abdominal injuries, but this is by no means always the case.

J M LONGMORE

Ferring,
West Sussex BN12 5HJ

1 Baskett PJF. Management of hypovolaemic shock. *Br Med J* 1990;**301**:179. (21 July.)
2 Ellis H. *Clinical anatomy*. 2nd ed. Oxford: Blackwell, 1963:196.

# *Drug Points*

## Hepatitis B vaccine associated with erythema nodosum and polyarthritis

Drs STEPHEN J ROGERSON and FRED J NYE (Fazakerley Hospital, Liverpool L9 7AL) write: Side effects of hepatitis B vaccine are rare but include erythema nodosum[1-3] and uveitis.[4] Polyarthritis has also been suggested in a Danish patient[5] and two other patients, whose adverse reactions are on file with the Committee on Safety of Medicines; arthralgia may be commoner. These are all symptoms of immune complex disease and suggest a possible aetiological link with the vaccine. A serum sickness-like illness due to circulating immune complexes occurs in 10-20% of patients with acute hepatitis B infection. We describe a patient who developed erythema nodosum and polyarthritis after the first dose of recombinant hepatitis B vaccine.

In May 1989 a 31 year old man was given a standard 20 μg dose of Engerix B vaccine. The next day he developed pain in the metacarpophalangeal and proximal interphalangeal joints of both hands and painful wrists, hips, elbows, knees, ankles, and sacroiliac joints with swelling, most notably of both ankles. He also noted tender, raised, purplish skin lesions with a red margin on the left shin, which lasted a few days and were consistent in appearance with erythema nodosum. He had no history of arthritis, eye or chest disease, or related problems and no evidence of intercurrent infection. He was taking no drugs.

By the time of our review he had only mild stiffness of the ankles with slight swelling of the right ankle. He had a normal full blood count and erythrocyte sedimentation rate and results of chest radiography, urine analysis, and microscopy; values for antinuclear factor and rheumatoid factor, titres of antistreptolysin O and brucella, serum IgE concentrations, and results of screening for HLA B27 were also normal. Hepatitis B surface antigen and IgG and IgM core antibodies were not detectable. The results of biochemical tests were normal apart from mildly elevated alkaline phosphatase (175 IU/l, range 30-130) and γ-glutamyltransferase (157 IU/l, 0-50) activities.

Erythema nodosum lasted for one week, but the arthritis persisted for six weeks and was initially severely incapacitating. The patient was subsequently free of symptoms for nine months. He was unwilling to receive further vaccination in view of the low perceived risk of hepatitis B infection and the possible risk of further arthritis.

Although it was not justifiable to rechallenge our patient, the similarity of his arthritis to that of acute viral hepatitis and its temporal relation to his hepatitis B vaccination, with the associated erythema nodosum, suggest an aetiological link with hepatitis B vaccine.

1 Di Giusto CA, Bernhard JD. Erythema nodosum provoked by hepatitis B vaccine. *Lancet* 1986;ii:1042.
2 Anonymous. Update on hepatitis B prevention. *MMWR* 1987;**36**:353-60.
3 Goolsby PL. Erythema nodosum after recombinant hepatitis B vaccine. *N Engl J Med* 1989;**321**:1198-9.
4 Fried M, Conen D, Conzelmann M, Steinemann E. Uveitis after hepatitis B vaccination. *Lancet* 1987;ii:631-2.
5 Christau B, Helin P. Reaktiv artrit efter vaccination mod hepatitis B. *Ugeskr Laeger* 1987;**149**:1882.

## Cushing's syndrome induced by medroxyprogesterone

Drs PETER K MERRIN and WILLIAM D ALEXANDER (Diabetic Unit, Queen Mary's Hospital, Sidcup, Kent DA14 6LT) write: A 65 year old man presented in 1980 with a hypernephroma. After nephrectomy he was started on medroxyprogesterone acetate (Provera) 100 mg four times daily. He remained well until 1983, when he presented with hyperglycaemia. Treatment was started with diet and twice daily biphasic isophane insulin.

Over the next four years he developed a sensory peripheral neuropathy and an increasingly cushingoid appearance. In 1987 investigations showed a plasma cortisol concentration at 9 am of less than 10 nmol/l, plasma corticotrophin concentration of 13 ng/l (normal 10-80 ng/l), and urinary free cortisol concentration of 13 nmol/l. A stimulation test was performed with corticotrophin at a dose of 80 IU intramuscularly twice daily for three days. Plasma cortisol concentration rose from 10 nmol/l on day one to 335 nmol/l on day three.

These results suggested that medroxyprogesterone acetate was acting as a glucocorticoid, suppressing adrenal function at the hypothalamic-pituitary level and producing iatrogenic Cushing's syndrome. The dose of medroxyprogesterone acetate was reduced to 50 mg twice daily. This resulted in recurrent hypoglycaemia, and it was therefore possible to stop the insulin and control his diabetes by diet alone. He became less cushingoid, but a month later he began to feel unwell with weakness, weight loss, and thirst. Insulin was restarted but his symptoms did not improve. Relative adrenal insufficiency secondary to glucocorticoid withdrawal was suspected. The plasma cortisol concentration at 9 am was now 53 nmol/l. The dose of medroxyprogesterone acetate was increased to 100 mg twice daily, his symptoms resolved, and he subsequently remained well with twice daily insulin and medroxyprogesterone acetate 100 mg twice daily.

Endocrinological effects of medroxyprogesterone acetate include adrenal suppression,[1 2] antioestrogen activity,[3] and gonadotrophin suppression.[4] It also causes a cushingoid appearance at the doses described above.[5] Cushing's syndrome associated with glucocorticoid deficiency on withdrawal of medroxyprogesterone acetate has been described but to our knowledge overt Cushing's syndrome associated with diabetes has not.[6] Although the dangers of withdrawal have been postulated,[1] it may be that because most patients treated with this drug are polysymptomatic and have a generally poor prognosis, adrenal insufficiency has not in practice been thought to be a problem. Whether or not the dose of medroxyprogesterone acetate itself should be increased or a different steroid started at times of potential stress is not clear. In our patient adequate adrenal replacement was apparently provided by restarting medroxyprogesterone acetate.

Even at relatively low doses medroxyprogesterone acetate may have considerable glucocorticoid activity, and patients should be monitored for glucose intolerance and adrenal insufficiency, especially during long term treatment. Both the Committee on Safety of Medicines and the manufacturer have been notified.

1 Van Veelan H, Houwerzijl J, Roding TJ, *et al*. Oral high dose medroxyprogesterone acetate causes adrenal suppression in patients with breast cancer. *Eur J Cancer Clin Oncol* 1983;**18**:1035-6.
2 Van Veelan H, Willemse PH, Sleijfer DT, Pratt JJ, Sluiter WJ, Doorenbos H. Adrenal suppression by oral high dose medroxyprogesterone acetate in breast cancer patients. *Cancer Chemother Pharmacol* 1984;**12**:83-6.
3 Sala G, Iannotta F, Facchinetti A. *Endocrinological properties of medroxyprogesterone acetate. Proceedings of an international symposium on medroxyprogesterone acetate, Geneva, 24-26 February 1982*.
4 Novak E, Hendrix JW, Seckman CE. Effects of medroxyprogesterone acetate on some healthy male volunteers. *Current Therapeutic Research* 1977;**21**:320-6.
5 Nemoto T, Patel J, Rosner D, Dao TL. Oral medroxyprogesterone acetate in the treatment of metastatic breast cancer. *J Surg Oncol* 1986;**32**:211-3.
6 Siminoski K, Goss P, Drucker DJ. The Cushing syndrome induced by medroxyprogesterone acetate. *Ann Intern Med* 1989;**111**:758-60.

## Myocardial infarction associated with the use of dextrofenfluramine

Drs P EVRARD, A F ALLAZ (Clinique Médicale Thérapeutique, University Hospital, 1211 Geneva), and P URBAN (Centre de Cardiologie, University Hospital, 1211 Geneva) write: Dextrofenfluramine, an anorexigenic drug, is the dextroisomer form of fenfluramine.[1] Adverse effects of fenfluramine include fixed or reversible pulmonary hypertension.[2-4] We describe a non-Q wave myocardial infarction that occurred in a woman taking dextrofenfluramine.

A 31 year old white woman was admitted with a two hour history of chest pain at rest that was relieved by intravenous nitroglycerin within 45 minutes. The patient was in excellent health with no family history of cardiovascular disease. She did not smoke or drink alcohol and had never used illicit drugs. She had been taking an oral contraceptive pill for the past three years (levonorgestrel 50-75-125 μg, ethinyloestradiol 30-40-30 μg). Eight days before admission she had started taking dextrofenfluramine 15 mg three times daily and had lost 6 kg in a week.

Physical examination was normal. She was 1 m 65 cm tall and weighed 54 kg. Electrocardiography showed ST elevation of 3 mm in leads V2 and V3, and cardiac enzymes were raised (creatine kinase 457 IU/l (normal range 0-27 IU/l), MB fraction 55 IU/l with a peak of 823 IU/l after five hours). Cardiac catheterisation showed moderate anterior hypokinesia, and findings on technetium-99 m scanning were also consistent with a non-Q wave myocardial infarction. Coronary angiography performed 15 hours after admission showed no abnormality, and the results of viral serology and blood coagulation tests were normal.

Acute and chronic cardiomyopathy as well as myocardial infarction have been described in association with amphetamine administration but not with oral administration of either fenfluramine or dextrofenfluramine.[5-7] Although we cannot exclude the contribution of the oral contraceptive pill in this patient,[8 9] the occurrence of a myocardial infarction a few days after the start of a course of dextrofenfluramine suggests that the drug may have helped to induce the event, possibly by inducing coronary spasm. Our patient took 45 mg a day instead of the recommended dose of 30 mg. Attention should be paid to the possible cardiovascular side effects of dextrofenfluramine, especially in higher dosages.

1 Silverstone T, Smith G, Richards R. A comparative evaluation of dextrofenfluramine and dl-fenfluramine on hunger, food intake, psychomotor function, and side effects in normal human subjects. In: Bender AE, Brockes LJ, eds. *Body weight control. The physiology, clinical treatment and prevention of obesity*. Edinburgh: Churchill Livingstone, 1987:240-6.
2 Guy-Grand B, Crepaldi G, Lefebvre P, Apfelbaum N, Gries A, Turner P. International trial of long term dexfenfluramine in obesity. *Lancet* 1989;ii:1142-5.
3 Douglas JG, Munro JF, Kitchin AH, Muir AL, Proudfoot AT. Pulmonary hypertension and fenfluramine. *Br Med J* 1981;**283**:881-3.
4 McMurray J, Bloomfield P, Miller HC. Irreversible pulmonary hypertension after treatment with fenfluramine. *Br Med J* 1986;**292**:239-40.
5 Call TD, Hartineck J. Acute cardiomyopathy secondary to intravenous amphetamine abuse. *Ann Intern Med* 1982;**97**:559-60.
6 Smith HF, Roche AHG, Jagusch MF, Herdson PB. Cardiomyopathy associated with amphetamine administration. *Am Heart J* 1976;**91**:792-7.
7 Carson P, Oldroyd K, Phadke K. Myocardial infarction due to amphetamine. *Br Med J* 1987;**294**:1525-6.
8 Shapiro S, Slone D, Rosenberg L, Kaufman DW, Stolley PD, Miettinen OS. Oral contraceptive use in relation to myocardial infarction. *Lancet* 1979;i:743-6.
9 Rosenberg L, Kaufman DW, Helmrich SP, Miller DR, Stolley PD, Shapiro S. Myocardial infarction and cigarette smoking in women younger than 50 years of age. *JAMA* 1985;**253**:2965-9.