SHORT REPORTS

Exacerbation of diazepam-induced phlebitis by oral penicillamine

Penicillamine, a heavy metal antagonist, is used in the treatment of Wilson's disease, cystinuria, rheumatoid arthritis, and various other conditions. Adverse reactions to the drug are many and frequent and range in severity from gastrointestinal distress, stomatitis, unpleasant skin odours, and rashes to proteinuria, leucopenia, and thrombocytopenia.¹ Up to one-third of patients given the drug for rheumatoid arthritis have to discontinue treatment because of toxicity.¹ Intravenous diazepam is widely used as a sedative, muscle relaxant, and anticonvulsant. Local complications with this drug, including pain at injection site, phlebitis, and thrombophlebitis, have likewise been reported frequently.²

We describe a patient who developed phlebitis from intravenous diazepam. The phlebitis resolved with local heat but recurred on two separate occasions after oral penicillamine.

Case report

A 33-year-old white man underwent endoscopic retrograde cholangiopancreatography for investigation of persistent raised activity of alkaline phosphatase and 5'-nucleotidase. He had had ulcerative colitis 10 years earlier which had been effectively treated with sulphasalazine. Five years later an asymptomatic rise of alkaline phosphatase and 5'-nucleotidase activities and findings on oral cholecystogram consistent with cholecystitis prompted a cholecystectomy. This showed acalculous cholecystitis. Minimal biliary duct inflammation was found on liver biopsy. Although the patient had remained asymptomatic the alkaline phosphatase activity remained raised at 70 to 225 IU/l (normal 13-40) as did the 5'-nucleotidase activity at more than 17 Bodansky units (normal 0.3-3.2). Results of tests for antimitochondrial and antismooth muscle antibodies were negative and serum bile acid concentrations were normal. An endoscopic retrograde cholangiopancreatography was performed using 5 mg of diazepam intravenously for sedation. This procedure showed mild beading and narrowing of the biliary ducts consistent with sclerosing cholangitis. Two days later mild phlebitis developed in the right forearm in the region of the antecubital fossa where diazepam had been injected. The pain, erythema, and warmth resolved after one week of treatment with local heat. Two weeks later penicillamine, in a daily dose of 250 mg orally, was started. Four days later the phlebitis recurred and persisted for the next two weeks. Penicillamine was discontinued, and the phlebitis resolved over three weeks in response to local heat. As haematological and renal values were stable and there were no other side effects penicillamine was restarted at the same dose. Two days later phlebitis recurred. Penicillamine was immediately discontinued, and the phlebitis resolved over four weeks. The patient was re-evaluated by another doctor, who felt that the clinical history and results on endoscopic retrograde cholangiopancreatography were more consistent with pericholangitis, and prednisone treatment was started. The alkaline phosphatase and 5'-nucleotidase activities returned to normal after five months of treatment, and prednisone was tapered off without adverse effects.

Comment

Phlebitis is a local inflammatory condition of the vein without induration characterised by erythema, oedema, and pain. Local complications after diazepam commonly start 24 to 48 hours after intravenous administration and last from a few days to several weeks.² Local treatment with heat is generally adequate, though antibiotics, anticoagulants, analgesics, or anti-inflammatory agents are sometimes used. Diazepam-induced local complications appear to be caused by an inflammatory reaction directly related to the chemical irritation of diazepam or its vehicle.²

The treatment of sclerosing cholangitis, a condition that may result in biliary cirrhosis and death, is not satisfactory. Since penicillamine has been used experimentally for primary biliary cirrhosis with encouraging results³ its use in sclerosing cholangitis seemed reasonable as a therapeutic trial.

The finding that phlebitis, presumably from intravenous diazepam, recurred after apparent healing after two separate courses of oral penicillamine was interesting. We found only one report describing the development of thrombophlebitis after beginning penicillamine treatment in a patient with a history of recurrent phlebitis.⁴ The thrombophlebitis resolved shortly after discontinuation of penicillamine.

Penicillamine has an influence on collagen synthesis which appears

to be dose-related. Evidence in animals treated with penicillamine suggests that wound healing is defective, possibly due to production of poor quality collagen.⁵ In this case the phlebitis though clinically resolved may still have been healing. Penicillamine may have prevented this subclinical healing and caused the exacerbation of phlebitis.

¹ Kean WF, Dwosh IL, Anastassiades TP, Ford PM, Kelly HG. The toxicity pattern of D-penicillamine therapy—guide to its use in rheumatoid arthritis. *Arthritis Rheum* 1980;**23**:158-64.

² Donaldson D, Gibson G. Local complications with intravenous diazepam. *Canadian Dental Association Journal* 1979;**45**:337-41.

³ Dickson ER, Fleming CR, Ludwig J. Primary biliary cirrhosis. *Prog Liver Dis* 1979;**6**:487-502.

⁴ Davis CM. D-penicillamine for the treatment of gold dermatitis. *Am J Med* 1969;**46**:472-4.

⁵ Burry HC. Penicillamine and wound healing—a potential hazard? *Postgrad Med J* 1974;**50**, suppl 2:75-6.

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Reversible renal damage due to glue sniffing

Glue sniffing and other forms of solvent abuse are becoming increasingly common. Toxic effects are rarely encountered, and a recent survey showed no evidence of renal or hepatic damage in 132 cases.¹ We report a case of reversible renal damage caused by sniffing a proprietary adhesive—one of the most widely abused agents in Britain—whose main solvents are toluene and acetone.

Case report

A 14-year-old boy presented to his general practitioner with a 24-hour history of sore throat and was prescribed cephalixin. The next day he returned complaining of haematuria, urinary frequency, and bilateral loin pain and was referred to hospital. He had abused solvents for two years and for eight months had "sniffed" a pint of adhesive daily. After three weeks of abstinence he had sniffed one pint of adhesive on each of the three days before his admission to hospital.

On examination he was flushed and had a fever of 38.6°C. Scabbed excoriations were present on the lower lip. The fauces were red and inflamed, his face was puffy, and several cervical nodes were palpable. There was no evidence of peripheral oedema or raised jugular venous pulsation. Blood pressure was 140/80 mm Hg on admission; this was the highest level recorded during his stay. The only other abnormal finding was bilateral loin tenderness. Plasma urea and creatinine concentrations on admission were normal. Urine analysis showed blood +++ and protein +++, and microscopy showed red blood cells but no casts.

In the 24 hours after admission he passed only 200 ml of urine, his face became more swollen, and the plasma urea concentration rose to 10.3 mmol/l (61.9 mg/100 ml) and creatinine concentration to 132 mmol/l (1493 mg/100 ml). Urine contained 2.2 g protein/l. Liver function tests showed normal results. Blood cultures, three midstream specimens of urine, and two throat swabs showed no growth. Antinuclear factor and antistreptolysin O titre were negative. Fluid intake was restricted and renal function closely monitored. Urine output increased daily, and by the fourth day after admission he was no longer oliguric. Plasma urea and creatinine concentrations returned to normal on the fifth day. Four weeks later his urine was free of blood, and protein and plasma urea and creatinine concentrations remained normal. Creatinine clearance was 112 ml/min.

Despite custodial care he contrived to sniff glue on two further occasions. Both of these episodes were associated with a recurrence of loin pain, haematuria, and proteinuria. Although urea and creatinine concentrations remained normal, microscopic haematuria persisted after six weeks' abstinence from glue.

Comment

We believe this case to be an example of renal damage caused by the inhalation of toluene in glue. Renal failure has been recorded after the abuse of other solvents such as carbon tetrachloride² and trichloroethylene.³ O'Brien *et al*⁴ reported a case of hepatorenal damage after inhalation of toluene from a liquid cleaner, but similar damage from the toluene in glue has not been recorded. Since this adhesive is now the most widely abused agent in the west of Scotland,¹ and probably in Britain, it is important to realise that renal damage may result from such abuse.

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¹ Watson JM. Clinical and laboratory investigation in 132 cases of solvent abuse. *Medicine, Science and the Law* 1978;**18**:40-3.

² New PS, Lubash GD, Scherr L, Rubin AL. Acute renal failure associated with carbon tetrachloride intoxication. *JAMA* 1962;**181**:903-6.

³ Baerg RD, Kinberg DV. Hepatic necrosis and acute renal failure in solvent sniffers. *Ann Intern Med* 1970;**73**:713-20.

⁴ O'Brien ET, Yeoman WB, Hobby JAE. Hepato-renal damage from toluene in a glue sniffer. *Br Med J* 1971;**iii**:29-30.

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Reactivation of vasculitis after influenza vaccination

In the past few years use of viral influenza vaccines has increased. Despite criteria regulating their administration, particularly in immunologically depressed patients, they are often overprescribed without consideration of possible adverse reactions.

Case report

A 55-year-old woman was admitted to hospital because of an ataxic gait and progressive weakness. She had been well until six months previously, when after an influenza-like syndrome she had become febrile and fatigued, with arthralgia and unsteady gait. During the next months these symptoms worsened and she lost weight. There was no history of allergic reactions. On admission she was alert but pale, weak, and febrile. She had brisk reflexes on her right side and an ataxic gait, tending to fall to the right.

Packed cell volume was 30%, white cell count $7.9 \times 10^9/l$ with neutrophils without eosinophils, platelet count $355 \times 10^9/l$, and erythrocyte sedimentation rate (Westergren) 85 mm in the first hour. Lupus erythematosus cells were not seen. Concentrations of C3, C4, immunoglobulins, cryoglobulins, blood urea, bilirubin, glucose, and lipids and results of liver function tests were normal. Serum creatinine concentration was $61.98 \mu\text{mol/l}$ (0.7 mg/100 ml), and protein electrophoresis showed 70 g total protein/l with an increase in α_2 -globulin. A lumbar puncture showed no abnormalities of cerebrospinal fluid. Urinary protein excretion was 1.5 g/24 hours, the sediment containing 40-50 red cells, 30-40 white cells, and many casts per high-power field. Urine cultures were negative. X-ray films of the chest, an intravenous urogram, an abdominal aortogram, and a carotid angiogram were normal. A renal biopsy specimen showed necrotising vasculitis of small- and medium-sized arteries and a focal glomerulonephritis with granulomatous infiltration around the glomerular tufts.

Prednisone 1 mg/kg/day was started. In a few weeks she showed clinical and biochemical improvement, the erythrocyte sedimentation rate being 15 mm in the first hour. The prednisone dose was decreased gradually to a maintenance dose of 12.5 mg/48 hours, and she remained well.

Eighteen months later 900 IU of a killed mixovirus influenza vaccine preparation was administered without our knowledge (315 IU of A/Bangkok/1/79(H_2N_2), 315 IU of A/USSR/90/77(H_1N_1), and 270 IU of B/Singapore/222/79). Ten days later she was readmitted to hospital with a recurrence of her original symptoms (fever, weakness, arthralgia, ataxic gait) and an

erythrocyte sedimentation rate of 84 mm in the first hour. Prednisone was increased to 1 mg/kg/day and cyclophosphamide added to treatment. In two weeks she had improved; prednisone was again gradually decreased and she was discharged. Twelve months later she remained well taking low-dose prednisone on alternate days and cyclophosphamide.

Comment

Vasculitis may be triggered by several types of antigenic substances,¹ but many unknown mechanisms exist to which it might be related. Often it appears after a short episode of an influenza-like syndrome, suggesting that viral infections may precede it, but this is difficult to prove. Traditionally the vasculitis syndrome may start with the same unspecific, non-infectious symptoms as influenza, making a distinction between both diseases almost impossible and therefore blurring the true incidence of their association.

Influenza vaccines are useful in certain subjects, particularly the immunologically depressed,⁵ but are often used more widely than is specifically indicated. Doctors should bear in mind that influenza vaccines, especially the broad-spectrum ones (trivalent), contain several types of attenuated viruses, all with their own antigenic power; thus the broad-spectrum vaccines are more likely to induce a wide antibody response and activate some immunological disturbance.

As knowledge of agents that cause systemic disease is still insufficient, doctors should be cautious in prescribing influenza vaccines as they may trigger some immunological illness that may itself be worse than most influenza syndromes.

¹ Mordes JA, Johnson MK, Soter NA. Possible naproxen-associated vasculitis. *Arch Intern Med* 1980;**140**:985.

² Phanuphak P, Kohler PF. Onset of polyarteritis nodosa during allergic hyposensitization treatment. *Am J Med* 1980;**68**:479-85.

³ Wharton CFP, Pietroni R. Polyarteritis after influenza vaccination. *Br Med J* 1974;**iii**:331-2.

⁴ Blumberg S, Bienfang D, Kantrowitz FG. A possible association between influenza vaccination and small vessel vasculitis. *Arch Intern Med* 1980;**140**:847-8.

⁵ Center for Disease Control. Influenza 1980-1981. Recommendation of the Public Health Service immunization practices advisory committee. *Ann Int Med* 1980;**93**:466-8.

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Recurrent pericarditis: a rare complication of influenza vaccination

Viral infection of the respiratory tract caused by influenza is common and widespread during the winter. The usual benign course of the disease is sometimes complicated by bacterial pneumonia, myocarditis, and pericarditis.¹ These complications are especially dangerous in the elderly and compromised hosts. A trivalent vaccine preparation of inactivated influenza virus antigen is available for this group of patients, and its composition is adjusted according to the new virus serotypes appearing each year. Adverse reactions to the vaccine that have been reported are local skin reactions, systemic symptoms of toxicity, allergic reactions, and the Guillain-Barré syndrome²⁻⁴; we report on a patient who developed pericarditis.

Case report

A 61-year-old man was admitted because of a fever of 38°C and a continuous chest pain aggravated by breathing and changing his position. A week before admission he had received an intramuscular injection of influenza vaccine containing A/Bangkok/1/79(H_2N_2), A/Brazil/11/78(H_1N_1), and B/Singapore/222/79 (Vaccigrip-Institut Maricux, Paris). Physical examination disclosed a fever of 37.5°C and a pericardial friction rub. Laboratory examination showed erythrocyte sedimentation rate 70 mm in