Drug points

Generalised chorea due to digoxin toxicity

Drs L J M M MULDER, R C van der MAST, and J D MEERWALDT (University Hospital "Dijkzigt," 3015 GD Rotterdam, The Netherlands) write: Digoxin is a widely prescribed drug with narrow therapeutic margins, and intoxication is a common complication. We report a case of severe generalised chorea, agitation, and emotional disturbance due to digoxin excess.

A 63 year old woman with a dissection of the ascending aorta had been treated conservatively for one month with digoxin 250 µg daily, labetalol 100 mg three times a day, dihydralazine 25 mg twice a day, isosorbide mononitrate 20 mg three times a day, bromazepam 1.5 mg three times a day, and triamterene one capsule daily. During the operation the defect of the intima was reconstructed with a haemoshield prosthesis (anaesthetic: fentanyl 36 ml and pancuronium 18 mg). The patient was haemodynamically stable immediately afterwards. Postoperatively she was treated with digoxin 250 µg daily, triamterene one capsule daily, and, for three days, prednisolone acetate 25 mg daily. Three days after the operation she started to complain of extreme fatigue, showed no clouding of consciousness but was disoriented in time, appeared to be frightened, and had an impaired memory. Generalised symmetric choreatic movements increased in severity during the next few days to such an extent that she injured herself. The patient had neither been treated with neuroleptic drugs nor received other medication in the past which could have caused chorea. There was no history of rheumatic fever. Computed tomography of the brain without contrast enhancement showed no abnormalities. Extensive laboratory values were repeatedly within normal ranges, except for urea and creatinine, which were temporarily raised, consistent with transient renal failure. The digoxin value, which had not been recorded previously, was 34 µg/l (therapeutic range 10-26 µg/l) one week after surgery. Digoxin was then discontinued and she was treated successfully with oral haloperidol 5 mg daily for one month. After the tapering off of haloperidol the abnormal involuntary movements did not return (follow up two years).

There are only limited data on the relation between non-cardiac symptoms of digoxin toxicity and serum digitalis concentrations.¹ Above 30 µg/l (in our patient 34 µg/l) there is a high incidence of intoxication, especially with renal failure.² In contrast to a previously reported patient, who had hemichorea due to digoxin toxicity,³ our patient had generalised symmetric chorea. After the withdrawal of digoxin haloperidol was discontinued and the choreatic movements did not return. The fact that haloperidol controlled the choreatic movements might suggest that digoxin toxicity induces a functional alteration in the activity of dopamine at the synaptic level.⁴ The involvement of dopaminergic pathways might also explain the psychotic symptoms of digoxin intoxication, as in the more common organic brain syndromes.^{5,6} Digoxin toxicity should be included in the differential diagnosis of iatrogenic choreatic disorders.

1 Smith TW, Antman EM, Friedman PL, Blatt CM, Marsh JD. Digitalis glycosides: mechanisms and manifestations of toxicity. *Prog Cardiovasc Dis* 1984;26:495-523.

2 Aronson JK. Digitalis intoxication. *Clin Sci* 1983;64:253-8.

3 Wedzicha JA, Lees AJ, Hoffbrand BI. Chorea in digoxin toxicity. *J Neurol Neurosurg Psychiatry* 1984;47:419.

4 Klawans HL, Werner WJ, eds. *Textbook of clinical neuropharmacology*. New York: Raven Press, 1981:49-67.

5 Closson RG. Visual hallucinations as the earliest symptom of digoxin intoxication. *Arch Neurol* 1983;40:386.

6 Cummings JL. Organic psychosis. *Psychosomatics* 1988;29:16-26.

Neutropenia caused by intravenous immunoglobulin

Drs R V MAJER and P J GREEN (St Mary's Hospital, Portsmouth PO3 6AG) write: Intravenous immunoglobulin is becoming widely used in childhood idiopathic thrombocytopenic purpura¹; we report two cases of reversible neutropenia occurring after each infusion of intravenous immunoglobulin.

A 6 year old boy developed an idiopathic autoimmune haemolytic anaemia which responded initially to corticosteroids and subsequently splenectomy.

When aged 11 years he developed idiopathic thrombocytopenic purpura with a platelet count of $5.0 \times 10^9/l$. Normal immunoglobulin (Sandoglobulin) 0.4 g/kg for five days restored his platelet count to normal for three weeks. The absolute neutrophil count fell from $7.55 \times 10^9/l$ by day 14. Two subsequent courses of normal immunoglobulin, 1 g/kg for two days and 0.4 g/kg for one day, were followed by nadirs in absolute neutrophil count of 0.05 and $0.1 \times 10^9/l$ respectively. The periods of neutropenia lasted for 7-10 days and then the count recovered spontaneously to normal levels as the platelet count began to decline. Troublesome mouth ulcers occurred during periods of neutropenia and immunoglobulin was therefore discontinued. The patient subsequently required corticosteroids to maintain a normal platelet count but relapsed three times on their withdrawal.

A 12 year old boy with idiopathic thrombocytopenic purpura gained a partial response from corticosteroids but relapsed on their withdrawal. Normal immunoglobulin 0.4 g/kg for five days restored his platelet count to normal for four weeks. Subsequent one day infusions of immunoglobulin 0.4 g/kg at four weekly intervals were required to maintain his platelet count at normal levels until a curative splenectomy was performed. His absolute neutrophil count fell after each course of intravenous immunoglobulin from previously normal levels to nadirs of 1.2 , 1.8 , 1.3 , and $1.3 \times 10^9/l$ respectively and recovered spontaneously as the platelet count declined. The neutropenia occurred 7-14 days after each infusion and lasted for 14 days. No infective problems were seen.

The neutropenia followed every course of intravenous immunoglobulin given to the two patients and followed a distinct pattern: the neutrophil count fell 7-14 days after treatment, remained low for 7-14 days, and recovered spontaneously over the next seven days as the platelet count was beginning to fall. The neutropenia seen in both cases never recurred subsequently and presumably was due to a perturbation of the immune system caused by the intravenous immunoglobulin. Immunoglobulin is a relatively safe agent, side effects being limited to mild pyrexial or anaphylactoid reactions, particularly in selective IgA deficient individuals. This side effect has not been previously reported to the Committee on Safety of Medicines or to the manufacturer. Interestingly, there are two reports of successful treatment of autoimmune neutropenia using intravenous immunoglobulin.^{2,3} Clearly neutrophil counts should be monitored when intravenous immunoglobulin is used.

- 1 Imbach P, Berchtold W, Hirt A, et al. Intravenous immunoglobulin versus oral corticosteroids in acute immune thrombocytopenic purpura in childhood. *Lancet* 1985;ii:464-8.
- 2 Pollack S, Cunningham-Rundles C, Smithwick EM, Baradun G, Good RA. High dose intravenous gammaglobulin for autoimmune neutropenia. *N Engl J Med* 1982;307:253.
- 3 Bussell JB, Lalezari P, Hilgartner MW, Purtil J, Fikrig S, O'Malley J. Reversal of neutropenia with intravenous gammaglobulin in auto-immune neutropenia of infancy. *Blood* 1983; 62:398-400.

Purpuric rash associated with slow release morphine

Drs R J WHISTON, C D M GRIFFITH, and B R HOPKINSON (Queen's Medical Centre, Nottingham NH7 2UH) write: A 70 year old man required strong analgesics for stump pain after a below knee amputation performed for peripheral vascular disease. He was prescribed slow release morphine sulphate (MST, Napp Laboratories) 20 mg twice a day by mouth for pain relief, his other long term medication being salbutamol and beclomethasone inhalers for chronic obstructive airways disease. He was also receiving vitamin B₁₂ injections for pernicious anaemia every two months.

Ten days after starting morphine he developed a purpuric rash on the extensor surface of his thighs, buttocks, and trunk. His full blood count showed haemoglobin of 100 g/l, a white cell count of $10 \times 10^9/l$, and a platelet count of $455 \times 10^9/l$ with an erythrocyte sedimentation rate of 12 mm in the first hour. Blood cultures were performed to eliminate sepsis as a cause of rash and were sterile. Echocardiography showed no evidence of mural thrombus or valve disease consistent with distal embolisation or infective endocarditis. After these negative investigations we attributed his rash to the morphine, which was

stopped, resulting in fading of the rash after 48 hours.

The opiate analgesics have many well known side effects but are only rarely associated with skin eruptions. We believe this to be the first reported case of an extensive rash associated with morphine sulphate. Napp Laboratories and the Committee on Safety of Medicines have no recorded cases of rash after administration of morphine sulphate. There have been three reported incidents of rash associated with dihydrocodeine reported to the committee.

Gynaecomastia associated with captopril

Drs H M MARKUSSE and R H B MEYBOOM (Department of Rheumatology, University Hospital, 2300 RC Leiden, The Netherlands) write: Captopril is associated with a wide variety of side effects including hypotensive episodes, granulocytopenia, proteinuria, loss of taste, angio-oedema, and coughing.¹ We report the first case of gynaecomastia associated with the use of captopril.

A 34 year old man suffered from systemic lupus erythematosus and mild biopsy proved mesangial glomerulonephritis with proteinuria and oedema, for which he had been treated with frusemide and low dose prednisone since 1984 (figure). A second renal

Time course of creatinine clearance and gynaecomastia in relation to administration of captopril, nifedipine, cyclophosphamide, prednisone, and frusemide.

biopsy, performed because of a deterioration in his renal function, showed diffuse proliferative glomerulonephritis. The renal function deteriorated further despite treatment with prednisone 60 mg a day and azathioprine, so monthly intravenous pulse therapy with cyclophosphamide (1000 mg) was started. The hypertension could not be controlled by nifedipine, but after captopril was given at 75 mg a day blood pressure returned to normal. Seven months later a painful gynaecomastia developed gradually on the left side. Normal values were obtained for liver enzymes, serum thyroxine, prolactin, testosterone, oestrone, and oestradiol, and 24 hour urinary excretion of 17 ketosteroids. Captopril was stopped, the left mammary pain vanished within two weeks, and over the following weeks the breast enlargement disappeared completely. No endocrine abnormalities were found and other causes of breast enlargement such as alcoholism, diabetes mellitus, and liver disease were excluded.

There are several reports of breast enlargement in women induced by penicillamine,² which is a second line antirheumatic drug with a molecular structure related to that of captopril. Both compounds contain a sulphhydryl group at one end of the molecule separated by a short chain of carbon atoms from an acid group at the other end. Both drugs bind copper, and they produce similar adverse side effects such as rash, nausea, loss of taste, proteinuria, and neutropenia. One case of penicillamine induced breast enlargement in a man has been reported,³ which showed a strong resemblance to our case. No gynaecomastia associated with captopril has been reported to the manufacturers or to the Netherlands Centre for Monitoring of Adverse Reactions to Drugs. The clinical course of this patient's gynaecomastia, the absence of hormonal disturbances, and the similarity between captopril and penicillamine, a drug with a possible breast enlarging action, suggest that in this case gynaecomastia was induced by captopril.