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Original Article

Association between Paralytic Ileus and Medication Including Psychotropics and Laxatives among Patients with Schizophrenia

Tokuya INAGUMA[1], Toshiaki NADAYA[2], Shohei IKEMOTO[3], Kae ITO[4]
1 Department of Psychiatry, Tokyo Metropolitan Matsuzawa Hospital
2 Department of Pharmacy, Tokyo Metropolitan Matsuzawa Hospital
3 Department of Internal Medicine, Tokyo Metropolitan Matsuzawa Hospital
4 Center for Promoting Dementia Support, Tokyo Metropolitan Geriatric Hospital and Institute of Gerontology
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Abstract

Patients with schizophrenia are susceptible to constipation, mainly due to the side effects of psychotropics. This constipation may advance to paralytic ileus, bowel ischemia, or bowel perforation, occasionally resulting in fatality. Despite numerous case reports of paralytic ileus in schizophrenia patients, few studies have explored the risk factors associated with this condition. The aim of this study was to investigate the relationship between paralytic ileus in schizophrenia patients, psychotropic medications, and laxative use.

The retrospective review of medical records included 3,775 consecutive patients diagnosed with schizophrenia admitted to the hospital between November 2014 and October 2019. Within this cohort, 25 patients received a diagnosis of paralytic ileus. Multivariable analysis revealed that the utilization of clozapine (OR: 71.815; 95%CI: 12.838-401.733; *P*< 0.001), magnesium oxide (OR: 3.536; 95%CI: 1.544-8.099; *P*=0.003), haloperidol (OR: 3.079; 95%CI: 1.192-7.954; *P*=0.020), sennoside (OR:

2.376; 95%CI: 1.048-5.388; *P*=0.038), and advanced age (OR: 1.053; 95%CI: 1.023-1.084; *P*=0.001) were associated with an elevated risk of paralytic ileus.

Therefore, caution is warranted when utilizing clozapine, haloperidol, or laxatives to avoid paralytic ileus, particularly among elderly patients with schizophrenia.

Keywords: schizophrenia, ileus, antipsychotics, laxative

Introduction

Patients with schizophrenia frequently suffer from reduced gastrointestinal motility. De Hert, M. et al. reported that 36.3% of individuals with schizophrenia experience constipation[2]. If not properly treated, constipation can progress to paralytic ileus, intestinal ischemia, or intestinal perforation. In severe cases, it can be fatal[3,7,15]. Consequently, the prevention, early identification, and management of gastrointestinal hypomotility are crucial concerns in psychiatric care.

Despite numerous case reports on ileus among those with schizophrenia[9,21,24], studies investigating risk factors are limited. In a case-control study, Nielsen, J et al. identified 123 cases of ileus among 26,720 patients with schizophrenia between 1996 and 2007 in Denmark[15]. They revealed that older age, female sex, clozapine, high-potency typical antipsychotics, tricyclic antidepressants, anticholinergic drugs, and opioids were independently associated with ileus. Similarly, in a retrospective cohort study, Chen, H.K. et al. monitored 27,178 patients with schizophrenia from 2001 to 2011 in Taiwan, identifying 419 cases of ileus and independently associating clozapine and typical high-potency antipsychotics with ileus[1]. However, these investigations lacked an exploration into laxative use as an associated factor.

In Japan, Kikuchi et al. conducted a case-control study comparing 31 cases of ileus during psychiatric hospitalization from 2002 to 2007 with 239 admitted patients in 2007[12]. They identified a history of ileus, severe psychiatric symptoms, laxative usage, antiparkinsonian drugs, low weight, low hemoglobin, and low triglyceride levels as risk factors through univariate analysis. However, the study's limitations included that the subjects were not limited to patients with

schizophrenia and the characteristics of the control group may have been different.

Hence, the purpose of this study was to elucidate the association between paralytic ileus and psychotropic drugs and laxatives, focusing specifically on patients with schizophrenia, through a case-control investigation.

I. Methods

1. Objectives

All individuals newly admitted to our hospital with a diagnosis of schizophrenia over a 5-year period between November 2014 and October 2019 were retrospectively reviewed using their medical records. Those individuals who developed paralytic ileus were specifically identified. The diagnosis of schizophrenia was determined by psychiatrists in accordance with ICD-10 criteria. Paralytic ileus diagnosis was established by gastroenterologists based on clinical observations and abdominal radiographs. Patients presenting with concurrent colon or rectal cancer or a history of abdominal surgery were excluded from the paralytic ileus diagnosis due to the consideration that adhesive ileus, not paralytic ileus, was the underlying mechanism.

2. Survey Items

The variables involved sex, age, height, weight, body mass index, and prescription. Prescriptions included typical antipsychotics (haloperidol, chlorpromazine, levomepromazine) and atypical antipsychotics (clozapine, olanzapine, quetiapine, risperidone, aripiprazole), antiparkinsonian drugs (biperiden, promethazine, trihexyphenidyl), stimulant laxatives (sennoside, picosulfate), and non-stimulant laxatives (magnesium oxide, lubiprostone, mosapride, dai-kenchu-to, probiotics). For individuals in the paralytic ileus group, prescriptions immediately before the onset of paralytic ileus were collected. For those in the non-paralytic ileus group, prescriptions were extracted at the peak chlorpromazine-equivalent value. The chlorpromazine-equivalent values were calculated using the equivalent conversion table for psychotropic drugs outlined by Inagaki et al.[10]. Tricyclic antidepressants and opioids, which are regarded as potential risk factors for paralytic ileus, were excluded from the study due to their infrequent prescription to patients with schizophrenia.

3. Statistical Analysis

Comparisons between the paralytic and non-paralytic ileus groups were conducted using the $\chi 2$ test for

categorical variables or Fisher's exact probability test for frequencies below 5, and the t-test for quantitative variables. The significance threshold was set at $P < 0.05$. Multivariate analysis was performed using logistic regression analysis. Independent variables included the usage of all drugs (haloperidol, clozapine, biperiden, sennoside, magnesium oxide, mosapride, dai-kenchu-to) and age, which exhibited significant differences based on univariate analysis. The statistical software SPSS (version 26.0; SPSS Inc., Chicago, IL, USA) was used for the analysis.

This study received approval from the Ethics Committee of Tokyo Metropolitan Matsuzawa Hospital, with due consideration for privacy concerns.

II. Results

During the observation period, there were 3,775 new admissions of individuals diagnosed with schizophrenia, among whom 25 developed paralytic ileus. The outcomes of univariate analysis of both paralytic and non-paralytic ileus groups are presented in Table 1. The paralytic ileus group exhibited a higher mean age compared with the non-paralytic ileus group (60.2±13.3 vs. 48.9±16.4 years, respectively, $P<0.001$). In terms of antipsychotics, the paralytic ileus group showed a higher rate of typical antipsychotics use than the non-paralytic ileus group (44.0 vs. 21.5%, respectively, $P=0.006$), especially haloperidol (24.0 vs. 8.2%, respectively, $P=0.014$). While the rate of atypical antipsychotics use did not significantly differ between the two groups (92.0 vs. 96.7%, respectively, $P=0.202$), the rate of clozapine use was significantly higher in the paralytic ileus group (8.0 vs. 0.3%, respectively, $P=0.004$). However, the chlorpromazine-equivalent value of total antipsychotic prescriptions showed no significant difference between the groups (1,006.1±600.7 vs. 1,030.7±743.1 mg, respectively, $P=0.987$). The rate of antiparkinsonian drug use was higher in the paralytic ileus group (56.0 vs. 36.1%, respectively, $P=0.039$). The rate of laxative use tended to be higher in the paralytic ileus group (76.0 vs. 59.0%, respectively, $P=0.085$). Regarding stimulant laxatives, the paralytic ileus group showed a significantly higher rate of sennoside use (44.0 vs. 22.2%, respectively, $P=0.009$) and a significantly lower rate of picosulfate use (8.0 vs. 26.8%, respectively, $P=0.034$).

The outcomes of multivariate analysis using logistic regression are presented in Table 2. The model's $\chi 2$ test yielded significant results at $P<0.01$, indicating independent associations with the use

of clozapine [odds ratio (OR): 71.815; 95% confidence interval (CI): 12.838 to 401.733; P<0.001), magnesium oxide use (OR: 3.536; 95% CI: 1.544 to 8.099; P=0.003), haloperidol use (OR: 3.079; 95% CI: 1.192 to 7.954; P=0.020), sennoside use (OR: 2.376; 95% CI: 1.048 to 5.388; P=0.038), and older age (OR: 1.053; 95% CI: 1.023 to 1.084; P=0.001). The Hosmer-Lemeshow test yielded a result of P=0.543, suggesting a satisfactory fit.

Among the 25 patients with paralytic ileus, two died of gastrointestinal hemorrhage or perforation of the gastrointestinal tract. Dose reduction of antipsychotics was attempted in 17 patients, of whom 3 required an increased dose due to worsening psychiatric symptoms during hospitalization. In four out of six patients previously administered haloperidol, the dosage was either reduced or discontinued. There was no worsening of psychiatric symptoms in all cases except one patient. Reduction or discontinuation of clozapine in two patients led to worsened psychiatric symptoms in one patient. Dose reduction of antiparkinsonian drugs was attempted in 8 patients. Sennoside usage was reduced or halted in 8 patients where continuous use was considered to affect gastrointestinal motility. Non-stimulant laxatives were introduced or increased in 17 patients. Frequently added non-stimulant laxatives included dai-kenchu-to (12 patients), magnesium oxide (8 patients), mosapride (8 patients), and lubiprostone (5 patients).

III. Discussion

1. Age

Older age was independently associated with the onset of paralytic ileus. It is widely recognized that gastrointestinal motility tends to decrease with advancing age. Reduced gastrointestinal motility in elderly patients is associated with various factors: reduced fluid intake, decreased levels of physical activity, comorbid health conditions, adverse effects of medications, challenges in swallowing due to tooth loss, and difficulty in consuming high-fiber diets[6]. Given that patients with schizophrenia require continuous antipsychotic treatment even in their advanced years, they might have a higher risk of decreased gastrointestinal motility compared with the general elderly population. A comprehensive approach to bowel movement management is indispensable for aged patients with schizophrenia, incorporating considerations of dietary patterns, physical activity routines, and oral health practices.

2. Haloperidol

Haloperidol showed an independent association with the onset of paralytic ileus. This is consistent with findings from Nielsen et al.'s case-control study and Chen et al.'s retrospective cohort study[1)15)]. Typical high-potency antipsychotics, such as haloperidol, are known for their weak anticholinergic properties. Nielsen et al. suggested that antiparkinsonian drugs, which are often used in combination with typical high-potency antipsychotics, may affect the development of ileus. Chen et al. conversely noted that despite the exclusion of antiparkinsonian drug effects, typical high-potency antipsychotics continued to be identified as a risk factor for ileus. The mechanism through which typical high-potency antipsychotics induce paralytic ileus remains unclear, necessitating further investigations.

Dose reduction of antipsychotics may be effective for gastrointestinal hypomotility. Suzuki et al. reported that reducing the bromperidol dose improved gastrointestinal hypomotility in a schizophrenic patient who developed paralytic ileus during bromperidol monotherapy[24)]. In this study, four out of six patients using haloperidol attempted dosage reduction during paralytic ileus treatment, observing no worsening of psychiatric symptoms except in one patient. The prescription of haloperidol in individuals with gastrointestinal hypomotility should be carefully evaluated and dose reduction should be considered.

3. Clozapine

Clozapine was independently associated with the occurrence of paralytic ileus. Possible reasons for the high OR are as follows. Clozapine's distribution is strictly controlled in Japan, resulting in the limited number of patients included in this study. Additionally, the rate of clozapine use was over 20-times higher in the paralytic ileus group compared with the non-paralytic ileus group. Multiple studies have reported the association between clozapine and gastrointestinal hypomotility. For example, a systematic review by Shirazi, A. et al. outlined a marked prevalence of constipation related to clozapine at 31.2%[23)]. Ingimarsson, O. et al. documented the occurrence of ileus in 4 (2.1%) out of 188 schizophrenia patients undergoing clozapine treatment[11)]. The underlying mechanism behind clozapine-induced gastrointestinal hypomotility is attributed to its significant anticholinergic effect, ranking highest among antipsychotics[19)]. Several studies demonstrated a decline in gastrointestinal motility associated with clozapine. Every-Palmer, S. et al. reported a fourfold prolongation of the

colonic transit time among individuals administered clozapine compared with those receiving alternative medications[4]. Moreover, Every-Palmer et al. explained the risk of worsening gastrointestinal motility induced by clozapine. They documented that among 102 patients experiencing gastrointestinal hypomotility while under clozapine treatment, 28 had a fatal outcome[3]. Vigilant monitoring of bowel movements remains crucial when using clozapine in clinical practice.

4. Antiparkinsonian Drugs

It is widely acknowledged that antiparkinsonian drugs induce gastrointestinal hypomotility owing to their anticholinergic effects[6]. Nonetheless, antiparkinsonian drugs were not selected as a variable in the current multivariate analysis. This result could be attributed to the decreased utilization of antiparkinsonian drugs among schizophrenia patients, owing to the widespread use of atypical antipsychotic drugs that cause fewer extrapyramidal symptoms. An extensive nationwide assessment of prescription patterns among patients with schizophrenia, conducted by the Psychiatric Clinical Pharmacy Research Group revealed a decline in the frequency of antiparkinsonian drug usage, dropping from 58.6% in 2010 to 42.8% in 2016[22]. The trend toward the reduced use of such drugs will lower the incidence of gastrointestinal hypomotility in patients with schizophrenia.

5. Sennoside

Sennoside was independently associated with the development of paralytic ileus. This suggests that severe constipation was present in the paralytic ileus group. Anthraquinone laxatives, such as sennoside, stimulate gastrointestinal motility by acting on Auerbach's plexus[17]. However, some research has reported that prolonged use of anthraquinone laxatives contributes to the degeneration of Auerbach's plexus, leading to reduced gastrointestinal motility[16][18][20]. The present results may indicate that sennoside causes damage to the gastrointestinal plexus. Further investigation is needed concerning the safety implications of prolonged sennoside administration. At present, utilizing sennoside for brief intervals is regarded as a safer approach[8].

6. Magnesium Oxide

Magnesium oxide was independently associated with the development of paralytic ileus. This suggests the extensive utilization of this medication as the first-line drug for constipation in Japan[13]. It also suggests that chronic constipation was present in the

paralytic ileus group. Magnesium oxide is an osmotic laxative that promotes the movement of water into the gastrointestinal tract[14]. Hypermagnesemia should be considered as a potential adverse effect of magnesium oxide. Special attention should be paid when dispensing high doses, for prolonged periods, or to patients with an impaired renal function[25]. Existing studies evaluating the effectiveness and safety of various laxatives concerning antipsychotic-related gastrointestinal hypomotility remain insufficient[5]. Future studies comparing the efficacy and safety of various laxatives are desirable.

7. Limitations of This Study

The limitations of this study were that it was observational, and the level of evidence was limited compared with intervention studies. In addition, items not measured, such as physical activity and diet, may be confounding factors. To achieve a more precise understanding of paralytic ileus in schizophrenia patients, conducting cohort studies or randomized controlled trials would be desirable. These studies should encompass the measurement of variables such as fiber intake and physical activity, recognized as prevalent risk factors for ileus. Assessing the severity of schizophrenia and extent of negative symptoms, which could influence these factors, is also crucial. Additionally, the analysis should include a detailed evaluation of prescription specifics, including antipsychotic drugs, antiparkinsonian drugs, and laxatives, in terms of the dosage and duration.

Conclusion

Caution should be exercised when elderly patients with schizophrenia are prescribed clozapine, haloperidol, or laxatives regarding the development of paralytic ileus. It is necessary to endeavor towards reducing the dosage of antipsychotic medications on a daily basis to prevent a decline in gastrointestinal motility.

We have no conflicts of interest to disclose in connection with this article.

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Table 1: Basic Attributes and Prescriptions for Paralytic Ileus and Non-paralytic Ileus Groups*

	Paralytic ileus group (n=25)		Non-paralytic ileus group (n=3750)		*P*
Male/female, n	14/11		1904/1846		0.602
Age, years	60.2	±13.3	48.9	±16.4	<0.001
Height, cm	163.2	±10.0	163.1	±10.7	0.978
Body weight, kg	55.9	±17.2	60.5	±17.6	0.193
Body mass index, kg/m2	20.6	±5.1	23.0	±11.4	0.303
Chlorpromazine equivalent, mg	1006.1	±600.7	1030.7	±743.1	0.987
Antipsychotic polypharmacy, n %	16	64.0%	2137	57.0%	0.480
Typical antipsychotic use, n %	11	44.0%	806	21.5%	0.006
Haloperidol	6	24.0%	308	8.2%	0.014
Chlorpromazine	2	8.0%	172	4.6%	0.321
Levomepromazine	5	20.0%	404	10.8%	0.126
Atypical antipsychotic use, n %	23	92.0%	3626	96.7%	0.202
Clozapine	2	8.0%	12	0.3%	0.004
Olanzapine	10	40.0%	1355	36.1%	0.688
Quetiapine	4	16.0%	552	14.7%	0.514
Risperidone	8	32.0%	1732	46.2%	0.156
Aripiprazole	2	8.0%	910	24.3%	0.058
Antiparkinsonian drug use, n %	14	56.0%	1354	36.1%	0.039
Biperiden	13	52.0%	1182	31.5%	0.028
Promethazine	2	8.0%	175	4.7%	0.329
Trihexyphenidyl	0	0.0%	125	3.3%	0.430
Laxative use, n %	19	76.0%	2213	59.0%	0.085
Stimulant laxative use, n %	11	44.0%	1579	42.1%	0.848
Sennoside	11	44.0%	831	22.2%	0.009
Picosulfate	2	8.0%	1006	26.8%	0.034
Non-stimulant laxative use, n %	18	72.0%	1123	29.9%	<0.001
Magnesium Oxide	15	60.0%	870	23.2%	<0.001
Lubiprostone	1	4.0%	248	6.6%	0.502
Mosapride	5	20.0%	203	5.4%	0.010
Dai-kenchu-to	4	16.0%	182	4.9%	0.032
Probiotics	3	12.0%	306	8.2%	0.336

Data are expressed as n% or mean ± standard deviation.

*Prescriptions: antipsychotics, antiparkinsonian drugs, and laxatives.

Table 2 Risk factors for paralytic ileus based on logistic regression analysis

	z	OR	95% CI	*P*
Age	0.052	1.053	1.023-1.084	0.001
Haloperidol	1.125	3.079	1.192-7.954	0.020
Clozapine	4.274	71.815	12.838-401.733	<0.001
Sennoside	0.865	2.376	1.048-5.388	0.038
Picosulfate	-1.332	0.264	0.061-1.147	0.076
Magnesium Oxide	1.263	3.536	1.544-8.099	0.003

Model $\chi 2$ test $P<0.01$, Hosmer-Lemeshow test $P=0.543$

OR: Odds ratio. CI: Confidence interval