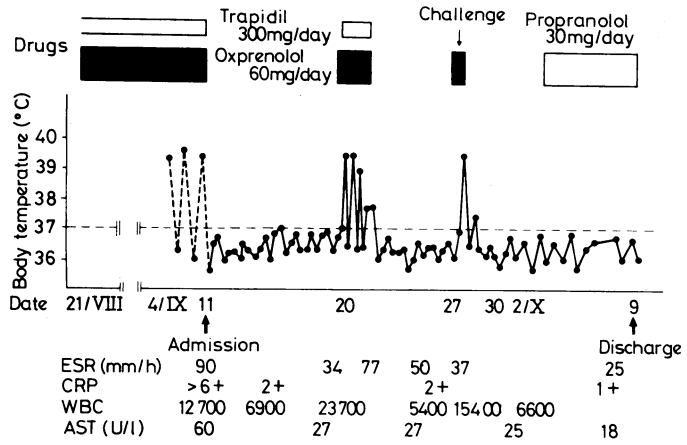
All drugs were withdrawn on admission, and no fever developed. The WBC became normal within a few days (figure). On 20 September (10 days after admission) oxprenolol and trapidil were resumed for aggravating chest pain. Twelve hours after the first dose the patient's temperature rose to 39°C; this was accompanied by chills with shaking and a leucocytosis of $23{\cdot}7 \times 10^9$/l (23 700/mm³) with shifting to the left. Drug fever was then suspected. On 27 September (17 days after admission) a challenge was made with oxprenolol alone: exactly the same clinical picture recurred within seven hours. He was then given propranolol 10 mg thrice daily without a febrile response. A lymphocyte stimulation test with oxprenolol showed a normal ^{3}H-thymidine uptake.



Temperature chart and clinical course in a case of fever induced by oxprenolol.

Comment

Side effects of oxprenolol in 13·7% of 4403 patients were reported by Forrest.[1] We were unable, however, to find a case of drug fever due to oxprenolol in English or Japanese reports. In our patient the diagnosis of drug-induced fever was established by a positive challenge test. The leucocytosis and liver dysfunction associated with the fever rapidly improved after oxprenolol was stopped. β-Adrenergic blocking agents, including oxprenolol, are widely used. This report shows that oxprenolol may cause hyperpyrexia.

[1] Forrest WA. A monitored release study: a clinical trial of oxprenolol in general practice. *Practitioner* 1972;**208**:412-6.

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Cryptococcosis treated by rapid infusion of amphotericin B

Amphotericin B, alone or in combination, is the drug of first choice for pulmonary cryptococcosis.[1] Because of adverse effects such as phlebitis, nausea, and rigors, amphotericin should be infused slowly over six hours.[2] We report the case of a patient with pulmonary cryptococcosis and early systemic spread, whose infection was successfully treated by rapid one-hour infusion of amphotericin B as part of combination chemotherapy. This subsequently allowed treatment as an outpatient.

Case report

A previously healthy 31-year-old Caucasian housewife developed unproductive cough, right-sided pleuritic chest pain, and minor systemic upset the day after cyclone Alby passed Perth in April 1978. Initially she was treated with co-trimoxazole and later with amoxycillin. The symptoms did not abate; a chest radiograph showed consolidation of lateral segment of right middle lobe. Physical examination showed nothing abnormal. Despite further antibiotics her symptoms continued and a repeat chest radiograph six weeks later showed persisting consolidation. Physical examination disclosed a pleural friction rub in the right axilla and no other abnormal findings. She was referred for further investigation.

Bronchoscopy showed an inflamed orifice of right middle lobe with a little inspissated, bloodstained mucus. Brush smears of the mucus subsequently stained positively with mucicarmine for *Cryptococcus neoformans*. Another specimen obtained by bronchoscopy three days later grew *C neoformans* after 48 hours' culture on Sabouraud's agar. The organisms subsequently proved sensitive to both amphotericin B (minimum inhibitory concentration = 0·25 mg/l) and flucytosine (minimum inhibitory concentration = 0·5 mg/l).[3] Diagnosis was confirmed by serology, which showed cryptococcal antigen present in a titre of 1024. The white cell count at the start of treatment was $11{\cdot}9 \times 10^9$/l with polymorph leucocytosis and some toxic granulation. Lumbar puncture produced clear cerebrospinal fluid (CSF) at normal pressure with glucose of 3·0 mmol/l (54 mg/100 ml (normal = 2·8-4·4 (50-79 mg/100 ml)) and protein of 0·42 g/l (normal = 0·15-0·45). Culture of CSF showed no growth at 48 hours, but at 72 hours three colonies of *C neoformans* were seen. Serum electrolyte, creatinine, and urea concentrations and liver function test results were normal. Urine and blood cultures were sterile. Treatment was a combination of amphotericin B and flucytosine. Flucytosine was given orally 150 mg/kg/day in four divided doses on all days. After a test dose of intravenous amphotericin 1 mg the dose was gradually increased to 30 mg on alternate days, in a suspension of 500 ml of 5% dextrose. Five hundred units of sodium heparin and 100 mg hydrocortisone were added to this to minimise phlebitis and rigors and the total dose infused over six hours.

Three days after treatment started the serum potassium concentration fell to 2·4 mmol (mEq/l) and she required potassium supplements of 40 mmol/day until amphotericin was withdrawn. This recognised complication of treatment[4] is reversible after stopping the drug. Creatinine clearance remained normal. After 15 days of alternate-day treatment, maintenance treatment was altered to a more rapid one-hour infusion on alternate days, with electrocardiographic monitoring over the first rapid infusions.[5] No abnormalities were seen on the electrocardiogram, nor did the patient report increased nausea or rigors at this time or subsequently. For domestic reasons the patient was discharged 17 days after admission; she returned on alternate days for hour-long infusions of amphotericin 30 mg. She received a total dose of 955 mg amphotericin over two months and flucytosine for five months. Titres of serum cryptococcal antigen fell to 1/32 within three months and remained unchanged 23 months after the presumed initial episode of infection. Serial chest radiographs showed resolution of the consolidation over two months, but there was persistent thickening of the horizontal fissure.

Comment

Amphotericin is excreted by the kidneys over several days after intravenous infusion,[2] and therefore the rationale for slow intravenous infusion is to minimise adverse effects rather than to sustain effective serum concentrations. In our patient rapid infusion of amphotericin B allowed outpatient treatment without major disruption of domestic responsibilities; treatment was well tolerated and convenient. There have been no further symptoms, radiological evidence of recurrence, or rise of antigen to *C neoformans* at 23 months after the initial infection and 16 months after oral treatment. We suggest that rapid infusion of amphotericin B is a safe, convenient, and effective way of treating pulmonary infection with *C neoformans*.

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[3] Bennett JE, Dismukes WE, Duma RJ, *et al*. A comparison of amphotericin B alone and combined with flucytosine in the treatment of cryptococcal meningitis. *N Engl J Med* 1979;**301**:126-31.
[4] Patterson RM, Ackerman GL. Renal tubular acidosis due to amphotericin B nephrotoxicity. *Arch Intern Med* 1971;**127**:241-4.
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