Comment

Continuous intravenous chlormethiazole is an effective anti-convulsant for status epilepticus, but because of the complications mentioned should be used carefully, preferably for short periods only.

We thank the scientific and technical branch of the DHSS and the Government Chemist for their interest and chemical analysis, and the manufacturers of Heminevrin (Astra Chemicals), for their analysis and pyrolysis tests.

¹ Harvey PKP, Higenbottam TW, Loh L. Chlormethiazole in treatment of status epilepticus. *Br Med J* 1975;iii:603-5.

(Accepted 12 November 1979)

The Hospital for Sick Children, Great Ormond Street, London WC1N 3JH

S LINGAM, DCH, MRCP, neurological registrar
HELEN BERTWISTLE, RSCN, SRN, neurological ward sister
HEATHER M ELLISTON, MPS, group chief pharmacist
JOHN WILSON, FRCP, PHD, consultant paediatric neurologist

Late displacement of central venous catheter resulting in vascular obstruction

The introduction of large-calibre plastic catheters into the central veins of patients has facilitated total parenteral nutrition and drug administration. These two procedures may be of critical importance in managing very sick people with bacterial endocarditis, acute leukaemia during initial induction chemotherapy, or after bone marrow transplantation. In each of these the peripheral vessels are unsatisfactory routes for intravenous infusion, since large volumes need to be given and also the high viscosity or hyperosmolality of some of the materials may result in thrombophlebitis and thus render small veins especially prone to occlusion. A number of techniques are available for achieving access to the high-flow veins within the thorax. To date these procedures have been relatively free from serious problems, but the catheters may become dislocated from the original desired site and then follow an abnormal route within the thoracic vessels, leading to complications.¹ In most reported cases the unsatisfactory results arise during the introduction process and we are not aware of late catheter migration, particularly against venous flow, with resulting vascular occlusion.

Case report

A 49-year-old woman was hospitalised for cytotoxic chemotherapy for stage IV lymphocytic lymphoma. In view of her poor physical state a 10-gauge Silastic catheter was introduced via the left subclavian line, using a previously described technique.² Postoperative chest x-ray examination confirmed that the end of the catheter was lying in the superior vena cava with its end 1 cm above the right atrium. For the next three weeks the patient received her intravenous drugs, hyperalimentation, and daily fluid requirements by this route without any problems. During the same period blood samples were collected from the catheter, since measurements in these correlate well with those in samples simultaneously collected from peripheral vessels.² On day 23 after introduction of the catheter the patient's left hand and arm started to swell and this progressed slowly for two days. Careful serial examination showed increasing tenderness and swelling of the left arm, supraclavicular space, and axilla. Radiological studies showed that the radio-opaque catheter had looped up inside the superior vena cava and wedged into the axillary vein, obstructing blood flow. The catheter was simply repositioned under x-ray control, and within two days all symptoms had disappeared. No late complications have occurred.

Comment

A survey of central venous catheters used in our hospital over a two-year period confirmed the finding of Fischer and his colleagues¹ that initial misplacement could occur and that intrathoracic complications may then arise. Nevertheless, once securely in position none of the catheters that we studied became displaced. Our case

was the first example of late dislocation we encountered over the same two-year period, when catheters were routinely employed for hyperalimentation, induction of cytotoxic chemotherapy in patients with leukaemia, and long-term support after bone marrow transplantation. The final resting place of the catheter is all the more surprising in view of the retrograde course followed by the large diameter and relative inflexibility of the plastic tubes. This complication should be recognised as soon as it occurs since the hypertonic and irritating solutions infused may lead to local endothelial damage and thrombus formation. One way to check the patency is by regular flushing, while direct determination of venous pressure is an easy method of monitoring freedom from obstruction. While radiological control is essential when introducing the catheter its subsequent use is of lower priority in the complex management of a critically ill patient. It is therefore not surprising that the symptoms of mechanical obstruction may not be immediately evident. Since delay in diagnosis is potentially serious we suggest that these patients should be regularly examined, with particular emphasis on catheter efficiency, and that x-ray studies should be undertaken whenever anxiety arises. A dislocation may then be promptly corrected and x-ray control will thus avoid venous complications.

¹ Fischer J, Lundstrom J, Ottander H-G. Central venous cannulation: a radiological determination of catheter positions and immediate intra-thoracic complications. *Acta Anaesthesiol Scand* 1977;21:45-9.

² Jacobs P, Jacobson J. A practical method for ensuring long-term venous access. *Proc R Soc Med* 1979;72:263-5.

(Accepted 1 November 1979)

Department of Haematology, University of Cape Town Medical School, Cape, South Africa

NICHOLAS NOVITSKY, MB, registrar
PETER JACOBS, MD, PHD, professor and head of department

Hydrallazine-induced cutaneous vasculitis

The commonest features of the hydrallazine-associated lupus syndrome are arthralgia and malaise. Erythematous rashes may occur but vasculitis has not been reported. We have recently seen two patients with ulcerating cutaneous vasculitis associated with hydrallazine treatment.

Case reports

(1) A 63-year-old woman had been treated for hypertension and stable renal impairment for 15 years. Hydrallazine was started in September 1977 and the daily dosage increased to 250 mg in addition to diuretic and beta-blocking drugs and methyl dopa. In July 1978 her serum antinuclear antibody (ANA) was positive at a titre of 1/40 and her erythrocyte sedimentation ratio (ESR) 33 mm in 1 h. In July 1979 the ANA titre was 1/160 and the ESR 70 mm in 1 h. In August 1979 she was admitted to hospital with a 10 × 5 cm ulcer on the lateral aspect of her left leg, which had developed over two weeks. She gave a six-month history of arthralgia, myalgia, and weight loss of 3 kg. Two days after admission she developed multiple vasculitic lesions over the buttocks, thighs, and arms. Hydrallazine was withdrawn and the lesions began to resolve. When one of them ulcerated, however, prednisone was given for five days, with rapid disappearance of the lesions and healing of the ulcer. Results of investigations included ESR 90 mm in 1 h; creatinine clearance 25 ml/min; no proteinuria; haemoglobin 11.4 g/dl; white cell count (WBC) $4.1 \times 10^9/l$ ($4100/mm^3$), normal differential and platelets; immunoglobulins IgG 13.0 g/l, IgA 1.75 g/l, IgM 2.60 g/l (normal IgM 0.5-1.8 g/l). IgG and IgM ANA titres were 1/2560, DNA binding 20%. No other autoantibodies were found, complement screen was normal, Clq binding negative, and cryoglobulins were present in trace only. Sulphamethazine phenotyping showed her to be a slow acetylator and her total intake of hydrallazine was estimated to be 120 g. Histology of a lesion from her thigh showed allergic vasculitis with fibrinoid necrosis of small vessels. Immunofluorescence microscopy showed deposits of IgM, fibrin, and C3 in small blood vessels.

(2) A 61-year-old woman with essential hypertension had received hydrallazine, propranolol, and cyclopentiazide K for two years. During this time her maximum daily dosage of hydrallazine was 100 mg and her estimated total intake 95 g. In 1979 she presented with a six-month history of pain and stiffness in her hands, wrists, elbows, shoulders, and knees

associated with malaise, and she reported the appearance a week previously of a crop of red patches on her legs. On examination she had a dark vasculitic rash with blisters and small superficial ulcers on the lower legs and dorsum of both feet (figure). Wrist movement was painful but no synovial swelling was present. Hydrallazine was stopped, and the skin lesions, arthralgia, and malaise resolved within two weeks. Results of investigations included

Skin lesions in case (case 2) of hydrallazine-induced cutaneous vasculitis.

ESR 69 mm in 1 h, creatinine clearance 79 ml/min, no proteinuria, haemoglobin 10 g/dl (hypochromic, microcytic film), WBC 3.5×10^9 (3500/mm³), normal differential and platelets, immunoglobulins IgG 8.2 g/l, IgA 1.3 g/l, IgM 6.8 g/l (normal IgM 0.5-1.8 g/l). ANA titre was 1/640 (IgM) and DNA binding 5%. No other autoantibodies were found, complement screen was normal, Clq binding and cryoglobulins negative. Sulphamethazine phenotyping showed her to be a slow acetylator. Histology of an ulcerated lesion

showed severe vasculitis with fibrinoid necrosis of dermal capillaries. No specific immunofluorescence was seen on frozen section.

Comment

The hydrallazine-induced lupus syndrome occurs almost exclusively in slow acetylators¹ and is rare when the daily dosage is less than 200 mg.² Our patients developed necrotising cutaneous vasculitis as part of such a syndrome together with the typical serological changes. The underlying metabolic and immunological mechanisms, however, are still not understood. ANA in low titre occur in up to 50% of patients receiving hydrallazine for two years. ANA in high titre with normal DNA binding are characteristic of hydrallazine-induced lupus. A rising titre of ANA preceded the emergence of symptoms in our first case, and further prospective studies are required to evaluate this as a predictive test.

We thank Professor C T Dollery and Dr S P Liyanage for permission to report these cases.

¹ Strandberg I, Boman G, Hassler L, Sjöqvist F. Acetylator phenotype in patients with hydrallazine-induced lupoid syndrome. *Acta Med Scand* 1976;200:367-71.

² Perry HM jun. Late toxicity to hydrallazine resembling systemic lupus erythematosus or rheumatoid arthritis. *Am J Med* 1973;54:58-72.

(Accepted 1 November 1979)

Rheumatology Unit and Department of Clinical Pharmacology, Hammersmith Hospital and Royal Postgraduate Medical School, London W12

R M BERNSTEIN, MA, MRCP, senior registrar (now ARC research fellow, division of rheumatic diseases, University of Colorado Medical Center, Denver, Colorado, USA)

J EGERTON-VERNON, MB, senior house officer

J WEBSTER, MRCP, honorary senior registrar

ONE HUNDRED YEARS AGO I will now mention a case in which jaundice prevailed to a greater or less degree for eighteen months, with ultimate cure. The patient, a Yorkshire gentleman sixty-six years old, had lived somewhat freely and taken enormous exercise. A year before his hepatic troubles came on, he had some head-affection, and was accordingly very strictly dieted; and to this restricted diet I really imputed his attack. After a long day's shooting, he was seized with agonising pain in the epigastrium and vomiting, etc., and quickly became jaundiced. The motions were never of a right colour again for a year and a half; the urine was always dark, and the skin deeply tinted. Occasionally the cuticle seemed to improve a little in colour, and the urine to become lighter; but the clay-colour of the motions was invariable. I am quite sure that the urine and the skin can assume their natural colour almost completely, and yet the obstruction to the flow of bile be as persistent as ever. The only explanation of this is diminished production of bile, through interference with the functions of the liver. Every few weeks, a paroxysm of pain and vomiting would come on, with great weakness; yet no stone could be discovered, and the most careful search was always made.

The patient lost flesh, the liver became large and hard, and, as he had taken freely of spirits, commencing cirrhosis was suspected. There was occasional albumen in the urine, and the appetite became very poor. At last, eighteen months after the first futile attack, an awful paroxysm ensued—pain, vomiting, rigors, oedema of lungs and feet, dry mahogany tongue, fearful thirst and anorexia, and the deepest jaundice. It would be an interesting question why the jaundice deepened at this time. The sweats drenched his bed. Two and three weeks passed, and remedies were of no avail, except as palliatives to his sufferings. But one day, I found a slight change in the colour of the stools, coincident with a cessation of pain. A day or two afterwards, I discovered the stone I now hand round. It has, of course, shrunk much by keeping, owing to its brittle structure. You will see that its ends have been ground off from rough treatment by the muscular coats of

the gall-bladder and duct. I would search through a thousand evacuations, however odorous, to witness the pleasure and satisfaction which the announcement of my discovery gave to my patient and his devoted family.

I did not find another stone, and convalescence, though naturally very slow, was complete. The oedema of lungs and legs faded away, and my friend has been shooting in the north this winter, the attack having taken place last March. For many days, he was at the point of death. One morning, after an awful rigor, I found him with a temperature of 105½° Fahr. Two days before the stone escaped, he became utterly collapsed, with intermitting irregular pulse and icy-cold extremities, and felt he was dying. Now, rigors and sweats are common in attacks of gall-stones; but I never saw such as these; and the fluctuations of temperature were remarkable. The extraordinary part of the case was the continuance of the rigors after the stone was gone: two, three, and four times a day, he had a paroxysm, simulating ague of the most severe type. My heart sank within me, and I began to fear lest extensive suppuration was going on from injury sustained by the passage of the stone. But I poured in large doses of quinine and digitalis, with a sort of forlorn hope, and had the infinite satisfaction of finding the attacks growing less and less frequent and severe, until at last they ceased altogether. No pus could be detected by a minute and constant examination of the stools. I thought some might possibly escape from a suppurating gall-bladder. None having been found, I can furnish no more rational explanation of these terrible rigors than that they were probably due to profound disturbance of the sympathetic system, inducing violent vas-motor storms. As to the position the stone occupied so long before its final discharge, although it is possible it blocked the cystic duct, and by its large size pressed upon and occluded the hepatic duct, yet I think it most probably occupied the common duct itself; for, otherwise, I cannot account for the permanent want of colour in the stools. (*British Medical Journal*, 1880.)