SHORT REPORTS

Phenytoin intoxication during treatment with parenteral miconazole

We describe a patient in whom phenytoin toxicity developed soon after treatment with parenteral miconazole.

Case report

A 51 year old man was admitted for treatment of recurrent severe haemoptysis associated with pulmonary aspergillosis. He was in chronic respiratory failure. He was a non-smoker. Biochemical indices of liver function were normal. There was a past history of asthma and also of epilepsy for 20 years, for which he was receiving phenytoin capsules 300 mg daily. The epilepsy was well controlled and the dose of phenytoin had remained unchanged for five years. During this time he had complained of intermittent dizziness and unsteadiness, but the plasma phenytoin concentration had not been estimated.

He began treatment with intravenous miconazole 500 mg every eight hours and oral flucytosine 2 g every six hours. The phenytoin dosage and formulation remained unchanged. The next day he complained of nausea, vomiting, and blurred vision and was treated with metoclopramide. Three days later his symptoms were more severe and pronounced nystagmus was noted. These symptoms and signs were attributed to the miconazole and the dose was decreased to 400 mg every eight hours; however, his symptoms persisted.

One week after beginning the antifungal treatment his plasma phenytoin concentration (EMIT, Syva Industries) was found to be 170 $\mu\text{mol/l}$ (43 $\mu\text{g/ml}$) (our recommended therapeutic range is 40-80 $\mu\text{mol/l}$; 10-20 $\mu\text{g/ml}$). Phenytoin was stopped for 12 days, during which time the plasma concentration fell to 39 $\mu\text{mol/l}$ (9.8 $\mu\text{g/ml}$) and his symptoms and signs subsided. During this time miconazole was stopped for four days and then reinstituted (figure).

Phenytoin was restarted at 100 mg/day, and 20 days later the plasma concentration was 91 $\mu\text{mol/l}$ (23 $\mu\text{g/ml}$). Miconazole and flucytosine were then stopped, and 10 days later the plasma phenytoin concentration had fallen to 57 $\mu\text{mol/l}$ (14.3 $\mu\text{g/ml}$).

When we realised that phenytoin toxicity was the cause of the patient's symptoms, two samples of blood which had been collected and stored for other purposes were analysed retrospectively for phenytoin concentration. The value from the day before beginning miconazole and flucytosine was 114 $\mu\text{mol/l}$ (29 $\mu\text{g/ml}$) (figure), which, together with his history of intermittent dizziness, suggested that he had had mild phenytoin toxicity before the antifungal treatment.

Plasma phenytoin concentrations during antifungal treatment. Dose of miconazole in first treatment period was 500 mg every eight hours, and in second treatment period 400 mg every eight hours. In both treatment periods flucytosine was given by mouth at a dose of 2 g every six hours.

Conversion: SI to traditional units—Phenytoin: 1 $\mu\text{mol/l} \approx 0.25 \mu\text{g/ml}$.

To eliminate spurious increases in EMIT phenytoin concentrations by miconazole or flucytosine these drugs were added, in concentrations up to five times those achieved therapeutically in plasma, to samples containing known concentrations of phenytoin: no effect was found.

Comment

The most likely mechanism for the increase of phenytoin concentrations was inhibition of phenytoin metabolism by miconazole. There are two reasons for this. Firstly, the plasma phenytoin concentration fell when antifungal treatment was stopped with no change in phenytoin dosage or formulation. Secondly, miconazole *in vitro* is a potent inhibitor of the hepatic cytochrome P-450 enzymes,¹ which are responsible for phenytoin metabolism. Also cimetidine, another imidazole structurally related to miconazole, inhibits phenytoin metabolism in man.^{2,3}

The only drug interaction with miconazole *in vivo* of which we are aware is potentiation of the effect of warfarin⁴; however, patients receiving parenteral miconazole concurrently with phenytoin or other drugs that are metabolised in the liver should be closely observed.

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³ Somogyi A, Gugler R. Drug interactions with cimetidine. *Clin Pharmacokinetics* 1982;**7**:23-41.

⁴ Watson RG, Locahn RG, Redding VJ. Drug interaction with coumarin derivative anticoagulants. *Br Med J* 1982;**285**:1045-6.

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Human cryptosporidiosis: a possible case of hospital cross infection

The protozoan *Cryptosporidium* causes enterocolitis in animals,^{1,2} and the importance of cryptosporidiosis in man was recently emphasised.³ Cases in man are being reported increasingly now that simple methods are available to detect oocysts in faeces.⁴ Severe infections occur in immunocompromised people, including those with acquired immune deficiency syndrome,⁵ but less severe, self limiting infection occurs in immunocompetent people.^{1,6} No effective chemotherapy is available.¹

We report two cases of human cryptosporidiosis which suggest that person to person transmission took place in hospital.

Case reports

Case 1—A 13 month old boy was admitted with vomiting, profuse watery diarrhoea, and dehydration which required correction with intravenous fluids. Gastroenteritis was diagnosed and he was nursed in isolation. Initial screening for enteropathogens yielded *Escherichia coli* 0111 only, which may have contributed to the initial diarrhoea. Jejunal aspirates and blood cultures also yielded *Candida*; this and the *E coli* were eliminated by appropriate chemotherapy. Despite temporary alleviation of diarrhoea by loperamide intravenous feeding for 52 days was necessary before a disaccharide free oral feed was tolerated. Diarrhoea (six to eight watery stools a day) recurred 16 days after starting loperamide, and faeces collected 16 days later (44 days after admission) were examined for *Cryptosporidium* oocysts in smears stained by Giemsa and modified Ziehl-Neelsen methods.⁴ Oocysts were seen in this specimen; earlier samples were not available. They were identical in size morphology staining and centrifugation characteristics with those in faeces from infected calves. Oocysts were seen in further samples taken over the next 25 days. Despite inquiries the source of infection was not traced, but we believe that the patient was infected before admission. Prolonged excretion of oocysts in otherwise normal patients is unusual.

Total and differential white cell counts were normal, as were numbers of B and T cells. There was possibly, however, a slight hypogammaglobulinaemia, concentrations of IgM (36 IU/ml), IgG (45 IU/ml), and IgD (13 IU/ml) being at the lower limits of normal. Concurrent chest infections probably also had a debilitating effect.

Case 2 was a nurse who had been doing night duty on the same ward as case 1. Fourteen days after cryptosporidiosis had been diagnosed in case 1 she presented with abdominal cramps and watery diarrhoea. No enteropathogenic bacteria or viruses were detected but *Cryptosporidium* oocysts ($10 \times 10^6/l$) were seen in the first faecal sample, taken on day 2 of her illness. Stools quickly returned to normal but diarrhoea recurred on day 7 and oocysts were detected. Excretion of oocysts reached a peak on day 9 ($10 \times 10^9/l$) but recovery was rapid and only low numbers ($>10^6/l$) were detected on days 11-18.

Comment

Reports of cryptosporidiosis in man describe unconnected cases, often with an unknown source (as in our case 1), or small clusters of patients in contact with animal reservoirs.⁶ Person to person transmission has not been established. Despite detailed inquiries, which ruled out animal sources, no source of infection outside the hospital was found for our second patient; we believe that she was infected while nursing case 1. If so, this represents not just person to person spread but also hospital cross infection. Although infection was transmitted from patient to nurse, spread in the opposite direction or to other patients would be more serious. Tests on patients and staff detected only one other case. This was in a 2 month old baby, who was admitted after the diagnosis had been established in case 2 and who was excreting oocysts on admission.

Cryptosporidium infects a wide range of animal species¹ but the incidence of infection in man is unknown. Mild or asymptomatic human infections with oocyst excretion do occur,² and oocysts are resistant to many disinfectants.¹ Consequently the possibility that cryptosporidiosis may be introduced into and transmitted within hospitals requires particular attention.

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Pemphigus associated with giant lymph node hyperplasia

Haematological abnormalities, fever, splenomegaly, peripheral lymphadenopathy, and the nephrotic syndrome have been associated with giant lymph node hyperplasia of the mediastinum and other sites. We report a case of pemphigus associated with the plasma cell type of lymph node hyperplasia.

Case report

A 21 year old woman presented with a four month history of blisters of the oral cavity, hands, and vulva. Daily treatment with prednisone (1 mg/kg body

Indirect immunofluorescence staining of mouse lip mucosa with pemphigus serum; staining of the intercellular substance is evident. $\times 122$.

weight) resulted in slight improvement. A biopsy specimen of the oral cavity showed an acantholytic bulla. Direct immunofluorescence microscopy showed IgG deposits in the epidermal intercellular bridges, and indirect immunofluorescence showed that her serum contained intercellular substance antibodies (titre 1/320) (figure), findings consistent with pemphigus vulgaris. Laboratory findings included: erythrocyte sedimentation rate 43 mm in first hour, haemoglobin 7.26 mmol/l (11.7 g/dl), leukocyte count $5.6 \times 10^9/l$ with a normal differential, serum iron concentration 10.02 $\mu\text{mol/l}$ (59 $\mu\text{g}/100\text{ ml}$), total iron binding capacity 51.9 $\mu\text{mol/l}$ (290 $\mu\text{g}/100\text{ ml}$), and total serum protein concentration 58.4 g/l (5.84 g/100 ml). Serum protein electrophoresis yielded normal results; immunoelectrophoresis showed an IgA, IgM polyclonal gammopathy. The following laboratory findings were either normal or negative: rheumatoid factor; clot test for lupus erythematosus cells; antinuclear, anti-DNA, antismooth muscle, antimitochondrial, anti-thyroglobulin, and antiparietal cell antibodies; Coombs tests; serum complement concentration; Clq activity; and immune complexes (Clq binding). HLA typing showed A2, A9, B5, and B13.

A roentgenogram of the thorax showed a left hilar mass. The tumour (14 cm in diameter) was removed together with remnants of the thymus by left thoracotomy. On microscopy extensive follicular hyperplasia and sheets of mature plasma cells were seen in the tumour.

The postoperative course was uneventful. The skin blisters resolved in 60 days. Gammopathy disappeared after excision of the tumour and results of indirect immunofluorescence were negative a year after surgery. Administration of prednisone was stopped in the sixth month after operation. Follow up examinations after three and six months did not show any abnormalities.

Comment

This patient presented with a four month history of multiple, painful, irregular, and persistent blisters of the oral cavity and hands, which had been poorly controlled by treatment with systemic corticosteroid. Considerable improvement occurred, however, with the same steroid doses after excision of the hyperplastic lymph nodes. The diagnosis of pemphigus vulgaris was confirmed by skin biopsy of a bullous lesion and by a high titre of intercellular substance antibody. Serum antibody levels are closely correlated with disease activity.

The patient had not taken penicillamine, phenylbutazone, propi-fenazone, or rifampicin and had no history of rheumatoid arthritis, systemic lupus erythematosus, Hodgkin's lymphoma, or solid neoplasms. Pemphigus has been seen in association with these conditions and after ingestion of the aforementioned drugs.¹ Thymoma was misdiagnosed in our patient because of the presence of mediastinal mass and pemphigus.² An increased prevalence of HLA-A10 and HLA-A7 was not observed.

An immune origin of pemphigus has been suggested recently,³ and some of the clinical manifestations associated with plasma cell lymph node hyperplasia (hypergammaglobulinaemia, autoimmune haemolytic anaemia, the nephrotic syndrome with minimal change pattern) may reflect immunological dysfunction.⁴ A serum blocking factor for in vitro lymphocyte transformation to phytohaemagglutinin and allogenic cells that disappeared after removal of the mediastinal mass have been reported in angiofollicular lymph node hyperplasia.⁵ The lymphoid tumour possibly altered lymphocyte function or cooperation, or both, in our patient, thus favouring the development of pemphigus as the systemic manifestation.

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