Suppression of prolonged fever during treatment of pulmonary tuberculosis: importance of using twice versus single daily dose of prednisolone

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Summary

We describe the clinical course of a patient with extensive pulmonary tuberculosis, in whom fever persisted despite adequate anti-tuberculous and broad-spectrum antibiotic treatment. A once daily morning dose of prednisolone failed to suppress the fever, but a twice daily regime was successful.

KEY WORDS: pulmonary tuberculosis, fever, prednisolone.

Introduction

Despite the advent of extremely effective anti-tuberculous drug regimes, fever may still persist for more than 2 weeks in many patients being treated for pulmonary tuberculosis (Kablawi *et al.*, 1981). We present such a patient in whom the fever was effectively suppressed by a twice-daily regime of prednisolone, but not by a single daily dose.

Case report

A 46-year-old single Irish museum attendant was admitted to hospital with a 3 month history of anorexia, severe weight loss, fever, night sweats and cough. On examination, he was pyrexial (38°C), cachectic and extremely weak, such that he could hardly stand up. The liver was palpable at 8 cm below the costal margin. There was no splenomegaly. The chest X-ray (Fig. 1) showed bilateral upper zone shadowing, more extensive at the left apex with cavitation. Sputum smears showed numerous acid-fast bacilli on Ziehl-Nielsen staining and, within 2 weeks of culture, *Mycobacterium tuberculosis* was grown. Other investigations were: haemoglobin 11.8 g/dl with normal white cell and differential counts; erythrocyte sedimentation rate (ESR) 100 mm/hr; plasma sodium 128 mmol/litre; plasma potassium 3.2 mmol/litre; urea 1.7 mmol/litre and creatinine 45 µmol/litre. A low plasma osmolality (259 mOsm/litre) in the presence of a urine osmolality of

FIG. 1. Chest X-ray on admission showing bilateral upper zone shadowing with cavitation.

638 mOsm/litre supported the presence of inappropriate antidiuretic hormone secretion.

Rifampicin, ethambutol and isoniazid, to which the mycobacterium was sensitive, were started after a week. Ampicillin was also given, as the sputum also grew *Pneumococcus*. A high protein and calorie diet with fluid restriction (1 litre/day) was commenced. The course of the fever is shown on Fig. 2. After a short period of abatement, the fever reappeared and was temporarily suppressed during a course of

FIG. 2. Temperature chart while an in-patient. The various medications as indicated are as follows: AMP=ampicillin; RIF=rifampicin; INH=isoniazid; ETM=ethambutol; TOB=tobramycin; GEN=gentamicin and PRE=prednisolone. The doses of prednisolone are in mg given either once daily (OD) or twice daily (BD). The vertical arrow indicates the day when the evening dose of prednisolone was omitted.

tobramycin. However, it recurred 2 days before tobramycin and ampicillin were stopped. Blood cultures taken after cessation of these antibiotics remained negative. Prednisolone as a single morning dose of 40 mg was started with the aim of increasing the patient's well-being and appetite. The pattern of fever became distinctive, with a single daily spike of fever at around 6-7 am, during which the patient looked pale and unwell and experienced rigors and sweating. Further blood cultures taken during these episodes were negative. A course of gentamicin and ampicillin had no effect. Prednisolone was gradually reduced to a single daily morning dose of 10 mg. To test whether the fever was secondary to drug sensitivity, all anti-tuberculous drugs were stopped for 2 weeks, but this had no effect on the pattern of fever. Finally, prednisolone, 10 mg given twice daily at 6 am and 6 pm, suppressed the fever. When one evening dose of prednisolone was deliberately omitted, the 6 am fever accompanied by rigors and sweating reappeared the following day.

The patient's general condition had started to improve shortly after prednisolone was commenced. At the time of discharge from hospital, he had gained 2.5 kg in weight, the ESR was 20 mm/hr and plasma sodium and potassium concentrations were within normal range. He continued on prednisolone 10 mg twice daily at home, in combination with rifampicin and isoniazid and denied any recurrence of morning fevers and rigors at home. Prednisolone was discontinued 3 months after discharge from hospital.

Discussion

In a recent study (Kablawi *et al.*, 1981), 36% of a group of 59 febrile patients with pulmonary tuberculosis being treated with isoniazid and ethambutol

plus either streptomycin or rifampicin had persistent fever for more than 2 weeks. Similar results were reported in an earlier study (Berger and Rosenbaum, 1968) where patients were treated with isoniazid and para-aminosalicylic acid with or without streptomycin. Patients with clinically and radiologically far-advanced disease, as in this patient, were more likely to experience prolonged fever (Kablawi *et al.*, 1981).

The cause of the prolonged fever in this patient is unlikely to be due to a pulmonary or extrapulmonary bacterial infection as the fever did not respond to intensive antibiotic therapy. Febrile reactions with spiking fever and rigors have been described in patients treated with isoniazid alone or in combination with other anti-tuberculous drugs (Dasta, Prior and Kurzok, 1979; Berte, DiMase and Christianson, 1964). However, discontinuation of all these drugs did not result in a reduction or disappearance of the fever. It is more likely that the prolonged fever was associated with the pulmonary tuberculosis itself, but the precise mechanism is unclear. Release of endogenous pyrogens from monocytes, which are activated by lymphokines released by specifically sensitized lymphocytes in cell-mediated immunity (Atkins, Francis and Bernheim, 1978) might be involved.

Corticosteroids were used in this patient in order to increase well-being and appetite (Horne, 1960) and a once-daily, morning dose of prednisolone was instituted so as to minimise pituitary-adrenal axis suppression (Nichols, Nugent and Tyler, 1965). The use of corticosteroids as an antipyretic agent in pulmonary tuberculosis has not been previously reported, though it has been used in other bacterial infections, in conjunction with antibiotic therapy (Klastersky, 1971). With a morning daily dose of prednisolone therapy, the pyrexia regularised and occurred at around 6 am daily, but was abolished when prednisolone was given twice-daily. The most likely explanation

tion for these observations is that prednisolone given orally in normal subjects has a relatively short plasma half-life of 2 to 3.5 hr (Pickup, 1979). Rifampicin may further decrease it through liver enzyme induction (Edwards *et al.*, 1974). Thus, the plasma concentration of prednisolone after a single morning dose would have been virtually nil in the mornings, thus allowing the pyrexia to occur then.

After exclusion of concomitant bacterial infections and of drug sensitivity, prednisolone may be used to suppress the prolonged fever of patients treated for advanced pulmonary tuberculosis, but it should, at least, be given on a 12-hr daily basis.

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