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Case Report Open Access

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 sings 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-N65L33M2	103	Urea-29 Creat-0.9	3.3	Negative	Negative	753
2.	Hb-14.3gm/ dl TLC-6700/ mm3 DLC-N60L31M9	84	Urea-32 Creat-1.0	1.8	Negative	Negative	590
3.	Hb-12.6gm/ dl TLC-9300/ mm3 DLC-N69L31	131	Urea-32 Creat-1.0	0.9	Negative	Negative	857
4.	Hb-12.6gm/ dl TLC-9300/ mm3 DLC-N71L27E2	92	Urea-32 Creat-1.0	2.0	Negative	Negative	609

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 (5)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 <5.0 uV 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	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
Posterior Tibial Nerve									

Distal Latency(ms)	≤5.8	4.90	5.12	6.73	6.12	5.7	5.9	6.02	5.23
NCV(m/s)	≥40	49.7	44.02	31.05	35.08	40.1	39.7	39.5	42.07
Amplitude(mV)	≥4.0	3.21	2.96	3.80	3.65	2.64	2.70	2.40	2.12
Sensory Function									
Median Nerve									
Distal Latency(ms)	≤3.5	2.89	3.08	4.14	3.95	2.57	2.98	3.05	3.12
NCV(m/s)	≥50	67.09	64.12	44.2	48.2	70.1	65.02	63.2	61.85
Amplitude(uV)	≥20	3.29	3.01	4.61	4.9	2.91	2.99	3.1	4.0
Ulnar Nerve									
Distal Latency(ms)	≤3.1	2.61	2.30	3.1	3.34	2.74	2.91	1.98	2.78
NCV(m/s)	≥50	63.0	68.09	49.2	44.02	60.01	57.01	72.13	58.7
Amplitude(uV)	≥17	4.3	4.03	4.19	4.85	4.9	3.8	4.66	3.96
Radial Nerve									
Distal Latency(ms)	≤2.9	2.1	1.91	2.0	2.2	1.68	1.92	1.78	1.97
NCV(m/s)	≥50	58.0	62.18	60.1	55.02	69.2	61.87	65.13	59.2
Amplitude(uV)	≥15	17.9	17.5	20.10	20.91	19.8	18.01	18.73	19.15
Sural Nerve									
Distal Latency(ms)	≤4.4	NR	NR	NR	NR	NR	NR	NR	NR
NCV(m/s)	≥40	NR	NR	NR	NR	NR	NR	NR	NR
Amplitude(uV)	≥6.0	NR	NR	NR	NR	NR	NR	NR	NR

Table 3: Nerve conduction parameters of patients, Distal Latency im milliseconds (ms), Nerve conduction velocity in meters per second(m/s) and, amplitude in millivolts (mV) and microvolts (uV)

They were asked to stop metronidazole intake and put on combination of drugs for neuropathic pain such as pregabalin, duoloxitine and amitriptylene. They started showing improvement in all symptoms within 2 to 3 days and was discharged after about a week. At 6 month of follow-up symptoms resolved up to 90% in 1st two patients while 3rd and 4th patient's symptoms resolved less than 30%.

Discussion

Identification of a toxic effect is simplest when acute or sub-acute onset of symptoms occurs soon after the initial drug exposure or a change of medication dosage. Most patients fall into this category. In contrast, it is much more problematic to diagnose a slowly progressive neuropathy starting many months or years after starting a chronic agent. Full investigation failed to elicit any possible cause for their neuropathy other than the drug they have been taking. The exact mechanism of metronidazole induced neuropathy is controversial and presumed to be probably the result of toxic accumulation of metronidazole leads to axonal degeneration. Most reported cases developed neuropathy following metronidazole doses of 1,000 - 2,400 mg/day, total doses of at least 50 gm and treatment duration of at least 30 days [7-10]. In my series patients took very low dose (range 11-18 gm) of metronidazole over a period of 7-15days and presented with 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 month after withdrawn 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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