

24 hour pH in the gastric lumen is about 1.5. This increases to about 2.5 with an H₂-receptor antagonist while PPIs in standard dosage can usually increase the median pH to about 4-5. This is of particular value when treating resistant gastro-oesophageal reflux disease. This elevation of pH also seems to be an advantage when acid suppression is used as part of the triple therapy strategies for treating *H. pylori* infection.¹

One interesting property of the current generation PPIs is that their effects can be a little more unpredictable when the dosage is lowered. For example, one study with omeprazole showed that a 10 mg dose once daily had little effect on 24 hour median pH in three of eight volunteers while several of the remainder had marked acid suppression. This phenomenon may be explained by variability in the rate of regeneration of acid pump molecules.

Tolerability

The PPIs are extremely well tolerated. In the trials that established their efficacy, the adverse events reported by patients taking the drugs were usually not statistically different from those of placebo. This presumably relates to the very specific drug delivery and the very tissue-specific localisation of this particular hydrogen/potassium pump.

Long-term safety

Initial concerns about potential risks from long-term acid suppression in humans seem to be unfounded. A slightly increased risk of some enteric infections (mainly *C. jejuni*) has been observed. Data accumulated over the first decade of use do not raise any significant concerns about neoplastic potential in humans. If there are any long-term risks, they are likely to be outweighed by the risks of **not** treating troublesome acid-related diseases adequately.²

Future developments

H₂-receptor antagonists appear to be a mature family of drugs, with further improvements probably unlikely. Blockade of the proton pump is still evolving, through the development of variants with even more predictable effects, as well as inhibitors that are shorter or longer acting than those currently marketed.

REFERENCES

1. Mohamed AH, Hunt RH. The rationale of acid suppression in the treatment of acid-related disease. *Aliment Pharmacol Ther* 1994;8 Suppl 1:3-10.
2. Yeomans ND, Dent J. Alarmism or legitimate concerns about long-term suppression of gastric acid secretion? *Aliment Pharmacol Ther* 2000;14:267.

FURTHER READING

Shamburek RD, Schubert ML. Pharmacology of gastric acid inhibition. In: Yeomans ND, editor. *Inhibition of gastric acid secretion*. Baillieres Clin Gastroenterol 1993;7:23-54.

Prewett EJ, Hudson M, Nwokolo CU, Sawyerr AM, Pounder RE. Nocturnal intragastric acidity during and after a period of dosing with either ranitidine or omeprazole. *Gastroenterology* 1991;100:873-7.

Sachs G, Zeng N, Prinz C. Physiology of isolated gastric endocrine cells. *Annu Rev Physiol* 1997;59:243-56.

Dockray GJ. Topical review. Gastrin and gastric epithelial physiology. *J Physiol (Lond)* 1999;518:315-24.

Piper DW, Yeomans ND, Shearman DJ. Omeprazole and acid peptic disease. *Med J Aust* 1991;154:374-5.

Self-test questions

The following statements are either true or false (answers on page 67)

3. Proton-pump inhibitors have a long duration of acid secretory inhibition because of their long plasma half-lives.
4. Histamine provides the most important final input to stimulate the gastric parietal cell to secrete acid.

Drug interactions

Warnings for cisapride

Cisapride will be withdrawn from the American market in July. The drug is being withdrawn because of concern about serious adverse effects. By the start of 2000, the Food and Drug Administration had reports of 341 cases of arrhythmia and 80 deaths. Many of these adverse reactions were the result of cisapride interacting with other drugs.

The metabolism of cisapride mainly involves cytochrome P450 3A4. If this metabolism is inhibited by other drugs (see box), plasma concentrations of cisapride increase. This prolongs the QT interval on the ECG and can provoke arrhythmias. These arrhythmias include torsades de pointes and ventricular fibrillation.

Cisapride is contraindicated in patients who already have a prolonged QT interval. This abnormality can be congenital,

but may be present in patients with:

- heart disease
- diabetes mellitus
- electrolyte abnormalities.

In the USA, cisapride was approved for the treatment of night-time heartburn due to gastro-oesophageal reflux disease. In Australia, the approved indication for reflux oesophagitis limits treatment with cisapride to six months or less.

Cisapride is contraindicated in combination with:

- macrolide antibiotics (e.g. erythromycin, clarithromycin)
- azole antifungals (e.g. fluconazole, itraconazole, ketoconazole, miconazole)
- HIV protease inhibitors (e.g. indinavir, ritonavir)
- nefazodone