Nitrofurantoin and peripheral neuropathy with megaloblastic anaemia

JOHN S. MORRIS¹

From St. Davids Hospital, Cardiff

Nitrofurantoin is a synthetic antibacterial drug derived from furan by the addition of a nitro group and a side chain containing hydantoin (Fig. 1). It has a bacteriostatic, and, in higher concentration, a bactericidal, action on a wide range of Gram-positive and Gram-negative organisms. It is widely used in the treatment of urinary tract infections.

Common complications caused by the drug are anorexia, nausea, vomiting, and diarrhoea. Less commonly skin rashes occur. Amongst other side effects are the development of an acute anaphylactic reaction (Khorsandian, Bremer, and Nodine, 1963), mild eosinophilia (Israel and Diamond, 1962), leucopenia (Hasen and Moore, 1954), and, rarely, haemolytic anaemia (Kimbro, Sachs, and Torbert, 1957). More recently it has been suggested that nitrofurantoin may produce a megaloblastic anaemia (Bass, 1963). One of the more serious complications is peripheral neuropathy (Collings, 1960; Martin, Corbin, and Utz, 1962; Loughridge, 1962; Ellis, 1962; Rubenstein, 1964).

The purpose of this communication is to stress this last complication, which recently occurred in four patients at this hospital. One of the patients had, in addition, a megaloblastic anaemia, and a possible relationship between the drug and the development of such anaemias will be discussed.

¹Present address: Llandough Hospital, Penarth, Glam.

CASE REPORTS

CASE 1² A 50-year-old woman (L.B.) was well until May 1964 when she developed symptoms of an urinary infection. She was treated at home with sulphamethizole in a dosage of 300 mg. daily. Recurrence of urinary symptoms led to her admission to hospital the following September. There it was found that the urine was infected with *E. coli* and intravenous pyelography revealed bilateral double ureters. The blood urea level was 36 mg. % and the haemoglobin was 6.9 g. % (three months earlier it had been 13.4 g. %). The haemoglobin rose to 9 g. % as the result of the transfusion of 2 pints of blood. One month after admission to hospital she was discharged on nitrofurantoin in a daily dosage of 400 mg.

Three weeks following the beginning of nitrofurantoin therapy, the patient developed paraesthesiae in all limbs. At that time she had taken 8 g. of the drug. Four days later she suddenly found that her limbs had become too weak to support her. She now stopped taking nitrofurantoin. Eight days after the onset of symptoms the patient was admitted to this hospital where examination showed marked wasting of the forearm, thigh and calf muscles (Fig. 2). She had a severe flaccid tetraparesis with little remaining movement in the hands or feet. The tendon reflexes were sluggish in the arms and absent in the legs. The plantar responses were flexor. Sensory testing showed that light touch and pain were impaired over the hands to the level of the wrists and over the lower limbs to the level of the knees. Vibration sense was

²Case 1 has previously been reported elsewhere (Wells, 1965).

FIG. 1. Derivation of nitrofurantoin from furan by the incorporation of a nitro group and a side chain containing hydantoin.

FIG. 2. Muscular wasting following the administration of nitrofurantoin.

absent in both legs to the level of the iliac crests. Joint position sense was everywhere intact.

Investigations The haemoglobin was 8.8 g.% and the peripheral blood film showed macrocytosis. The serum levels of vitamin B₁₂ and folate were 171 $\mu\text{g./ml.}$ (normal $>150 \mu\text{g./ml.}$) and 2 ng./ml. (normal 5.9-21.0 ng./ml.) respectively. The anaemia did not respond to vitamin B₁₂ but as a result of folic acid in a dose of 15 mg. daily the haemoglobin rose to 13.8 g.%. Faecal fat estimations averaged 2.5g./24 hours over a five-day period. The glucose tolerance test was normal. Excretion of a 25 g. dose of d-xylose was low, being less than 2 g. on two separate occasions. A fractional test meal showed histamine-fast achlorhydria. A barium meal and follow-through examination was normal. Intestinal biopsy was unsuccessful since the patient was unable to swallow a Crosby capsule.

The blood urea level during the weeks that the patient was in hospital ranged from 64 to 70 mg.%. The serum phosphocreatine kinase was 0.56 i.u./litre (normal $<0.7 \text{ i.u./litre}$). The *E. coli* urinary infection persisted. No urinary porphyrins were found. The cerebrospinal fluid was clear and colourless and under normal pressure, containing 30 mg.% of protein and no cells. The Wassermann reaction of the fluid was negative. The vitamin B₁₂, folate, and phosphocreatine kinase levels of the cerebro-

spinal fluid were 8 $\mu\text{g./ml.}$ (normal 0-30 $\mu\text{g./ml.}$), 13 ng./ml. (normal 9-60 ng./ml.), and 5.82 i.u./litre (normal $<0.06 \text{ i.u./ml.}$) respectively. Electromyography showed extensive fibrillation with a poor volitional pattern. Nerve muscle biopsy showed atrophy of the peripheral nerves but the muscle was histologically normal.

Treatment with vitamins and physiotherapy was of little avail, and when seen six months later, the patient was still unable to walk unaided. The wasting of the limbs persisted, so had the reflex changes, but the sensory changes had largely resolved.

CASE 2 A 60-year-old man (A.D.) was first seen in 1960 with hypertension and albuminuria. Subsequent investigations showed that his blood urea level was 45 mg.% and the creatine clearance was 46 ml./min. Renal biopsy showed the changes of chronic pyelonephritis. Treatment with nitrofurantoin, 400 mg. daily, and hypotensive agents was started. In 1963 he developed a carcinoma of the bladder which was treated by partial cystectomy. In December 1964, having by that time taken over 1 kg. of nitrofurantoin, he suddenly developed pain in both lower limbs, followed by rapidly progressive weakness of the legs so that within a week he was unable to walk. Examination showed a flaccid paraparesis with bilateral foot drop. There was marked wasting of the calf muscles.

The right ankle and both knee reflexes were absent and the plantar responses were flexor. There was no sensory loss.

Investigations The impairment of renal function first noted in 1960 had progressed, the blood urea being 130 mg.% and the creatinine clearance 73 ml./min. The haemoglobin was 12.2 g.% and a peripheral blood film was normal. The serum level of vitamin B₁₂ was 222 µµg./ml. and that of folate was 4.2 ng./ml. Bone marrow examination was normal. The cerebrospinal fluid was clear and colourless containing 30 mg.% of protein. There were no cells and the Wassermann reaction of the fluid was negative. The phosphocreatine kinase level was nil. The folate level of the fluid was 22.0 ng./ml. and that of vitamin B₁₂ 3 µµg./ml. Faecal fat estimations averaged 4 g./24 hours over a five-day period. The excretion of a 25 g. dose of d-xylose was 3.6 g. in a five-hour collection of urine. The glucose tolerance test was normal. Cystoscopic examination did not reveal any recurrence of the bladder carcinoma.

Physiotherapy and treatment with vitamins were begun soon after the patient was admitted to hospital. Within two months he was able to walk unaided and to return to work. The reflex changes and the muscle wasting, however, persisted.

CASE 3 A 75-year-old woman (C.G.) was first seen in 1962 when she was diagnosed as having chronic pyelonephritis. Renal function was at that time impaired and over the succeeding three years her blood urea level ranged from 19 to 94 mg.%. In February 1965 she was admitted to hospital complaining of frequency of micturition and burning dysuria. She was shown to have an *E. coli* urinary infection. Long-term therapy with nitrofurantoin, 100 mg. three times a day, was started.

Eleven weeks after leaving hospital, having by that time received 25.5 g. of the drug, she developed numbness in the finger tips and later weakness in the legs. Examination showed that the grip in both hands was weak and that she had bilateral foot drop. The reflexes were absent at the ankles and sluggish elsewhere. Sensory testing showed that there was impairment of the sense of pain, light touch, and vibration in all four limbs peripherally. She refused further hospital admission.

Some four weeks after stopping nitrofurantoin power was returning to the limbs although the patient was not fully mobile.

CASE 4 A 36-year-old woman (M.L.) was first seen in 1962 when she gave a six-year history of exertional dyspnoea, ankle swelling, and recurrent attacks of burning dysuria. She had persistent albuminuria and culture of the urine grew *E. coli*. Renal biopsy showed the changes of chronic pyelonephritis. The blood urea was 40 mg.% and the creatinine clearance was 54 ml./min. She commenced long-term therapy with nitrofurantoin in a dosage of 300 mg. daily. Over the following three years she was seen at varying intervals in the Out-patient Department. In 1964 the blood urea level was 60 mg.% and levels of between 70 and 110 mg.% were recorded at later dates. She continued to take nitrofurantoin.

During the early months of 1965 symptoms of burning dysuria and of frequency of micturition became worse and

she had increased, on her own initiative, the dosage of nitrofurantoin to 100 mg. five times a day. In June 1965 she presented with a five-week history of numbness of the fingers, toes, and lower parts of the legs. Examination showed slight weakness of dorsiflexion at the right ankle. The reflexes were all present and equally brisk; the plantar responses were flexor. The sensation of pain and light touch was impaired over her hands to a few centimetres above her wrists and over her feet to the level of her ankles.

Investigations Renal function was impaired with a blood urea level of 100 mg.%. Creatinine clearance was 62 ml./min. The urine was infected with *E. coli*. The haemoglobin was 11.6 g.% with a normochromic, normocytic peripheral blood film. The serum vitamin B₁₂ level was 198 µµg./ml. and that of folate 4.25 ng./ml. Faecal fat estimations over a five-day period averaged 3 g./24 hours, the glucose tolerance test was normal, and the excretion of a 25 g. dose of d-xylose was 1 g. in a five-hour collection of urine. The cerebrospinal fluid was clear and colourless, containing 20 mg.% of protein; there were no cells and the Wassermann reaction of the fluid was negative. The cerebrospinal fluid vitamin B₁₂ content was 8 µµg./ml., and the phosphocreatine kinase level was 0.05 i.u./litre.

Within a few days of stopping the drug there was no evidence of weakness of dorsiflexion at the right ankle and the sensory signs had considerably improved.

DISCUSSION

PERIPHERAL NEUROPATHY ASSOCIATED WITH NITROFURANTOIN THERAPY Despite the widespread use of nitrofurantoin in the treatment of urinary tract infection, reported cases of a peripheral neuropathy, resulting from such therapy, are few. The literature has already been adequately reviewed (Rubenstein, 1964; Uesu, 1962).

The manner in which the neuropathy is produced is unknown. Previously reported cases have had impaired renal function and this finding is reflected in each of the four patients described. Long-standing renal failure itself may cause peripheral neuropathy (Asbury, Victor, and Adams, 1963), but this alone is an unlikely cause of the neuropathy which occurred in the four patients described, for there was a close relationship between therapy with nitrofurantoin and the onset of the neuropathy and, in two patients, symptoms improved after the drug was stopped.

Nitrofurantoin has been shown to have an effect on carbohydrate metabolism. Paul, Paul, Kopko, Bryson, and Harrington (1954) showed that, *in vitro*, the drug inhibits the formation of citrate, the inhibition being reversible and occurring at the stage of the production of acetyl coenzyme A from pyruvate and coenzyme A. It has also been shown that, under conditions of renal failure, blood levels of the drug are higher than in patients on the same dosage who

have normal renal function (Loughridge, 1962). It may be that in higher concentration the drug affects carbohydrate metabolism in nervous tissue in the same manner as it has been shown to act *in vitro*.

There is no evidence that the drug affects vitamin B metabolism; indeed, one of the cases reported in the literature was receiving vitamin therapy at the time that signs of a neuropathy appeared (Collings, 1960). Also the clinical course of the neuropathy in the above four patients and in previously reported cases has not apparently been affected by vitamin therapy.

Nitrofurantoin neuropathy may appear after a few days' treatment or may be delayed as long as five years (case 4). The total dose of the drug under these circumstances will of course vary also. The duration of treatment and the total dose of the drug taken, therefore, do not appear to be as important as hitherto supposed (Collings, 1960; Willett, 1963). Of the four patients described above the milder neuropathies occurred in those (cases 2, 4) who had been on the drug for longer periods.

Nitrofurantoin neuropathy resembles other toxic neuropathies. The onset is rapid, regardless of the duration of therapy, and is often associated with a considerable degree of pain. Sensory symptoms, such as paraesthesiae and dysaesthesiae, are common and are followed by muscle weakness and wasting. When muscle wasting has occurred the ultimate prognosis is said to be poor (Rubenstein, 1964). Involvement of cranial nerves has not been reported, although this has occurred with furaldalone, a drug of similar chemical structure (Hussain and Koilpillai, 1960).

Pathological changes include disintegration of the peripheral nerves and nerve roots (Collings, 1960) and sarcolemmic proliferation with atrophy of striated muscle and degenerative changes in the peripheral nerves (Uesu, 1962). Nerve muscle biopsy in the first patient showed atrophic changes in the peripheral nerves.

In the absence of any specific underlying cause treatment must, of necessity, be symptomatic. Vitamin therapy, with in two patients treatment with cyanocobalamin, appeared not to affect the clinical course of the four patients. Physiotherapy was apparently of most value and this must be intensive and protracted before any improvement is manifest.

NITROFURANTOIN AND MEGALOBlastic ANAEMIA Hydantoin derivatives, particularly anticonvulsant drugs, are known to produce megaloblastic anaemia of the folic acid deficiency type (Badenoch, 1954). It is not surprising therefore that nitrofurantoin, also a hydantoin derivative, should be similarly implicated and indeed two such cases have been re-

ported (Bass, 1963; De Veber and Valentine, 1964).

The manner in which hydantoin derivatives produce folic-acid-deficiency anaemia is not known. The anaemia has been shown to respond to the administration of folic acid and sometimes to the withdrawal of the hydantoin drug (Christenson, Ultmann, and Roseman, 1957). This latter observation has led to the suggestion that hydantoin derivatives interfere with the metabolism of available folic acid (Chanarin, Elmes, and Mollin, 1958), perhaps because of the structural similarity between hydantoin and the pyrimidine ring of folic acid (Girdwood and Lenman, 1956). This, however, is probably not the only factor, since the incidence of megaloblastic anaemia in epileptic patients is low: dietary deficiency may be another factor (Flexner and Hartmann, 1960).

Definite evidence relating nitrofurantoin to megaloblastic anaemia has not yet been produced. It has been suggested that the drug produces malabsorption thus leading to folic acid deficiency (De Veber and Valentine, 1964); malabsorption was also subsequently demonstrated (Peaston, 1964) in the case originally described by Bass (1963). Apart from the lowered excretion of d-xylose, which may have been due to renal impairment, there was no evidence of malabsorption in either the patient with megaloblastic anaemia (case 1) or in the two other cases investigated (cases 2, 4). It is probable that if nitrofurantoin produces a megaloblastic anaemia it does so by virtue of its hydantoin component in the same manner as megaloblastic anaemia is produced by other hydantoin derivatives. This has yet to be satisfactorily demonstrated.

In case 1 megaloblastic anaemia of the folic acid deficiency type was present. The patient was known to have some form of anaemia before treatment with nitrofurantoin was started so that the drug cannot be held wholly responsible for the megaloblastic anaemia. It is possible of course that the drug precipitated a folic acid deficiency state in the patient who was already anaemic. Serum folate levels in two of the other three patients were normal.

COMMENT

Hitherto nitrofurantoin has been accepted as a fairly safe urinary antibiotic but the possibility of a peripheral neuropathy developing in a patient who has renal failure must be recognized and caution exercised in the use of the drug. Given orally the drug does not reach bacteriostatic levels in the tissues (Jawetz, Hopper, and Smith, 1957), and when there is renal impairment urinary concentration of the drug is below that required therapeutically (Lipmann, Wrobelm, Rees, and Hoyt, 1958). For

these reasons nitrofurantoin should be discarded in favour of some other urinary antibiotic when renal function is impaired.

SUMMARY

Four patients are described in whom peripheral neuropathy appeared following a course of nitrofurantoin. The clinical picture of such a neuropathy is described and possible precipitating factors are discussed.

A possible relationship between nitrofurantoin therapy and the development of a megaloblastic anaemia is noted and it is suggested that the drug may produce such an anaemia because of the incorporation of hydantoin into its structure.

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