tion be part of the treatment of anorexia nervosa? Even though only some patients show depletion of tissue zinc, all patients require zinc as they regain weight. In extreme cases of weight loss, or when patients fail to gain weight, supplementation is probably indicated. Zinc supplementation of subjects who are not deficient, however, may cause copper deficiency with anaemia and may impair immunity. At present, therefore, widespread treatment of anorexia nervosa with zinc is not indicated.

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Subacute encephalopathy associated with human immunodeficiency virus in haemophilia A

Neurological complications associated with the acquired immune deficiency syndrome (AIDS) have been well described in homosexuals and drug abusers but not in haemophiliacs. We report on two haemophiliacs who suffered fatal subacute encephalopathy after seroconverting to human immunodeficiency virus (HIV). This is a new manifestation of the disease as seen in haemophilia and has important implications.

Case reports

Case 1—A 25 year old man receiving regular treatment with factor VIII concentrate for severe haemophilia A developed anti-HIV antibody in 1981. In October 1985 he developed axillary lymphadenopathy, a polyclonal increase in immunoglobulin, lymphopenia with a low T4:T8 ratio, and weight loss. The diagnosis was AIDS related complex. In November he was admitted with a *Streptococcus pneumoniae* chest infection. Subsequently he complained of lethargy, poor concentration, and difficulty with micturition. Examination disclosed diminished cognitive function and brisk reflexes. Computed tomography (CT) of the brain showed dilated lateral ventricles and widened sulci consistent with cerebral atrophy. By March 1986 he was incontinent and had difficulty walking and showed signs of a pyramidal tract lesion. A myelogram was normal and lumbar puncture yielded no evidence of infection with bacteria, fungus, toxoplasma, herpes simplex, herpes zoster, cytomegalovirus, or papovavirus. Serological findings were negative for syphilis, hepatitis B, herpes virus, and cytomegalovirus. He remained positive for HIV antibody. One month later he was admitted unable to walk and with paranoid delusions. Relentless neurological deterioration followed with painful spastic quadriparesis and convulsions. He died in July after four months in hospital. Permission for a necropsy was refused.

Case 2—A 48 year old haemophiliac who had been treated with factor VIII concentrate developed anti-HIV antibody in March 1983. In July 1984 he was noted to have axillary lymphadenopathy, thrombocytopenia, and lymphopenia with a low T4:T8 ratio. AIDS related complex was diagnosed. Additionally, he had chronic persistent hepatitis as a legacy of non-A, non-B hepatitis some years previously. He was admitted in August 1985 with weight loss, confusion, unilateral cerebellar dysfunction, and diplopia which was diagnosed clinically as an internuclear ophthalmoplegia. A cerebral CT scan showed low attenuation areas in the white matter of the frontal lobes and also in the right parietal lobe. Cerebrospinal fluid contained no evidence of infection by any of the agents sought in case 1. Similarly, serology and blood culture gave no evidence of infection with any agent other than HIV. He continued to deteriorate and, having progressed to coma, died in October 1985. Permission for necropsy was refused.

Comment

Several neurological syndromes associated with HIV infection have been described in patients with AIDS and also in patients with AIDS related complex.[1]

While an acute encephalopathy occurring as a reversible complication of primary HIV infection has been described in haemophilia A,[2] fatal subacute encephalopathy has not been recognised as a risk for these patients. The probability that the aetiological agent in our patients was HIV is increased by reports that the virus is neurotropic and replicates in brain cells.[3] Additionally, HIV is morphologically and genetically related to the visna virus, a neurotropic retrovirus affecting sheep and goats.[3] The occurrence of subacute encephalitis and other neurological syndromes associated with HIV infection in haemophilia A casts doubt on the recently expressed hope that viral pathogenicity may have been attenuated during preparation of factor VIII concentrate.[4]

Several practical difficulties arose during the investigation and subsequent management of these two patients. Firstly, we were unable to find a laboratory willing to test for HIV antigen in the cerebrospinal fluid of either patient at the time of lumbar puncture. Secondly, the patients required three to four months of barrier nursing and terminal care in facilities usually reserved for acute admissions. In view of the potential number of patients at risk[5] we suggest that consideration should be given to providing supra-regional laboratory and clinical facilities within the National Health Service for the diagnosis and management of syndromes associated with HIV.

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Hypothyroidism after treatment with ketoconazole

I report on two patients, a father and his son, who both developed hypothyroidism after treatment with ketoconazole.

Case 1

This patient, a 40 year old white man, had had severe chronic mucocutaneous candidiasis since the age of 5. The diagnosis had been confirmed by nail biopsy, and he had subsequently remained infected in the mouth, pharynx, larynx, oesophagus, and nails despite numerous and varied treatments, including treatment with vitamin B complex, dilute hydrochloric acid, and sodium thiosulphate in the 1950s; with dequalinium chloride paint, nystatin, amphotericin lotion and lozenges, and polynoxylin in the 1960s; and with intramuscular iron, clotrimazole, flucytosine, and miconazole in the 1970s. All of these treatments had been stopped because they were either ineffective or toxic.

In May 1982 he was given ketoconazole 200 mg orally twice daily, which

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.

I thank Dr Graham Bird, of Newcastle General Hospital, for the results of the thyroid antibody studies; Mr Alan Rutter, of the biochemistry department, North Tees General Hospital, for the results of the assays of thyroxine and thyroid stimulating hormone; Dr David Carr, of North Tees General Hospital, for his considerable help in the preparation of this paper; and Dr P Hood and Dr K O'Byrne for permission to report details of case 2.

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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 H_2 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 H_2 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 (Hässle, 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 H_2 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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