

Thrombotic thrombocytopenic purpura due to rifampicin

Drs I H FAHAL, P S WILLIAMS, R E CLARK, and G M BELL (Royal Liverpool University Hospital, Liverpool L7 8XP) write: Thrombotic thrombocytopenic purpura is usually rapidly progressive with 75% mortality in three months if untreated.¹ Plasma exchange has improved the prognosis, though the mortality is still 30%. Haematological and renal abnormalities have been noted in patients receiving rifampicin but the syndrome of thrombotic thrombocytopenic purpura has not. We report a case of thrombotic thrombocytopenic purpura in a patient taking rifampicin.

A 57 year old white man with renal tuberculosis started treatment with rifampicin 450 mg, isoniazid 300 mg, and ethambutol 1200 mg daily. Three weeks later he complained of nausea, vomiting, and malaise. On examination he was confused, anaemic, and jaundiced. His pulse was regular at 100 beats/min, and his blood pressure was 80/50 mm Hg. His liver was palpable 1 cm below the costal margin, but there was no splenomegaly or lymphadenopathy. Rectal examination showed melaena.

His serum concentration of urea was 36.1 mmol/l, creatinine 402 µmol/l, haemoglobin 100 g/l, and platelets 13×10^9 /l. His white cell count was normal. Examination of a blood film showed schistocytes, spherocytes, and increased polychromasia, which are typical features of microangiopathic haemolytic anaemia. Serum bilirubin concentration was 85 µmol/l (indirect bilirubin 65 µmol/l), alanine aminotransferase 46 IU/l, γ -glutamyltransferase 23 IU/l, and alkaline phosphatase 73 IU/l.

Serum concentrations of auto-antibodies, antibodies to neutrophil cytoplasm, complement, and immunoglobulin were normal. Blood and protein were present in the urine. Blood, urine, and stool cultures gave negative results, and sequential studies showed no rise in the titre of viral antibodies. Gastroscopy showed petechial haemorrhage and oozing of blood from the lesser curvature of the stomach. Renal ultrasound examination showed normal sized kidneys with no obstruction. A renal biopsy was not performed because of his severe thrombocytopenia.

Rifampicin was stopped. During the next 48 hours he received six units of fresh frozen plasma, 18 units of platelets, and six units of blood, but his condition continued to deteriorate. He became confused, his level of consciousness fluctuated, and he developed a purpuric rash. His platelet count fell to 5×10^9 /l and his haemoglobin concentration to 41 g/l. He underwent daily plasma exchange. By the ninth day of treat-

ment his platelet count had risen to 188×10^9 /l and examination of a blood film showed less severe signs of microangiopathic haemolytic anaemia. His general condition improved, and four weeks later his serum creatinine concentration was 120 µmol/l, haemoglobin 125 g/l, and platelet count 210×10^9 /l.

Thrombotic thrombocytopenic purpura has been associated with infection, autoimmune disease, and drugs including penicillin, penicillamine, and the contraceptive pill,^{2,4} none of which were implicated in our patient. Rifampicin may cause haemolysis, thrombocytopenia, and, rarely, acute renal failure, particularly during intermittent treatment, but there are no reports of it causing thrombotic thrombocytopenic purpura. In our case the symptoms began shortly after the start of anti-tuberculous treatment. Rifampicin, which is known to cause haematological abnormalities, probably through an immunological mechanism,³ is the likely cause of the thrombotic thrombocytopenic purpura in this patient.

- 1 Amorosis EL, Ultman JE. Thrombotic thrombocytopenic purpura: report of 16 cases and review of the literature. *Medicine* 1966;45:139-59.
- 2 Parker JC, Barret DA, Hill C. Microangiopathic hemolysis and thrombocytopenia related to penicillin drugs. *Arch Intern Med* 1971;127:474-7.
- 3 Ahmed F, Sumalno V, Spain DM, Tobin MS. Thrombolytic thrombocytopenic purpura during penicillamine therapy. *Arch Intern Med* 1987;138:1292-3.
- 4 McShane PM, Bern MM, Schiff I. Thrombotic thrombocytopenic purpura associated with oral contraceptives: a case report. *Am J Obstet Gynecol* 1983;145:762-3.
- 5 Poole G, Stradling P, Worledge S. Potential serious side effects of high-dose twice weekly rifampicin. *BMJ* 1971;iii:343-7.

Parotitis due to nicardipine

Drs X BOSCH, J SOBRINO, A LOPEZ-SOTO, and A URBANO-MARQUEZ (Hospital Clínic i Provincial, 08036 Barcelona, Spain) write: Several adverse reactions associated with nicardipine have been described, including headache, dizziness, flushing, and swelling of the ankles. Uncommon serious adverse effects include arrhythmias, exacerbation of angina, and myocardial infarction.^{1,5} We report on a patient who developed a painful swelling of the parotid glands after taking nicardipine.

A 63 year old man was admitted to hospital for investigation of an asymptomatic pulmonary mass. Two years earlier mild essential hypertension had been diagnosed and he had been advised to restrict his dietary intake of salt. On admission his blood pressure was

180/105 mm Hg and he had grade I-II hypertensive retinopathy. Physical examination was otherwise normal. Routine laboratory data were unremarkable. He was treated with nicardipine 30 mg three times daily. One hour after the first dose he complained of a dry mouth and had bilateral painful enlargement of the parotid glands. He had no fever, rash, or eosinophilia. The swelling resolved over four hours. The second dose of nicardipine produced similar temporary painful swelling of the parotid glands. Nicardipine was stopped and captopril given without any adverse effect.

Parotid swelling has been reported with drugs such as iodide compounds, nitrofurantoin, oxyphenbutazone, phenylbutazone, methyldopa, and nifedipine. Parotid pain without enlargement of the salivary glands has been reported with antihypertensive drugs including clonidine, guanacine, and bretylium.⁶⁻¹⁰ To our knowledge there are no published reports of nicardipine causing these effects. Oedema and spasm of smooth muscle in the salivary ducts have been suggested as the cause of the enlargement of the salivary glands.⁸ In the case of methyldopa and bretylium the enlargement has been attributed to excessive hyperaemia in the parotid glands when they are deprived of the normal vasoconstrictor action on the sympathetic neurones.⁷ A hypersensitivity reaction has been suggested in cases of parotitis due to nifedipine, oxyphenbutazone, phenylbutazone, and nitrofurantoin.^{6,8,10} We do not know how nicardipine produces parotitis.

- 1 Scheidt S, LeWinter MM, Hermanovich J, Venkataraman K, Freedman D. Efficacy and safety of nicardipine for chronic, stable angina pectoris: a multicenter randomized trial. *Am J Cardiol* 1986;58:715-21.
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- 3 Wallin JD, Cook ME, Blanski L, Bienvienn GS, Clifton GG, Langford H, et al. Intravenous nicardipine for the treatment of severe hypertension. *Am J Med* 1988;85:331-8.
- 4 Gheorghide M, Weiner DA, Chakko S, Lessem JN, Klein MD. Monotherapy of stable angina with nicardipine hydrochloride: double-blind, placebo-controlled, randomized study. *Eur Heart J* 1989;10:695-701.
- 5 Dubois C, Blanchard D. Efficacy and safety of nicardipine in 29104 patients with hypertension. *Clin Ther* 1989;11:452-60.
- 6 Pellinen T. Nitrofurantoin-induced parotitis. *BMJ* 1982;285:344.
- 7 Mardh P-A, Belfrage I, Naversten E. Sialadenitis following treatment with alpha-methyldopa. *Acta Med Scand* 1974;195:333-5.
- 8 Chen JH, Ottolenghi P, Distenfeld A. Oxyphenbutazone-induced sialadenitis. *JAMA* 1977;238:1399.
- 9 Bosch X, Campistol JM, Botey A, Cases A, Revert L. Nifedipine-induced parotitis. *Lancet* 1986;iii:467.
- 10 Massimo C, Sebastianelli G, Noera G. Nifedipine-induced parotitis: a hypersensitivity reaction. *Am J Cardiol* 1988;61:874.

Acute hypothermia due to penicillin

Dr Bjørnar Hassel (Division of Environmental Toxicology, Norwegian Defence Research Establishment, N-2007 Kjeller, Norway) writes: Hypothermia during antibiotic treatment has been reported once in association with erythromycin.¹ I report on a patient who developed acute hypothermia during treatment with phenoxymethylpenicillin.

A previously healthy 45 year old man, with no known allergies developed a gingival abscess. He did not have malaise or fever. He started treatment with phenoxymethylpenicillin 600 mg four times daily. After taking the third dose he felt increasingly drowsy and cold. After the fifth dose he slept for 12 hours and woke up feeling well. Twenty minutes after taking the next dose he started to feel drowsy and dizzy. His gait became unsteady and his vision blurred. When examined two hours later he was somnolent, and his skin was pale, cold, and dry. He was not shivering. He had a blood pressure of 180/110 mm Hg and a pulse of 64 beats/min. Rectal temperature was 35.1°C. He had not taken any drug other than the penicillin. Penicillin intolerance was suspected and the treatment stopped. Four hours after the last dose of penicillin he began sweating profusely. Over the next eight hours he gradually became more alert, and his rectal temperature rose to 36.8°C. His blood pressure fell to 120/85 mm Hg, and his pulse rose to 70 beats/min. Erythromycin 250 mg four times daily was started. Subsequent measurements showed that his rectal temperature varied between 36.8 and 37.1°C.

The hypothermia in this patient was probably caused by the penicillin as it occurred shortly after ingestion of the drug and ended after a period sufficient to allow clearance of the drug. No other causative agent could be identified. Neither the drug's manufacturer nor the Norwegian Medicines Control Authority has received reports, national or international, of hypothermia associated with penicillin treatment.

Though clearly a rare side effect of penicillin treatment, hypothermia may easily be overlooked, partly because of the inadequacy of standard thermometers² and partly because the cerebral symptoms of hypothermia may be attributed to the infections for which the drug is being given.

- 1 Hassel B. Acute hypothermia during erythromycin therapy. *Ann Intern Med* 1991;115:69-70.
- 2 Reuler JB. Hypothermia: pathophysiology, clinical settings, and management. *Ann Intern Med* 1978;89:519-27.