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Case-controlled Study on Risk Factors for the Development of Constipation in Hospitalized Patients

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Constipation is a common problem in hospitalized patients; however, the relative risks of its development with various factors have not been clarified. To clarify the risk factors associated with constipation, we performed a case-controlled study of 165 hospitalized patients who were not laxative users on admission. They were divided into case ($n=35$) and control ($n=130$) groups according to laxative administration during hospitalization. Comparison of the patient backgrounds in the two groups revealed significant differences in the activities of daily living, length of fasting, rest level on admission, cerebrovascular disease, and administration of hypnotics. Multiple logistic regression analysis using these five factors as autonomous variables showed that administration of hypnotics (odds ratio, 2.79; 95% confidence interval, 1.10–7.06; $p=0.031$) was significantly related to laxative use. Therefore, the administration of hypnotics may be the principal cause of constipation development in hospitalized patients and they should be used with caution.

Key words——constipation; hypnotics; laxative; adverse drug reaction; hospitalized patient; risk factor

INTRODUCTION

Constipation is one of the most common gastrointestinal complaints[1–3] and is associated with implications for healthcare costs and patients' quality of life.[4–6]. Constipation more frequently occurs in hospitalized patients[7] and the reasons for this are multi-factorial.[8] Factors known to increase the risk of constipation are age, diet, being bedridden, and drugs.[8–12] In particular, adverse effects and inappropriate use of drugs may be the principal causes.[13,14] A few previous reports have shown that constipating drugs are antidepressants, calcium channel blockers, iron preparations, opioids, diuretics, antihistamines, antispasmodics, anticonvulsants, and aluminum antacids.[15,16] In addition, hypnotics were strongly related to constipation in our recent cross-sectional study;[17] however, the degree of influence of the various factors for the development of constipation is uncertain. Moreover, little is known about the relative risks among individual drugs in the hospital setting. In the present study, we analyzed the factors affecting the development of constipation in hospitalized patients.

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PATIENTS AND METHODS

Patients This study was approved by the Ethics Committee of Nagasaki University Graduate School of Biomedical Sciences and was conducted at Kitakyushu City Yahata Hospital. The patients included in the study were admitted to the internal medicine ward from February to April 2007, and the cardiovascular disease ward from November 2007 to January 2008. Patients who were transferred from other hospitals, were prescription or over-the-counter laxative users on admission, or were oldest old (85 years or older,[18] because of their low functional status and decreased physical activity) were excluded, as were patients who were hospitalized for less than 7 days. The exclusion criteria of length of hospitalization set in reference to the normal stool frequency limits of three or more bowel movements weekly up to three movements daily.[19]

Methods The authors interviewed the patients directly at any time, and confirmed the drugs which they took before admission and during hospitalization, and recorded them. The administration of laxatives to these patients during hospitalization was surveyed. The laxatives were defined based on the Standard Commodity Classification of Japan, but drugs

prescribed prior to examination or for surgical pretreatment, and lactulose used in the treatment of hyperammonemia were excluded.

The patients were divided into case and control groups according to the administration of laxatives. Newly administrated drugs were surveyed retrospectively from the day of laxative administration in the case group and from the day of discharge in the control group. Newly administrated drugs were defined as follows: non-use before admission, increasing dosage, and/or changing the route of administration such as from oral to injection, but changes to other brands were excluded.

For these two groups, patient backgrounds were compared with respect to length of hospitalization, age, gender, number of regularly used drugs on admission (excluding laxatives), history of allergy or adverse drug reactions, history of gastrointestinal resection, body mass index, activities of daily living (ADL; the criterion using an independent degree of daily living in the handicapped elderly), days of fasting, rest level on admission, total parenteral nutrition therapy, type of underlying disease (a disease class was excluded if fewer than 5 patients had it), and the types of newly administrated drugs (a drug class was excluded if it had been administered to fewer than 5 patients). Significantly different factors that could be specific to constipation were identified. Multivariable analysis was performed using these factors excluding length of hospitalization. Drugs significantly related to constipation were investigated in further detail.

Statistical Analysis To compare the two groups by means of continuous variables, the two-tailed Mann-Whitney test was used. For discrete variables, the χ^2 or Fisher's exact test was employed. Multivariable analysis was applied to multiple logistic regression analysis. $p<0.05$ was considered significant. Statistical analyses were performed using Stat View-J version 5.0 (SAS Institute Inc.).

RESULTS

Patients A total of 341 patients were examined, of which 172 had been admitted to the internal medicine ward and 169 to the cardiovascular disease ward. Those excluded were 13 who had been transferred from other hospitals, 99 who had been laxative users, 21 who were 85 years or older, and 43 who had been hospitalized for less than 7 days. This left 165 (male 103, female 62) patients whose data were analyzed in the study.

The subjects were not suffering from Hirschsprung disease or sigmoid dolichocolon with a congenital cause of organic constipation, and were not pregnant. There were 4 patients with colon cancer, 3 with hypothyroidism, 2 with ileus, and 1 with Parkinson's disease.

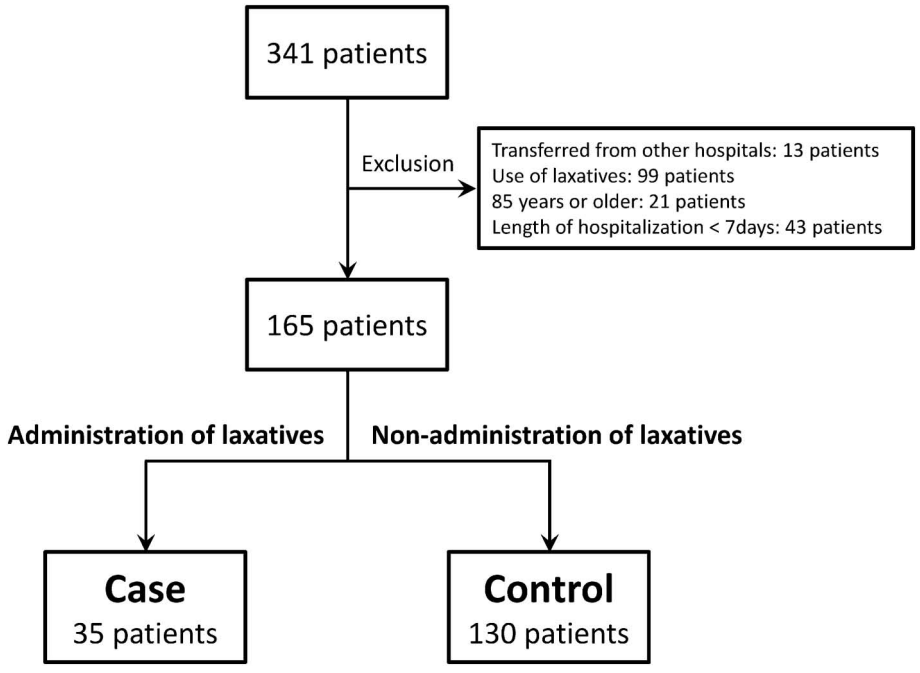

Fig. 1. Classification of Case and Control Groups According to Administration of Laxatives

Classification of Case and Control Groups Of the 165 patients, 35 received laxatives during hospitalization; therefore, 35 were classified into the case group, and 130 into the control group (Fig. 1). There were no cases of preventive administration of laxatives for the constipating drugs such as opioids and antipsychotics.

Comparison of Patient Backgrounds between Case and Control Groups Patient backgrounds and newly administrated drugs in the two groups are compared in Tables 1 and 2, respectively. Significant differences were found for the five factors of ADL ($p=0.003$), days of fasting ($p=0.014$), rest level on admission ($p=0.003$), cerebrovascular disease ($p=0.011$), and administration of hypnotics ($p=0.003$).

Multivariable Analysis Multiple logistic regression analysis was performed using the autonomous variables of significant differences in the five factors from the patient backgrounds and new administrated drugs between the two groups. As a result, administration of hypnotics (odds ratio, 2.79; 95% confidence interval, 1.10–7.06; $p=0.031$) was found to be significantly related to the use of laxatives (Fig. 2). Furthermore, to check for the possibility of bias, patient backgrounds and newly administrated drugs in the patients who received hypnotics between the case and control groups are compared in Table 3 and 4, respectively. Significantly different factors were not found in the two groups.

Types of Hypnotics Six kinds of hypnotics

Table 1. Comparison of Patient Backgrounds between Case and Control Groups

Patient backgrounds	Overall ($n=165$)	Case ($n=35$)	Control ($n=130$)	p-value
Length of hospitalization (days)	20 (7–182)	29 (11–182)	17 (7–137)	$<0.001^{c}$
Age (years)	67 (18–83)	69 (39–83)	66.5 (18–83)	0.185^{c}
Gender (male/female)	103/62	22/13	81/49	0.952^{b}
Number of regularly used drugs	2 (0–16)	2 (0–11)	2 (0–16)	0.549^{c}
History of allergy or adverse drug reactions	23	2	21	0.089^{a}
History of gastrointestinal resection	15	6	9	0.068^{a}
Body mass index (kg/m^2)	23.1 (11.5–53.3)	22.7 (12.4–30.9)	23.1 (11.5–53.3)	0.984^{c}
ADL independence scale (dependence/independence)	81/84	25/10	56/74	0.003^{b}
Defecation interval before admission (days)	1 (0.2–7)	1 (0.33–7)	1 (0.2–7)	0.064^{c}
Length of fasting (days)	0 (0–18)	0 (0–18)	0 (0–11)	0.014^{c}
Rest level on admission (bed rest/non-bed rest)	86/79	26/9	60/70	0.003^{b}
Total parenteral nutrition therapy	5	2	3	0.287^{a}
Underlying diseases				
Hypertension	81	19	62	0.489^{b}
Diabetes mellitus	47	7	40	0.210^{b}
Hyperlipidemia	30	3	27	0.097^{b}
Cerebrovascular disease	18	8	10	0.011^{b}
Bronchial asthma	11	0	11	0.066^{a}
Chronic obstructive pulmonary disease	9	3	6	0.292^{a}
Renal failure	7	2	5	0.459^{a}
Heart failure	28	6	22	0.975^{b}
Liver disease	29	5	24	0.565^{b}
Ischemic heart disease	30	6	24	0.858^{b}
Gastric cancer	6	3	3	0.110^{a}
Hepatocellular carcinoma	5	1	4	0.713^{a}
Lung cancer	6	3	3	0.110^{a}
Depression	5	2	3	0.287^{a}
Anemia	13	2	11	0.452^{a}

Age, number of regularly used drugs, body mass index, and defecation interval before admission indicate median (range). Other data indicate number of patients. Laxatives were excluded from the number of regularly used drugs. Body mass index was measured in 120 patients (23 cases and 97 controls). Defecation intervals before admission were self-reported, and were surveyed in 138 patients (23 cases and 115 controls). ADL denotes activities of daily living. Statistical analyses were applied to (a) Fisher's exact test, (b) χ^2-test, (c) Mann-Whitney test.

Table 2. Comparison of Administrated Drugs between Case and Control Groups

Drugs	Overall (n=165)	Case (n=35)	Control (n=130)	p-value
Calcium channel blockers	24	2	22	0.095[b]
Angiotensin converting enzyme inhibitors	12	1	11	0.231[a]
Angiotensin II receptor blockers	24	4	20	0.556[b]
β-Blockers	11	2	9	0.576[a]
Diuretics	29	9	20	0.154[b]
α-Human atrial natriuretic peptide	13	4	9	0.286[a]
Coronary vasodilators	19	6	13	0.187[a]
HMG-CoA reductase inhibitors	22	2	20	0.108[a]
Anticoagulants	22	6	16	0.310[a]
Antiplatelet drugs	23	2	21	0.089[a]
Antiarrhythmic drugs	9	2	7	0.606[a]
Histamine-2 receptor antagonists	37	12	25	0.058[b]
Proton pump inhibitors	17	4	13	0.507[a]
Antacids containing aluminum	5	0	5	0.299[a]
Antipsychotics	12	5	7	0.082[a]
Hypnotics	32	13	19	0.003[b]
Antianxiety drugs	20	5	15	0.424[a]
NSAIDs including low-dose aspirin	69	10	59	0.073[b]
Hypoglycemic drugs	34	5	29	0.298[b]
α-Glucosidase inhibitors	9	1	8	0.394[a]
Theophylline	8	1	7	0.464[a]
Steroids	14	3	11	0.605[a]
Antiallergic drugs	8	0	8	0.142[a]
Opioids	17	6	11	0.120[a]
Potassium preparations	11	2	9	0.576[a]
Iron preparations	8	0	8	0.142[a]
Hemostatics	16	2	14	0.296[a]
Cold remedies	12	1	11	0.231[a]
Antipyretic analgesics	9	1	8	0.394[a]
Antimicrobials	102	22	80	0.887[b]
Expectorants	11	2	9	0.576[a]
Antitussives	11	0	11	0.066[a]
Probiotics	24	4	20	0.556[b]
Prokinetics (Dopamine antagonists)	19	5	14	0.374[a]
Glycyrrhizin preparations	8	1	7	0.464[a]
Protease inhibitors	8	3	5	0.227[a]

NSAIDs denotes non-steroidal anti-inflammatory drugs. Statistical analyses were applied to (a) Fisher's exact test, (b) χ^2-test. Data indicate number of patients.

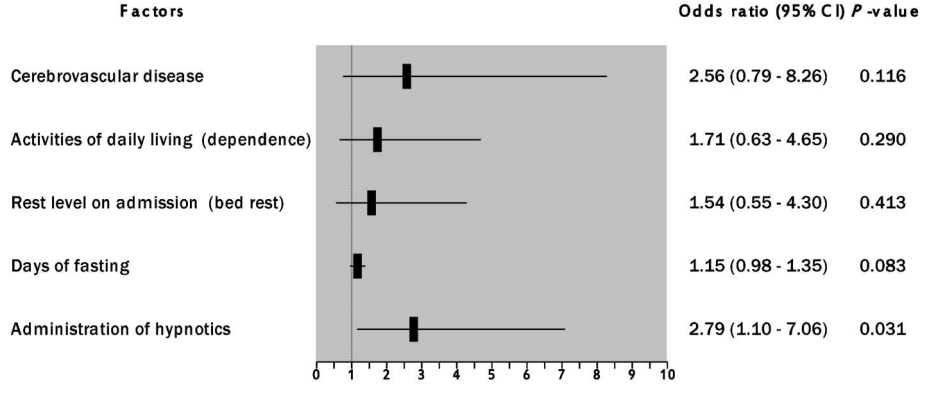

Fig. 2. Multiple Logistic Regression Analysis for the Risk Factors Related to Constipation during Hospitalization

Table 3. Comparison of Patient Backgrounds in Hypnotics Users between Case and Control Groups

Patient backgrounds	Overall (n=32)	Case (n=13)	Control (n=19)	p-value
Length of hospitalization (days)	23 (8–75)	23 (14–75)	23 (8–60)	0.645[b]
Age (years)	66.5 (35–81)	60 (39–80)	69 (35–81)	0.878[b]
Gender (male/female)	22/10	9/4	13/6	0.636[a]
Number of regularly used drugs	3 (0–14)	1.5 (0–11)	3 (0–14)	0.935[b]
History of allergy or adverse drug reactions	6	1	5	0.197[a]
History of gastrointestinal resection	2	2	0	0.157[a]
Body mass index (kg/m^2)	21.8 (15.4–42.1)	21.8 (15.4–26.6)	21.5 (16.4–42.1)	0.949[b]
ADL independence scale (dependence/independence)	20/12	10/3	10/9	0.153[a]
Defecation interval before admission (days)	1 (0.2–3)	1 (0.33–1)	1 (0.2–3)	0.194[b]
Length of fasting (days)	0 (0–17)	1 (0–17)	0 (0–3)	0.098[b]
Rest level on admission (bed rest/non-bed rest)	24/8	11/2	13/6	0.271[a]
Total parenteral nutrition therapy	2	2	0	0.157[a]
Underlying diseases				
Hypertension	12	6	6	0.320[a]
Diabetes mellitus	8	2	6	0.271[a]
Hyperlipidemia	7	1	6	0.120[a]
Cerebrovascular disease	3	3	0	0.058[a]
Bronchial asthma	4	0	4	0.108[a]
Chronic obstructive pulmonary disease	4	2	2	0.542[a]
Renal failure	1	0	1	0.594[a]
Heart failure	6	2	4	0.530[a]
Liver disease	6	2	4	0.530[a]
Ischemic heart disease	7	2	5	0.389[a]
Gastric cancer	1	1	0	0.406[a]
Hepatocellular carcinoma	1	0	1	0.594[a]
Lung cancer	2	2	0	0.157[a]
Depression	2	1	1	0.655[a]
Anemia	3	2	1	0.356[a]

Age, number of regularly used drugs, body mass index, and defecation interval before admission indicate median (range). Other data indicate number of patients. Laxatives were excluded from the number of regularly used drugs. Body mass index was measured in 23 patients (9 cases and 14 controls). Defecation intervals before admission were self-reported, and were surveyed in 24 patients (7 cases and 17 controls). ADL denotes activities of daily living. Statistical analyses were applied to (a) Fisher's exact test, (b) Mann-Whitney test.

were used for the subjects. Examination of the types of hypnotics revealed a higher proportion of constipation in patients who had been injected with a drug such as midazolam. Also, benzodiazepines showed a tendency to increase the proportion than non-benzodiazepines such as zolpidem tartrate and zopiclone (Table 5). The elapsed times to the administration of laxatives after the first administration of hypnotics were varying from 3 to 22 days, and the median was 7 days and the mode was 3 days (Fig. 3).

DISCUSSION

The relative risks of various factors for hospitalization-induced constipation have not yet been reported. Thus, this study aimed at clarifying the factors affecting the development of constipation in hospitalized patients. Our data indicated a causal relation between hypnotics and the use of laxatives with small bias. The hypnotics may contribute strongly to the development of constipation. Most reports have shown that constipation can be induced by most central nervous system drugs; however, hypnotics are not really known as drugs causing constipation.

One possible mechanism of constipation by hypnotics is based on anticholinergic and myorelaxant effects. The pharmacological actions of hypnotics are similar to those of anti-anxiety drugs, and their anticholinergic effects are weaker than those of anticholinergic drugs, such as antipsychotics; however, our data showed that only hypnotics were significant-

Table 4. Comparison of Administrated Drugs in Hypnotics Users between Case and Control Groups

Drugs	Overall (n=32)	Case (n=13)	Control (n=19)	p-value
Calcium channel blockers	4	2	2	0.542[a]
Angiotensin converting enzyme inhibitors	4	1	3	0.458[a]
Angiotensin II receptor blockers	5	2	3	0.683[a]
β-Blockers	2	1	1	0.655[a]
Diuretics	9	5	4	0.248[a]
α-Human atrial natriuretic peptide	6	2	4	0.530[a]
Coronary vasodilators	7	2	5	0.389[a]
HMG-CoA reductase inhibitors	6	1	5	0.197[a]
Anticoagulants	9	3	6	0.455[a]
Antiplatelet drugs	6	1	5	0.197[a]
Antiarrhythmic drugs	5	2	3	0.683[a]
Histamine-2 receptor antagonists	19	9	10	0.348[b]
Proton pump inhibitors	6	3	3	0.467[a]
Antacids containing aluminum	1	0	1	0.594[a]
Antipsychotics	7	3	4	0.611[a]
Antianxiety drugs	10	4	6	0.636[a]
NSAIDs including low-dose aspirin	17	6	11	0.513[b]
Hypoglycemic drugs	9	4	5	0.545[a]
α-Glucosidase inhibitors	2	0	2	0.345[a]
Theophylline	3	0	3	0.195[a]
Steroids	5	2	3	0.683[a]
Antiallergic drugs	2	0	2	0.345[a]
Opioids	10	6	4	0.133[a]
Potassium preparations	3	1	2	0.644[a]
Iron preparations	0	0	0	—
Hemostatics	5	1	4	0.308[a]
Cold remedies	3	1	2	0.644[a]
Antipyretic analgesics	2	1	1	0.655[a]
Antimicrobials	25	10	15	0.719[a]
Expectorants	0	0	0	—
Antitussives	1	0	1	0.594[a]
Probiotics	3	1	2	0.644[a]
Prokinetics (Dopamine antagonists)	5	3	2	0.317[a]
Glycyrrhizin preparations	3	1	2	0.644[a]
Protease inhibitors	5	2	3	0.683[a]

NSAIDs denotes non-steroidal anti-inflammatory drugs. Statistical analyses were applied to (a) Fisher's exact test, (b) χ^2-test.

Table 5. Types of Hypnotics and Proportion of Constipation

Route of administration		Generic name	
Injection	6/10(60%)	Midazolam	6/9 (67%)
		Flunitrazepam	0/1 (0%)
Oral	7/25(28%)	Zolpidem tartrate	5/18(28%)
		Zopiclone	0/3 (0%)
		Triazolam	1/2 (50%)
		Brotizolam	1/2 (50%)

Data indicate number of patients in case group/number of hypnotic users (%).

ly related to constipation. One explanation may be a difference in the timing of drug administration. Enterokinesis is active during sleep when the parasympathetic nervous system is dominant. This means that hypnotics taken before going to bed are maximally active during sleep; therefore, they may inhibit enterokinesis and lead to the occurrence of constipation. Also, the administration of laxatives was frequent with hypnotic injections rather than oral agents, and with benzodiazepines rather than non-benzodiazepines which exhibit fewer myorelaxant

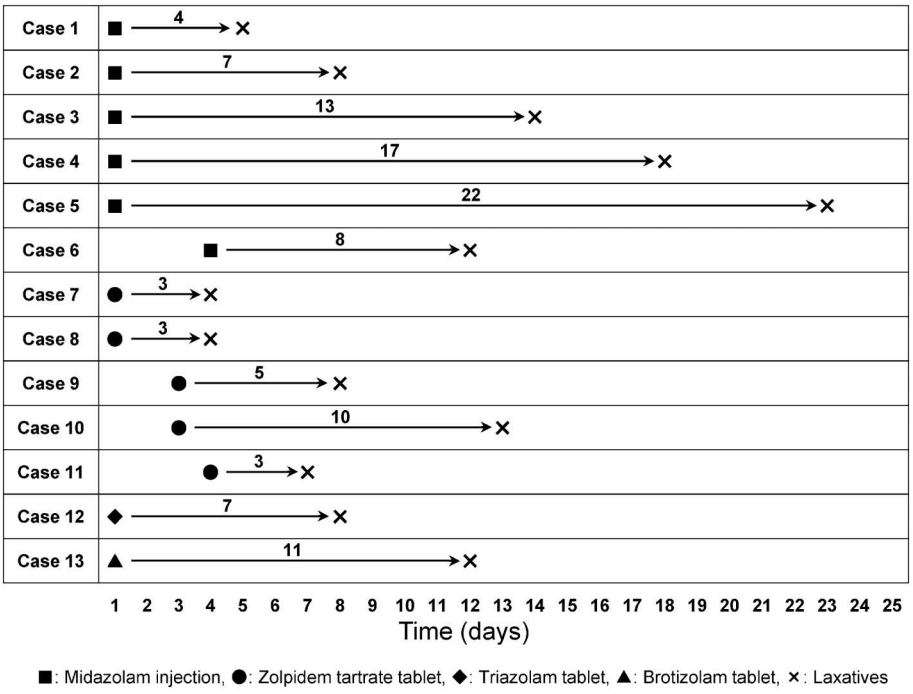

Fig. 3. Elapsed Time for the Administration of Laxatives in Case Group
The number in the figure indicates the elapsed days for the administration of laxatives after the first administration of hypnotics in 13 patients.

effects.[20] Thus, the pharmacological action of hypnotics seems to affect the occurrence of constipation.

The median time to the administration of laxatives after the hypnotics use was 7 days, and the mode was 3 days. Constipation may occur more for one week after the beginning of hypnotic administration. In particular, this period should be monitored for the development of constipation with caution.

In fact, the development of constipation in hospitalized patients is caused by multiple factors and therefore does not result from a single factor. Comparison of the cases and controls showed significant differences in the patient backgrounds of ADL, days of fasting, rest level, and cerebrovascular disease, which are already known to cause constipation. Also, while females suffer from constipation more than males according to epidemiological studies,[1–3] hospitalization-induced constipation may be little influenced by gender.

In Japan, constipation as an adverse drug reaction is described in the package inserts of about 600 clinically used drugs. Constipation can be induced by many drugs; for example, the constipating effect of opioids is widely acknowledged.[21] As for opioid use in this study, most cases were administrated pentazocine injection as needed, and there was little regular administration.

Although our results are informative for clinical pharmacy practice, our study has some limitations. We examined about the types of drugs, but the dosage and the duration of administration were not considered. Also, the subjects were limited to the internal medicine and cardiovascular disease wards of our hospital. More study needs to be done on the administration of several types of drugs; the number of such patients in this study was too small to reach any conclusions.

On the other hand, it has been reported that sleep disorders are associated with gastrointestinal symptoms,[22–24] so constipation might be induced by sleep disorders. Our results indicated a significant relationship between hypnotics and the use of laxatives, but it is not clear whether this is due to the clinical conditions of sleep disorders or the adverse effects of hypnotics. We aim to clarify this, and the results are due to be reported soon.

In hospitalized patients, here we conclude that the strongest risk factor with the development of constipation is the administration of hypnotics. This view is also supported by our previous cross-sectional study.[17] Therefore, the administration of hypnotics may be undesirable for patients who should avoid development of constipation such as ileus patients. Care should be taken to prevent hypnotics-induced consti-

pation.

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