SIDE EFFECTS OF DRUGS

Severe allergic reaction to chlormethiazole

Allergic reactions are not a recognised side effect of treatment with chlormethiazole. This paper describes a patient who suffered such a reaction after being treated for acute alcoholic withdrawal symptoms with chlormethiazole.

Case report

The patient was a married woman aged 48 years, Scottish by birth and unemployed. She was of medium build and weighed 57 kg. She was admitted to Hill Hospital, Hartwood, for treatment of chronic alcoholism. On admission she smelt of alcohol and was visually hallucinated with delirium tremens. On physical examination she was healthy, and all systems were normal.

Treatment—She was started on oral chlormethiazole (Heminevrin), 2 capsules three times a day. No other drugs were prescribed.

Adverse effect—Twelve hours later the patient developed a severe allergic reaction with profuse rash on her face, neck, and arms. The rash was blotchy in distribution with severe itching. Her face was swollen and she was in pain. The drug was withdrawn and she was started on the antihistamine chlorpheniramine maleate, one tablet three times a day, and given an antihistamine cream for local application. The rash and swelling disappeared after 24 hours, leaving behind some chaffing of the skin.

Comment

Chlormethiazole seems to have been responsible for causing the severe allergic reaction, as the patient had no personal or family history of allergic reaction to the drug, food, or clothes. The patient had been drinking heavily for several years, and as she had had her last drink 48 hours before admission the possibility of chlormethiazole interaction with alcohol is rather remote. In any case chlormethiazole is indicated for treating the withdrawal symptoms of alcoholism. We would be interested to know whether a similar case has been noted by others.

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Two cases of ethambutol nephrotoxicity

Ethambutol has found wide acceptance for treating tuberculosis and is often used in first-line triple treatment of the disease instead of para-aminosalicylic acid (PAS). Ethambutol may cause ocular damage,[1] and it has also been associated with hyperuricaemia,[2] peripheral neuropathy,[3] and a false-positive screening result for phaeochromocytoma.[4] We describe two patients in whom ethambutol may have caused renal failure.

Case 1

A 56-year-old man was treated for pulmonary tuberculosis in 1963 and discharged from follow-up in 1972. In July 1974 he was readmitted for investigation of a pleural effusion but attempts to isolate tubercle bacilli were unsuccessful. Plasma urea concentration was 4·3 mmol/l (26 mg/100 ml). He was readmitted in March 1975 with fever, anorexia, dyspnoea, brown sputum, and weight loss. He was cachetic (weight 54 kg) with reduced chest movements and signs of left-sided bronchopneumonia. Sputum culture was positive for tubercle bacilli.

Treatment—He was immediately started on antituberculous treatment with rifampicin 450 mg (9 mg/kg) daily, isoniazid 300 mg (6 mg/kg) daily, and ethambutol 1 g (20 mg/kg) daily. Urine was normal on microscopy and sterile on culture. Plasma urea was 5·7 mmol/l (34 mg/100 ml). He reported no drug allergies.

Adverse effects—In April 1975 he developed a left foot drop without clinical evidence of sensory loss. Electromyography and nerve conduction tests confirmed partial denervation of the left lateral popliteal nerve. The following month his plasma urea had risen to 38 mmol/l (229 mg/100 ml) and plasma creatinine was 630 μmol/l (7·1 mg/100 ml). Urine volume was maintained between 1½ and 2 litres with an osmolarity of 320-390 mmol (mosm)/kg, but the uncorrected creatinine clearance was 6 ml/min. There was slight intermittent proteinuria and glycosuria with some granular casts on microscopy. Blood pressure was 130/70 mm Hg. Immunofluorescent test for antinuclear factor (ANF) was negative. High-dose intravenous urography showed bilaterally poor contrast excretion with normal renal size and configuration, without evidence of obstructive uropathy. Rifampicin was stopped immediately and dietary protein restricted. The plasma urea fell, but plasma creatinine concentration continued to rise, reaching a peak of 730 μmol/l (8·3 mg/100 ml). Creatinine clearance remained at 6 ml/min. Culture of a percutaneous renal biopsy specimen taken three weeks later was sterile. Histological examination showed some fibrosis of occasional glomerular tufts; considerable tubular damage with diffuse atrophy and some dilatation; diffuse interstitial fibrosis and infiltration with lymphocytes, plasma cells, and some eosinophils; some focal nephrocalcinosis; and hyaline thickening of the walls in glomerular afferent arterioles. Electron microscopy showed endothelial cell swelling and proliferation. The glomerular basement membrane appeared normal. Light and electron microscopy showed no amyloid material. Immunofluorescence showed no IgG, IgA, IgM, IgE, C3, or fibrin. After 30 days without rifampicin, isoniazid and ethambutol were stopped. Plasma creatinine concentration fell immediately, and settled at 150 μmol/l (1·7 mg/100 ml) after six weeks; creatinine clearance reached 15 ml/min by six weeks and after six months (December 1975) was 40 ml/min.

After two weeks without antituberculous treatment the patient was started on isoniazid 300 mg and PAS 12 g daily. Rifampicin 450 mg/day was reintroduced in October 1975 without subsequent deterioration of renal function.

Case 2

A 69-year-old man was admitted with cough, anorexia, and dyspnoea in May 1970. A chest radiograph showed miliary mottling in both lungs with infiltration in the left upper mid-zones. Urine and sputum cultures grew *Mycobacterium tuberculosis* "fully sensitive to all current drugs." Plasma urea was 6 mmol/l (36 mg/100 ml).

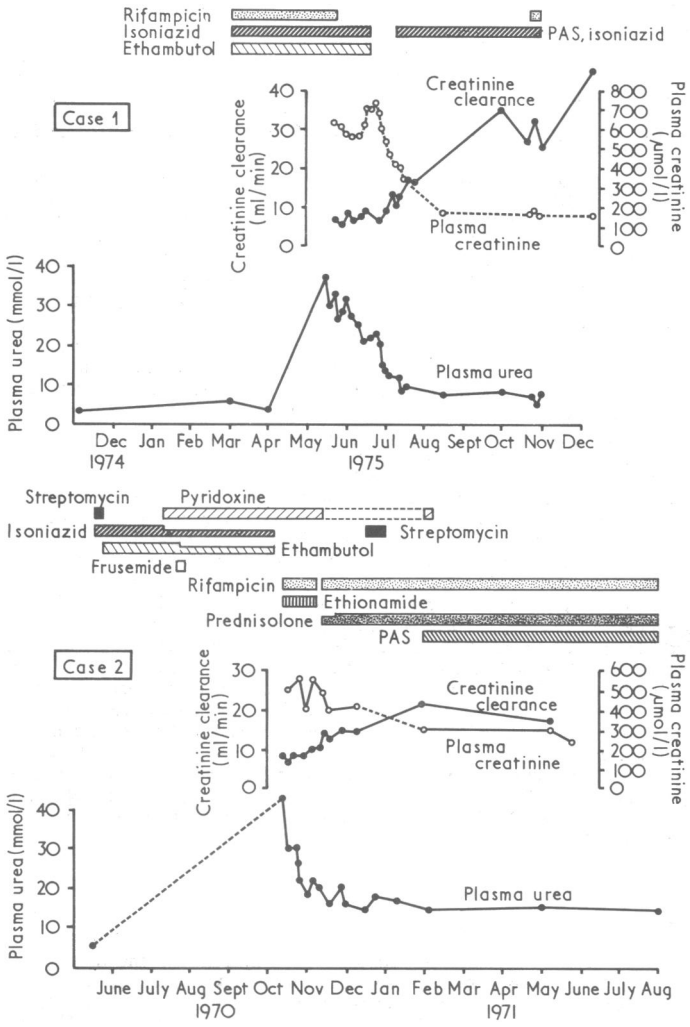
Treatment—Chemotherapy was started five days after admission with streptomycin 0·75 mg/day and isoniazid 500 mg/day. After five days the patient developed a rash and streptomycin was replaced by ethambutol 1·2 g/day. After two months the ethambutol was reduced to 1 g/day and the isoniazid to 300 mg/day. Pyridoxine 60 mg/day was given for burning paraesthesiae of the feet, and frusemide 40 mg/day was also prescribed.

Adverse effects—The patient was readmitted to hospital in October 1970 with blurred vision and exacerbation of his paraesthesiae. He weighed 59 kg. Blood pressure was 150/80 mm Hg, plasma urea 42 mmol/l (253 mg/100 ml), and plasma creatinine 520 μmol/l (5·9 mg/100 ml) with an uncorrected creatinine clearance of 8 ml/min. Urine volumes were 1 to 2 litres daily with a specific gravity of 1·006. There was slight proteinuria and glycosuria with some granular casts on microscopy. Ethambutol and isoniazid were stopped and dietary protein restricted. Treatment continued with rifampicin 600 mg/day and ethionamide 250 mg twice daily. Intravenous urography (standard dose) showed poor excretion with normal renal contour and no evidence of obstruction. Culture of a percutaneous renal biopsy specimen taken three weeks later was sterile. Histological examination showed some sclerosed glomeruli with a moderate degree of tubular atrophy and fibrosed interstitium infiltrated with lymphocytes. Some collections of chronic inflammatory cells formed small granulomata but no caseation or tubercle bacilli was seen. Light microscopy showed no amyloid material. Plasma creatinine began to fall in early November 1970, three weeks after stopping ethambutol and isoniazid, and fell over the next 10 days to 400 μmol/l (4·5 mg/100 ml). Creatinine clearance rose simultaneously to 14 ml/min. Ethionamide was stopped and prednisolone 60 mg/day added to the treatment. Prednisolone was continued in slowly reducing dosage for two years. PAS was started in early 1971. By February 1971 the plasma creatinine was 310 μmol/l (3·5 mg/100 ml) and the creatinine clearance was 22 ml/min. This improvement has been maintained. Intradermal injection of ethambutol in December 1970 elicited no response, but the drug was not reintroduced orally.

Treatment and laboratory values in both patients are shown in the figure.

Comment

Elucidating possible drug toxicity in the treatment of tuberculosis is especially difficult because of multiple drug treatment. Tuberculous infection, amyloidosis, obstruction subsequent to renal tract tuber-



Treatment and progression of renal failure in two patients.

Conversion: SI to traditional units—Creatinine: 1 μmol/l ≈ 0·0113 mg/100 ml. Urea: 1 mmol/l ≈ 6 mg/100 ml.

culosis, and coincidental intercurrent disease may also cause renal failure.

In our cases we excluded amyloid deposition and obstructive uropathy. Renal function usually deteriorates only in the advanced stages of renal tuberculosis,[5] and tuberculosis is unlikely to have caused the renal failure in case 1, as there was no indication of renal infection. The other patient did have positive urine cultures with suggestive lesions in the renal biopsy, but if infection caused the renal failure the initial deterioration and rapid improvement after the change in treatment has to be explained. The mycobacteria may have been resistant to the first drugs used (isoniazid and ethambutol) and sensitive to their substitutes (rifampicin and ethionamide), but initial testing showed the organisms to be fully sensitive to the current drugs. Moreover, the pulmonary tuberculosis responded satisfactorily to treatment.

No intercurrent illness caused renal failure in these patients, and we had to determine which drug or drugs may have had a nephrotoxic effect.

Both patients received isoniazid and ethambutol before developing renal failure. Isoniazid is well known to induce systemic lupus erythematosus (SLE), which in turn may precipitate renal failure.[6] Neither patient had typical features of SLE clinically or in the biopsy specimen. The first patient was also negative for ANF and subsequently received isoniazid without deterioration of renal function. During the period of presumed decreasing renal function he also received rifampicin, which is known to cause acute renal failure. Nearly all patients who have developed renal failure after taking rifampicin[7] have had an allergic type of illness characterised by acute onset of fever, malaise, arthralgia, backache, chills, nausea, and vomiting. Most are oliguric. Haemolysis, eosinophilia, thrombocytopenia, and icterus are often associated. One tablet is enough to precipitate the syndrome in the predisposed person. Renal biopsy typically shows evidence of acute tubular necrosis and interstitial nephritis. The renal damage appears to result from a drug-induced immune reaction, either directly or, more probably, as a result of the anaphylactic vascular disturbances. Our patient showed none of these clinical features and subsequently received rifampicin without ill effect.

In both cases dietary protein restriction probably caused the early fall of the plasma urea level. Plasma creatinine continued to rise until ethambutol was stopped. Its subsequent fall occurred immediately in case 1, but was delayed for three weeks in case 2. The second patient also had another toxic effect of ethambutol—blurred vision—and the peripheral neuropathy experienced by both patients may also have been a manifestation of ethambutol toxicity.

There is, therefore, strong evidence that ethambutol caused the renal failure in these patients. There was little likelihood that pre-existing renal failure had allowed toxic accumulation of drugs. Moreover, although ethambutol excretion has been reported to be about 80% renal,[8] pharmacodynamic studies in renal failure have shown that reducing the dose below 15 mg/kg/day is unnecessary except when there is severe renal impairment.[9 10] There is, therefore, no suggestion of ethambutol overdose.

Rats treated with several antibiotics separately, including ethambutol, were monitored for renal damage by observing renal enzyme excretion.[11] Neither rifampicin nor ethambutol were incriminated. The observation of ethambutol-induced hyperuricaemia is of interest in the present context.[2 12] In our cases, however, plasma urate levels were normal on several occasions during the acute phase and, clearly, ethambutol did not cause renal damage in our patients through induced hyperuricaemia. Postlethwaite and Kelly showed reduced renal clearance of urate after a single oral dose of ethambutol.[12] Endogenous creatinine clearance was unaffected in their acute study. Although renal clearances of urate were reduced in our patients, there seemed to be no selective reduction of urate clearance compared with creatinine clearance.

Although some evidence of renal toxicity has been mentioned in a few reports of adverse reactions to antituberculous drugs received by the Committee on Safety of Medicines, none has linked the association clearly with the use of ethambutol.[13] Patients have usually been exposed to at least two and often up to five antituberculous drugs simultaneously and it is difficult to draw conclusions from these spontaneous reports.

On the basis of the histological appearances and the time course of the disease, we suggest that the renal damage in these two patients was probably due to a toxic rather than an allergic effect producing an interstitial nephritis and tubular lesions. This may be an idiosyncratic side effect, but renal function should be carefully monitored in all patients taking this drug.

Requests for reprints should be addressed to FDT.

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