

Intravenous Metronidazole-Induced Neuropathy with Autonomic Dysfunction - Report of A Case

Chien-Chung Chen; Win-Jie Kuo; Jyh-Chou Yang¹;
Yang-Chyuan Chang¹

Department of Neurology, St. Martin De Porres Hospital, Chiayi;

¹Department of Neurology, National Taiwan University Hospital,
Taipei, Taiwan

Abstract - We reported the first case of intravenous metronidazole-induced axonal sensory polyneuropathy in Taiwan. The prominent clinical and electrophysiologic evidences for dysautonomia in this case had never been found in literature review.

Key Word : Metronidazole, Neuropathy, Autonomic dysfunction

Acta Neurol Sin 1995; 4: 195-197

INTRODUCTION

Metronidazole, known as an agent for protozoal and anaerobic infections, is also used in the treatment of Crohn's disease^(1,2) and as a radio-sensitizing agent before the administration of radiotherapy⁽³⁾.

Neuropathy is an uncommon but well-established side effect after long term use of metronidazole⁽²⁻¹³⁾. Majority of the reported cases with metronidazole-induced neuropathy were Crohn's disease patients treated with high dose oral metronidazole. Predominantly sensory neuropathy characterized the neurotoxicity in these patients. Dysautonomia had never been described following prolonged use of metronidazole in previous reports.

CASE REPORT

This 29-year-old male was a victim of complex cyanotic congenital heart disease (transposition of great arteries, pulmonary arterial atresia, ventricular septal defect, and situs solitus). He had received a systemic-

pulmonary shunt procedure in September 1985.

He was admitted to the National Taiwan University Hospital in February 1993, with a one-week history of headache, fever, neck stiffness, and consciousness disturbance. A cerebrospinal fluid (CSF) study revealed elevation of initial pressure (235 mm H₂O), mild pleocytosis with neutrophil dominant, and positive Pandy test. However, there was no hypoglycorrhachia and no microorganisms were cultured from CSF. The head computed tomography scan revealed a contrast-enhanced lesion in the right frontal epidural space with perifocal edema. Under a diagnosis of epidural abscess with parameningeal reaction, metronidazole (500 mg 4 times a day, intravenous infusion) was administered in addition to oxacillin and ceftriaxone. The clinical condition improved gradually. Fifty days after continuous administration of these antibiotic agents (the total dose of metronidazole was 100 grams), he gradually developed distressing paresthesia at the distal part of four limbs and an unsteady gait.

Received June 31, 1995. Revised August 10, 1995. Accepted September 17, 1995.

Address correspondence to Dr. Yang-Chyuan Chang, Department of Neurology, National Taiwan University Hospital, 7, Chung-Shan South Road, Taipei, Taiwan 100, R.O.C.

Meanwhile, he had frequent episodic dizziness related to postural changes. Watery diarrhea supervened but repeated stool cultures were unyielding. Neurologic examination revealed diminished sensibility to pin-prick and light touch in a glove and stocking distribution, absence of joint position sense in the toes, reduced vibration sense in the malleoli, knees, and fingers, positive Romberg's sign, and all the muscular stretch reflexes were absent. There were no abnormalities in the cranial nerves and no weakness in the limbs.

The serum vitamin B₁₂ level and fasting blood sugar were within normal ranges.

Electrophysiologic investigations showed absence of sensory action potentials in the median, ulnar, and sural nerves. Motor conduction velocities were normal in the median, ulnar, peroneal, and tibial nerves except for mildly decreased amplitudes of compound muscle action potentials. Autonomic function tests revealed abnormal heart rate variation (R-R interval variation, RRIV) and absence of sympathetic skin response (SSR). The RRIVs during quiet breathing and hyperventilation were 5.78 % and 5.82 %, respectively (normal control values for aged 20-29: 29.2 ± 17.4 % during quiet breathing; 40.4 ± 21.2 % during hyperventilation)⁽¹⁴⁾. His symptoms improved gradually after discontinuation of metronidazole. In the subsequent 11-month period of follow-up, he still had mild distal limb paresthesia.

DISCUSSION

Metronidazole can induce serious neurologic complications including peripheral neuropathy⁽²⁻¹³⁾, seizures⁽¹⁶⁾, optic neuropathy⁽¹⁷⁾, and encephalopathy⁽¹⁸⁾. Since 1968, metronidazole-induced peripheral neuropathy has been reported in about 40 patients⁽²⁻¹³⁾. Majority of the reported cases occurred in Crohn's disease patients after prolonged use of oral metronidazole. The neuropathy induced by metronidazole is sensory-predominant in nature, which results in distal hypoesthesia, paresthesia, and sensory ataxia. These findings were evident in our patient. After discontinuation of metronidazole, the

symptoms of neuropathy may recover completely or partially. Our patient had persistent mild distal paresthesia till 11 months after onset, which suggests a neuropathy with axonal degeneration.

Most reported cases developed neuropathy following oral metronidazole doses of 1000-2400 mg/d, total doses of at least 50 g, and treatment durations of at least 30 days⁽²⁻¹³⁾. In some of these cases, intravenous form was concomitantly used. But there was no report concerning the neuropathy following intravenous route alone. Our patient received intravenous metronidazole only, at a dose of 2000 mg/d for 50 days, resulting in a cumulative dose of 100 g, prior to the onset of neuropathy.

Autonomic dysfunctions had never been reported in the patients with metronidazole-induced neuropathy. The dysautonomia in our patient, i.e., posture-related dizziness, diarrhea, narrowed RRIV and absence of SSR, was believed to be caused by metronidazole because: (1) the autonomic dysfunctions appeared after prolonged use of metronidazole and resolved gradually after drug discontinuation; (2) there was no other explainable cause for dysautonomia; and (3) oxacillin or ceftriaxone had never been reported to cause any peripheral neuropathy⁽¹⁹⁾.

The mechanism of metronidazole-induced neuropathy is not clear. In the rodent experiments, metronidazole was found to bind selectively to neuronal RNA. After binding, metronidazole or its metabolites inhibit protein synthesis and result in axonal degeneration⁽⁷⁾. Human sural nerve biopsy revealed loss of myelinated fibers⁽¹⁰⁾. In the future, the pathologic changes of unmyelinated fibers under electron microscope in metronidazole-induced neuropathy might be helpful in elucidating the dysautonomic component.

Recently metronidazole has been indicated as an integral part of *Helicobacter pylori* eradication therapy^(20,21). Metronidazole-induced neuropathy has been reported in one patient who received an 8-week course of oral metronidazole 500 mg q8h for the treatment of endoscopically documented *H. pylori* gastritis⁽²²⁾. We would like to emphasize that

the incidence of metronidazole-induced neuropathy might increase if the triple-drug therapy (metronidazole, amoxicillin or tetracycline, and a bismuth salt) becomes more popular in the future.

REFERENCES

- Rosen A, Ursing B, Alm T, et al. A comparative study of metronidazole and sulfasalazine for active Crohn's disease: the Cooperative Crohn's Disease Study in Sweden. I. Design and methodological considerations. *Gastroenterology* 1982;83:541-9.
- Ursing B, Kamme C. Metronidazole for Crohn's disease. *Lancet* 1975;1:775-7.
- Urtasun RC, Rabin HR, Partington J. Human pharmacokinetics and toxicity of high-dose metronidazole administered orally and intravenously. *Surgery* 1983;93:145-8.
- Ramsay ID. Endocrine ophthalmopathy (letter). *Br Med J (Clin Res)* 1968;4:706.
- Holdstock DJ. Drug treatment in Crohn's disease (letter). *Lancet* 1975;2:1260.
- Coxon A, Pallis CA. Metronidazole neuropathy. *J Neurol Neurosurg Psychiatry* 1976;39:403-5.
- Bradley WG, Karlsson IJ, Rassol CG. Metronidazole neuropathy. *Br Med J (Clin Res)* 1977;2:610-1.
- Karlsson IJ, Hamlyn AN. Metronidazole neuropathy (letter). *Br Med J (Clin Res)* 1977;2:832.
- Hishon S, Pilling J. Metronidazole neuropathy (letter). *Br Med J (Clin Res)* 1977;2:832.
- Said G, Goasguen J, Laverdant C. Polynevrites au cours des traitements prolongés par le metronidazole. *Rev Neurol* 1978;134:515-21.
- George WL, Kirby BD, Sutter VL, et al. Intravenous metronidazole for treatment of infections involving anaerobic bacteria. *Antimicrob Agents Chemother* 1982;21:441-9.
- Duffy LF, Daum F, Fisher SE, et al. Peripheral neuropathy in Crohn's disease patients treated with metronidazole. *Gastroenterology* 1985;88:681-4.
- Boyce EG, Cookson ET, Bond WS. Persistent metronidazole-induced peripheral neuropathy. *DICP Ann Pharmacother* 1990;24:19-21.
- Persson A, Solders G. R-R variations, a test of autonomic dysfunction. *Acta Neurol Scand* 1983; 67:285-93.
- Glickman RM. Inflammatory bowel disease. In: Wilson JD, Braunwald E, Isselbacher KJ, Petersdorf RG, Martin JB, Fauci AS, Root RK eds. *Harrison's Principles of Internal Medicine*. 12th ed. New York:McGraw-Hill 1991:1268-81.
- Frytak S, Moertel CG, Childs DS, et al. Neurologic toxicity associated with high-dose metronidazole therapy. *Ann Intern Med* 1978;88:361-2.
- Putnam D, Fraunfelder FT, Dreis M. Metronidazole and optic neuritis (letter). *Am J Ophthalmol* 1991;112:737.
- Kusumi RK, Plouffe JF, Wyatt RH, et al. Central nervous system toxicity associated with metronidazole therapy. *Ann Intern Med* 1980;93:59-60.
- Snively SR, Hodges GR. The neurotoxicity of antibacterial agents. *Ann Intern Med* 1984;101:92-104.
- Seppala K, Farkkila M, Nuutinen H, et al. Triple therapy of *Helicobacter pylori* infection in peptic ulcer. A 12-month follow-up study of 93 patients. *Scand J Gastroenterol* 1992;27:973-6.
- Hentschel E, Brandstatter G, Dragosics B, et al. Effect of ranitidine and amoxicillin plus metronidazole on the eradication of *Helicobacter pylori* and the recurrence of duodenal ulcer. *N Engl J Med* 1993;328:308-12.
- Learned-Coughlin S. Peripheral neuropathy induced by metronidazole (letter). *DICP Ann Pharmacother* 1994;28:536.