Toxicity of co-trimoxazole in nutritional haematinic deficiency

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Summary

A woman of 47 habituated to analgesics and living on an inadequate diet was deficient in iron, folate and vitamin B₁₂. Treatment of pyelonephritis with co-trimoxazole precipitated pancytopenia with a megaloblastic bone marrow. She recovered following withdrawal of the drug and administration of iron, folate and vitamin B₁₂.

Introduction

Co-trimoxazole is an antibacterial combination of trimethoprim and sulphamethoxazole which acts by sequentially blocking folate metabolism (Elion, Singer & Hitchings, 1954; Darrell, Garrod & Waterworth, 1968). Cases of haematological toxicity have been reported following its use in patients with initially normal haematological status (Kahn, Fein & Brodsky, 1968; Paulley, 1970; McPherson & Raik, 1970; Geddes *et al.*, 1971; Jewkes, Edwards & Grant, 1970; Jenkins, Hughes & Hall, 1970; Hulme & Reeves, 1971) but only a few have been of such severity as to be clinically significant.

Chanarin & England (1972) reported the use of co-trimoxazole in four patients with known megaloblastic anaemia due to vitamin B₁₂ or folate deficiency. There was suppression of the reticulocyte response in all, pancytopenia in two and anaemia with neutropenia in a third. We report serious pancytopenia following the administration of co-trimoxazole to a patient with iron, folate and vitamin B₁₂ deficiency.

Case report

Mrs M.M., a 47-year-old restaurant manageress, was admitted with acute renal failure precipitated by pyelonephritis with a coliform organism. She had taken 100 Compound Codeine tablets BPC per week for many years, with a recent increase in dose. Due to overwork and the constant smell of cooking she had a poor appetite for at least 5 years and her standard meal was jam and bread. She was pale, dehydrated, semiconscious and had Kussmaul breathing and bilateral loin tenderness. Her plasma urea was 240 mg/100 ml, sodium 114, potassium 5.4, chloride 74, and bicarbonate 9 mEq/l, haemoglobin 9.1 g/100 ml, MCHC 29%, WCC 8600,

Fig. 1. Response of blood urea and urine output to treatment.

platelets 220,000/mm³, serum iron 80, iron binding capacity 302 mg/100 ml. Serum folate and vitamin B₁₂ levels were requested but were not reported until 10 days later.

She was treated by rehydration, peritoneal dialysis and co-trimoxazole two tablets twice a day for 14 days. Her renal function rapidly improved (Fig. 1). Eighteen months later her serum creatinine is 0.8 mg/100 ml and her creatinine clearance has risen to 70 ml/min. Her haematological changes are shown in Fig. 2. The haemoglobin dropped to 7.4 g/100 ml after rehydration and fell further to 5.7 g/100 ml on the 10th day, by which time she had a leukopenia of 1400/mm³ and a thrombocytopenia of 60,000/mm³. Bone marrow aspirate showed megaloblastic haematopoiesis, and at this time it was ascertained that her initial folate level was 1.4 ng/ml and her vitamin B₁₂ was less than 100 pg/ml.

Her drug therapy was reviewed. She had received sulphamethizole and nalidixic acid for 1 week prior to admission and oral sodium bicarbonate, sodium chloride, slow release potassium chloride, ferrous gluconate, co-trimoxazole and intravenous saline in the ward. Of these, co-trimoxazole seemed much the most likely precipitant of her pancytopenia at a time when her renal function was improving. She was given 5 mg folic acid orally three times a day and vitamin B₁₂ 100 µg intramuscularly, daily at first

FIG. 2. Peripheral blood changes during co-trimoxazole therapy and treatment with oral iron and folic acid and intramuscular vitamin B₁₂.

then at wider intervals; co-trimoxazole was withdrawn on the 14th day. There was a peak reticulocyte response of only 6%, possibly due to a septicaemia which was detected 1 week later, and on discharge after 3 weeks of haematinic therapy her haemoglobin was 7.7 g/100 ml, WCC 9400 and platelets 300,000/mm³. Folate and vitamin B₁₂ were discontinued after 2 months and with improved diet she has maintained normal blood counts apart from a slight anaemia for 18 months.

During the period of leukopenia she developed a low grade fever and coliforms were grown from her blood stream on two occasions, and from her urine on one occasion. She responded to a 6-week course of nalidixic acid. Her urine has remained sterile, though she has the persistent pyuria typical of analgesic nephropathy (Dawborn *et al.*, 1966; Bell *et al.*, 1969).

Discussion

We presume that Mrs M.M. was suffering from early analgesic nephropathy complicated by acute pyelonephritis, which is a common and sometimes lethal complication of this disease (Bell *et al.*, 1969). Her IVP after recovery was normal, but this by no means excludes analgesic nephropathy (Fairley & Kincaid-Smith, 1968). The recovery of good renal function after withdrawal of analgesics is charac-

teristic of the disease at an early stage (Bell *et al.*, 1969; Murray, Lawson & Linton, 1971). However, it implies that she could not have had severe renal impairment before her pyelonephritis and her initial anaemia was therefore out of proportion to her renal dysfunction (Pennington & Kincaid-Smith, 1971). This anaemia was partly due to iron deficiency, presumably resulting from gastric bleeding induced by the analgesic, menstruation and her poor diet. The folate and vitamin B₁₂ deficiency were attributed to dietary inadequacy as barium meal and follow-through examination, faecal fat excretion, xylose excretion, and absorption studies of vitamin B₁₂ and folate were all normal.

We do not know for certain that her haematopoiesis was normoblastic on admission, but her blood film showed no evidence of macrocytic anaemia and her white cell and platelet counts were not depressed. The precipitation of life-threatening pancytopenia was probably the result of co-trimoxazole administration to a patient with subclinical deficiency of folate and vitamin B₁₂. Since this complication with megaloblastic anaemia is not produced by sulphonamides alone trimethoprim is the presumptive cause (Chanarin & England, 1972).

Co-trimoxazole is a very effective antibacterial increasingly popular in the treatment of many infections, notably those of the urinary tract (Dargie *et al.*, 1971; Gavras, Lawson & Linton, 1971; Cattell *et al.*, 1971). In view of this experience, and those of Chanarin & Edwards, patients who are at risk of folate deficiency—pregnant women on poor diets, those taking anticonvulsants, the debilitated elderly, etc.—should be assessed for folate and B₁₂ deficiency before treatment with long courses of co-trimoxazole. Particular care should be taken with patients on immunosuppressive drugs (Hulme & Reeves, 1971).

Addendum

Since this manuscript was accepted Yuill (1973) has described megaloblastic anaemia following administration of co-trimoxazole to a patient probably depleted of folic acid by dietary restriction and peritoneal dialysis.

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Pseudo-pseudo-hypoparathyroidism with coarctation of the aorta— a clinical syndrome?

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Summary

Two cases of pseudo-pseudo-hypoparathyroidism are described, associated with coarctation of the aorta, suggesting a further common clinical link (besides those already recognized) between the former condition and Turner's syndrome. The need for a change of nomenclature of pseudo-pseudo-hypoparathyroidism is emphasized.

Case no. 1.

A single woman, aged 50, was referred for opinion because of recent dyspnoea. She had not been allowed to play games at school because of 'some heart condition', but had led a normal life in all other respects, and had always menstruated normally. Her father had died of 'a heart complaint', her mother was alive but was being treated for pernicious anaemia, and her sister had 'rheumatism'.

On examination she was short (height 145 cm) and weighed 62 kg. She had a rounded facies, small hands and feet, and a recessed knuckle of the left

fifth finger. BP 240/100 mmHg in the right arm. No femoral or other leg pulses could be felt, but there was a prominent carotid pulse bilaterally and collateral arterial pulsations were felt over the thorax. No thrills were felt, but there was a loud, high-pitched ejection-type systolic murmur all over the front of the chest. A chest X-ray showed gross notching of several ribs, an elongated aortic knuckle, and post-stenotic dilatation of the descending aorta. X-ray of the hands confirmed their small appearance and the shortening of the left fifth metacarpal. An ECG showed left ventricular hypertrophy with negative T waves in leads 1, VL and V6. The patient refused admission to hospital for further investigation to confirm the clinical diagnosis of coarctation, and to exclude associated cardiac lesions; but it was felt that the diagnosis was reasonably certain in view of the physical signs and radiological features. The following investigations were normal: blood urea and electrolytes, routine urinalysis, serum calcium, phosphorus and alkaline phosphatase, haematological