between parts of the NHS. There is a good argument for expanding hospital pharmacies immensely given their expertise and scale of economies. But as long as the philosophy of disintegration prevails hospital pharmacies will fight their own corner and the zeitgeist will screw the gestalt.

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Drug Points

Interaction between fluconazole and rifampicin

Drs R J COKER, D R TOMLINSON, J PARKIN, J R W HARRIS, and A J PINCHING (St Mary's Hospital, London W2 1NY) write: *Cryptococcus neoformans* causes infection in up to 10% of patients with AIDS.[1] Fluconazole is the first line treatment for cryptococcal meningitis, both in the acute presentation[2] and as maintenance suppressive treatment,[3] because of its effectiveness in penetrating the blood-brain barrier,[4] lack of toxicity, and ease of administration. We report on three patients with cryptococcal meningitis in whom clinical relapse seemed to be associated with concurrent administration of fluconazole and rifampicin.

Case 1—A 42 year old man who was positive for antibodies to HIV was admitted with a three week history of headaches and fever. Cryptococcal meningitis was confirmed by lumbar puncture and treatment started with fluconazole (400 mg/day), to which he made a good initial response. This was confirmed at repeat lumbar puncture two weeks after treatment had been started, when *C neoformans* antigen titres had fallen from 1 in 20 000 to 1 in 2000. Radiological changes suggestive of tuberculosis (later confirmed by bronchoscopy) led to the introduction of rifampicin, isoniazid, pyrazinamide, and ethambutol. Neurological symptoms returned and fever increased five days later. Although these symptoms improved, he remained mildly symptomatic for several weeks despite continuing treatment. A repeat examination of the cerebrospinal fluid at five weeks showed the persistence of cryptococci. Amphotericin was instituted with clinical and microbiological resolution.

Case 2—A 26 year old man infected with HIV was admitted with a week's history of frontal headache. Positive titres of cryptoccocal antigen in the cerebrospinal fluid confirmed cryptococcal meningitis, and he responded well to treatment with fluconazole (400 mg/day). At a repeat examination of the cerebrospinal fluid one month later cryptococcal antigen was undetectable. He was kept on maintenance fluconazole (100 mg/day). Rifampicin, pyrazinamide, and ethambutol were started three months later when pulmonary tuberculosis was suspected. Symptomatic cryptococcal meningitis with cerebrospinal fluid positive for cryptococcal antigen recurred two months later but resolved with amphotericin.

Case 3—A 41 year old man infected with HIV was admitted with a three month history of weight loss, fevers, and lethargy. Cryptococci were found in the cerebrospinal fluid, and he was treated with fluconazole (400 mg/day), to which he responded. Two weeks later he started rifampicin, isoniazid, and ethambutol when pulmonary tuberculosis was suspected. This was confirmed by bone marrow culture. Cryptococcal meningitis recurred five months later and amphotericin was instituted.

No published data have suggested an interaction between fluconazole and rifampicin, although unpublished phase 1 data showed a 20% reduction in the half life of fluconazole and a 25% reduction in its serum concentration when it was coadministered with rifampicin (Pfizer, personal communication). A study of the response of 35 patients with cryptococcal meningitis to fluconazole found that 18 had cerebrospinal fluid cultures negative for cryptococcus at day 60 (B Dupont. Abstract from symposium on fluconazole, a novel advance in therapy for systemic fungal infections, Dorado, Puerto Rico, 1988). Though we recognise that the relapse rate of cryptococcal meningitis is high (roughly 50%)[5] and that the long half life of fluconazole (30 hours) makes failure of treatment difficult to assess retrospectively, we believe that these cases provide some clinical support for the observation that rifampicin interferes with the pharmacokinetics of fluconazole. In our experience the relapse rate of cryptococcal meningitis is 43% (6/14) and the mean time to relapse from diagnosis 20 weeks (range two to 46), similar to those quoted by Dupont.[5] These cases show a possible drug interaction with important clinical consequences, and we suggest that doctors should be vigilant when these drugs are used concurrently and alert to the possibility of relapse.

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Ciprofloxacin and myasthenia gravis

Drs COLIN J MUMFORD and LIONEL GINSBERG (Addenbrooke's Hospital, Cambridge CB2 2QQ) write: We describe a patient in whom exposure to ciprofloxacin unmasked subclinical myasthenia gravis.

A 73 year old man with a history of rheumatoid arthritis and cranial arteritis was receiving long term oral antibiotics for chronic osteomyelitis secondary to knee surgery. He was also taking prednisolone (5 mg daily) and cimetidine (400 mg twice daily), the last for peptic ulcer disease. In October 1989 ciprofloxacin (250 mg twice daily) was introduced into the antibiotic regimen and within 48 hours he developed severe dysphagia, dysarthria, and left sided ptosis that varied with fatigue. Further questioning showed that he had been mildly dysphagic for some months before the introduction of ciprofloxacin. When this drug was withdrawn the severe bulbar symptoms resolved within days but the ptosis persisted. Ptosis was reversed by intravenous injection of edrophonium and by oral pyridostigmine. An assay for acetylcholine receptor antibodies gave strongly positive results. Thyroid function was normal. There was no radiographic evidence of thymoma.

In retrospect, this patient had had mild myasthenic symptoms before exposure to ciprofloxacin. Many drugs, particularly antibiotics, can aggravate or unmask myasthenia gravis by prejunctional and postjunctional blocking in a setting where the "safety margin" for neuromuscular transmission has already been affected by disease.[1] We propose that ciprofloxacin exerted such an action in our patient, as evidenced by the close temporal relation between the onset of his severe symptoms and the introduction of the drug and by the resolution of symptoms on its withdrawal.

Possible exacerbation of symptoms by ciprofloxacin has been reported in a patient with known myasthenia gravis.[2] The interpretation of that case was hampered by the presence of additional factors (upper respiratory infection, emotional stress) coincident with the administration of the drug, which might have contributed to the exacerbation. In our patient ciprofloxacin was introduced in the context of long term antibiotic treatment for chronic sepsis. We therefore may conclude with greater certainty that the drug exposure was causally related to the severe myasthenic symptoms, particularly as the disease had been subclinical until being unmasked by ciprofloxacin. This case underlines the need for observation and caution in patients with myasthenia gravis given this antibiotic.

We thank Professor D A S Compston and Dr R J Dickinson for permission to report this case.

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Nephrotic syndrome associated with sulphasalazine

Drs V M BARBOUR and P F WILLIAMS (Ipswich Hospital, Ipswich IP4 5PD) write: Treatment of ulcerative colitis with sulphasalazine is usually well tolerated. Any side effects are usually attributed to the sulphapyridine moiety, and mesalazine, which contains only 5-aminosalicylic acid, may be useful in patients intolerant of sulphasalazine. We describe a patient with ulcerative colitis who developed the nephrotic syndrome while taking sulphasalazine.

A 28 year old man with an 18 month history of ulcerative colitis who had been treated since diagnosis with sulphasalazine presented with a two week history suggestive of nephrotic syndrome. His 24 hour urinary protein excretion was 11·9 g and serum albumin concentration 19 g/l. Diuretic treatment was started and sulphasalazine changed to mesalazine. Three weeks later, as there had been no improvement in the nephrotic syndrome, a kidney biopsy was performed. The results were thought to be compatible with minimal change nephropathy, possibly drug induced.

His clinical condition deteriorated, with increasing oedema and decreasing urine output. Mesalazine was stopped, and he was started on oral prednisolone (60 mg/day), with a rapid clinical improvement. Two weeks after starting steroids he had no oedema, a serum albumin concentration of 30 g/l, and a 24 hour urinary protein excretion of 0·13 g. Nine months later his steroid treatment was reduced and he remained on a small dose of azathioprine to control ulcerative colitis.

There has been one report of the nephrotic syndrome associated with mesalazine but none with sulphasalazine.[1] The therapeutic moiety of sulphasalazine is 5-aminosalicylic acid, which is released in the large bowel, where about a fifth is absorbed and excreted renally.[2,3] We suggest that the nephrotic syndrome in patients with ulcerative colitis treated with sulphasalazine or mesalazine may be caused by 5-aminosalicylic acid, which is common to both these drugs. Short term corticosteroid treatment should be successful in minimal change lesions, and other drugs such as azathioprine may then be required for the long term control of ulcerative colitis.

We thank Dr G D Bell for permission to report this case.

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