Rapid Onset Metronidazole Induced Sensory Neuropathy: Case series and Review of Literature

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Abstract

Background: Metronidazole has been widely used to treat various anaerobic infections for many years without producing major side effects. Some of its new therapeutic indications, however, necessitate prolonged treatment with relatively high doses. Peripheral neuropathy is clearly one of the complications that can arise with such use. Case Report: Four young male patients with history of intake of metronidazole for treatment of amoebic liver abscess and diarrhoea developed very rapid onset distal symmetrical sensory neuropathy. Patients being treated with metronidazole particularly those on high doses even for short period should be monitored for neurotoxicity. Conclusion: This drug which is widely and empirically prescribed and is an over the counter (OTC) drug for any types of diarrhoea in our country is clearly associated with neurotoxicity. Metronidazole should be used with some caution and with clear indications even when is prescribing for short course and low doses.

Keywords: Metronidazole; Sensory Neuropathy; Axonal; Rapid-onset

Introduction

Metronidazole is a 5-nitroimidazole derivative and has potent activity against anaerobic bacteria, several protozoa including Entamoeba, Giardia, Trichomonas and B. coli, H. pylori and Guinea worm and hepatic encephalopathy. Common side-effects of metronidazole include mild abdominal pain, headache, nausea, and a persistent metallic taste. Other serious and rare side-effects include pseudomembranous colitis, seizures, and encephalopathy [1-3]. It is generally well tolerated and peripheral neuropathy is its rare side effect [4]. We are presenting a case series of patients who developed acute sensory neuropathy after intake of short course of metronidazole.

Case Report

Four male patients with history of intake of metronidazole for treatment of liver abscess and diarrhoea presented with distressing paresthesia in form of tingling and burning pain in glove and stocking distribution. Symptoms started first in soles and dorsa of feet and gradually progressed. They have distressing paresthesia in form of tingling, burning and severe tearing pain from toes up to knees in lower limbs and in glove distribution in upper limbs. Patients were taking metronidazole for different disease, dose and duration. (Table1). All were non-alcoholic. Family history was negative.

| Sl no. | Age (yrs) | Sex (M/F) | Duration of Drug intake (Days) | Onset (Days) | Duration of Symptoms and signs (Days) | Disease Condition (Suffering from) | Dose (mg/day) | Cumulative Dose (gm) | Prognosis /Outcome |
|-------|-----------|-----------|-------------------------------|-------------|--------------------------------------|----------------------------------|--------------|----------------------|-------------------|
| 1.    | 16        | M         | 13                            | 6           | 15                                   | Liver abscess                     | 1200         | 15.6                 | Good              |
| 2.    | 33        | M         | 7                             | 3           | 8                                    | Diarrhoea                         | 1600         | 11.2                 | Good              |
| 3.    | 38        | M         | 15                            | 10          | 21                                   | Liver abscess                     | 1200         | 18.0                 | Poor              |
| 4.    | 25        | M         | 11                            | 12          | 28                                   | Liver abscess                     | 1600         | 17.6                 | Poor              |

Table 1: Demographic and Clinical Profile of Patients

Neurological examination revealed no abnormalities in the cranial nerves and no focal weakness or wasting in the limbs. There were graded impaired sensation for tactile and pain over knees and down in lower limbs and mid of forearm and down (20 to 80%) in upper limbs, but postural sense and deep pain sense were well preserved. Vibration sense was absent at the malleoli and over the tibial tuberosities. 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.

They were unable to walk unassisted due to intolerable paresthesia. No cerebellar signs were present. Haematological investigations (Complete Blood Count, Blood sugar, Urea/creatinine, thyroid profile tests and serum Vitamin B12) including CSF examination were unremarkable (Table 2).

| Sl no. | Comlete Blood Count | Random blood sugar (mg/dl) | RFT (mg/dl) | TSH (mIU/L) | HBsAg /HCV | HIV I and II | S. Vit B12 level (pg/ml) |
|-------|---------------------|-----------------------------|-------------|-------------|-------------|-------------|--------------------------|
| 1.    | Hb-13gm/dl TLC-5000/ mm3 DLC- N85L33M2 | 103 | Urea-2 9 Creat-0.9 | 3.3 | Negati ve | Negati ve | 753 |
| 2.    | Hb-14.3gm/ dl TLC-6700/ mm3 DLC- N60L31M9 | 84 | Urea-3 2 Creat-1.0 | 1.8 | Negati ve | Negati ve | 590 |
| 3.    | Hb-12.6gm/ dl TLC-9300/ mm3 | 131 | Urea-3 2 | 0.9 | Negati ve | Negati ve | 857 |

Table 2: Haematological Profile of patients, Normal Thyroid Stimulating Hormone level 0.4 - 4.0 milli-international units per liter (mIU/L), Normal Serum Vitamine B12 level—200-900picogram per millilitre (pg/ml)

Electrophysiological Studies: The sensory nerve conduction studies were recorded orthodromically in upper limbs and antidromically in lower limbs. This confirmed the presence of a sensory neuropathy predominantly axonal except in case no. 2 which have mixed (both axonal and demyelinating) picture, affecting both upper and lower limbs. Motor conduction velocities (m/s) were normal in median and ulnar nerves (>60.0 m/s) in upper limbs and lateral popliteal (>40.0 m/s) nerves in lower limbs. The amplitude of the sensory action potential in the ulnar and median nerves (<5.0uV at 2.35 ms and <5.0uV at 3.0 ms respectively) was markedly reduced (6). Normal sensory nerve action potentials were elicited in radial (17.5uV at 2.2 ms) nerves. No sensory nerve action potentials could be elicited from both sural nerves in all patients (Table 3).

| Electrophysiological function | Normal Values | case no.1 | case no. 2 | case no. 3 | case no. 4 |
|-------------------------------|---------------|------------|------------|------------|------------|
| Motor Function                |               | Right      | Left       | Right      | Left       | Right      | Left       |
| Median Nerve                  |               |            |            |            |            |            |            |
| Distal Latency (ms)           | ≤4.2          | 2.63       | 2.95       | 4.82       | 4.54       | 3.15       | 3.52       | 3.0        | 2.91       |
| NCV (m/s)                     | ≥60           | 67.0       | 61.3       | 48.1       | 50.3       | 59.6       | 62.7       | 64.0       | 63.1       |
| Amplitude (mV)                | ≥4            | 3.12       | 2.9        | 3.8        | 3.4        | 2.1        | 1.9        | 1.6        | 2.0        |
| Ulnar Nerve                   |               |            |            |            |            |            |            |            |            |
| Distal Latency (ms)           | ≤3.3          | 1.94       | 2.08       | 3.51       | 3.78       | 2.04       | 2.19       | 2.97       | 3.21       |
| NCV (m/s)                     | ≥60           | 58.0       | 55.1       | 49.2       | 43.8       | 61.0       | 63.2       | 56.6       | 54.0       |
| Amplitude (mV)                | ≥6            | 4.1        | 3.2        | 4.9        | 5.13       | 3.10       | 3.80       | 2.96       | 2.80       |
| Radial Nerve                  |               |            |            |            |            |            |            |            |            |
| Distal Latency (ms)           | ≤2.9          | 1.96       | 2.11       | 3.12       | 2.99       | 2.04       | 2.39       | 2.81       | 2.56       |
| NCV (m/s)                     | ≥60           | 61.8       | 57.9       | 45.8       | 51.0       | 60.1       | 55.9       | 50.0       | 53.2       |
| Amplitude (mV)                | ≥2.0          | 1.91       | 1.81       | 2.62       | 2.81       | 1.32       | 1.52       | 1.22       | 1.10       |
| Common Peroneal Nerve         |               |            |            |            |            |            |            |            |            |
| Distal Latency (ms)           | ≤6.5          | 5.90       | 6.06       | 7.12       | 6.87       | 5.15       | 5.32       | 5.05       | 5.90       |
| NCV (m/s)                     | ≥40           | 42.21      | 40.09      | 33.17      | 36.03      | 44.9       | 41.03      | 46.4       | 39.6       |
| Amplitude (mV)                | ≥2.0          | 1.60       | 1.85       | 2.05       | 1.91       | 1.39       | 1.69       | 1.31       | 0.9        |
Table 3: Nerve conduction parameters of patients, Distal Latency in milliseconds (ms), Nerve conduction velocity in meters per second (m/s) and, amplitude in millivolts (mV) and microvolts (uV)

The rapid onset (range 3-12 days) distal symmetrical axonal sensory neuropathy. It is noteworthy that, in case reports from India, the cumulative dose of metronidazole was low (8-20 gm), and latency of symptoms onset very short (10-18 days) when compared to patients from the West [11,12]. This may reflect a genetic susceptibility to neurotoxic effects of metronidazole or a genetic variation in the metabolism of metronidazole in Indian patients. Most toxic neuropathies, including medication-induced forms, principally induce axonal degeneration in a “dying back” pattern disproportionately affecting the distal segments of the most vulnerable, usually longest nerves. Electron microscopic studies of human sural nerve biopsy specimen have also confirmed axonal degeneration of both the myelinated and unmyelinated fibers [13]. Complete or partial resolution may occur after discontinuation of therapy. However symptoms may take up to two years to completely resolve [10]. Neuropathic symptoms improved up to 90% in next 6 months after withdrawal of metronidazole and giving supportive treatment.

To sum up I suggest that a careful neurological examination and studies of sensory and motor nerve conduction should be performed in patients who complain of paresthesia, pain, muscle cramps, weakness or other abnormal sensation during treatment with metronidazole.
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