Aliment. Pharmacol. Ther. (1992) **6**, 399–406.

Review article: metabolic consequences of long-term inhibition of acid secretion by omeprazole

H. KOOP

Division of Gastroenterology and Metabolism, Department of Medicine, Philipps-University, Marburg, Germany

Accepted for publication 20 March 1992

SUMMARY

Metabolic sequelae of profound and long-lasting inhibition of gastric acid secretion by omeprazole have largely been neglected. Data from long-term studies suggest that vitamin B_{12} stores decrease slightly over several years, although this was not clinically relevant within the first 4 years of therapy. Additionally, it cannot be completely ruled out that patients with an increased iron demand may develop iron deficiency, but data available at present do not provide any evidence that iron malabsorption is to be expected under normal conditions. Protein homeostasis and calcium metabolism seem to be unaffected by long-term omeprazole therapy. Based upon present experience, serum cobalamin concentration should be monitored in patients undergoing omeprazole therapy for several years.

INTRODUCTION

The proton pump inhibitor omeprazole is generally established as an effective and safe drug for primary short-term therapy of acid peptic diseases.[1] Increasing interest is focused on possible side-effects of this compound during prolonged treatment, which is mandatory particularly in patients with reflux oesophagitis.[2]

Correspondence to: Professor Dr Herbert Koop, Department of Medicine, Philipps-University, Baldingerstrasse, D-W-3550 Marburg, Germany.

During long-term administration omeprazole has been shown to prevent relapses effectively even in severe ulcer disease and reflux oesophagitis.[2–5] While the risk of omeprazole to induce hypergastrinaemia and consequently lead to development of carcinoids has been extensively studied (for review see Refs 6, 7), the metabolic sequelae of profound and long-lasting acid inhibition have raised little attention so far. This review focuses on this safety aspect of continuing proton pump inhibition and provides additional insight into the physiological role of gastric acid in the absorption process of protein, vitamin B_{12} and some minerals.

PROTEIN ABSORPTION

Digestion of protein starts in the stomach by the protease pepsin. Omeprazole in general does not influence pepsin secretion.[8–10] Only in the complete absence of acid, pepsin concentrations in gastric juice may be decreased.[9] This may be due to either lack of direct topical stimulation of chief cells by hydrochloric acid[11] or caused by degradation of pepsin at neutral pH.[12] Independent of changes in pepsin secretion, the enzymatic activity of pepsin which has its pH optimum at pH 1.8[12, 13] declines with increasing pH to less than 5% at pH 5.

There is little information available whether omeprazole has any effect on the process of protein digestion and absorption. Omeprazole induces profound and long-lasting inhibition of parietal cell function. Although it usually does not induce achlorhydria at doses of 20–40 mg daily,[14, 15] complete suppression of acid secretion

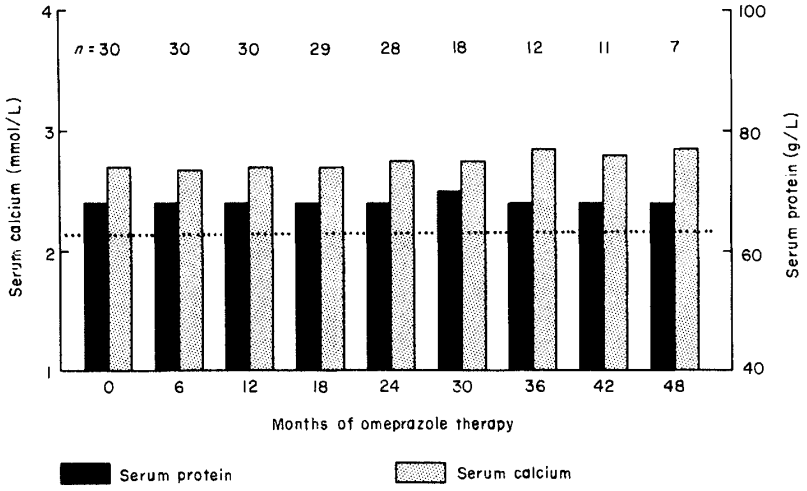

Figure 1. Effect of prolonged omeprazole therapy on serum concentrations of total protein and calcium. Measurements were performed in 30 patients prior to and during omeprazole treatment of varying duration (12–48 months). Medians are given. The dotted line indicates the lower limit of normal.

might occur in some individuals. The question has been raised whether this decrease in intragastric acidity leads to a clinically relevant decrease of peptic activity.[16]

We have performed serial determinations of total protein concentration in serum before and during prolonged omeprazole therapy (Fig. 1). Though plasma proteins consist of numerous different components, many of which are largely independent of protein intake, the major constituent of plasma proteins is albumin which accounts for almost two-thirds of total protein concentration. Adequate protein absorption is the major prerequisite in order to maintain a constant serum albumin level—apart from undisturbed hepatic albumin synthesis and in the absence of renal or intestinal albumin losses. In cases of protein malabsorption, hypoproteinaemia will develop. Results from measurements of serum protein concentration during long-term omeprazole administration did not reveal any changes even after therapy for several years. Since hypoproteinaemia is not a common feature in chronic atrophic gastritis (pernicious anaemia) either, intestinal proteolytic activity deriving from the exocrine pancreas must compensate for any decrease of gastric proteolysis. Thus, protein malabsorption is very unlikely to occur even during long-term treatment with proton pump inhibitors.

COBALAMIN ABSORPTION

Under normal circumstances, vitamin B_{12} is freed from dietary sources (predominantly apoenzymes) under the action of gastric acid whereas pepsin secretion does not appear to play a major role.[17] In the stomach cobalamin binds to salivary R protein; at acidic pH the affinity of cobalamin to R protein is much greater than to intrinsic factor predominantly (about 50 times higher at pH 2).[18] Cobalamin is transferred from R protein to intrinsic factor in the proximal small bowel after the R protein is degraded by pancreatic proteases.[18]

Complete absence of gastric acid may lead to inefficient extraction of cobalamin from food, despite sufficient intrinsic factor secretion and unaltered absorption of crystalline vitamin B_{12}.[19] This observation has to be attributed to achlorhydria itself.[20, 21] It has been demonstrated that inhibition of acid secretion by H_2-receptor antagonists decreases absorption of protein-bound cobalamin,[22–25] even though intrinsic factor secretion is only slightly diminished. However, any clinically relevant vitamin B_{12} deficiency or even megaloblastic anaemia has not been reported in patients on maintenance treatment with H_2-receptor antagonists. This may be due to the usual nocturnal administration of H_2-blockers which leaves acid secretion undisturbed over the day.

Somewhat different conditions apply for continuous omeprazole therapy since acid secretion is decreased more efficiently and acid suppression persists for the whole 24-h period. This constant decrease in intragastric acidity resembles that found after vagotomy, and cobalamin deficiency is known to develop in some patients after vagotomy.[26] Like H_2-receptor antagonists, omeprazole decreases absorption of food-bound cobalamin,[27] while intrinsic factor secretion is not affected

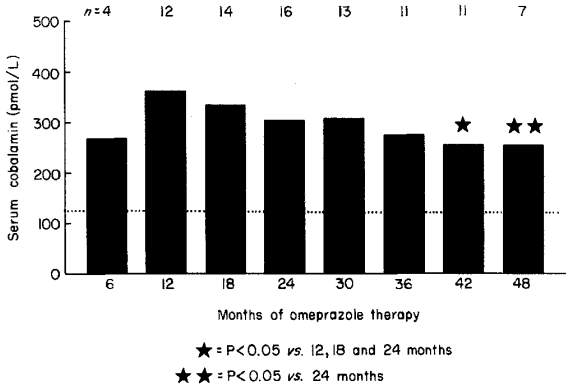

Figure 2. Effect of prolonged omeprazole therapy on serum concentrations of vitamin B_{12} (medians) in 34 patients with H_2-blocker resistant peptic diseases. Measurements were carried out during continuous omeprazole therapy; however, data from pre-treatment values were not available. The numbers placed above the columns indicate the number of individual observations. The dotted line indicates the lower limit of normal.

by the proton pump inhibitor due to its specific mode of action.[8] Data from long-term therapy with omeprazole (Fig. 2) indicate that serum vitamin B_{12} concentration remains constant within the initial 3 years of treatment.[28] However, significant decreases of serum cobalamin level developed after more extended periods of therapy (Fig. 2); circulating vitamin B_{12} concentrations showed a subtle downward trend during therapy and were found to be diminished significantly after more than 3 years of therapy. The observation that serum cobalamin remained in the normal range in all cases is probably due to large cobalamin stores which are able to maintain normal serum levels for several years[29] despite diminished vitamin B_{12} absorption. Data from larger populations and periods of 5–10 years duration are mandatory to clarify whether clinically relevant vitamin B_{12} malabsorption develops. From the practical point of view, regular determination of serum cobalamin concentration is recommended in patients undergoing prolonged omeprazole therapy.

IRON ABSORPTION

Gastric acid is an important factor for iron absorption: HCl facilitates transformation of trivalent ferric iron to soluble bivalent ferrous iron[30] and prevents formation of insoluble iron complexes of non-haem iron;[31] such insoluble iron complexes (making up about 90% of dietary iron in the western world) are poorly absorbed.[32] On the other hand, absorption of haem-iron (present predominantly in meat) is largely undisturbed in the absence of gastric acid.[32] Along with observations that gastric resection, vagotomy, and severe atrophic gastritis[30, 33–35] may lead to iron deficiency

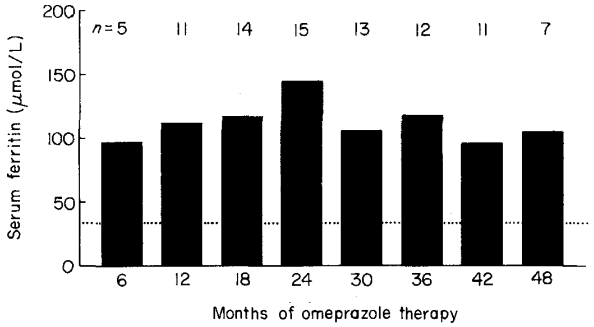

Figure 3. Serum ferritin levels (medians) during long-term administration of omeprazole in 34 patients with H_2-blocker refractory peptic diseases. The numbers placed above the columns indicate the number of individual observations at those time intervals. The dotted line indicates the lower limit of normal.

(particularly when associated with diets containing little meat), drug-induced inhibition of acid secretion may also have some impact on iron absorption.

Slight inhibition of iron absorption by the H_2-blocker cimetidine[36] is without clinical relevance. However, it has been suggested that more profound inhibition of gastric acidity induced by omeprazole may cause iron malabsorption.[37] In rat experiments, iron deficiency developed within a short period of time during omeprazole administration (given in doses to mimick the extent of acid suppression in humans) while the animals were maintained on a low-iron diet whereas in rats exposed to a normal iron-containing diet, iron absorption was affected.[38] Recent findings in man[28] show that iron malabsorption might not be anticipated at least within the initial years of continuous omeprazole treatment (Fig. 3): serum iron and ferritin levels (the latter of which served as a marker for iron stores) remained largely within the normal range up to 4 years of treatment. Slightly decreased serum iron levels were observed in very few patients, but there was no evidence that these changes were related to omeprazole therapy.[28] Undisturbed iron homeostasis during omeprazole therapy may have two major reasons: first, omeprazole at doses administered in clinical practice does not induce complete achlorhydria in most patients; second, dietary iron sources less dependent on low intragastric acidity (such as haem-iron in meat) seem to provide sufficient amounts of iron maintaining normal iron and ferritin levels. However, particular care should be taken in patients with an increased iron demand (for example, menstruating women) while on long-term omeprazole.

CALCIUM ABSORPTION

Absorption of calcium is a complex process and dependent on a number of different factors such as dietary calcium content, solubility of calcium ions, dietary fibre content, vitamin D, etc. (for review see Ref. 39). One of these factors is thought to

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.