The Occurrence of Metronidazole-Induced Encephalopathy in Cancer Patients: A Hospital-Based Retrospective Study

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Abstract

Background: Metronidazole-induced encephalopathy (MIE) is a rare but serious complication caused by metronidazole, a widely used antianaerobic drug. Previous studies prescribed MIE including dysarthria, cerebellar ataxia, and confusion after long-term use of metronidazole. Malignancy has been proposed one of the predisposing conditions for MIE. However, the occurrence of MIE in cancer patients remains unknown. **Methodology:** We investigated the occurrence of MIE and analyzed retrospectively by hospital-based data of 4160 cancer patients from January 2014 to December 2016. **Results:** Findings in 793 cancer patients who underwent metronidazole therapy for anaerobic infection revealed two cases of MIE. One had renal cell carcinoma and the other had bladder urothelial carcinoma. Both of their initial presentation were cerebellar dysfunction. The occurrence of MIE was 8.6% for cases who received >30 g of cumulative dose. Hypertension was the most common comorbidity, followed by chronic renal disease and diabetes mellitus. **Conclusion:** In cancer patients, MIE should be monitored in those with genitourinary cancer,

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DOI: 10.4103/aian.AIAN_523_18

especially with renal dysfunction. Longer duration with more cumulative dose also has a greater risk of MIE. Early consideration of MIE with prompt cessation of metronidazole may result in better outcome.

Keywords: Anaerobic infection, cancer, encephalopathy, metronidazole

Introduction

Metronidazole, a synthetic 5-nitroimidazole antibiotic, has been widely used for infection treatment for >50 years and still considered as the drug of choice for the most anaerobic infections.[1,2] While metronidazole is fairly safe and well tolerated, it can rarely cause serious adverse effects, including peripheral neuropathy, dysarthria, cerebellar ataxia, and encephalopathy.[3] To our knowledge, metronidazole-induced encephalopathy (MIE) appears accompanied by patients with malignancy,[4,5] which may render them more susceptible to neurotoxicity. In cancer patients, there is a higher incidence of anaerobic infections in fact and usually treated with metronidazole.[6,7] However, the occurrence of MIE in cancer patients was not known in real-world practice.[8] Due to the limited amount of data, the study investigated retrospectively the epidemiology and occurrence of MIE in cancer patients over a 3-year period at a tertiary hospital. The study aimed to investigate the occurrence and risk factors of MIE and to increase the awareness of MIE in cancer patients among physicians.

Methodology

The study was approved by the Institutional Review Board of the hospital (TMU-JIRB no. N201709066). This is a retrospective study of metronidazole encephalopathy in patients with malignancy seen in our unit between January 2014 and December 2016. All patients had been administered metronidazole therapy. Patients' records extracted from the institutional database and medical records were reviewed to extract the following information, such as metronidazole dose, duration of administration, indication for metronidazole (infection source), cancer types, initial presentation of MIE, duration of MIE, clinical symptoms, and outcome. Pediatric patients (under 18 years of age) and those without malignancy were excluded from the study. Descriptive statistics were generated in the forms of rates, ratio, and proportions using Excel statistical program.

Results

In this study, we analyzed retrospectively clinical information of 4160 cancer patients admitted or visited to Taipei Medical University Hospital from January 2014 to December 2016. During this period, a total of 793 cancer patients who underwent metronidazole therapy for anaerobic infection were recorded [Table 1]. There were 370 men and 423 women, with age ranging from 22 to 95 years. There was almost equal ratio of gender in the study participants (male:female, 46.7%:53.3%). In those patients, respiratory tract infection (27.7%) was the most common indication of metronidazole therapy. The average period of administration was 10.4 days (range: 1–70 days), although 35.6% had taken <10 days. The mean cumulative dose was 8.73 g (range: 1.75–90 g). The most common cancer type, metastasis type, and double cancer

Table 1: Clinical data and demographic characteristics of 793 study participants

Categories	*n* (%)
Gender	
Male	370 (46.7)
Female	423 (53.3)
Age group (years)	
<40	28 (3.5)
40-60	378 (47.7)
60-80	335 (42.2)
>80	52 (6.6)
Infectious focus	
Bloodstream	162 (20.4)
Urinary tract	154 (19.4)
Pelvic cavity	58 (7.3)
Hepatobiliary system	0 (0)
Soft tissue	13 (1.6)
Joint	0 (0)
Central nervous system	0 (0)
Head and neck	0 (0)
Respiratory tract	220 (27.7)
Others	186 (23.5)
Administration duration (days)	
1-10	587 (74)
11-20	39 (5)
21-30	143 (18)
31-40	10 (1.3)
41-50	7 (0.9)
51-60	4 (0.5)
>61	3 (0.4)
Cumulative dose (g)	
1-10	647 (81.6)
11-20	85 (10.7)
21-30	38 (4.8)
31-40	15 (1.9)
41-50	4 (0.5)
51-60	3 (0.4)
>61	1 (0.1)
Comorbidity	
Liver disease	93 (11.8)
Renal disease	116 (14.6)
Diabetes mellitus	102 (12.9)
Hypertension	239 (30.1)
Congestive heart failure	32 (4.0)

type were colorectal cancer (57.2%), colorectal cancer with liver metastasis (25.5%), and ovarian cancer combined with cervical cancer (94.4%), respectively. Hypertension (30.1%) was the most common comorbidity, followed by chronic renal disease (14.6%) and diabetes mellitus (12.9%).

Among those participants, two patients of MIE were documented. The occurrence of MIE in our study was 0.25%. The observations of MIE in this study indicate predominant male gender, and the mean age was 69 years old. One had been diagnosed with renal cell carcinoma and the other had high-grade bladder urothelial carcinoma. The onset of MIE symptoms developed after total metronidazole duration/dosage of 38 g/38 days and 90 g/60 days, respectively. The occurrence of MIE was 8.6% (2/23) for cases who received >30-g metronidazole in our series, and no case who received <30-g metronidazole had developed MIE (0/770). The first neurological symptom was cerebellar dysfunction, such as slurred speech, incoordination, and unsteadiness of gait. The diagnosis of them was confirmed by brain magnetic resonance imaging (MRI) and T2-weighted or fluid-attenuated inversion recovery imaging, prominently in cerebellar dentate nucleus bilaterally. It was noticed that complete resolution in clinical symptoms after discontinuation of metronidazole was 14 days and 10 days, respectively, in both the cases.

Patient 1

A 64-year-old male had the histories of left renal cell carcinoma status postnephrectomy and rectal cancer status postconcurrent chemoradiation and radical proctectomy with coloanal anastomosis as well as diverting colostomy, hypertension, and chronic kidney disease Stage 3 (estimated glomerular filtration rate [eGFR]: 50 mL/min/1.73 m^2). Due to intermittent anal abscess discharge, he visited infection outpatient clinic, where oral form metronidazole 1 g daily was prescribed. After about 1 month, insidious onset of progressive dizziness and unsteady gait was noted. Dizziness exacerbated with action accompanied with nausea and vomiting. He denied fever, headache, diplopia, slurred speech, paresthesias, limbs weakness, or involuntary movements. The symptoms did not improve with antihistamines or prokinetics. According to the records, the first symptom appeared after total metronidazole dosage of 38 g. His liver function was unremarkable at symptom onset. When he stopped use after about 2 months, he had ingested 61 g. Neurological examinations were positive for Romberg sign, slurred speech, and failed tandem gait. Muscle tone, power, and reflexes were normal. Brain MRI showed focal edematous lesions over the splenium of the corpus callosum [Figure 1a] and dorsal pons [Figure 1b]. After discontinuation of the drug for 2 weeks, the patient's gait greatly returned to normal with minimal dizziness. Six months later, the follow-up brain MRI revealed disappearance of previous lesions [Figure 1c and d]. Although there is no typical cerebellar lesions in this case, the reversibility of splenium and pons lesions is also an important finding to establish the diagnosis of MIE.

Patient 2

A 74-year-old male had the histories of diabetes mellitus (hemoglobin A1c: 6.5%), hypertension, chronic kidney disease Stage 2 (eGFR: 77 mL/min/1.73 m^2), bladder urothelial carcinoma, papillary, noninvasive, high grade, cTaN0M0, status posttransurethral resection of bladder tumor, and chemotherapy. Due to uncertain source of infection, suspect pelvic region involved, our infection physician has prescribed ciprofloxacin 2 g and oral form metronidazole 1.5 g daily. After 2 months, acute onset of slurred speech and gait disturbance was noted. There was no dizziness, vertigo, nausea/vomiting, fever, headache, diplopia, paresthesia, limbs weakness, or involuntary movements. The first symptom appeared after total metronidazole dosage of 90 g. When he stopped use after about 2 months, he had ingested 97.5 g. Neurological examinations revealed failed tandem gait. Muscle tone, power, and reflexes were normal. His brain MRI showed hyperintense lesions of bilateral cerebellar dentate nuclei [Figure 2a]. His liver function was normal with stationary renal function at symptom onset. After cessation of metronidazole for 10 days, the patient's gait greatly returned to normal with mild unsteady gait. Three months later, the follow-up MRI showed disappearance of previous hyperintense change of bilateral cerebellar dentate nuclei [Figure 2b], which suggests metronidazole intoxication and complete recovery after discontinuation of the drug.

Discussion

Regardless in general population or cancer patients, the incidence or occurrence of MIE has never been reported before.[8,9] Summary of the findings, the occurrence of MIE in cancer patients received metronidazole therapy is 0.25%. Moreover, the study showed that the infection rate of anaerobes in cancer patients undergoing metronidazole therapy accounts for 19% yearly, significantly higher than noncancer hospitalized patients accounting for 0.5%–9% in recent studies.[6,7] An increase of infection rate due to anaerobic infection in cancer patients may be attributed to underlying malignancy and various modalities used (radiation or chemotherapy) for treatment.

The mechanism of MIE is not fully understood. Recent studies have proposed that metronidazole can pass through blood–brain barrier (BBB) and has therapeutic effects in cerebrospinal fluid.[10-12] In patients with malignancy, dysfunction of BBB integrity and permeability may result from reversible mitochondrial dysfunction, triggered by cancer-derived mediators through the release of proteins and microRNAs.[13] Binding of metronidazole to neural RNA may also affect the modulation of inhibitory neurotransmitters and gamma-aminobutyric acid receptors within cerebellar and vestibular systems.[14] We supposed that in cancer patients, high probability of BBB disruption may render the brain more vulnerable to metronidazole-induced toxic-metabolic process and lead to cerebral axonal swelling and demyelination.[8,9] Another suggested that mechanism includes vascular spasms that may produce mild localized ischemia.[8] In this study, hypertension is the most common comorbidity in cancer patients. Hypertension can result in hypertensive encephalopathy and endothelial dysfunction,

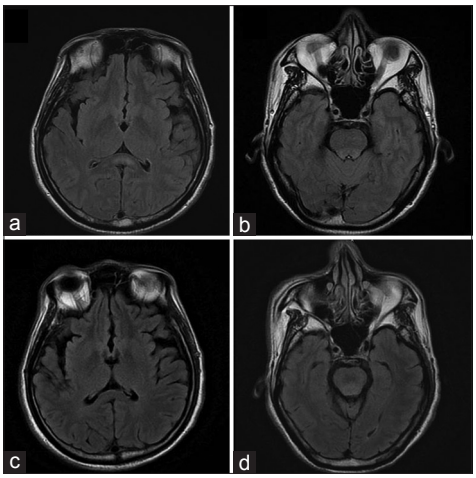

Figure 1: Patient 1 of metronidazole-induced encephalopathy. Mildly focal edematous lesions, splenium of the corpus callosum (a) and dorsal pons (b) on T2-weighted image and fluid-attenuated inversion recovery Previously noted hyperintense lesions of the splenium of the corpus callosum (c) and dorsal pons (d) have completely resolved on follow-up magnetic resonance imaging

leading to a breakdown of BBB and vasospasm. We supposed that in patients with hypertension and malignancy, angiogenesis mediated by vascular endothelial growth factor produced by cancer cell may aggravate endothelial dysfunction and reversibly occur localized ischemia, causing greater probability of focal brain edema and vasospasm.[15] Further research is clearly necessary to elucidate the issue.

MIE has been found to be associated with higher dose and duration of metronidazole therapy.[5] The duration of a course of metronidazole for the treatment of anaerobic infection is about 10–15 days, but it will depend on the patient's condition. Our infection specialist may decide prolonged regimens of antimicrobial therapy in severe illness or immunosuppressed patients, especially in those with chemotherapy, nonresolution, or unknown origin of infection. Mostly, a dose above 1 g/day for at least 30 days or total dosage of 50 g can result in cerebellar ataxia.[16] Our data revealed that the occurrence of MIE is 8.6% for those cancer patients who receive totally >30-g metronidazole. The prolong use with more cumulative doses of oral form metronidazole therapy revealed a greater opportunity to develop MIE. However, the difference of administration between intravenous and oral form metronidazole remains undetermined. The investigation is warranted in the future to further clarify this issue. Previous studies and our study both confirmed that discontinuation of metronidazole almost always results in rapid resolution of symptoms and structural lesions of MIE.[9]

Otherwise, MIE is related to wide ranges of cumulative dosage and therapeutic duration.[4,17] It does not seem fully a dose- or duration-related phenomenon for MIE.[14] Some factors may predispose metronidazole-induced neurotoxicity. Knorr *et al*. described severe liver dysfunction as an important risk factor for MIE.[18] According to Menéndez *et al*.,[19] the intermediate metabolite of metronidazole rather than by the

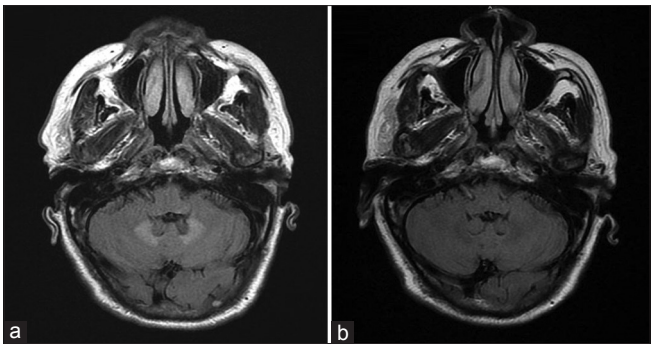

Figure 2: Patient 2 of metronidazole-induced encephalopathy. Hyperintense changes of bilateral dentate nuclei (a) on T2-weighted image and fluid-attenuated inversion recovery. Follow-up magnetic resonance imaging showed that complete resolution of hyperintense changes of bilateral dentate nuclei (b) after cessation of metronidazole

parent drug may lead to observed DNA damage on the human neuronal cell.[19] In our cases who developed MIE, chronic kidney disease combined with genitourinary cancer may be a predisposing condition. The half-life of metronidazole in patients with normal renal function is 6–9 h and unchanged in those with renal insufficiency. Previous studies showed that renal insufficiency may not alter metabolites disposition but may be associated with significant accumulation of metabolites of metronidazole, possibly requiring a dose reduction in patients with renal failure.[20] Postulated mechanisms may include the reduction of clearance of metronidazole and the prolonged excretion of metronidazole and its renal metabolites in patients with genitourinary cancer coupled with renal dysfunction.

Moreover, the comorbidities are common among cancer patients and potentially may affect the treatment and outcome of people with cancer. In this study, the most common comorbidity in cancer patients is hypertension, similar to previous studies.[21,22] The second and third comorbidities among our cancer patients are chronic kidney disease and diabetes mellitus, dividedly. Both of the chronic conditions lead to increased susceptibility to infections and increase the use of metronidazole, which may raise the possibility of neurological complication after metronidazole therapy.

Conclusion

Metronidazole is a widely used antibiotic for anaerobic infection. In cancer patients, the neurological complications of metronidazole should be monitored in those with genitourinary cancer, particularly combined with chronic kidney disease. Longer duration with more cumulative dose also has a greater risk of MIE in cancer patients. Early consideration for MIE in cancer patients with timely cessation of metronidazole may result in better outcome.

Acknowledgments

This work is granted by Taipei Medical University Hospital (107TMUH-NE-01).

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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