Metronidazole neuropathy

A. COXON AND C. A. PALLIS

From the Department of Medicine (Neurology), Royal Postgraduate Medical School, London

SYNOPSIS Two patients are described who developed sensory neuropathy after the ingestion of 30.6 and 114 g metronidazole respectively. The drug, widely used in gastroenterological and gynaecological practice, has not hitherto been considered neurotoxic. The implications are stressed in relation to the differential diagnosis of patients with gastroenterological disorders who develop peripheral neuropathy.

In view of the recent advocacy, from Sweden, of long-term metronidazole therapy for Crohn's disease (Ursing and Kamme, 1975) and of discussions as to whether the drug might prove useful as a 'radio-sensitizing' agent before the administration of radiotherapy (Urtasun *et al.*, 1974), we feel it worth stressing the possible neurotoxic effects of this substance. We here report two personally observed cases of sensory neuropathy, almost certainly due to metronidazole.

CASE 1

M.B., a 60 year old Caucasian woman, had suffered from intermittent abdominal pain and episodic diarrhoea for nearly 40 years. In 1966 a barium meal and follow-through had established a diagnosis of Crohn's disease. Investigations at this stage had revealed histamine-fast achlorhydria, no anti-intrinsic factor antibodies, mild steatorrhoea (with a normal Lundh test), a rather flat glucose tolerance test, impaired absorption of vitamin B₁₂ (not improved by concomitant administration of intrinsic factor), a low-normal serum vitamin B₁₂ (128 ng/l), normal serum folate (8.8 µg/l), and a mild sideroblastic anaemia, which later improved spontaneously. Rectal biopsy was normal. At this stage there were no abnormal neurological signs.

Steroids, and later azothiaprime, induced temporary remissions, but the patient relapsed on each occasion.

On 22 June 1975, she was started on metronidazole (200 mg thrice daily). When seen on 12 August 1975 (after having been given a total of 30.6 g of the drug) she complained of the recent development of numb-

ness in the toes. Within a few days this had spread to involve the soles and the dorsa of the feet. She could not feel the ground under her properly, and was not sure whether she was wearing shoes or not. Distressing paraesthesiae had developed in the wake of this numbness. For a few days she had also been aware of 'soreness' in the fingers, which constantly felt cold.

Neurological examination revealed no abnormalities in the cranial nerves and no focal weakness or wasting in the limbs. Tactile sense and pain sense were impaired over the toes and distal half of each foot, but postural sense and deep pain sense were well preserved. Vibration sense was absent at the malleoli and over the tibial tuberosities. No sensory abnormalities could be elicited in the upper limbs. Both ankle jerks were absent, but all other tendon reflexes were preserved and symmetrical. The plantar responses were flexor. There were no stigmata of malnutrition.

The serum vitamin B₁₂ was 180 ng/l and the serum folate 8.8 µg/l. There was no evidence of diabetes.

ELECTROPHYSIOLOGICAL INVESTIGATION This confirmed the presence of a sensory neuropathy, affecting predominantly the lower limbs. Motor conduction velocities (Thomas *et al.*, 1959) were normal in the right median (59.7 m/s) and right lateral popliteal (40 m/s) nerves. The amplitude of the sensory action potential in the right ulnar nerve (6 µV at 2.1 ms) was at the lower end of the normal range (Gilliat and Sears, 1958). Normal sensory nerve action potentials were elicited in the right median (10 µV at 2.6 ms) and radial (15 µV at 2.5 ms) nerves. No sensory nerve action potentials could be elicited from the sural nerves or—antidromically—from the anterior tibial nerves at the instep.

Administration of the drug was stopped. A month

later there had been slight improvement in her symptoms. Full investigation failed to reveal any obvious cause for her neuropathy, other than the metronidazole she had been receiving.

CASE 2

B.R., a 40 year old Caucasian, had developed diarrhoea while in West Africa, three weeks before his admission to Hammersmith Hospital as a surgical emergency on 21 March 1975. The diarrhoea had settled after a fortnight and his admission had been precipitated by the development of central abdominal pain radiating to the right iliac fossa. There had been no recurrence of diarrhoea.

At laparotomy for suspected appendicitis, he was found to have an abscess in the right iliac fossa. Repeated examinations of warm stool specimens failed to reveal any amoebae or cysts but fluorescent amoebic antibody tests showed a rising titre (from 1/32 on 26 March 1975 to 1/256 10 days later) consistent with active amoebic infection.

The clinical course was stormy, being complicated by faecal fistulae, a left paracolic abscess, a Gram negative septicaemia and multiple liver abscesses.

He received a total of 114 g metronidazole (800 mg thrice daily from 1 April 1975 to 2 June 1975), 460 mg emetine hydrochloride (30 mg twice daily from 9 April 1975 to 17 April 1975), and 32.5 g diloxanide (500 mg thrice daily from 25 April 1975 to 16 May 1975).

On 2 June 1975 he was referred to the Neurology Unit complaining of paraesthesiae in the toes, feet, and calves of two weeks' duration and of similar symptoms in the finger tips for about 10 days. Examination revealed a generally wasted man without stigmata of avitaminosis. No focal atrophy was seen in the limbs, where power was well preserved. There was questionable hypalgesia over the finger tips, where the threshold to two-point discrimination was 4 mm. Both tactile and pain sense were impaired up to mid-calf level, above which there was an area of hyperalgesia extending up to about 10 cm above each knee. Vibration sense was depressed at the malleoli and he made errors in perception of passive movement at the toes. Deep pain sense in the Achilles tendons was preserved. The Romberg sign was negative and his gait was normal. The knee and ankle jerks were present. The plantar responses were flexor.

There was nothing of significance in his past history and no history of exposure to other potentially neurotoxic substances. His consumption of alcohol was very moderate.

The metronidazole was immediately discontinued.

Full investigation failed to elicit any possible

cause for his neuropathy other than the drugs he had been taking. A glucose tolerance test was normal, the serum vitamin B₁₂ was 320 ng/l, and the serum folate 52 µg/l. The spinal fluid was normal in every respect.

The dysaesthesiae became extremely distressing over the next three or four weeks, assuming a constant burning quality. The sensory signs progressed somewhat, but no motor deficit developed and the tendon reflexes never disappeared. Steroid therapy was deferred, on surgical advice, due to the presence of a persistently discharging abdominal sinus.

On 4 August 1975, some 10 weeks after the onset of his neuropathy, he was started on daily ACTH injections. There was no dramatic response and a month later he was still experiencing distressing dysaesthesiae.

ELECTROPHYSIOLOGICAL INVESTIGATION These were carried out on 9 September 1975. They confirmed the clinical diagnosis of sensory neuropathy. Motor conduction velocities in the left median nerve (63.5 m/s) and left lateral popliteal nerve (54 m/s) were normal, but no sensory nerve action potentials could be elicited from the sural nerves, or in the left lateral popliteal nerve, from stimulation of the anterior tibial nerve at the instep.

DISCUSSION

There is strong presumptive evidence to incriminate metronidazole in the pathogenesis of the sensory neuropathy in both these patients. In case 1 the patient had suffered from Crohn's disease for many years but, although the terminal ileum was involved (as evidenced by both the barium follow-through and the impaired absorption of vitamin B₁₂), the serum B₁₂ was not in the range deemed necessary for the production of neurological signs. Neuropathy is not a feature of Crohn's disease (Pallis and Lewis, 1974) and we have found only one dubious reference to its occurrence (Soltoft *et al.*, 1972).

In case 2, metronidazole was the only drug taken in an unusually large amount. Emetine hydrochloride, was at one time an accepted cause of 'neuromuscular disorders', but these occurrences antedated the widespread availability of modern neurophysiological techniques for the elucidation of their mechanism. Modern views are that emetine overdosage occasionally causes muscle necrosis (Goodman and Gilman, 1970), but not peripheral neuropathy. In our

patient the prescribed dose of emetine was well within the acceptable range.

In the doses usually prescribed for the treatment of trichomonal or giardial infections—or even for acute amoebiasis—that is, up to 12 g over a period of five days (Wilcocks and Manson-Bahr, 1972)—metronidazole is an effective drug and probably quite safe, although attention has recently been drawn to its carcinogenicity in rodents (*Medical Letter*, 1975). The drug is, however, known to have neurotoxic effects in dogs (Goodman and Gilman, 1970) and the same authors mention numbness and paraesthesiae as occasional complications in man but give no references. In 1968 Ramsay recorded the occurrence of a severe sensory neuropathy in a 43 year old man given 135 g metronidazole (over a period of 113 days) for ‘endocrine ophthalmopathy’. The neuropathy slowly improved when the drug was stopped. Of the five recently reported cases from Scandinavia given long-term metronidazole therapy for Crohn’s disease (Ursing and Kamme, 1975), two (cases 1 and 2) developed neurological symptoms suggestive of peripheral neuropathy, which cleared up on discontinuing (case 1) or reducing (case 2) the administration of metronidazole. The first patient had received over 50 g (over a period estimated at about a month) and the second 75.6 g (over a period of 42 days).

The whole question of neuropathy occurring in the course of therapy for various gastroenterological disorders was highlighted by the recent controversy concerning subacute myelo-optic neuropathy (SMON) and its possible relation to clioquinol therapy (Pallis and Lewis, 1974; Meade, 1975). Metronidazole is widely prescribed in the management of intestinal amoebiasis (either proven or assumed) and, if the potentially neurotoxic effects of the drug be confirmed, the differential diagnosis of ‘SMON’ (often made on the basis of neuropathy alone) could prove to be even wider than it already is.

As yet the metabolic disturbance induced by metronidazole (and presumably responsible for the neuropathy) is unknown, but it seems unlikely that it is related to the now well-established effect of the drug on anaerobic organisms (Freeman *et al.*, 1968).

Metronidazole, in our opinion, should be added to the large list of potentially neurotoxic agents and the possibility of its administration kept in mind, when dealing with obscure cases of sensory neuropathy occurring in patients with gastroenterological disease.

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