and aluminium hydroxide mixture, and (5) 0.3 m sodium citrate are included for comparison.

N = number of trials; n = total number of patients in trials; pH < 2.5 = number (%) of patients with gastric pH of 2.5 or less; Vol > 25 ml = Number (%) of patients with gastric juice volume of 25 ml or more; pH < 2.5 + Vol > 25 ml = number (%) of patients with gastric pH of 2.5 or less and volume of 25 ml or more.

The trial of cimetidine as the sole antacid in labouring patients shows encouraging results.[61] One problem of cimetidine used in this way is its relatively short length of action, which requires precise timing of dosage to achieve optimal effect.[59,61] The longer action of ranitidine offers a real potential advantage in this situation, and deserves clinical trial.

Overall, H_2 receptor blockers can be as effective as oral antacids in reducing gastric acidity preoperatively, and are probably superior in reducing gastric volume. They are also free of the possible risk of oral antacids having a direct toxic action on the lung. However, in emergency situations, oral antacids can act rapidly,[37] whereas H_2 receptor antagonists, even given parenterally, need at least 45 minutes to act,[5,59] and can have no effect on gastric contents present before administration.

No form of antacid prophylaxis completely eliminates "at risk" patients, and effective prevention of acid aspiration syndrome depends on the skilled use of appropriate techniques, including regional anaesthesia where suitable.

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