Risk factor analysis for metronidazole-associated neurologic adverse events

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Background

- Metronidazole is one of the most widely used antibiotics worldwide.
- However, little is known about the risk factors of metronidazole-associated neurological adverse events.

Objectives

- To investigate the risk factors of metronidazole-associated neurological adverse events.

Methods

- We conducted a matched case-control study based on patients treated with metronidazole between January 2006 and July 2021 at a tertiary hospital in South Korea.
- Case patients were defined as those diagnosed with metronidazole-associated encephalopathy or peripheral neuropathy during the study period with causal assessment.
- In a ratio of 1:3, case patients were compared to a control group of patients prescribed metronidazole without neurologic adverse events matched for age and cumulative dose of metronidazole.

Results

Table 1. Clinical characteristics and outcomes of the study population

	Without neurologic adverse event (n=162)	Neurologic adverse event (n=54)	P-value
Age, median (IQR), years	62.5 (50.5–75.0)	60.0 (48.0–67.0)	0.087[a]
Sex, No. (%)			0.374
Male	103 (63.6%)	30 (55.6%)	
Body weight, median (IQR), kg	56.1 (51.1–66.7)	54.0 (43.2–63.0)	0.007[a]
Comorbidity, No. (%)			
Hypertension	76 (46.9%)	23 (42.6%)	0.693
Diabetes mellitus	38 (23.5%)	20 (37.0%)	0.076
Chronic kidney disease	24 (14.8%)	22 (40.7%)	<0.001
Chronic lung disease	7 (4.3%)	4 (7.4%)	0.592
Solid cancer	68 (42.0%)	17 (31.5%)	0.228
Solid organ transplant	7 (4.3%)	9 (16.7%)	0.007
Liver cirrhosis	6 (3.7%)	14 (25.9%)	<0.001
Cerebrovascular accident	18 (11.1%)	4 (7.4%)	0.603
Charlson comorbidity index, median (IQR)	4.0 (2.0–7.0)	5.0 (2.5–6.5)	0.643[a]
Alcohol history, No. (%)			0.166
No significant alcohol consumption	138 (85.2%)	43 (79.6%)	
History of significant alcohol consumption	16 (9.9%)	10 (18.5%)	
Current significant alcohol consumption	8 (4.9%)	1 (1.9%)	
Cumulative dose of metronidazole, median (IQR), g	63.5 (32.2–115.8)	69.8 (36.0–126.8)	0.297[a]
Duration of therapy, median (IQR), days	44.5 (24.5–84.5)	51.0 (28.0–81.0)	0.392[a]
Dosage Form, No. (%)			0.004
Oral administration	110 (67.9%)	24 (44.4%)	
Intravenous administration	52 (32.1%)	30 (55.6%)	
Concomitant medication, No. (%)			
β-lactams	120 (74.1%)	42 (77.8%)	0.717
Glycopeptide	15 (9.3%)	9 (16.7%)	0.211
Anti-fungal agents	7 (4.3%)	7 (13.0%)	0.056
Proton pump inhibitor	26 (16.0%)	22 (40.7%)	<0.001
Immunosuppressant	33 (20.4%)	19 (35.2%)	0.043
Psychiatric medication	19 (11.7%)	11 (20.4%)	0.173
Laboratory data, median (IQR)			
Haemoglobin, g/dL, mean (SD)	11.0 (2.2)	9.9 (1.8)	0.001
Blood urea nitrogen, mg/dL	15.0 (10.8–22.0)	18.8 (10.9–33.6)	0.088[a]
Creatinine, mg/dL	0.8 (0.6–1.1)	1.0 (0.8–1.5)	0.001[a]
Aspartate aminotransferase, IU/L	23.0 (16.0–33.0)	23.5 (15.5–34.0)	0.805[a]
Alanine aminotransferase, IU/L	16.5 (11.0–25.5)	14.0 (10.0–24.0)	0.199[a]
Total bilirubin	0.6 (0.4–0.9)	0.7 (0.4–1.4)	0.183[a]
Albumin, mg/dL, mean (SD)	3.3 (0.7)	3.0 (0.6)	0.018
SOFA score, median (IQR)	0.0 (0.0–2.0)	2.0 (0.0–4.0)	0.001[a]

IQR, Inter-quartile range; SOFA, Sequential Organ Failure Assessment

Table 2. Risk factor analysis for central nervous system or peripheral nervous system adverse events

	Univariate analysis				Multivariate analysis			
	OR	2.5%	97.5%	p-value	OR	2.5%	97.5%	p-value
Liver cirrhosis	9.59	3.14	29.3	<0.001	15.74	3.95	62.76	<0.001
Chronic kidney disease	3.56	1.81	6.97	<0.001	4.57	1.88	11.08	<0.001
Intravenous administration	2.72	1.38	5.36	0.004	3.57	1.42	8.97	0.007
Body weight	0.95	0.93	0.98	0.003	0.95	0.91	0.99	0.015
Proton pump inhibitor	3.57	1.76	7.24	<0.001	2.42	0.92	6.36	0.072
Hemoglobin	0.77	0.65	0.91	0.002				
SOFA score	1.24	1.08	1.43	0.003				
Solid organ transplant	4.74	1.57	14.33	0.006				
Albumin	0.54	0.32	0.90	0.019				

OR, Odds ratio;
SOFA, Sequential Organ Failure Assessment

Major Findings

- A total of 92,838 patients were prescribed metronidazole during the study period at the Severance Hospital.
- Fifty-four patients were diagnosed with metronidazole-associated encephalopathy or peripheral neuropathy, 40 patients with central and 28 patients with peripheral nervous system adverse events.
- The incidence of metronidazole-associated neurological adverse events was 0.05 per 1,000 patient-days.
- Liver cirrhosis, chronic kidney disease, intravenous administration, and low body weight were identified as risk factors for these adverse events.

Conclusions

- Prolonged metronidazole treatment in patients with risk factors requires careful examination for neurological adverse events.