produced definite improvement in the mouth and resulted in easier swallowing within two weeks. After a further two weeks the dose was reduced to 200 mg once daily, and improvement was maintained. After 12 weeks at this dose ketoconazole was stopped, but the candidiasis relapsed and it was therefore restarted after one month at 200 mg once daily, which partially controlled his candidiasis.

In August, three months after starting ketoconazole, he began to put on weight and suffer muscle cramps. By May 1983 he had overt features of myxoedema with slurring of speech, weight increase of about 8 kg, and tiredness. Hypothyroidism was confirmed by a serum total thyroxine concentration of less than 10 nmol/l (0.8 µg/100 ml) (normal 50-160 nmol/l (3.9-12.4 µg/100 ml)) and a serum thyroid stimulating hormone concentration of over 128 mU/l (normal 1-6 mU/l). Tests for thyroid microsomal and thyroglobulin antibodies, including immunofluorescence screening and serum electrophoresis, yielded negative results. He continued to take ketoconazole and became clinically and biochemically euthyroid when thyroxine sodium 0.2 mg a day was added.

Case 2

The son of the above patient, aged 6, developed oral candidiasis and was given ketoconazole 100 mg once daily for two months beginning in December 1983, and then for one month in June 1984. In September 1984 he became myxoedematous with weight increase and sluggishness, first recognised by his father; this was confirmed by a serum thyroxine concentration of 10 nmol/l (0.8 µg/100 ml) and a thyroid stimulating hormone concentration of 100 mU/l. Testing for thyroid microsomal and thyroglobulin antibodies by both immunofluorescence and serum electrophoresis yielded negative results. Thyroxine sodium 0.1 mg once daily was started, and he became euthyroid.

Comment

Neither of the two patients developed a goitre. They came from a large family with no history of hypothyroidism or other organ specific autoimmune diseases. Neither was receiving any other drugs. The doses of ketoconazole used here were unremarkable, and this drug has been widely used in patients suffering from chronic mucocutaneous candidiasis. Interestingly, the son's hypothyroidism persisted after he stopped taking ketoconazole.

A computer search failed to find any similar reports, and no other cases are known to the Committee on Safety of Medicines or to the manufacturers of ketoconazole (Janssen). There do not seem to be any structural similarities between ketoconazole and thyroxine or propylthiouracil, and the mechanism of action of ketoconazole on the thyroid gland is unknown.

The coincidence of hypothyroidism and treatment with ketoconazole in these cases was striking, although it is not possible to say with certainty what the exact cause of the hypothyroidism was. The close family relationship between the two patients suggests the possibility of some genetically determined susceptibility to hypothyroidism as a rare side effect of ketoconazole.

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Omeprazole as adjunct to enzyme replacement treatment in severe pancreatic insufficiency

The efficacy of enzyme replacement treatment in patients with severe steatorrhoea due to pancreatic insufficiency is usually low^{1,2} because of a low quantity of lipase in the enzyme preparation or an irreversible inactivation of lipase by acid. To improve efficacy of enzyme treatment in such patients at least 30 000 IU of lipase must be taken with each meal, and luminal pH lower than 4 must be avoided by adding antacids or H₂ receptor antagonists.^{1,2} The effect of this treatment, however, is disappointing, and the optimal adjuvant treatment has yet to be devised.

Two patients with acid related symptoms resistant to H₂ receptor antagonists and severe pancreatic insufficiency were treated with omeprazole, a potent and long acting antisecretory drug acting through inhibition of the H⁺/K⁺ adenosine triphosphatase in the parietal cell.^{3,4} This resulted in not only alleviation of the acid related symptoms but also an appreciable improvement of steatorrhoea.

Case reports

Case 1—A 49 year old man with Zollinger-Ellison syndrome had severe diarrhoea and steatorrhoea due to pancreatic insufficiency resulting from idiopathic calcifying pancreatitis. He was treated with cimetidine 600 mg four times daily and 10 g pancreatic granulate containing 225 000 IU lipase (Organon, Oss, The Netherlands) with each meal, but severe steatorrhoea persisted. His basal acid output was 56.2 mmol/h, which was reduced to 12.0 mmol/h two hours after ingestion of 600 mg cimetidine. Treatment with omeprazole (Hässel, Mölndal, Sweden) was started, which inhibited gastric acid secretion to 5.7 mmol/h 24 hours after ingestion of 80 mg of the enteric coated preparation. This more pronounced inhibition of gastric acid secretion was accompanied by a notable reduction in steatorrhoea from 96(SEM14)g/48 h during treatment with cimetidine (n=5) to 35(4)g/48 h during treatment with omeprazole (n=4), achieved without changing the dose of pancreatic enzyme treatment (p<0.01). Furthermore, the change from cimetidine to omeprazole resulted in a weight gain of 3.5 kg and in the return to normal of plasma concentrations of cholesterol, vitamin E, and albumin.

Case 2—A 56 year old woman had steatorrhoea due to pancreatic insufficiency resulting from alcoholic calcifying pancreatitis. The steatorrhoea was treated by increasing doses of pancreatic enzymes with cimetidine and subsequently ranitidine as adjuvant treatment. She continued to have severe steatorrhoea despite being given a high dose of 10 g pancreatic granulate and 150 mg ranitidine thrice daily. On upper gastrointestinal endoscopy, performed because of progressive upper abdominal pain and anaemia, a large prepyloric ulcer was found. The size of the ulcer was not affected by treatment with ranitidine 300 mg/24 h given intravenously for one week, followed by 150 mg ranitidine four times a day by mouth for three weeks. Two hours after ingestion of 150 mg ranitidine basal acid output, which was 3.2 mmol/h before antisecretory treatment, was 0.7 mmol/h with pH levels of 2.40 to 4.85. Treatment with 40 mg omeprazole once a day was started, resulting in healing of the ulcer within eight weeks. Basal acid output, measured 24 hours after the last dose of omeprazole, was 0.0 mmol/h with pH levels between 7.80 and 8.21. With no change in the dose of pancreatic enzymes there was a notable reduction of steatorrhoea from 122(21)g/48 h (n=6) during treatment with ranitidine to 21(6)g/48 h (n=2) during treatment with omeprazole (p<0.05). This pronounced reduction of steatorrhoea was accompanied by a weight gain of 5.2 kg and a rise in plasma cholesterol concentration from 3.1 to 4.4 mmol/l (120 to 170 mg/100 ml) and in plasma vitamin E from 6.1 to 15.5 µmol/l (2.5 to 6.5 µg/ml) during the eight weeks of omeprazole treatment.

Comment

These results show that profound inhibition of gastric acid secretion by omeprazole, a substituted benzimidazole inhibitor of the enzyme H⁺/K⁺ adenosine triphosphatase within the parietal cell,^{3,4} results in appreciable reduction of steatorrhoea during enzyme replacement treatment of patients with severe pancreatic insufficiency. Although such inhibition of gastric acid secretion may not be needed in all patients with severe pancreatic insufficiency, omeprazole treatment will probably also be beneficial to patients with cystic fibrosis, who are known to secrete fairly large amounts of gastric acid.⁵ Other advantages of omeprazole treatment over antacids and histamine H₂ receptor antagonists are the profound reduction in gastric volume, which prevents dilution of pancreatic enzymes, and the long duration of antisecretory activity of the drug, which allows a once daily dosage regimen, which will probably improve patient compliance and circumvent the problem of timing of the adjuvant treatment.

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