Phenindione-induced Neuropathy

Brit. med. J., 1967, 3, 218

Mononeuritis has been well recognized in diabetes, alcoholism, polyarteritis nodosa, carcinomatosis, and leprosy. Traumatic mononeuritis was not uncommon during wars. Of the blood disorders haemophilia, thrombotic thrombocytopenic purpura, porphyria, macroglobulinaemia, and myelomatosis are too well known. Two cases of neuropathy due to anticoagulant therapy are reported.

CASE 1

The patient, an old case of malignant hypertension (for which he had had a sympathectomy 13 years previously, followed by control of blood pressure on hexamethonium), was admitted to hospital on 22 May 1963 with a history of sudden onset of retrosternal pain lasting for 45 minutes. Diagnosis of myocardial infarct was confirmed by E.C.G. He was given analgesics, sedatives, and anticoagulants—heparin 10,000 i.u. stat. and 5,000 i.u. six-hourly for five doses intravenously, along with phenindione 200 mg. stat. and 150 mg. next day. The prothrombin time was 17 seconds with a control of 13 seconds on 23 May; subsequently it was controlled two to two and a half times the control (prothrombin time ranging from 24 to 32 seconds against a control of 12 to 16 seconds), with varying doses of phenindione ranging from 25 to 50 mg. twice a day. On 8 June he complained of severe pain in his right buttock and thigh. On examination there was evidence of right sciatic nerve palsy with motor and sensory changes. Later strength curves showed denervation. Haemoglobin was 14.4 g./100 ml.; it dropped to 9 g., but returned gradually to normal. Prothrombin time was 24 seconds, with a control of 16 seconds. Prothrombin activity was raised by vitamin-K injections. Total W.B.C., blood urea, E.S.R., electrolytes, liver-function tests, serum proteins, and cerebrospinal fluid were normal.

He was treated with intensive physiotherapy and electrical stimulation of paralysed muscles. Severe pain continued, though after three months there was a good recovery of his hamstring muscles but little improvement in his leg muscles, and the right-foot drop was well marked. Sensations were impaired on the lateral aspects of the right leg and foot. Physiotherapy was continued along with analgesics and tranquillizers.

He was followed up for a year. He continued having pain similar to that encountered in some cases of brachial plexus palsy, with little recovery of muscles below the knee.

CASE 2

This patient, an old case of recurrent myocardial infarction, had been on long-term anticoagulants (phenindione) since his discharge from hospital on 5 June 1965. He was having 50 mg. of phenindione twice a day. His prothrombin time on 8 August was 32 seconds against the control of 14 seconds. While on holiday on 20 August he started having bruising and pain in his left arm, with tingling and numbness in his fingers. Examination showed the clinical picture of a complete median nerve lesion on the left side with motor and sensory features, though no bruising was seen at the time of examination. The lesion was thought to be in the arm between the origin of the nerve and the site of the first muscular

branch in the antecubital fossa. Strength-duration curves showed denervation. Investigations included prothrombin time of 83 seconds against a control of 12, which fell to 17 after phenindione was stopped. Haemoglobin was 15 g./100 ml., total W.B.C. 11,000/cu. mm. Platelet count, bleeding-time, and coagulation-time were normal. Blood urea, electrolytes, liver-function tests, pyruvate metabolism test, serum proteins, electrophoresis, chest x-ray picture, and cerebrospinal fluid were within normal limits.

He was put on analgesics, after which he was admitted to hospital for a course of corticosteroid therapy to reduce fibrosis around and within the nerve, and electrical treatment. After six weeks' treatment the power in his left hand had improved, and sensations were impaired over the distal interphalangeal joints of thumb, index, middle, and medial half of the ring finger only. He continued to improve with physiotherapy and electrical treatment. Initially he also had a severe causalgic type of pain in the hand and forearm, but this improved with corticosteroid treatment.

COMMENT

Adverse reactions to phenindione are well known. Perkins (1962) reviewed 133 reported cases and three of his own. The most common complication was a rash (100 cases), fever (34 cases), diarrhoea (20 cases), granulocytopenia (18 cases), stomatitis (14 cases), jaundice (10 cases), and nephropathy (5 cases). Occasional cases had vomiting, misty vision, thrombocytopenia, lymphadenopathy, conjunctivitis, loss of hair, and gangrene of the breast. Devanney and Osher (1952) described a case of spontaneous spinal epidural haemorrhage. Further cases were mentioned by Jacobson *et al.* (1966), who added three of their own.

Haematuria and bruising are the presenting features of phenindione overdose in most of the patients. The above cases are of interest, because there was no history of trauma or subcutaneous haemorrhage formation, and I believe the spontaneous haemorrhage into the nerve sheaths due to an unknown local factor, resulting in ischaemic neuritis of the nerve, caused the palsy in both cases. Persistent pain in Case 1 was presumably due to fibrosis in and around the sciatic nerve. The cases differ in the fact that in Case 1 the anticoagulant control was reasonable, though in Case 2 the prothrombin time was prolonged. There was no history of trauma in either case. It is therefore unlikely that either trauma sensitivity to phenindione or prolonged prothrombin time was the sole factor, and the combination of both factors seems to have been more than likely.

I should like to thank Dr. W. A. Elliott, consultant physician, and Mr. R. H. Sewell, consultant orthopaedic surgeon, for allowing me to publish these cases, and for their necessary advice and guidance.

T. N. MEHROTRA, M.D., B.SC., M.R.C.P.ED.,
Medical Registrar, St. Alfege's Hospital, London S.E.10.

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