Comment

Although other drugs could not always be excluded, in most of the cases reported here chloroquine appeared to be responsible for the involuntary movements. In a previous case of involuntary movements attributed to amodiaquine[1] the patient had also taken chloroquine, so either drug may have produced the side effects. Benztropine, which is well recognised in the treatment of Parkinsonian syndromes, was successfully used in this case,[1] although it was not available to us. We would recommend the same treatment for chloroquine-induced involuntary movements. Although chlorpromazine may produce extrapyramidal effects it was successful in controlling involuntary movements in one of our patients, who responded rapidly when the drug was given parenterally.

Normal therapeutic doses of chloroquine may induce involuntary movements whether it is given by mouth or by injection. Furthermore, some of the patients had taken chloroquine before without adverse reactions. In the past five years we have used chloroquine to treat over 25 000 patients with malaria, and these five patients are the only ones to develop this side effect. The incidence is less than 1/5000. It is also notable that all our patients were under the age of 30, which appeared to be the case in those reported previously,[1] though the ages were not always stated.

[1] Akindele, M O, and Odejide, A O, *British Medical Journal*, 1976, **2**, 214.
[2] Rollo, I M, in *The Pharmacological Basis of Therapeutics*, ed by L S Goodman and A Gilman, 5th edition, p 1052. New York, Macmillan, 1975.
[3] Echelberger, A A S, *et al*, *Journal of Clinical Investigation*, 1948, **27**, 60.
[4] Hart, C W, and Nauton, R F, *Archives of Otolaryngology*, 1964, **80**, 407.

(*Accepted 7 December 1976*)

University of Nigeria Teaching Hospital, Enugu, Nigeria
E M UMEZ-ERONINI, MB, MRCP, lecturer and consultant physician

Umezuruike Hospital, Owerri, Nigeria
ELSPETH A ERONINI, MB, DCH, consultant paediatrician

Intramuscular iron and local oncogenesis

Seven cases of sarcomas arising in the area of a previous iron injection site have been reported in man.[1-3] We report here what seems to be another such case.

Case report

A 35-year-old White Caucasian woman (para 2+0) was referred to our outpatient clinic with a four-month history of pain and swelling in the left hip. Examination showed a large craggy mass in the left gluteal region. Biopsy of this mass showed a poorly differentiated spindle cell fibrosarcoma. There was no stainable iron present. The patient received radiotherapy to the tumour site.

Further questioning showed that 14 years earlier this patient had received a short course of intramuscular iron dextran (Imferon) after delivery of one of her children. Her haemoglobin concentration had been 9·4 g/dl at the time. She received one injection into the right gluteal muscles, after which she developed a mass in that area. The lesion resolved slowly over three weeks. The other four injections were therefore given into the left gluteal muscles. A few days after the end of this short course of injections the patient developed an itchy purpuric rash on her legs. More detailed information on the dose and frequency of the injections was not available as the case notes had been destroyed. The proprietary name was mentioned only in a discharge letter lodged in her general practitioner's records.

There was no history of other allergies or of any other intramuscular injections having been given to either buttock. The only other injections the patient could remember having received were childhood vaccinations into the deltoid muscle. The patient did not take any regular medication.

Comment

The carcinogenic risks of iron dextran were discussed in an editorial in the *British Medical Journal* in 1960.[4] Extensive animal studies had shown that sarcomas readily arose at the sites of large intramuscular iron injections, and this raised the possibility that sarcomas might arise at the sites of such injections in man. It was thought, however, that oncogenesis was local and dose-dependent,[5 6] and the product was not removed from the market.

The average interval between injection and the appearance of the neoplasm in the other seven cases reported in man was five years (range a few months to 13 years). In our case it was 14 years. Other unusual features, although they have been reported before,[7] were the development of swelling at the injection site and the occurrence of a rash after the iron dextran injections.

Sarcomas arising at the site of intramuscular iron injections are much rarer in man than in animals, possibly because of the different sizes of the muscles. The much larger human gluteal muscle may allow the iron to be dispersed to such an extent that the concentration necessary to trigger the induction mechanism is rarely achieved in humans. There may also be a long induction period in man. For this reason we think that it is important that this and all similar cases should be recorded.

We thank Dr O'Hare and technical staff of the pathology department, Glasgow Royal Infirmary, for preparing the histology slides.

[1] Robinson, C E G, Bell, D N, and Sturdy, J H, *British Medical Journal*, 1960, **2**, 648.
[2] MacKinnon, A E, and Bancewicz, J, *British Medical Journal*, 1973, **2**, 277.
[3] Greenberg, G, *British Medical Journal*, 1976, **1**, 1508.
[4] *British Medical Journal*, 1960, **1**, 788.
[5] Goldberg, L, Martin, L E, and Smith, J P, *Toxic and Applied Pharmacology*, 1960, **2**, 683.
[6] Fielding, J, in *Jectofer—Proceedings of a Symposium*, p 40. Washington, DC, Astra Pharmaceuticals, 1962.
[7] Fielding, J, in *Jectofer—Proceedings of a Symposium*, p 136. Washington, DC, Astra Pharmaceuticals, 1962.

(*Accepted 7 December 1976*)

The Centre for Rheumatic Diseases and University Department of Medicine, Royal Infirmary, Glasgow G4 OSF
A G ROBERTSON, MB, PHD, senior house officer in radiotherapy
W C DICK, MD, MRCP, consultant physician

Guanidine treatment and impaired renal function in the Eaton-Lambert syndrome

The myasthenic-myopathic or Eaton-Lambert syndrome and its electrophysiological characteristics were described in 1956[1] and 1957.[2] The case reported here is unusual in that guanidine, which was essential for maintaining power,[3] seemed to produce renal impairment.

Case report

A 61-year-old White post office engineer weighing 72·6 kg suddenly developed diplopia and severe muscular weakness in March 1969. Examination by one of us (JM) six weeks later showed bilateral ptosis, diplopia, and variable muscle weakness. At worst he could not raise his arms to the horizontal nor rise from the squatting position; at best he could do both, albeit with effort. There was no wasting or fasciculation. Tendon reflexes were sluggish but became brisker after strong contraction of the muscles. Plantar responses were flexor, and sensation and co-ordination were normal. The blood pressure was 150/85 mm Hg with no abnormality in the cardiovascular or other systems. Edrophonium (Tensilon) 10 mg intravenously produced a very slight increase in power, much less than that expected in myasthenia gravis.

Investigation for carcinoma was negative; in particular a chest radiograph was normal and tomography showed no evidence of a mediastinal mass. Plasma urea was 4·1 mmol/l (25 mg/100 ml), and alkaline phosphatase was slightly raised at 121 IU/l (normal 12-65 IU/l). The muscle action potential in abductor digiti minimi in response to stimulation of the ulnar nerve was of low amplitude with a post-tetanic contraction potentiation of two and a half times the baseline value.

The Eaton-Lambert syndrome was diagnosed and guanidine hydrochloride, 250 mg four times daily by mouth, started. Post-contraction enhancement of tendon reflexes was abolished[3] and by January 1970 power was normal and he had no diplopia.

TREATMENT

Guanidine hydrochloride 250 mg four times a day by mouth was continued from May 1969 until the patient's death in August 1976 except for three short intervals of a few days, in each of which profound weakness recurred. The patient had no other drugs until October 1974, when methyldopa 250 mg four times a day and clonidine 0·15 mg three times a day were added. There was no personal or family history of adverse drug effects.

ADVERSE EFFECTS

In January 1971 a rash on the right shin appeared which biopsy showed as subacute dermatitis, and in June he developed a generalised dermatitis, which cleared by October. In November 1971 he presented with haemoptysis. Chest radiography, electrocardiography (ECG), and bronchoscopy showed nothing abnormal and sputum did not contain malignant cells. The haemptysis settled. Plasma urea was noted to be raised at 9·3 mmol/l (56 mg/100 mg).

He continued well on guanidine until May 1974, when he developed exertional dyspnoea and haemoptysis. Blood pressure was 170/95 mm Hg. Chest radiographs, ECG, and bronchoscopy were again normal. Sputum was free from malignant cells. Plasma urea had risen to 13·0 mmol/l (78 mg/100 ml) and alkaline phosphatase was 94 and 92 IU/l. Other liver function tests gave normal results.

He retired from work but remained active until September 1974, when he developed dysphagia with nasal regurgitation. Two weeks later he began to vomit and so stopped the guanidine. He became so weak that he could not get out of bed and so resumed the tablets after four days.

Examination showed bilateral ptosis, third degree nystagmus to the right, and gross disorganisation of eye movements. Gait and stance were severely ataxic. Blood pressure was 180/110 mm Hg.

A brain stem vascular lesion associated with the high blood pressure was diagnosed. Alkaline phosphatase was 211 IU/l, plasma urea 14·6 mmol/l (88 mg/100 ml), and plasma creatinine 221 μmol/l (2·5 mg/100 ml), with creatinine clearance reduced to 40 ml/min. An intravenous urogram showed normal kidney sizes and upper urinary tracts. The bladder shadow was normal but there was a large residue after micturition. A percutaneous kidney biopsy done by one of us (AMJ) showed normal glomeruli but considerable hypertrophy and subintimal fibrosis with hyaline degeneration of the interlobular arteries and the glomerular afferent arterioles. The most noticeable feature was a considerable amount of interstitial fibrosis in both cortex and medulla. The medullary tubules were atrophic and the interstitium contained small collections of lymphocytes and polymorphs and a focus of nephrocalcinosis. Electron microscopy showed nothing further. Immunofluorescence to IgG, IgA, IgM, IgE, C3, and fibrin(ogen) was negative.

In October 1974 he had a further brain stem disturbance, his blood pressure rising to 220/120 mm Hg. Methyldopa 250 mg four times a day was started. He improved but a few days later had an acute confusional state with a blood pressure of 240/140 mm Hg, for which clonidine 0·15 mg three times a day was introduced. Blood pressure fell to 145/100 mm Hg, and he recovered. A further attempt to stop guanidine was abandoned when he immediately became profoundly weak.

By June 1976 renal function had deteriorated: plasma creatinine was 380 μmol/l (4·2 mg/100 ml) and ^{51}Cr-EDTA glomerular filtration rate was 21 ml/min. He had daytime frequency, dysuria, and nocturia. An intravenous urogram showed dilated upper urinary tracts, a distended bladder, and bladder neck outflow obstruction. Transurethral resection of the bladder neck and a small benign adenoma of the prostate was performed under general anaesthesia without mishap. There was an immediate symptomatic improvement.

Two months later, after an upper respiratory tract infection, the patient died. Necropsy showed bronchopneumonia as the cause of death. The heart was enlarged with normal valves and coronary arteries. Detailed examination of the respiratory system showed no evidence of carcinoma nor was there evidence of malignant disease elsewhere. The prostate showed benign hypertrophy. Macroscopic sections of the cerebral hemispheres, brain stem, cerebellum, and spinal cord showed no abnormality. Postmortem examination of the kidney showed appearances essentially similar to those seen in the biopsy two years earlier.

Comment

The clinical and electrophysiological evidence, together with the response to guanidine leave no doubt about the diagnosis of the Eaton-Lambert syndrome. The episodes in September and October 1974 were thought to be brain stem vascular disturbances associated with his high blood pressure.

Guanidine might have been responsible for the transient dermatitis which has been seen in a few patients. A relation with renal failure is, however, difficult to establish. Lambert and Howards[4] mentioned five patients on guanidine in whom impaired renal function was observed, but three had pre-existing kidney disease. The two with no evidence of pre-existing kidney disease had raised serum creatinine levels, which fell when guanidine was withdrawn.

Guanidine has been tried in motor neurone disease. One patient developed retention of urine and was found to have a flaccid bladder. Plasma creatinine was 389 μmol/l (4·4 mg/100 ml) and fell to 239 μmol/l (2·7 mg/100 ml) on catheter drainage.[5] Another patient who also had calcium sodium edetate developed acute tubular necrosis from which he recovered.[6]

Our patient had no evidence of a renal lesion when first seen and his plasma urea and blood pressure were normal. Two and a half years after starting guanidine both started to rise and continued to do so until five years after treatment started, when the patient suffered a brain stem vascular lesion. Kidney biopsy at this stage must be interpreted as showing a severe fibrosing interstitial nephritis. Although the appearances could be attributed to aging nephrosclerosis such a large amount of fibrosis is rarely seen except in Balkan nephritis.[7] In the absence of analgesic abuse or any other aetiology we think that guanidine hydrochloride may have been responsible for this change. Stopping the drug produced such profound weakness that we decided to continue it despite its putative side effects. Its toxicity might be apparent to a greater degree in the kidney than elsewhere because, like other organic bases, guanidine probably diffuses across cell membranes by non-ionic diffusion,[8] and thus inordinately large amounts might accumulate in the interstitium and the medulla.

The subsequent course of the illness resembles the reported case with the flaccid bladder.[5] In our patient there was definite evidence of bladder neck obstruction relieved by transurethral resection. It is difficult to know whether guanidine was responsible for the bladder neck dysfunction, but careful monitoring of patients treated by guanidine hydrochloride should clarify this point.

Dr R Willison, Dr F J V Jenner, Mr H Nohl-Oser, Mr P H L Worth, Dr M Erdohazi, and Dr R C B Pugh helped with the management and investigation of this patient.

[1] Lambert, E H, Eaton, L M, and Rooke, E D, *American Journal of Physiology*, 1956, **187**, 612.
[2] Eaton, L M, and Lambert, E H, *Journal of the American Medical Association*, 1957, **163**, 1117.
[3] Lambert, E H, *Annals of the New York Academy of Sciences*, 1966, **135**, 367.
[4] Lambert, E H, and Howards, F M, paper presented at Annual Scientific Meeting of Myasthenia Gravis Foundation, New York, 1972.
[5] Norris, F H, jun, Fallot, R J, and Calanchini, P R, *Neurology*, 1974, **24**, 135.
[6] Norris, F H, *New England Journal of Medicine*, 1973, **288**, 690.
[7] Hepstinstall, R H, *Pathology of the Kidney*, 2nd edn, vol II, p 830. Boston, Little Brown and Co, 1974.
[8] Davidoff, F, *New England Journal of Medicine*, 1973, **289**, 141.

(*Accepted 11 February 1977*)

Institute of Neurology, National Hospital for Nervous Diseases, and Institute of Urology, St Philip's Hospital, London
L D BLUMHARDT, BSC, MRACP, registrar in neurology
A M JOEKES, MA, FRCP, consultant nephrologist
JOHN MARSHALL, MD, FRCP, professor of clinical neurology
P E PHILALITHIS, MD, MRCP, senior lecturer in nephrology