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Pharmacokinetic Optimisation in the Treatment of Gastro-Oesophageal Reflux Disease

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Summary

Gastro-oesophageal reflux disease (GORD) is a very common disorder of upper gastro-intestinal motility, differing widely in severity and prognosis. Medical therapy of GORD has involved antacids, alginates, prokinetic agents and antisecretory compounds, primarily H_2 receptor antagonists and proton pump inhibitors. Knowledge of the pharmacokinetics of these compounds is important, to optimise the therapeutic benefit in each patient.

GORD patients are often elderly and pharmacokinetics are more variable in this group. Furthermore, they often suffer from other diseases needing medical therapy and may need a combination of drugs to heal reflux oesophagitis and relieve reflux symptoms. The ideal therapy for GORD will have linear pharmacokinetics, a relatively long plasma half-life ($t_{1/2}$), a duration of action allowing once

daily administration, and a stable effect independent of interactions with food, antacids and other drugs.

Over-the-counter antacids and alginates are widely used, but may affect absorption of H_2 receptor antagonists like cimetidine and ranitidine. Aluminium-containing antacids may, over time, cause toxicity in patients with renal insufficiency. In the treatment of GORD, cisapride presents important advantages over earlier prokinetic compounds, with a longer plasma $t_{1/2}$, low penetration of the blood-brain barrier and fewer adverse effects.

The group of H_2 receptor antagonists is still the most frequently used therapy for GORD. Linear pharmacokinetics make dose adjustments easy and safe. In individual patients, suppression of gastric secretion is related to the area under the plasma concentration-time curve (AUC), but there is wide interindividual variation in the effect of the same oral dose. Only with frequent administration and high doses will acid suppression approximate that of proton pump inhibitors. Tolerance, with loss of effect over time, however, is most pronounced in this situation.

H_2 receptor antagonists seem well suited for on-demand treatment of reflux symptoms, due to the rapid onset of effect and a decreased likelihood of the development of tolerance. Effervescent formulations provide more rapid absorption and almost immediate clinical effect. Cimetidine, however, causes interference with the metabolism of several other drugs in common use. In elderly patients elimination is delayed and in patients with renal insufficiency, dose reductions of all H_2 receptor antagonists are recommended.

The most effective medical therapy for any severity of GORD, particularly in severe oesophagitis, are the proton pump inhibitors. The substituted benzimidazoles (omeprazole, lansoprazole and pantoprazole), are prodrugs which once trapped and activated in the acid milieu of the gastric glands potently suppress gastric secretion of acid and pepsin. Their long duration of action, more related to the slow turnover of parietal cell H^+-K^+ ATPase molecules, allows once daily administration in most patients. Interindividual variation in bioavailability sometimes calls for higher doses or twice daily administration.

Acid suppression is closely related to the AUC. Omeprazole is prone to interaction with the metabolism of other drugs, some of which may be clinically important. Lansoprazole seems to have an earlier onset of action than omeprazole, ascribed to higher bioavailability during the first days of treatment. Proton pump inhibitors have a slow onset of action, which makes them unsuited for on-demand therapy.

Clinical practice in GORD calls for the use of not one but several substances, according to the severity and symptom pattern of the patient. Pharmacokinetic optimisation in the treatment of GORD is a question of selecting the most suitable substances and administration schemes within each group. Cisapride is superior to other prokinetics in terms of longer plasma $t_{1/2}$ and less toxicity. Amongst H_2 receptor antagonists, the more long-acting compounds, ranitidine and famotidine, will improve acidity control throughout 24 hours and also cause less metabolic interaction with other drugs than cimetidine.

Lansoprazole has a higher bioavailability than omeprazole from the first day of therapy, resulting in the more rapid relief of symptoms. Pantoprazole may cause fewer drug interactions than other proton pump inhibitors.

Gastro-oesophageal reflux disease (GORD) has a complex and perhaps somewhat differing pathogenetic background, the common pathway of which is reflux of gastric contents to the oesophagus. By reducing acid load on the oesophageal mucosa, lesions are allowed to heal and the sensitivity of the mucosa is reduced. It has been shown, by Bell et al.,[1] that the healing of reflux oesophagitis is highly dependent on the normalisation of contact time between refluxed material and the oesophageal mucosa. Acid load is commonly quantified as the proportion of time when oesophageal pH is less than 4.0, as measured by 24-hour ambulatory intra-oesophageal pH-measurement.

Besides being a routine diagnostic procedure, pH-measurement is increasingly used to assess the effect of drugs on gastro-oesophageal reflux, in cases of therapeutic failure, and in clinical research. The relationship of gastro-oesophageal reflux to both motility disturbances and gastric secretion creates a heavy challenge for medical treatment.

Over the last 20 years, new drugs have become available enabling us to treat almost any grade of reflux oesophagitis. The harmful action of refluxate on the oesophageal mucosa can be reduced by several methods:

- neutralising the gastric acidity (antacids)
- decreasing gastric secretion of acid and pepsin
- improving upper gastro-intestinal motility (prokinetics)
- topically acting agents which may neutralise pepsin and bile acids.

These drugs comprise several chemical classes.

1. Pharmacokinetic Considerations in the Therapy of Gastro-oesophageal Reflux Disease (GORD)

Insight into the pharmacokinetic characteristics of drugs is important for choosing the right drug for the right patient, and in a dose and dosage scheme that will benefit the healing of the disease. This is particularly important in such situations as therapy resistant disease, when combinations of drugs are needed, and in patients with concomitant diseases.

The majority of pharmacokinetic data available for all drugs used in treating GORD has been obtained from young, healthy individuals or in peptic ulcer patients, therefore the paucicity of data from GORD patients is a problem. Antisecretory drugs have been in widespread use for the treatment of peptic ulcer disease, a condition with characteristics sufficiently different from those of GORD to call for specific considerations.

Pharmacokinetic optimisation is aimed at creating good conditions for bringing the active drug to its site of action in concentrations enabling it to work effectively for the healing and symptom relief of the disease. Several important pharmacokinetic considerations must be taken into account:

- Intake with food will reduce the bioavailability of several drugs and intake of these drugs in the fasting state should therefore be recommended.
- Prokinetics, due to their mechanism of action, and their short $t_{1/2}$, should be administered prior to meals.
- The elimination of several drugs, particularly H_2 receptor antagonists, is affected by renal failure, while hepatic failure will tend to reduce metabolism of the proton pump inhibitors.

First order pharmacokinetics, which exist for most compounds, facilitate dosage adjustments, and will ensure safer administration and evaluation of treatment failures. More frequent administration of prokinetics, H_2 receptor antagonists and even proton pump inhibitors will sometimes increase effectiveness. On the other hand, once daily administration will improve compliance and compounds with longer $t_{1/2}$ may show advantages. Amongst related considerations is the effects of ageing, intake of alcohol and use of other concomitant medication.

The ideal drug therapy for GORD does not exist, but would have to fulfil most of the following requirements. The onset of action should be rapid, particularly when given as on-demand treatment and in cases of severe symptoms. Currently, this favours antacids and effervescent formulations of H_2 receptor antagonists which rapidly raise the pH of the gastric contents. High bioavailability from

the first day of therapy will contribute to early symptom relief. The majority of patients will need treatment on a continuous basis and for long periods of time. The effect of treatment on acid secretion and amount of reflux should be stable, as tachyphylaxis may compromise symptom relief and healing. Adverse effects should be negligible, even in the long run.

Even though recurring symptoms will remind GORD patients to take drugs as prescribed, compliance is a problem and a drug regimen should comprise as few daily doses as possible. For practical use, interference with food should be minimal, because diurnal symptoms often dominate and it is easier to take drugs with meals.

All but the most effective medication will sometimes be supplemented by antacids, which should therefore not interfere with the absorption or action of the compound. It will sometimes be necessary to combine 2 compounds, most often an antisecretory and a prokinetic drug to improve symptom relief and healing. It is important that each one should not affect the absorption, metabolism, excretion or the effect of the other.

Patients with GORD are often elderly and drug metabolism and excretion is slower in this patient group. This may increase the effect of therapy, and the patients susceptibility to adverse effects. Patients with GORD often have other concomitant diseases, so clinically interactions with other drugs may be an important consideration.

2. Antacids and Alginates

Traditionally, antacids were the cornerstone of medical therapy for GORD symptoms but do not heal oesophagitis. The majority of heavy users of antacids have reflux disease.[2] Alginate-antacid combinations have been shown to form a foam-like layer in the fundic region of the stomach,[3] but whether this reduces oesophageal acid reflux is not clear.[4]

Acid neutralisation is probably the most important mechanism by which antacids work in GORD. Antacids like calcium carbonate or calcium bicarbonate, which both have a rapid onset of action, are often preferred by patients with heartburn. The same may be true for liquid formulations of aluminium antacids which are sometimes used in very high doses.[2]

The optimal dosage and formulation of antacids in GORD is not known. The direct effect of acid-neutralising agents is measurable by intragastric pH-measurement. When 1 single antacid tablet (acid-neutralising capacity 30 mmol) was administered to patients with duodenal ulcers, intragastric pH was elevated above pH 2.0, 3.0 and 4.0 for 35, 12 and 2 minutes, respectively, compared with placebo.[5]

Treatment with 4 antacid tablets a day reduced intragastric acidity considerably less than treatment with cimetidine 400mg twice daily.[6] Increasing the dose may increase efficacy, but can also increase the chances of adverse effects and possibly absorption of aluminium.[7] Antacids should be considered only symptomatic therapy in GORD. Frequent administration is logical, on-demand during the day and prophylactically at bedtime if nighttime symptoms are expected.

3. Sucralfate

Sucralfate is a topically acting aluminium salt of sucrose octasulfate containing 21% Al bodyweight. Clinical studies in reflux oesophagitis have shown that both healing and symptom relief following treatment with sucralfate is equal to that following alginate plus antacid[8] or cimetidine[9] and significantly better than placebo.[10] Suralfate is available as 1g chewable tablets or suspension. It is practically devoid of antacid effect even though the aluminium content is similar to that of conventional antacids.

Upon acidification, sucralfate forms a viscid, yellow-white gel that adheres to ulcer bases and epithelium, protecting the tissues for a period of around 6 hours. Acidification slowly releases aluminium ions, the gastrointestinal absorption of which is normally low (< 0.02%), but approximately equal to that after antacid administration when the drugs are compared in doses of 1 tablet 4 times daily.[11]

In patients with renal failure, the accumulation of aluminium ions may cause hyperaluminiumaemia, due to reduced elimination.[12]

Antacids and food do not seem to interact with the actions of sucralfate, but antacids should not be taken less than 30 minutes before sucralfate, as pH-dependent activation of the gel may be affected. The bioavailability of certain drugs is reduced if taken at the same time as sucralfate, presumably due to binding to sucralfate. Administration is recommended 2 to 4 times a day, 30 minutes before meals and at bedtime.

4. Prokinetic Agents

Prokinetic drugs act by stimulating gastro-intestinal motility, which is in some way pathological in most GORD patients. Prokinetics may increase lower oesophageal sphincter (LES) tone, improve oesophageal peristalsis and stimulate gastric emptying, whether pathological or not. In a reflux patient, this may decrease the total acid exposure on the oesophageal mucosa. The presently available prokinetics do not seem to affect the important reflex-mediated transient LES relaxations (TLESRs). In GORD, an additive effect of prokinetics and antisecretory medication on oesophageal acid exposure has been demonstrated.[13]

4.1 Metoclopramide

Metoclopramide acts both as a dopaminergic D_2-receptor antagonist and indirectly as a cholinergomimetic, by stimulating the release of acetylcholine from postganglionic nerve terminals of the gut wall. It has been speculated that blockade of $5HT_3$-receptors may contribute to the effect. It is possible that some of the gastro-intestinal effects of metoclopramide are mediated through receptors in the central nervous system.[14]

The effect of metoclopramide in reflux disease is thought to be partly due to increase in the rate of gastric emptying.[15,16] Most studies have shown an increase in LES tone after intravenous and oral administration. The effect on LES tone and gastro-oesophageal reflux has been established only in the fasting and late postprandial state.[15]

Metoclopramide hydrochloride is available as tablets and suspension for oral administration. Absorption from the intestine is complete, but hepatic first-pass metabolism reduces systemic bioavailability to about 75%. The maximum plasma drug concentration after single dose administration (C_{max}) of 84 μg/L after oral intake of metoclopramide 20mg is reached within 30 minutes.

In humans, most of the ingested dose is metabolised through hepatic conjugation and excreted partly in the bile and urine, while 30% is excreted unchanged.[17] The elimination half-life ($t_{½β}$) in plasma is in the order of 3 to 6 hours, but increased up to 4-times in patients with renal failure, while clearance is reduced by about 70%.[18] Metoclopramide passes the blood-brain barrier to a large extent and has been shown to induce extrapyramidal adverse effects.[19,20] This occurs in 1 to 2% of patients treated, but more often in patients treated for more than 12 months and in patients treated concomitantly with monoamine oxidase inhibitors, tricyclic antidepressants, phenothiazines or butyrophenones. The recommended regimen of metoclopramide for oral treatment is 10mg taken 20 to 30 minutes prior to 3 main meals and at bedtime (i.e. 4 times a day).

4.2 Domperidone

Domperidone improves gastric emptying in healthy individuals and in patients with gastroparesis, and this effect may be more important than the effect on LES and oesophageal peristalsis. Domperidone is primarily a dopaminergic antagonist acting on D_2 receptors in the gastrointestinal smooth muscle. It is available as tablets and an oral solution.

After oral administration of doperidone tablets of 10 or 60mg, mean peak plasma concentrations of 23 and 80 ng/L respectively, are reached after around 30 minutes.[21] In this dosage range, the pharmacokinetics of domperidone is of first order. Bioavailability of oral domperidone is low, with a mean of around 13% in a fasting person, because of the extensive first-pass metabolism. If the drug is taken 90 minutes after a meal, absorption is sig-

nificantly delayed but the bioavailability is increased to 17.6%, this is thought to be because of the lower intramural metabolism.[21] Plasma half-life ($t_{1/2}$) is 7.5 hours.[21] Protein binding is high, in the order of 91-93%.[21] Metabolism by hydroxylation and N-dealkylation is extensive, and only small amounts are excreted unchanged.[22] After oral administration, two-thirds of radiolabelled drug is excreted in the faeces, and the rest in urine.[22] In patients with severe renal failure, plasma concentrations are lower, but as protein binding is also decreased, the activity of the drug may be unchanged or actually increased.[23]

4.3 Cisapride

Cisapride, at least partially, acts by stimulating $5HT_4$-receptors in the presynaptic nerve endings in the myenteric plexus of the intestine. This stimulates the release of acetylcholine at the neuromuscular junction, strengthening tone and contractions of the gut wall.

Several studies have demonstrated that intravenous and oral doses of cisapride increase LES tone in healthy individuals and GORD patients,[24-28] most effectively in patients with a hypotonic oesophageal sphincter.[27,28] Smout and associates found that cisapride had a significant effect on the sphincter only in the late postprandial and fasting periods.[29] Similarly, studies of gastro-oesophageal reflux employing 16 to 23 hour pH-measurement show reduced gastro-oesophageal reflux, most pronounced in the fasting state.[30,31]

Cisapride is available in tablets of 5, 10 and 20mg. First-pass metabolism reduces bioavailability to 40 to 50%.[32] Single and repeated oral doses of cisapride 10mg taken 15 minutes prior to a meal give a C_{max} of between 45 and 65 μg/L, but this is higher if taken with food than in the fasting state, indicating reduced first-pass metabolism with food.[33]

Hypochlorhydria as induced by cimetidine and sodium bicarbonate will reduce C_{max} and bioavailability considerably.[32] Under such conditions, intake of cisapride 15 minutes prior to a meal will improve bioavailability.[32]

Cisapride acts on the LES primarily in the late postprandial and fasting state, which may indicate a need for frequent administration during the day. When cisapride is given 3 or 4 times a day, both daytime and nocturnal gastro-oesophageal reflux is reduced.[31] Single doses of cisapride 5 to 10mg are used in other motility disorders, but single doses below 10mg are not effective in GORD.[26]

In patients with delayed gastric emptying, 10mg 3 times daily has been shown to be more effective than either cisapride 10mg or 20mg twice daily.[34] Within the recommended dose range, after single and repeated doses, there are linear pharmacokinetics.[32]

Cisapride is metabolised in the liver to hydroxylated derivatives and via oxydative *N*-dealkylation to norcisapride, all virtually inactive.[33] In healthy humans, 41 to 45% of an ingested dose is excreted in the urine as norcisapride, with only 0.2% in the urine and 4 to 6% in faeces as unaltered cisapride.[35] The $t_{1/2\beta}$ of cisapride is 7 to 10 hours[32] in healthy volunteers. $t_{1/2\beta}$ is somewhat prolonged in patients with hepatic disorders, but not in renal insufficiency.[32]

After repeated administration, the area under the concentration-time curve (AUC) for the cisapride concentration curve was higher in elderly patients, indicating some degree of accumulation.[32] Cisapride accelerates the absorption of diazepam, cimetidine and ranitidine.

5. Histamine H_2 Receptor Antagonists

The compounds of this group act by inhibiting histamine H_2 receptors located on the basal membrane of gastric parietal cells. Histamine is released from enterochromaffin-like cells and possibly mast cells and mediates acid secretion by the parietal cell from a variety of stimuli, including the vagal nerve.

The direct effect of antisecretory agents can be measured by gastric secretion studies and by intragastric pH-measurement. Increasing doses of all H_2 receptor antagonists will inhibit basal, meal stimulated and pharmacologically stimulated gastric acid output in a dose-related manner. Data are

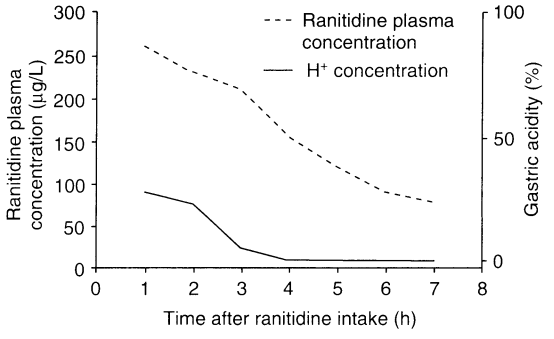

Fig. 1. Plasma drug concentration and gastric acidity after a single dose of ranitidine, showing that gastric acidity continues to fall at a time when plasma ranitidine is very low (reproduced from Berstad et al.,[42] with permission)

mostly available from healthy individuals and patients with peptic ulcer, but the effect of H_2 receptor antagonists on gastric pH in patients with GORD is thought to be comparable. Collen and associates[36] did, however, find that of 23 patients with long-lasting severe GORD, 12 patients were characterised by basal acid hypersecretion, high oesophageal acid exposure and oesophageal epithelial metaplasia. These patients had little symptomatic effect of ranitidine 150mg twice daily, but 10 of these responded to daily doses of 600 to 1800mg.[36] Direct comparisons of acid-suppressive effect between H_2 receptor antagonists are few, and have not been done in patients with GORD.

In 30 healthy individuals, Merki et al.[37] compared 24-hour intragastric acidity in 30 healthy volunteers receiving cimetidine 800mg, ranitidine 300mg, famotidine 40mg and placebo in the late evening in randomised order, finding that with the doses given, ranitidine and famotidine were significantly more effective, and famotidine was the only drug to inhibit acidity in the late morning.

The major physiological stimulus for gastric secretion is the intake of a meal, which increases acid and pepsin secretion by neural and endocrine mechanisms. Studies by Berstad et al.[38] in human volunteers show that meal stimulated acid (but not pepsin) secretion is inhibited by ranitidine, but significantly less effectively than basal secretion.[39] An inverse dose-response relationship between the size of the meal and the degree of acid inhibition by ranitidine has been established in dogs.[40] The impaired effect of ranitidine lasts longer than the duration of meal-stimulated acid secretion. The kinetics of the interaction of a meal with the effect of ranitidine is clearly competitive, suggesting that the meal releases histamine competing for the H_2 receptor.[40] The effect of competitive H_2 receptor antagonists on acid secretion seems to be most pronounced during periods of fasting, for example during the night. The effect of an evening dose of ranitidine 300mg on gastric acidity in patients with reflux oesophagitis lasts longer than that of a morning dose.[41]

H_2 receptor antagonism is prone to development of tolerance, a diminishing effect of a fixed daily dose on gastric acidity with time. This phenomenon has been described in volunteers[43,44] as well as in patients with reflux,[41] on intravenous and oral administration. Tolerance develops within the first few days of therapy,[45] is not progressive[46] and disappears shortly after the cession of medication. The higher the dose and the shorter the dose interval, the more pronounced the tolerance. Consequently, on-demand treatment, resulting in a lower consumption of drugs, might reduce this problem. It seems that even though there is a loss of effect on gastric acidity, tolerance affects gastro-oesophageal reflux to a lesser extent.[41]

No changes in the pharmacokinetics of H_2 receptor antagonists has been found over time.[47] While some patients describe loss of symptom relief over time, this refers to a minority only. Similarly, rebound hypersecretion on stopping medication with H_2 receptor antagonists has been described in volunteers,[48] but has not been established in patients with GORD. Tolerance may explain why it has been difficult to demonstrate a long term effect of H_2 receptor antagonists on the healing of reflux oesophagitis in clinical studies. Only a high dose of famotidine, 40mg twice daily, has proven to be superior to placebo in 1 large study,[49] thought to be due to a more pronounced suppression of gastric acidity.

From studies of intragastric acidity, the time of onset of different H_2 receptor antagonists after oral intake is around 45 minutes, but the rise in gastric pH occurs significantly earlier for effervescent formulations of cimetidine and ranitidine,[50] partly the initial antacid effect of sodium bicarbonate. The gastric acidity profile is often twin-peaked, representing first an acid-buffering effect of sodium bicarbonate, followed by the antisecretory effect of the H_2 receptor antagonist.[51] Because of its immediate *and* long-lasting effect, effervescent formulations of H_2 receptor antagonists may seem well suited for on-demand treatment.

The main effect of interest in GORD is decrease in oesophageal acid exposure, expressed as reflux time, i.e. percentage of 24 hours when pH is less than 4.0. Thomson et al.[52] compared the effect of increasing doses of ranitidine in patients with GORD, finding that 150mg twice daily and 300mg twice daily dose-dependently reduced 24-hour acid exposure, while 300mg 4 times daily did not contribute further. Only the highest dose reduced the number of reflux episodes significantly.

A significant relationship exists between intra-oesophageal acid exposure and the suppression of gastric acidity.[1,52] Jansen and associates[53] found that in 8 patients with reflux oesophagitis and a resistant to healing with ranitidine 150mg twice daily, the reflux time was reduced from a median of 26.4% on placebo to 10.2% with ranitidine 300mg twice daily and 5.4% with 300mg 4 times daily. Orr et al.[54] compared famotidine 40mg at night with 20mg twice daily and 40mg twice daily in 12 patients with GORD. They found that while all 3 regimens were effective in reducing reflux time, only the 2 twice daily regimens significantly reduced upright daytime reflux.[54]

5.1 Cimetidine

Cimetidine is an analogue of histamine retaining the imidazole ring of the physiological ligand. Cimetidine hydrochloride is at present available as tablets, as effervescent tablets and for intravenous administration. Key pharmacological data are given in table I. The absorption of cimetidine after oral administration is rapid, and a peak plasma concentration of 1.5 to 2.9 mg/L after intake of a 400mg tablet is reached within 60 to 90 minutes in a fasting person. Within the dose range of 200 to 400mg there are linear pharmacokinetics, while higher doses are followed by disproportionally high peak plasma concentrations. After oral intake, a systemic bioavailability of around 70% is found.[75]

The effervescent formulation of cimetidine contains sodium bicarbonate and citric acid and gives an almost immediate pH-increase to above pH 4.0.[51] The time to reach an effective plasma concentration (0.5 mg/L) was significantly shorter than with the standard 800mg tablet (11 *vs* 34 minutes).[51] A second peak on the plasma concentration profile of cimetidine is observed after about 3 hours in fasting individuals[76] when cimetidine is administered orally, but not on intravenous administration.

Table I. Pharmacokinetic and pharmacodynamic parameters for antisecretory drugs used in treating gastro-oesophageal reflux disease

Drug	V_{ss} (L/kg)	CL (L/h)	IC_{50} (μg/L)	$t_{1/2}$ (h)	Reference
Cimetidine	0.8-1.4	26.9-48.5	500-780	1.5-2.3	55,56
Ranitidine	1.2-1.8	32.6-42.5	80-165	1.6-2.7	57-60
Famotidine	0.9-1.3	18.5-29.3	13	2.2-4.0	37,61-64
Nizatidine	1.1-1.4	40.0-51.0		1.4-1.9	65,66
Roxatidine	1.7-3.2	21.2-29.3		4.0-8.0	67-69
Omeprazole	0.2-0.5	60		0.6-1.0	70
Lansoprazole	0.5	11-17		1.3-2.9	71,72
Pantoprazole	0.15-0.17	9.0		0.9-1.9	73,74

Abbreviations: CL = clearance; IC_{50} = concentration of drug producing 50% effect; $t_{1/2}$ = half-life; V_{ss} = apparent volume of distribution at steady-state.

The peak plasma concentrations of cimetidine are lower and reached later if cimetidine is taken with food,[76,77] but bioavailability is not significantly reduced. Studies in patients with peptic ulcers show that the bioavailability of cimetidine is reduced by around one-third when administered concomitantly with high doses of aluminium hydroxide antacids.[78,79,84]

Cimetidine is metabolised in the liver, by oxidative hydroxylation and conjugation. Up to 80 to 88% of a single dose of cimetidine is excreted in the urine; and up to 70% of the ingested drug is excreted in an unchanged form. The $t_{1/2\beta}$ is about 2 hours in healthy volunteers, but significantly prolonged in patients with renal insufficiency, and this is related to creatinine clearance (CL_{CR}). Total body clearance (CL) is between 27.0 and 48.5 L/h, reduced to between 3.1 and 16.3 L/h in patients with renal failure.[80] A $t_{1/2}$ of up to 5 hours was found in patients with severe renal impairment, and high peak concentrations of cimetidine were found,[81] necessitating a dose reduction.

Metabolism by enzymes of the cytochrome P450 (CYP) system gives multiple possibilities for interaction with hepatic metabolism of other drugs as well as endogenous mediators. Cimetidine inhibits several enzymes of families I, II and III of the microsomal CYP system, and thereby decreases hepatic clearance of several drugs in widespread clinical use. Amongst well-established interactions with a potential for pharmacodynamic effects are those with warfarin, diazepam, theophylline, phenytoin, carbamazepine, phenacetin and alcohol (ethanol).[82] The serum concentrations of lidocaine (lignocaine), propranolol, labetolol and metoprolol also increase, but are of less clinical importance. Interaction with the metabolism of psychotherapeutic agents may cause sedation and other CNS adverse effects.

5.2 Ranitidine

Ranitidine is an analogue of histamine with a furane ring replacing the imidazole ring. For oral treatment, ranitidine hydrochloride is available as tablets and effervescent tablets. Key pharmacological data are given in table I.

After oral administration of ranitidine 150mg twice daily in healthy volunteers, a peak plasma concentration of around 400 μg/L was found within 2 to 3 hours, but with considerable interindividual variation. A weak dose/plasma concentration linearity is found. A second peak in the plasma concentration profile of ranitidine, about 2 hours after the first, has been observed in several studies in volunteers,[83] after both oral and intravenous administration, thought to be caused by the biliary accumulation of the drug, postcibal (postprandial) emptying and intestinal reabsorption of ranitidine.[57] The bioavailability of ranitidine has been calculated at about 55%. Administration with a meal does not seem to reduce the bioavailability of ranitidine.[58]

It has recently been shown that ranitidine 300mg in an effervescent formulation results in a more rapid absorption (shorter t_{max},) and significantly higher plasma concentrations for the first 90 minutes after oral intake when compared with the standard tablet formulation.[85] This may contribute to the rapid onset of effect found in gastric pH studies with this formulation.[50] In a different study comparing oral intake of single doses of ranitidine 300mg in standard and effervescent tablet form, the AUC for the first 4 hours after intake was not significantly different, indicating similar systemic bioavailability.[86]

A study by Mihaly et al.[87] showed that concomitant administration of ranitidine with relatively large doses of aluminium/magnesium antacids resulted in the reduced bioavailability of ranitidine. As pointed out by Frislid and Berstad,[88] ranitidine and other H_2 receptor antagonists are customarily taken prior to a meal, while antacids may be needed only later to relieve postprandial reflux symptoms. In a study in volunteers, ranitidine was taken with a meal with an antacid added 1 and 3 hours later.[88] Under these more clinically realistic conditions, no interaction with the bioavailability of ranitidine was found. Sucralfate, another aluminium-containing salt, reduced the bio-

availability of ranitidine by 29%, when administered concomitantly to 10 volunteers in 1 study,[89] but this was not found in another study.[90]

Ranitidine is metabolised in the liver and excreted mostly in the urine, but also to some degree in bile. In elderly persons, plasma ranitidine AUC, trough plasma concentrations and $t_{½\beta}$ are moderately increased compared with the concentrations found in young individuals.[91]

Few clinically important interactions with other medication has been found, in particular, no interaction with the metabolism of diazepam, tricyclic antidepressants or antiepileptic drugs has been found, while the bioavailability of midazolam is increased. Recent studies have found no interaction with the pharmacokinetics of theophylline. A significant increase in peak concentrations and AUC of alcohol, with no change in the elimination rate was found after moderate alcohol intake in healthy young men.[92]

The CL and renal clearance (CL_R) of ranitidine in healthy individuals have been found between 32.6 to 42.5 L/h and 25.8 to 31.2 L/h, respectively.[80] Absorption is delayed in patients with renal insufficiency, but bioavailability is not altered. The $t_{½\beta}$ is prolonged, from 1.6 to 3.1 hours in healthy individuals, up to 9.7 hours, depending on the severity of the renal impairment. CL is reduced to between 7.6 and 14.0 L/min and CL_R to between 0.6 and 6.2 L/min.[80] The dose should be adjusted according to CL_{CR}, as the clearance of ranitidine is closely related to CL_{CR}. No specific compensation seems necessary when patients start haemodialysis or peritoneal dialysis, although plasma concentrations are reduced. Haemofiltration contributed to a ranitidine clearance of 4.0 L/min and removed, on average, 17.1% of the ranitidine dose after a mean filtration duration of 3.5 hours.[93]

5.3 Famotidine

Famotidine is a histamine analogue possessing a thiazole ring structure. Key pharmacological data are given in table I.

After oral intake of a single dose of famotidine 20 or 40mg, a maximum serum concentration of 0.043 to 0.070 mg/L is reached after 1.9 to 2.3 hours in a young healthy individuals, but C_{max} is reached later and is higher in elderly persons. Plasma concentrations are proportional to the dose taken in the recommended dosage range (first order pharmacokinetics). Bioavailability in a fasting person is in the order of 45%. The intake of famotidine with breakfast did not delay absorption or reduce bioavailability of the drug significantly, while administration with an aluminium magnesium hydroxide antacid resulted in delayed absorption and reduced bioavailability.[94]

Up to 38% of an oral dose of famotidine is recovered in the urine within 120 hours. Metabolism to an *S*-oxide recovered in the urine is of minor importance. The potential for drug interactions with famotidine seems to be lower than that of cimetidine and ranitidine, in particular, no interaction with the pharmacokinetics of diazepam, theophylline, phenytoin, warfarin or alcohol has been found.[95] The plasma $t_{½\beta}$ is short, about 3 hours in young healthy adults, but slightly increased in elderly people (4.1 to 6.7 hours) and significantly increased in patients with renal impairment (up to 18 to 27 hours).[96] CL of famotidine is between 18.5 and 27.8 L/min, but reduced to 2.0 to 14.5 L/min in patients with a varying degree of renal failure.[80]

The inhibitory effect of famotidine on gastric acidity in healthy volunteers lasts around 9 hours, but was increased to more than 24 hours in 4 out of 7 patients with severe renal failure,[96] necessitating a dose reduction. In 11 patients with various degrees of hepatic dysfunction, the pharmacokinetic parameters for famotidine were not significantly different from those found in 5 healthy individuals.[97]

A special wafer formulation (RAPIDISC wafer) of famotidine allowing dissolution of the tablet in the oral cavity, facilitates ingestion in patients with dysphagia and when water is not readily available. The famotidine in this formulation has been shown to have a similar bioavailability to the ordinary tablet formulation of famotidine.[98] It has no acid

buffering capacity, which limits its use in on-demand treatment, where an immediate effect is called for.

5.4 Nizatidine

Nizatidine, like famotidine, has a thiazole ring replacing the imidazole ring of histamine. Key pharmacological data are given in table I.

After an oral dose of nizatidine 150mg, the maximal plasma concentration is reached within 3 hours, with a bioavailability of 98%. Increasing oral doses result in proportionally increased plasma concentrations (linear pharmacokinetics). Bioavailability is unaffected by food intake, while concomitant intake of aluminium containing antacids decreased absorption by a modest 10%.[99]

Nizatidine is mainly excreted in urine, either unchanged or as an active metabolite, with an $t_{½\beta}$ of 1.1 to 1.4 hours in young healthy individuals.[66] The $t_{½\beta}$ has been found to be significantly longer in a group of elderly patients[100] and in patients with impaired renal function. In a group of haemodialysis patients $t_{½}$ was up to 8.5 hours.[65] CL_R is normally between 40.0 and 51.0 L/h, but reduced to between 12.4 and 26.8 L/h[80] in patients with renal failure. Up to 16.4% of an ingested dose was removed by 5 hours of haemodialysis, while chronic ambulatory peritoneal dialysis removed less. A reduced dose will be necessary in patients with moderate to severe reduction in CL_{CR} (<3 L/h).

5.5 Roxatidine

Roxatidine has a piperidine ring structure in place of the imidazole ring of histamine and cimetidine. For oral use, roxatidine is available as slow-release capsules with granules containing 150mg of roxatidine acetate. Key pharmacological data are given in table I.

Roxatidine is almost completely absorbed from the gastrointestinal tract and rapidly converted into its active form, roxatidine, by esterases present in the intestinal wall, liver and plasma. After oral administration to healthy volunteers, a peak plasma concentration of 264 μg/L was reached within 3 hours.[67] $t_{½\beta}$ has been found to be between 4 and 8 hours.[68] 69% of an oral dose of radiolabelled roxatidine acetate 75mg was recovered as unchanged roxatidine, while the rest was recovered as inactive metabolites. The $t_{½\beta}$ is significantly prolonged in patients with various degree of renal insufficiency, up to 18.1 hours was found in patients with uraemia.[69] The CL of roxatidine is between 21.2 and 25.9 L/min, but is reduced to 5.1 to 13.9 L/min in patients with renal failure.[80] This will give increased plasma concentrations and AUC for plasma roxatidine, which may necessitate a dose reduction.[69]

6. Proton Pump Inhibitors

The compounds of this class, lansoprazole, omeprazole and pantoprazole, are substituted benzamidazoles and act as non-competitive inhibitors of the parietal cell H^+-K^+ ATPase mediating gastric acid secretion. The prodrugs are weak bases and are rapidly accumulated in the acid environment of the luminal canaliculi of the parietal cell membrane, are converted to the active sulphenamide derivatives and bind covalently to cysteine residues in 1 to 3 positions on the α subunit of the ATPase molecule. This blocks the action of the proton pump since dissociation of the complex is very slow. Acid secretion is gradually restored only when new ATPase molecules are synthesised. E-3810, a new member of the group, has a shorter duration of action, thought to be due to endogenous gluthathione dissociating the drug from binding sites more rapidly.[101]

Clinical studies comparing lansoprazole and omeprazole in mild to moderate reflux oesophagitis document similar healing rates, but earlier symptom relief with lansoprazole 30mg daily than with omeprazole 20mg daily.[102] Some, but not all, studies indicate that lansoprazole 30mg inhibits gastric acidity to a greater extent than omeprazole 20mg,[103] partly explaining the clinical observations. Furthermore, there are data indicating a much higher systemic bioavailability of lansoprazole 15 and 30mg during the first days of treatment, explaining the more rapid onset of effect.

All benzimidazole compounds are metabolised by enzymes of the CYP system in the liver, to hydroxylated and sulphone derivatives of the compounds. A minority of Caucasians (<5%), but around 15% of Chinese individuals are poor metabolisers of omeprazole and certain other drugs (diazepam and phenytoin) that are metabolised by a hydroxylase belonging to the CYP2C group.

6.1 Omeprazole

Omeprazole is very unstable at a low pH and will degrade unless protected against the acid in the stomach. Key pharmacological data are given in table I.

For oral intake, omeprazole is available as encapsulated enteric-coated granules, causing the drug to released only when reaching the small intestine. t_{max} is delayed by this formulation, relative to a buffered solution of the drug, but has been found to be reached within 3 to 4 hours.[104] The rate and extent of absorption of omeprazole given as enterocoated granules is highly variable. Systemic bioavailability after an oral dose of omeprazole 20mg is 35%, increasing to 60% on repeated dose administration, indicating that suppression of gastric acidity reduces preabsorption degradation of the drug.[104]

The absorption of omeprazole is markedly delayed by a meal, but bioavailability is not reduced. The exact timing of medication prior to a morning meal seems to be less important.[105] Administration concomitantly with an aluminium magnesium hydroxide antacid did not alter bioavailability of omeprazole in 1 study.[105] Linear pharmacokinetics has not been found for omeprazole.

Omeprazole is rapidly eliminated from plasma, with a $t_{½β}$ of 2.8 hours, not significantly longer after repeated administration.[104] Metabolism in the liver gives hydroxyomeprazole and a sulphide derivative of the molecule, neither of which are pharmacologically active. Genetic differences in CYP2C (*S*-mephenytoin hydroxylase) activity result in a group of slow metabolisers with a $t_{½β}$ for omeprazole more than 2 hours. The clinical implications of this are unknown, but an increased effect is expected. Excretion is mainly renal, and around 80% of an ingested dose is found in the urine; CL is in the order of 60 L/h.

In patients with renal insufficiency, the elimination of omeprazole is unchanged, while renal excretion of its metabolites is reduced, partly compensated for by increased biliary excretion. Liver cirrhosis with a decreased hepatocellular tissue mass is followed by an increased $t_{½β}$ in excess of 3 hours. In elderly individuals, hepatic metabolism is also decreased.

Potentially important interactions with the metabolism of other drugs have been noted for diazepam and phenytoin, which are both metabolised by CYP enzymes of subfamily 2C. A statistically significant increase in concentration of the *R*-isomer of warfarin, and a decrease in 'Thrombotest' values was noted in 1 study, being of uncertain importance.[106]

Several studies have demonstrated very effective inhibition of gastric secretion and acidity by the proton pump inhibitor omeprazole, showing a dose-response relationship in the range of 5 to 80mg in groups of healthy volunteers, with the highest doses resulting in virtual anacidity (>95% suppression), but with wide interindividual variation in the response to each dose.[107] When compared with ranitidine 300mg 4 times daily, a significantly more effective suppression of daytime (but not nighttime) acidity was found after only 2 days of omeprazole 40mg each morning.[45] Whereas the antisecretory effect of ranitidine decreased significantly between day 1 and 7, that of omeprazole increased during the first week.

6.2 Lansoprazole

Like other compounds in this group, lansoprazole is acid labile and is for oral use formulated as acid-stable enteric-coated granules in hard gelatine capsules, containing 15 or 30mg of biologically inactive lansoprazole. Key pharmacological data are given in table I.

On oral administration of a single dose of lansoprazole 30mg, it reaches a plasma C_{max} of between 0.75 and 1.15 mg/L within 1.5 to 2.2 hours

in fasting healthy volunteers. The C_{max} was found to be delayed by a meal, but was similar in young and elderly individuals.[71] Within the dose range of 15 to 60mg, lansoprazole shows linear pharmacokinetics.[108] On repeated administration of lansoprazole 15 or 30mg daily for 7 days, plasma AUC were significantly (40 to 53%) higher in elderly persons compared with young individuals,[109] this is thought to be caused by a longer $t_{1/2\beta}$. In a French study,[71] mean $t_{1/2}$ was 2.9 *vs* 1.4 hours for elderly versus young patients; no accumulation occurred. A mean absolute bioavailability of 85% has been found in healthy individuals on daily intake of lansoprazole,[110] but with a 6-fold interindividual variation.[72] The systemic bioavailability of lansoprazole 15 and 30mg is high from the first day of oral intake.[71]

The $t_{1/2\beta}$ of lansoprazole in oral doses between 15 and 60mg is between 1.3 and 1.7 hours, through hepatic metabolism to hydroxy-lansoprazole by enzymes of the CYP group and lansoprazole-sulphone and -sulphide. Elimination is significantly slower in elderly persons[71] and in patients with hepatic failure (terminal $t_{1/2}$ 3.2 to 7.2 hours, oral CL 2.8 to 4.9 L/h, dependent on the degree of hepatocellular loss).[110] In hepatic failure, elimination characteristics remain constant on repeated administration for 9 days, showing no signs of accumulation.[111] When compensating for older age, patients with renal failure (aged 34 to 74 years) did not seem to eliminate lansoprazole more slowly than a control group (aged 20 to 32) in 1 study.[110]

One study investigated the importance of lansoprazole as a morning dose rather than a bedtime dose,[112] showing increased bioavailability, but no difference in gastric 24-hour acidity. There is conflicting evidence as to the importance of administrating lansoprazole in the fasting state, 1 study shows delayed absorption and a 27% reduction in bioavailability when given with a morning meal,[113] while another study[114] found a similar reduction in gastric acidity caused by lansoprazole 30mg given either 30 minutes before or 30 minutes after breakfast for 7 days. One study has examined the effect of antacids on lansoprazole bioavailability, finding a decrease in t_{max} and a small decrease in bioavailability.[113]

Increasing daily doses of lansoprazole will result in higher gastric 24-hour mean pH values, increasing from pH 4.3 with 30mg once daily, and pH 5.1 with 60mg 3 times daily, while dividing a single daily dosage into 2 or 3 doses did not seem to increase the acid inhibition in a group of healthy volunteers.[115] The effect of lansoprazole 15 and 30mg daily on gastric acidity was recently compared to that of omeprazole 20mg[103] in healthy volunteers. On the fifth day of medication, no significant difference was found between lansoprazole 15mg (median 24-hour pH 4.03) and omeprazole 20mg (median 24-hour pH 4.16), while lansoprazole 30mg was found to be significantly more effective (median 24-hour pH 4.91). A greater suppression of gastric acidity was found in elderly versus young persons.[116]

No clinically significant interaction has been found with the pharmacokinetics of propranolol, phenytoin, warfarin, prednisone, theophylline, oral combination contraceptives, diazepam or alcohol.

6.3 Pantoprazole

For clinical and oral pharmacokinetic studies, pantoprazole has been administered as enterocoated tablets. Key pharmacological data are given in table I.

After oral intake of a single dose of pantoprazole 40mg, a mean C_{max} of 2.09 mg/L was reached after a median time of 2.8 hours. Mean absolute bioavailability was calculated at 77%, and was relatively stable on repeated administration.[117] The serum concentration of pantoprazole was found to be proportional to the oral dose, when volunteers were given daily doses of 20, 40 and 80mg for 7 days (linear pharmacokinetics). Median gastric 24-hour pH was not significantly different with the 40 and 80mg doses, both being superior to 20mg, which is in turn significantly superior to placebo.[118]

Pantoprazole is mainly metabolised in the liver and inactive metabolites are excreted in the urine. In 12 patients with severe renal impairment, no sig-

nificant differences were found in the C_{max}, $t_{1/2}$ or 24-hour AUC of pantoprazole.[119] Aluminium antacids ('Maalox' 10ml) taken concomitantly with pantoprazole 40mg did not significantly influence the pharmacokinetic properties of the drug in healthy volunteers.[73]

In a study in 73 healthy women, treatment with pantoprazole 40mg daily did not cause failure in oral contraception in any of the patient,[120] nor was there any influence on the pharmacokinetic parameters of a single dose of phenytoin.[121] No interaction was found with warfarin.[122]

7. Plasma Concentration and Clinical Response

A desired effect of therapy in gastro-oesophageal reflux disease is the decrease in oesophageal acid exposure, which can be achieved by medical therapy acting by different pharmacological principles. Control of oesophageal acid loads is important to promote the healing of oesophagitis and relief from symptoms. Optimal or effective plasma concentrations of the individual drugs for treating GORD have not been published, partly because a well-defined parameter of effect has been difficult to define. Oesophageal acid exposure, as measured by 24-hour pH-measurement might seem to be an ideal parameter, and plasma concentrations and dosage regimens of drugs that would normalise oesophageal acid exposure could be compared. Oesophageal acid exposure does, however, show considerable intraindividual variation. During antisecretory therapy, oesophageal acid load is related to suppression of gastric acidity,[1] which is a more reproducible parameter.

Antisecretory agents reduce oesophageal acid load by decreasing the acidity and, to less extent, the volume of gastric acid secretion available for reflux. The plasma concentration of a drug associated with a 50% reduction in pentagastrin-stimulated acid secretion (IC_{50}), has been used by some authors to compare the potency of acid-lowering drugs used in treating peptic ulcer disease. Values of IC_{50} are of less interest in GORD, in which a more profound acid inhibition is called for than in other acid-related diseases. Fraction of time above a certain gastric pH-level at which reliable healing of oesophagitis and relief of symptoms is achieved is a more relevant measure for comparing the efficacy of different drugs and dosages.

Which gastric pH threshold to aim at is not well studied, but as shown in a metaanalysis by Bell et al.,[1] treatment which (in groups of patients) elevates median gastric pH to above 4 for more than 21 out of 24 hours leads to healing in more than 90% of patients. The best effect is seen with proton pump inhibitors, omeprazole 20, 30 and 60mg resulting in pH above 4.0 for 15, 19 and 21 hours respectively. Standard doses of H_2 receptor antagonists raise pH above 4.0 for 4 to 9 hours. These data only relate acid suppression to ingested doses and not to plasma concentration of drugs. Interindividual variation is also considerable. Even at a pH of 4, full healing may not be achieved in all patients and/or some reflux symptoms may persist. Symptom relief may be achieved at a lower pH than healing, but may differ more between individuals.[123]

All H_2 receptor antagonists act on receptors on the parietal cell basal membrane to reduce the secretion of acid. There is no direct time relationship between the peak plasma concentration of the drug and its maximum antisecretory effect. In a study in 11 healthy volunteers,[42] a single dose of ranitidine hydrochloride or placebo was administered with a meal, and the plasma concentration of the drug and inhibition of acid secretion were studied. Although the plasma concentration of ranitidine was highest after just 1 hour and then declined rapidly, the reduction in gastric acidity due to ranitidine increased after that and reached nearly 100% after 4 hours (fig. 1).[42] This discrepancy in time between ranitidine concentration and its effect is attributed to delayed and prolonged ligand-receptor binding in the gastric mucosa, as the plasma ranitidine concentration does not reflect the amount of ranitidine bound to receptors. The effect lasts longer in a fasting patient; this is thought to be because of the dissociation of the drug from receptors by meal-induced histamine secretion.[39] Nevertheless, acid

inhibition is related to the ingested oral dose and the mean plasma concentration or AUC,[124] as shown mainly in patients receiving H_2 receptor antagonists as prophylaxis against stress-induced ulceration and bleeding.

Interindividual variation in acid inhibition achieved with the same plasma concentration is also considerable. While maximum antisecretory response to famotidine was fairly constant in a group of ulcer patients and healthy individuals, plasma concentrations necessary to maintain gastric pH at 4 showed a wide interindividual variation.[123] Furthermore, interindividual variation in plasma concentration will add to the problem of predicting acid suppression from the dosage of the drug in individual patients. In different studies IC_{50} was found to be 13 μg/L with famotidine, 80 to 165 μg/L with ranitidine and about 500 to 780 μg/L with cimetidine (table I).

The relationship between plasma concentrations of H_2 receptor antagonists and acid suppression is not constant over time, but is altered by the development of tolerance. Tolerance developed in healthy volunteers,[43,44] patients with duodenal ulcers and patients with reflux oesophagitis,[41] on both intravenous and oral administration. Tolerance has been shown not to be related to any pharmacokinetic parameter[47] but is thought to be caused by alterations at either a hormonal or receptor level.

Tolerance reduces the effect on acid suppression from the first day of therapy, when an H_2 receptor antagonist can be more effective than a proton pump inhibitor, to a more modest level. Tolerance develops within the first few days of therapy,[44] but is not progressive[45] and disappears shortly after the cession of medication. The higher the dose and the shorter the administration interval, the more pronounced the tolerance. One study shows that tolerance has little effect on gastro-oesophageal reflux in patients with moderate reflux oesophagitis.[40]

The substituted benzimidazole compounds act directly on the parietal cell H^+-K^+ ATPase molecule to inhibit H^+ secretion. By inhibiting gastric acid secretion at a late step in the process, several important physiological stimuli, including the stimulation by a meal, are inhibited, this partly explains the high effectiveness of acid suppression compared with H_2 receptor antagonists.

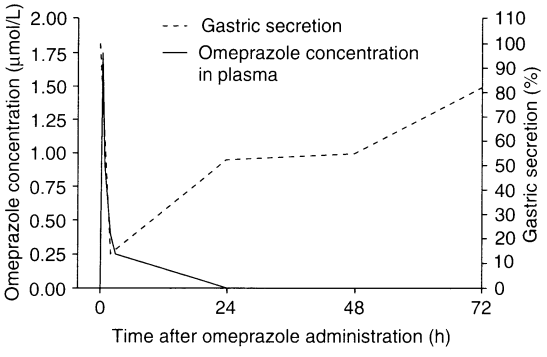

Fig. 2. Plasma drug concentration and gastric acidity after a bolus injection of omeprazole, showing that gastric secretion is suppressed when plasma omeprazole is no longer detectable.[125]

There is no temporal association between the peak plasma concentration and the maximum acid suppression caused by the proton pump inhibitors (fig. 2). While plasma $t_{1/2}$ is short, in the order of 1 to 2 hours, the duration of acid suppression even after single doses is much longer. The duration of action of these drugs depends more on the rate of synthesis of the ATPase molecules than on the plasma concentrations of the drug itself. Basal secretion is still inhibited by on average 70% 24 hours after the intake of an oral dose of omeprazole 20mg, but interindividual variation is considerable.[126]

In a study involving healthy volunteers, the plasma concentration peak was reached 30 to 40 minutes after the intake of oral suspension and maximum inhibition of pentagastrin-stimulated acid secretion was recorded during the second hour. Although no omeprazole could be found in plasma 24 hours after a single oral dose of 40mg, stimulated gastric secretion was still inhibited by 48, 34 and 18% after 24, 48 and 72 hours, respectively.[125] After repeated daily oral doses of 15mg, a stable mean inhibition of 30 to 40% prior to and 75 to 80% 2 hours after intake was reached by day 3.[125] With omeprazole, a dose-response relationship has been

found for single oral doses in the range of 5 to 80mg, although not a linear relationship.[107]

Interindividual variation in first-pass metabolism for these drugs makes it difficult to predict acid suppression from the dosage given. A significant correlation exists between the AUC for the drug and suppression of gastric acidity.[125] There have not been any studies to date which look at whether this relationship is stable over a long time.

During the first days of administration, the effect on acid suppression is less than expected from plasma concentrations of the drugs, as only active proton pump molecules in the parietal cell are available for inhibition, while continued administration will lead to progressive inhibition. Frequent administration may increase acid suppression by inhibiting newly synthesised ATPase molecules at an early time.

Prokinetics may decrease oesophageal acid exposure by stimulating upper gastrointestinal motility, notably LES tone, oesophageal peristalsis and gastric emptying. The blood concentrations of prokinetics with different administration regimens and their relationship to motility effects have not been published. With metoclopramide, single intravenous doses of 10 and 20mg are, however, known to result in dose-dependent increases in LES tone, proportional to baseline tone.[127] With single doses of cisapride, the effect on motility is most consistently seen after intravenous doses, and in the dose range of 5 to 20mg, the effect on LES tone is dose-dependent. Similar effects are seen after single oral doses of 20mg and repeated oral doses. After oral intake of a single dose, cisapride reaches a plasma peak concentration after 1 to 2 hours and can still be measured after 24 hours. A significant effect on resting LES tone has been found to last for only 2 hours.

8. Pharmacokinetic Optimisation of Therapy

Pharmacokinetic optimisation in GORD is aimed at creating the optimal conditions for bringing active drugs to their sites of action in concentrations enabling them to work effectively for healing and symptom relief. Optimal plasma concentrations of drugs in treating GORD have not been defined and may seem to be of limited clinical use. H_2 receptor antagonists and proton pump inhibitors have short $t_{1/2}$ and only AUC relates to acid suppression. In individual patients, tailoring the medication regimen to achieve the optimal plasma concentrations is of theoretical interest, but not necessarily adequate to ensure effective therapy. With antisecretory therapy, it is clear that a more profound acid inhibition is needed than has been considered necessary to heal the majority of gastro-duodenal ulcers. Furthermore, there are indications that more aggressive acid suppression is needed when the anti-reflux barrier is weak.[1]

While severe or complicated reflux oesophagitis seems dependent on effective suppression of gastric acidity to achieve normalisation of gastric acid exposure and heal, less severe disease will often respond well to prokinetics or less aggressive antisecretory therapy. In cases of therapeutic failure, the adequacy of medication is more directly monitored by combined oesophageal and gastric pH-measurement during ongoing treatment.

Cisapride is the drug of choice among prokinetics, partly because of the lower incidence of CNS adverse effects than for metoclopramide. In the group of prokinetics, cisapride has a longer plasma $t_{1/2}$ and longer duration of action than metoclopramide and domperidone, which allows twice daily administration. In both functional dyspepsia and GORD, the required oral dose for clinical effect varies considerably between individuals; linear pharmacokinetics facilitate dosage adjustments. Administration regimens which mean frequent doses of prokinetics and antisecretory drugs may improve the effects of the drug, but may jeopardise patient compliance. The combinations of antisecretory drugs and antacids may decrease the absorption of cisapride, but the extent of this is reduced when cisapride is taken prior to a meal. Patients with GORD often suffer from concurrent bloating and upper abdominal discomfort related to meals, which may also respond well to prokinetic therapy.

With H_2 receptor antagonists, competitive inhibition of gastric secretion and linear pharmacokinetics ensure an easily controlled inhibition of acid secretion, but with limitations in maximum efficiency. Acid inhibition is related to the AUC, but interindividual variation with the same dose is wide. Tolerance will reduce the effect of the drug without affecting its plasma concentration.[47] While single doses of H_2 receptor antagonists are highly effective, the acid suppression provided by continued doses is lower, and may not be adequate for the relief of symptoms and healing of oesophagitis in individual patients.

Both night-time and daytime reflux is considered important in patients with GORD, so the treatment effect should cover 24 hours. The short duration of action found in studies of gastric acidity indicates a need for twice daily administration.[41] Twice, instead of once, daily administration of famotidine has been shown to improve acid suppression but not healing. Some data indicate that frequent administration is as important as the total daily dose and when taken 3 or 4 times daily H_2 receptor antagonists may approach proton pump inhibitors in effectiveness, at least initially. In patients with renal failure, a dose reduction is needed. Some limitation of effect may result from a high concomitant intake of antacids. Effervescent formulations, with improved absorption and rapid onset of action are a good alternative in on-demand therapy.

With proton pump inhibitors like omeprazole, lansoprazole and pantoprazole, plasma concentrations vary considerably, even when in steady state, due to interindividual variation in first-pass metabolism. Suppression of gastric acid secretion is closely related to the AUC for omeprazole when at steady state.[125] This indicates that the amount of drug absorbed is the important factor for inhibition, more so than the plasma concentration, probably due to the redistribution and irreversible binding of the drug in the gastric parietal cell.[128] During the first days of administration however, acid suppression is lower than expected from plasma AUC values, which can be explained by progressive binding of the drug to the gastric H^+,K^+ ATPase molecules. Since it is difficult to predict the response to standard oral doses of proton pump inhibitors, some patients will have little effect, while others will reach virtual anacidity, with possible long term adverse effects, like reduced absorption of iron and cyanocobalamin (vitamin B12).[129]

The acid-suppressive effect of omeprazole is significantly higher in *Helicobacter pylori* positive patients. Several studies show that morning administration results in the higher bioavailability of proton pump inhibitors,[112] which is of therapeutic importance. Administering lansoprazole in the fasting state may be more important than with omeprazole.[72,116] Because of the long duration of action of proton pump inhibitors, they are usually taken once daily. However, the duration of action varies considerably, and in some patients an additional early evening dose is needed.[130] Only a minority of patients do not respond to omeprazole at all, this is considered to represent a form of resistance.[131] It is not yet clear whether this phenomenon applies equally to all drugs in the group.

9. Conclusion

During the last decades we have seen the introduction of new drugs leading to the improved treatment of GORD. Different patients need different types of treatment, involving differences in potency and drug combinations. We have reviewed the key pharmacokinetic and pharmacodynamic data necessary in the process of optimising therapy. Important data are summarised in table I. The different classes of drugs represent different principles of action and certain data may therefore be of varying importance.

Cisapride is undoubtedly superior to earlier prokinetics, metoclopramide and domperidone, with a longer $t_{1/2}$ and duration of action, allowing twice daily administration and less CNS effects. Administration 15 minutes before meals is important to achieve adequate bioavailability.

Among H_2 receptor antagonists the compounds with the longest $t_{1/2}$, famotidine and ranitidine, provide the most effective acid suppression throughout 24 hours. Cimetidine interacts with the meta-

bolism of several other drugs in common use and should be avoided when patients use other medication. The need for administration at least twice daily may affect patient compliance when compared with proton pump inhibitors. H_2 receptor antagonists in effervescent formulation have improved bioavailability and are most effective in on-demand therapy of GORD.

Through their profound inhibition of gastric acid secretion, the proton pump inhibitors omeprazole, lansoprazole and pantoprazole are beyond doubt the most effective drugs for the treatment of GORD. Their long duration of action allows once daily administration in the majority of patients. The linear pharmacokinetics and high bioavailability of lansoprazole and pantoprazole are of clinical importance when starting therapy. Interaction with the absorption and metabolism of other drugs are few and will seldom be a clinical problem. Pantoprazole is less prone to drug interactions than omeprazole.

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