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Comparison and Analysis of Delirium Induced by Histamine H₂ Receptor Antagonists and Proton Pump Inhibitors in Cancer Patients

Shiro Fujii^a Hitoshi Tanimukai^{b, c} Yujiro Kashiwagi^d

^aDepartment of Psychosomatic and Palliative Medicine, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, ^bOncology Center, Osaka University Hospital, and ^cDepartment of Psychiatry, Osaka University Graduate School of Medicine, Suita, and ^dDepartment of Clinical Psychology, Faculty of Social Welfare, Kansai University of Welfare Sciences, Kashiwara, Japan

Key Words

Delirium · H₂ blockers · Proton pump inhibitors · Switching · Prevention

Abstract

Objective: H₂ blockers have been reported to be responsible for drug-induced delirium. We compared the incidence of delirium between two groups of patients who were treated with H₂ blockers (H₂ group) or proton pump inhibitors (PPI group) for anastomotic ulcer prevention following surgical treatment of esophageal cancer.

Method: The incidence and severity of delirium were retrospectively compared in patients of the H₂ group (30 cases; age, 65.2 ± 8.1 years) and the PPI group (30 cases; 65.2 ± 6.5 years). The diagnosis of delirium was based on the Diagnostic and Statistical Manual of Mental Disorders-IV-Text Revision. Delirium severity was rated on the Delirium Rating Scale (DRS).

Results: The incidence of delirium was significantly lower in the PPI group than in the H₂ group ($p = 0.047$). In the 11 patients from the H₂ group who developed delirium, discontinuation of H₂ blockers resulted in a significant reduction in the DRS score ($p = 0.009$). In three patients for whom H₂ blockers were discontinued, DRS scores decreased by 50% or more three days after discontinuation compared to the prediscontinuation score.

Conclusions: These results suggested that switching antiulcer drugs from H₂ blockers to PPIs reduced delirium and thus provided an appropriate coping method for drug-induced delirium from antiulcer drugs.

Histamine H₂ receptor antagonists (H₂ blockers) are antiulcer agents which may cause drug-induced delirium. However, few reports are available on the association between proton pump inhibitors (PPIs) and delirium [1, 2]. To the best of our

knowledge, there have been no reports comparing the incidence of delirium between patients treated with H₂ blockers and PPIs. Therefore, we compared the incidence of delirium in patients taking either H₂ blockers (H₂ group) or PPIs (PPI group) for preventing anastomotic ulcers after surgical resections of esophageal cancer in Osaka Medical Center for Cancer and Cardiovascular Diseases between January 2006 and July 2007. Patients with a history of organic brain disease, severely compromised hepatic function (bilirubin levels, >2.0 mg/dl), or severely compromised renal function (creatinine levels, >2.0 mg/dl) were excluded. The incidence and severity of delirium were retrospectively compared in patients of the H₂ group (30 cases; age, 65.2 ± 8.1 years) and PPI group (30 cases; age, 65.2 ± 6.5 years). The diagnosis of delirium was based on the Diagnostic and Statistical Manual of Mental Disorders-IV-Text Revision. Delirium severity was rated on the Delirium Rating Scale (DRS). Statistical comparisons of the incidence of delirium between the two groups were conducted with Fisher's exact tests. Wilcoxon matched-pairs signed-rank tests were employed to compare the DRS scores before and after H₂ blocker discontinuation. Statistical analyses were conducted with PASW Statistics 17.0 2 (IBM Corporation, Armonk, N.Y., USA). p values less than 0.05 were considered significant. Parameters are expressed as mean ± SD.

Delirium incidence was significantly lower in the PPI group (16.7%; five cases; two from lansoprazole and three from omeprazole; age, 69.4 ± 4.8 years) than in the H₂ group (43.3%; 13 cases, 12 from famotidine and one from ranitidine; age, 67.6 ± 4.8 years) (p = 0.047) with an odds ratio in the H₂ group relative to the PPI group of 3.824 and a 95% confidence interval of 1.150–12.713 ([table 1](#)).

Of the 13 H₂ group patients who developed delirium, two continued H₂ blocker treatment. The remaining 11 patients were evaluated on the DRS the day before and three days after H₂ blocker discontinuation or after switching to PPIs ([fig. 1](#)). For these 11 patients, the average DRS score three days after H₂ blocker discontinuation was significantly lower (11.8 ± 5.1) than that the day before discontinuation (16.6 ± 3.1) (p = 0.009) ([fig. 2](#)). Notably, three patients (two treated with famotidine and one with ranitidine; age, 71.0 ± 5.0 years) showed a >50% decrease in DRS scores ([fig. 1](#)). These patients had used other drugs that may induce delirium such as benzodiazepines or anticholinergic drugs, but their dose levels were not changed before or after H₂ blocker discontinuation. Among these patients, two patients (67 and 68 years) had compromised renal function, and both were rated with moderate nephropathy. Inotsume et al. [3] reported that the half-life of famotidine was significantly extended and exceeded 20 h when it was administered to elderly patients with compromised renal function. Schentag et al. [4] detected cimetidine in the cerebrospinal fluid of patients presenting with psychiatric symptoms during cimetidine treatment. Taken together, the marked improvement in DRS scores in these two patients after H₂ blocker discontinuation may reflect the underlying conditions in which the blood and cerebrospinal drug levels were likely to rise because of the aging-related fragile blood-brain barrier [5] combined with compromised renal function.

In the present study, H₂ blocker discontinuation in the H₂ group patients who had developed delirium resulted in significant alleviation of the delirium, suggesting that H₂ blocker discontinuation or switching to PPIs is an appropriate intervention in cases with drug-induced delirium attributable to H₂ blockers. Even though this study has the following limitations: (1) it was a retrospective study and sample size was small, (2) it did not have randomized comparisons, and (3) it lacked measures of H₂ blocker levels

in blood and cerebrospinal fluid in each case, this is the first report to compare the incidence of delirium induced by H₂ blockers and PPIs and analyze the efficacy of antiulcer agent switching. Antiulcer agent switching is expected to rapidly reduce delirium-related suffering and contribute to improving the patients' and their family's quality of life. The results additionally suggested that for patients at an elevated risk for delirium, the use of PPIs as a first-choice drug for preventing delirium may reduce the incidence of delirium.

Table 1. Incidence of delirium in the H₂ group and the PPI group

Delirium	H ₂ group, n/N	PPI group, n/N	OR (95% CI)	p value*
Positive	13/30 (43%)	5/30 (17%)	3.824 (1.150–12.713)	0.047
Negative	17/30 (57%)	25/30 (83%)		

OR = Odds ratio; CI = confidence interval. * Fisher's exact test.

Fig. 1. Changes in Delirium Rating Scale (DRS) scores from the day before histamine H₂ receptor antagonist (H₂ blockers) discontinuation to three days after discontinuation in the 11 patients from the H₂ group who developed delirium.

Fig. 2. Among the 11 patients from the H₂ group who developed delirium, the average DRS score three days after H₂ blocker discontinuation (11.8 ± 5.1) was significantly lower than the score on the day before discontinuation (16.6 ± 3.1). * $p = 0.009$ (Wilcoxon matched-pairs signed-rank test).

References

- 1 Heckmann JG, Birklein F, Neundorfer B: Omeprazole-induced delirium. *J Neurol* 2000;247:56–57.
- 2 Bebartá VS, King JA, McDonough M: Proton pump inhibitor-induced rhabdomyolysis and hyponatremic delirium. *Am J Emerg Med* 2008;26:519.e1–e2.
- 3 Inotsume N, Nishimura M, Fujiyama S, Sagara K, Sato T, Imai Y, Matsui H, Nakano M: Pharmacokinetics of famotidine in elderly patients with and without renal insufficiency and in healthy young volunteers. *Eur J Clin Pharmacol* 1989;36:517–520.
- 4 Schentag JJ, Cerra FB, Calleri G, DeGlopper E, Rose JQ, Bernhard H: Pharmacokinetic and clinical studies in patients with cimetidine-associated mental confusion. *Lancet* 1979;1:177–181.
- 5 Farrall AJ, Wardlaw JM: Blood-brain barrier: ageing and microvascular disease – systematic review and meta-analysis. *Neurobiol Aging* 2009;30:337–352.