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Safety of proton pump inhibitors—an overview

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SUMMARY

Drug-induced achlorhydria in experimental animals results in excessive hypergastrinaemia, ECL-cell hyperplasia and ECL-cell carcinoidosis. However, these events have not been observed in long-term studies in patients receiving proton pump inhibitors. Serum gastrin levels increase only modestly during acute and long-term treatment. It is concluded that monitoring of serum gastrin levels and of fundic ECL cells is of no clinical relevance even during long-term therapy with proton pump inhibitors. The clinically available proton pump inhibitors such as pantoprazole, omeprazole and lansoprazole are well tolerated, with a low incidence of side-effects. Minor and serious side-effects classified as possibly related to proton pump therapy have been described in up to 2.5% of patients. This is the same order of magnitude as that found in patients treated with H_2-receptor blockers and in placebo-treated controls. In most cases, therefore, the observed side-effects are unrelated to the intake of proton pump inhibitors. Minor adverse events include headache, diarrhoea, dizziness, pruritus and rash. Proton pump inhibitors are metabolized mainly in the liver via the cytochrome P450 system and interactions with drugs metabolized by the same system are possible. Evidence is becoming available which suggests that pantoprazole may have less potential to interact with the cytochrome P450 system than the other proton pump inhibitors. In the case of diazepam metabolism, pantoprazole had the least effect on prolongation of the diazepam effect. This may well be an advantage in the clinical use of the drug.

INTRODUCTION

Over the past 15 years, major advances have been made in the therapeutic control of acid secretion. The advent of H_2-receptor antagonists provided an effective class of drugs, and their widespread use has brought relief to millions of patients without significant side-effects.[1–4] Earlier in this symposium, Professor Sachs described the limitations of the H_2-receptor antagonists and provided a biological basis for the therapeutic control of acid secretion by an entirely new class of antisecretory drugs, the substituted benzimidazoles, which act as inhibitors of gastric H^+,K^+-ATPase, the gastric acid pump.[5] Many investigators have demonstrated advantages of proton pump inhibitors in the treatment of peptic ulcers resistant to high doses of H_2-receptor antagonists.[6–10]

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The safety and long-term use of proton pump inhibitors have been discussed extensively in this symposium. This paper will provide an overview of the current overall safety data available. First of all, it is important to begin with the gastrin hypothesis and its relation to therapy with proton pump inhibitors.

The gastrin hypothesis

The gastrin hypothesis implies that hypergastrinaemia can arise, either because of the Zollinger–Ellison syndrome, or via achlorhydria. The state of achlorhydria can be achieved by pharmacological induction in animals or by atrophic gastritis, for instance, in the case of pernicious anaemia in humans. Achlorhydria leads to hypergastrinaemia, which then exerts a trophic effect leading to enterochromaffin-like (ECL)-cell hyperplasia.[11] In his paper, Professor Sachs also described the presence of a receptor on the ECL cells for progastrin[5] and it follows

that ECL-cell hyperplasia is the physiological or pathophysiological consequence of every case of hypergastrinaemia, whether or not it arises from the Zollinger–Ellison syndrome, pernicious anaemia or following pharmacological induction. However, ECL-cell hyperplasia does not necessarily lead to the appearance of either ECL-cell dysplasia or ECL-cell carcinoidosis. There may be important cofactors involved which have still to be identified. For example, in humans, carcinoids have only been observed in patients with pernicious anaemia and gastrinoma patients associated with the Multiple Endocrine Neoplasia (MEN) I syndrome.[12,13] In contrast, patients with sporadic gastrinoma do not develop carcinoid tumours.[13] This indicates that the presence of atrophic gastritis (pernicious anaemia) or of a genetic trait (MEN I syndrome) could be such cofactors.

When rats were treated experimentally with BY308 (a predecessor of pantoprazole), there was a marked rise in serum gastrin levels paralleled by a rise in the number of ECL cells, compared with control values (Figure 1).[14]

Measurement of the ECL-cell labelling index reveals the extent of cells which are dividing. Figure 2 shows the dividing capacity of ECL cells in rats under the influence of BY308. It can be seen that in contrast to control values, the ECL-cell labelling index increased rapidly within 10 days of treatment after which time a plateau occurred through to 70 days. This corresponds with the linear increase in ECL cell numbers over this 70-day period. (Figure 2).[14]

When the experiments were repeated with BY308 in rats in the presence of a specific gastrin receptor antagonist, it was possible to reverse the increases both in the number of ECL cells and in the ECL-cell labelling index despite persisting hypergastrinaemia. This normalization of the ECL-cell labelling index demonstrated that the ECL-cell hyperplasia observed was gastrin-mediated.[15]

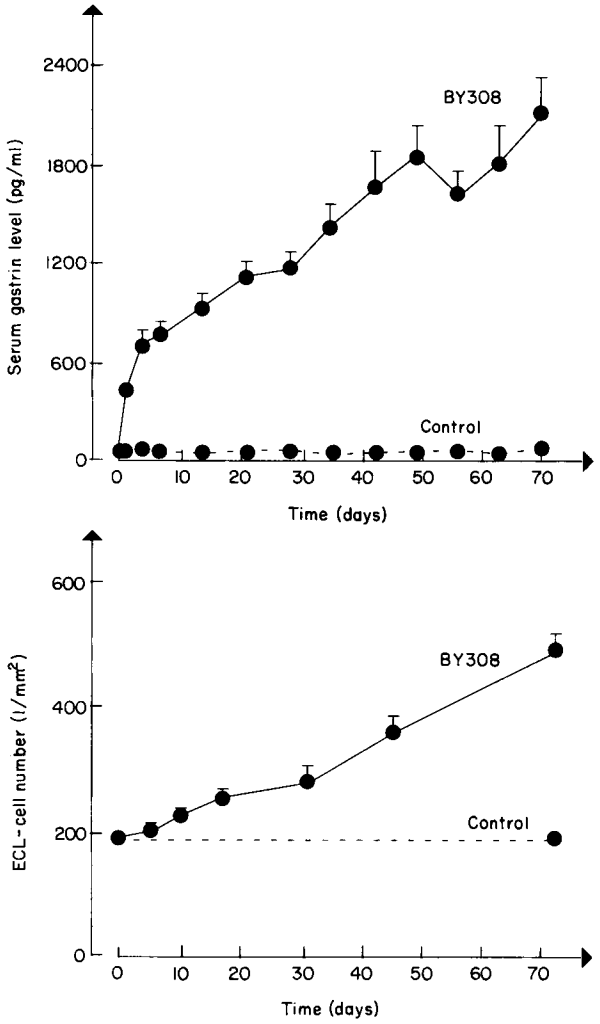

Figure 1. Serum gastrin levels and number of ECL-cells in rats treated with BY308, and untreated controls (data from Eissele *et al*).[14]

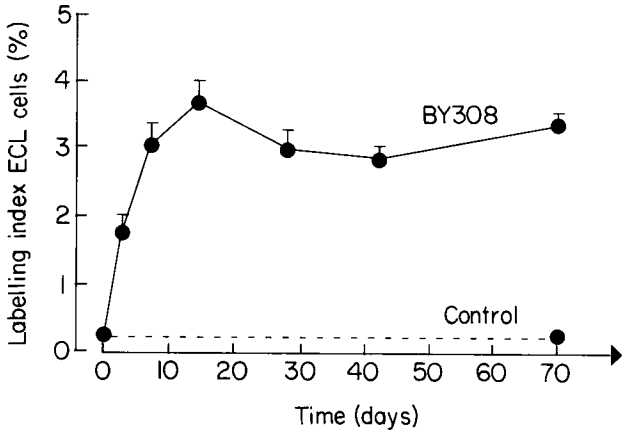

Figure 2. Percentage labelling index of ECL cells in rats treated with BY308, and untreated controls (data from Eissele *et al*).[14]

Types of ECL-cell hyperplasia

Several types of ECL-cell hyperplasia have been identified, namely diffuse, linear and micronodular.[16] Linear and diffuse ECL-cell hyperplasia is often observed in patients with duodenal and gastric ulcer disease in which *H. pylori*-associated gastritis of the antral and fundic mucosa is a common finding. Changes in ECL-cell morphology in these patients seem to be independent of the mode of treatment (H_2-blockers, proton pump inhibitors) as similar events have been described even in untreated

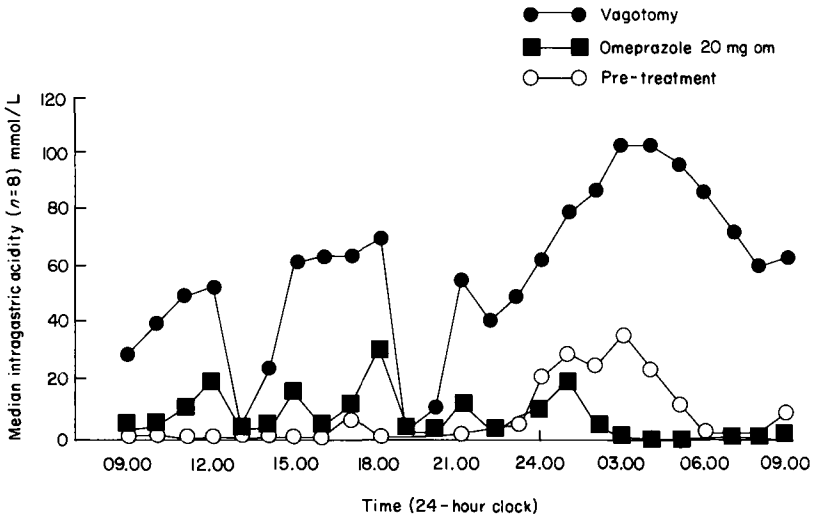

Figure 3. 24-hour intragastric acidity in duodenal ulcer patients, treated with omeprazole during or after selective proximal vagotomy (data from Lind *et al*).[20]

patients.[16–19] Micronodular ECL-cell hyperplasia can also be observed in patients with atrophic gastritis due to pernicious anaemia, resulting from atrophy of the glands where parietal cells are destroyed.[12,16] From these observations it has been concluded that there is a correlation between the grade of gastritis and the development of linear, diffuse and micronodular ECL-cell hyperplasia.

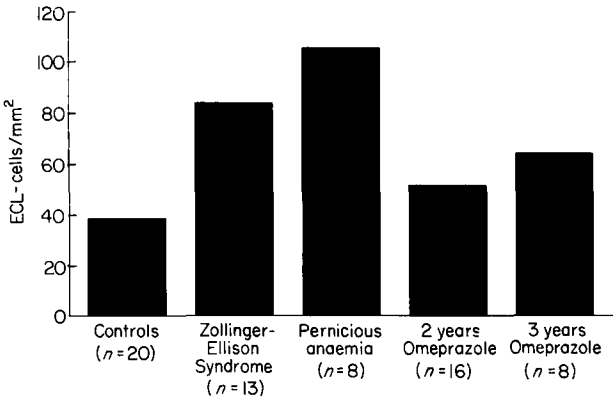

Figure 4. Median ECL-cell number in various conditions (data from Arnold *et al.*).[19]

Serum gastrin and ECL cells in patients treated with proton pump inhibitors

In contrast to patients with pernicious anaemia and Zollinger–Ellison syndrome, only moderate increases in serum gastrin levels have been observed during acute and long-term treatment with either the proton pump inhibitor, omeprazole, or with ranitidine.[17,19] These moderate increases mirror the levels in serum gastrin obtained during or after selective proximal vagotomy (SPV) (Figure 3).[20] Selective proximal vagotomy has been

Table 1. Side-effects in patients receiving pantoprazole, ranitidine or omeprazole

Description	Pantoprazole	Ranitidine	Omeprazole
Oedema	0	1	0
Vasodilation	1	0	0
Peripheral vascular disorder	0	1	0
Tremor	0	1	0
Taste perversion	0	1	0
Sleep disorder	0	1	0
Bilirubinaemia	0	1	1
Arthritis	0	0	1
Chills	0	1	0
Exfoliative dermatitis	1	0	0
Depression	0	1	0
Anorexia	0	1	0
Apathy	0	1	0

Table 2. Frequency of adverse events (percentages in parentheses) for patients receiving pantoprazole (20, 40 or 80 mg), ranitidine (300 mg) or omeprazole (20 mg)

Parameter	Pantoprazole 20 mg	Pantoprazole 40 mg	Pantoprazole 80 mg	Ranitidine 300 mg	Omeprazole 20 mg
Episodes	6	180	23	114	20
Patients with episodes					
All episodes	6 (7.0%)	170 (10.6%)	21 (15.2%)	105 (12.3%)	19 (11.0%)
Serious episodes	1 (1.2%)	17 (1.1%)	0 (0.0%)	9 (1.1%)	3 (1.7%)
Patients treated	86	1610	138	854	173

proven as safe for more than 30 years. In a recent publication we described the ECL cell density in patients several years after SPV, and the results showed that there was a modest increase in ECL cell density, similar to that observed after proton pump treatment.[21]

Treatment with omeprazole for up to 6 years induces only a modest increase in the ECL cell density, which is much lower than that observed in patients with Zollinger–Ellison syndrome or with pernicious anaemia (Figure 4).[17,19] A doubling of the mean argyrophil cell volume density was paralleled by a decrease in the normal endocrine cell growth pattern[17] and an increase in micronodular hyperplasia.[17] These changes correlate with the severity of corpus gastritis and seem to be more disease- than drug-related.[17] Similarly, only modest increases in serum gastrin levels are observed in humans with pantoprazole, increases which are not clinically significant.[22] From the present studies it can be concluded that the monitoring of serum gastrin levels and of the ECL cell numbers in fundic biopsies in patients treated with proton pump inhibitors is of no clinical relevance, even during the longer term.

Safety of proton pump inhibitors

There are numerous studies on the side-effects of proton pump inhibitors which demonstrate that proton pump inhibitors are as safe as H_2-receptor antagonists. Most studies compared the safety of omeprazole in comparison with the H_2-blockers cimetidine and ranitidine.[23,24] Studies involving almost 3500 patients with peptic ulcer and reflux oesophagitis indicated that the incidence of the major side-effects in the short term, such as headache, diarrhoea, abdominal pain, fatigue and flatulence, was very similar following treatment with either drug. Omeprazole had no clinically relevant effects on laboratory variables including: haematology; liver function; electrolytes; renal function; thyroid hormones; blood pressure; heart rate; ECG. Available data indicate that pantoprazole is similarly well tolerated in humans.[25–28]

There is, in addition, ample evidence that the pattern and frequency of adverse events following omeprazole therapy did not increase, even during long-term treatment.[29,30] In this symposium, Dr Schepp has presented comparative data of side-effects in patients receiving pantoprazole, ranitidine or omeprazole and observed very little differences between them (Table 1).[31]

Similarly, Table 2 shows percentages of all episodes, and of serious episodes, of adverse events in patients receiving pantoprazole (20, 40 or 80 mg/day), ranitidine (300 mg/day) or omeprazole (20 mg/day) for 4–8 weeks. There was little difference between the three drugs in terms of the frequency of serious episodes.

Interactions with pharmaceutical compounds

Proton pump inhibitors are metabolized mainly in the liver via the cytochrome P450 system and it is possible that interactions could occur with other drugs metabolized by the same system. Interactions of omeprazole with phenytoin, warfarin, diazepam, digoxin and nifedipine have been described, some of which could possibly achieve clinical significance. Pantoprazole has a much lower potential than omeprazole for interaction with the cytochrome P450 system and is likely to exhibit fewer interactions with any of the above-mentioned drugs.[32,33] Indeed, it has been shown in rats that pantoprazole interacts less with the metabolism of diazepam and theophylline in comparison with either of the other two proton pump inhibitors or with cimetidine.[32,34] Furthermore, clinical studies with pantoprazole have demonstrated no interaction with diazepam.[35]

CONCLUSIONS

The clinically available proton pump inhibitors, pantoprazole, omeprazole and lansoprazole, are well tolerated. This holds true for overall safety, unwanted effects with drug-metabolizing enzymes and the consequences of the gastrin hypothesis. With proton pump inhibitors, there is a low incidence of side-effects. Minor and serious side-effects, classified as possibly related to proton pump therapy, have been described in up to 2.5% of patients, which is the same order of magnitude as that found in patients treated with H_2-receptor blockers and in placebo-treated controls. In most cases, the observed side-effects are unrelated to the intake of proton pump inhibitors. Moreover, clinical monitoring of serum gastrin levels is deemed unnecessary. With this overall good safety profile, the proton pump inhibitors represent a very useful treatment for the management of peptic ulcers and other acid-related diseases.

Proton pump inhibitors are metabolized mainly in the liver via the cytochrome P450 system, and interactions with drugs metabolized by the same system are possible. It appears that pantoprazole has considerably less potential to interact with the cytochrome P450 system than the other proton pump inhibitors and, in the case of diazepam metabolism, pantoprazole in rats had the least effect on prolongation of the diazepam effect. In clinical use this may well be an advantage of the drug.

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