—Regular Article—

Cross-sectional Study on Relationship between Constipation and Medication in Consideration of Sleep Disorder

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(Received January 14, 2011; Accepted May 17, 2011; Published online May 20, 2011)

Constipation can be caused by adverse drug reactions as a result of many drugs and might be induced by sleep disorders; however, the relative risk of its occurrence with individual drugs and the influence of sleep conditions have not been clarified. To clarify the relationship between constipation and various drugs in consideration of sleep disorders, we investigated the self-reported bowel habits, use of laxatives, and the Athens Insomnia Scale (AIS, a self-administered psychometric instrument to measure insomnia) in 344 inpatients on admission. They were divided into a constipation group (self-reported bowel habits of ''Constipation'' or ''Occasional constipation'' and/or use of laxatives, $n=161$) and a non-constipation group (both ''Normal'' and the non-use of laxatives, $n=183$). A comparison of the backgrounds of the two patient groups revealed significant differences in age, gender, number of used drugs, AIS score, hypothyroidism, chronic obstructive pulmonary disease, use of diuretics, coronary vasodilators, thyroid hormones, non-steroidal anti-inflammatory drugs, proton pump inhibitors, antidepressants, anti-anxiety drugs, and hypnotics. Multiple logistic regression analysis using these fourteen factors as autonomous variables showed that age (odds ratio [OR], 1.03; 95% confidence interval [CI], 1.01–1.04; $p=0.007$), female gender (OR, 1.96; 95% CI, 1.21–3.18; $p=0.006$), the AIS score (OR, 1.10; 95% CI, 1.02–1.18; $p=0.010$), and the use of hypnotics (OR, 2.33; 95% CI, 1.30–4.16; $p=0.004$) were significantly related to constipation; therefore, as hypnotics appear more likely to cause constipation than other drugs, they should be used with caution.

Key words——constipation; hypnotic; sleep disorder; adverse drug reaction

INTRODUCTION

Constipation is one of the most common gastrointestinal complaints[1–3] and is associated with adverse implications for economic costs and patients' quality of life.[4–6] Most epidemiological studies have reported prevalence rates between 12% and 19% in the general population.[1–3] These high rates make constipation a major public health issue.

The reasons for constipation are multi-factorial. In general, constipation occurs more frequently in older adults and females.[1–3,7–9] Secondary constipation is induced by diseases such as hypothyroidism.[7–9] Further, constipation is an adverse effect caused by many drugs.[7–9] A few previous reports have shown that constipating drugs are antidepressants, calcium channel blockers, iron preparations, opioids, diuretics, antihistamines, antispasmodics, anticonvulsants, aluminum antacids, and hypnotics.[10–13]

It has been reported that sleep disorders are associated with gastrointestinal symptoms,[14] and therefore constipation might be induced by sleep disorders. Epidemiological surveys[15,16] by Ono *et al.* have suggested a relationship between bowel movement abnormality, including constipation and sleep disorder. They also studied this relation by actigraphy measurement and fecal flora analysis;[17] however, those studies did not consider the influence of drug use. On the other hand, hypnotics were strongly related to constipation in our recent studies,[12,13] but it was not clear whether this was due to the clinical condition of sleep disorder or adverse effects of the hypnotics.

Adverse effects and the inappropriate use of drugs may be the principal causes of constipation;[9,18] however, little is known about the relative risks of individual drugs. Moreover, with respect to the con-

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sideration of both sleep conditions and drug use, no reports are available. In the present study, we analyzed the relationship between constipation and drugs by considering the patient background, including sleep conditions.

PATIENTS AND METHODS

Patients This study was approved by the Ethics Committee of the Nagasaki University Graduate School of Biomedical Sciences and was conducted at Kitakyushu City Yahata Hospital. The patients included in the study consented to the study after admission to the hospital from February 2007 to October 2009.

Methods The self-reported bowel habits, use of laxatives, defecation frequency, and sleep conditions of these patients were surveyed on admission. Bowel habits, based on subjectivity, were classified into five groups of ''Normal'', ''Constipation'', ''Occasional constipation'', ''Diarrhea'', or ''Constipation and diarrhea''. The laxatives were prescription or over-the-counter (OTC) drugs indicated for constipation, but drugs prescribed prior to examination or for operation pre-treatment, and lactulose used in the treatment of hyperammonemia were excluded. The drugs were categorized based on the Standard Commodity Classification of Japan. Defecation frequencies were expressed as the number of days between defecation (defecation interval). The sleep conditions were evaluated using the Athens Insomnia Scale (AIS),[19] a self-administered psychometric instrument consisting of eight items. The items assessed difficulty with sleep induction, awakening during the night, early morning awakening, total sleep time, overall quality of sleep, and problems with sense of well-being, functioning, and sleepiness during the day. Each item was rated 0 to 3, (with 0 corresponding to ''no problem at all'' and 3 ''very serious problem''); therefore, the total AIS score ranges from 0 (denoting absence of any sleep-related problem) to 24 (representing the most severe degree of insomnia).[19] The total score of 6 or more in the AIS showed the presence of insomnia with high sensitivity and specificity.[20]

The patients included in the analysis were those who reported bowel habits of ''Normal'', ''Constipation'', and ''Occasional constipation''. Patients who reported ''Diarrhea'' and ''Constipation and diarrhea'' were excluded from the study. The patients were divided into two groups according to their self-reported bowel habits and use of laxatives. The constipation group reported ''Constipation'' or ''Occasional constipation'' and/or the use of laxatives, and the non-constipation group reported both ''Normal'' and the non-use of laxatives. For these two groups, patient backgrounds were compared with respect to age, gender, number of used drugs (excluding laxatives), history of allergy or adverse drug reactions, history of gastrointestinal resection, body mass index, AIS score, type of disease (a disease class was excluded if fewer than 5 patients had it), and the types of drugs taken (a drug class was excluded if fewer than 5 patients were taking those drugs). Significantly different factors that could be specific to constipation were identified. Multivariable analysis was performed using these factors. 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 and Self-reported Bowel Habits A total of 372 patients were examined, 165 of which had been admitted to the department of cardiovascular disease, 143 to internal medicine, 27 to orthopedics, 22 to surgery, 11 to neurosurgery, 1 to ophthalmology, 1 to otolaryngology, 1 to urology, and 1 to plastic surgery.

Of the 372 patients, 212 (57.0%) reported bowel habits of ''Normal'', 50 (13.4%) ''Occasional constipation'', 82 (22.0%) ''Constipation'', 20 (5.4%) ''Diarrhea'', and 8 (2.2%) ''Constipation and diarrhea''. Those excluded were the 20 who reported ''Diarrhea'' and 8 who reported ''Constipation and diarrhea''. This left 344 (male 174, female 170) 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 3 patients with ileus and 2 with Parkinson's disease. Only 1 patient was using opioids.

Use of Laxatives and Defecation Frequency Of

the 344 patients, 119 (34.6%) were using laxatives. Among 119 laxative users, 70 (58.9%) were taking them regularly and 49 (41.1%) occasionally, and 100 (84.0%) were using prescription drugs, 18 (15.1%) were using OTC drugs, and 1 (0.8%) was using both prescription and OTC drugs. In 28 (23.5%) of cases, two or more laxatives were used together. The most commonly taken laxatives were sennoside in 72 patients, magnesium oxide in 51, bisacodyl in 8, glycerin enema in 4, rhubarb-containing preparations in 4, and sodium picosulfate in 2.

Defecation intervals in the patients with ''Normal'', ''Occasional constipation'', and ''Constipation'' bowel habits were a mean of 1.1 (median 1.0), 1.9 (2.0), and 2.7 (2.0) days, respectively.

Classification of Constipation and Non-constipation Groups Of the 212 patients who reported bowel habits of ''Normal'', 29 were using laxatives; therefore, 161 were classified into the constipation group (''Constipation'' or ''Occasional constipation'' and/or use of laxatives), and 183 were classified into the non-constipation group (both ''Normal'' and non-use of laxatives) (Fig. 1).

Comparison of Patient Backgrounds between Constipation and Non-constipation Groups Patient backgrounds and drugs taken by the two groups are compared in Tables 1 and 2, respectively. Significant differences were found for fourteen factors of age ($p<0.001$), gender ($p=0.002$), number of used drugs ($p<0.001$), AIS score ($p<0.001$), hypothyroidism ($p=0.046$), chronic obstructive pulmonary disease ($p=0.044$), use of diuretics ($p=0.036$), use of coronary vasodilators ($p=0.013$), use of thyroid hormones ($p=0.046$), use of non-steroidal anti-inflammatory drugs (NSAIDs), including low-dose aspirin ($p=0.019$), use of proton pump inhibitors ($p=0.038$), use of antidepressants ($p=0.004$), use of anti-anxiety drugs ($p=0.047$), and use of hypnotics ($p<0.001$).

The distribution of the total AIS scores in the constipation group was different from that in the non-constipation group, as depicted in Fig. 2. Furthermore, the proportion of the total AIS score of 6 or more in the constipation group was significantly higher than in the non-constipation group ($p<0.001$) (Fig. 3).

Multivariable Analysis Multiple logistic regression analysis was performed using the dependent variables of constipation and non-constipation, and the autonomous variables of the significant difference of the fourteen factors from the patient backgrounds between the two groups (Table 3). As a result, age (odds ratio [OR], 1.03; 95% confidence interval [CI], 1.01–1.04; $p=0.007$), female gender (OR, 1.96; 95% CI, 1.21–3.18; $p=0.006$), the AIS score (OR, 1.10; 95% CI, 1.02–1.18; $p=0.010$), and the

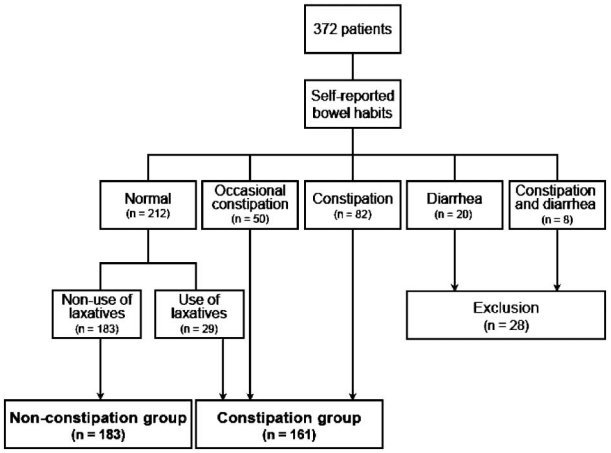

Fig. 1. Classification of Constipation and Non-constipation Groups according to Self-reported Bowel Habits and Use of Laxatives

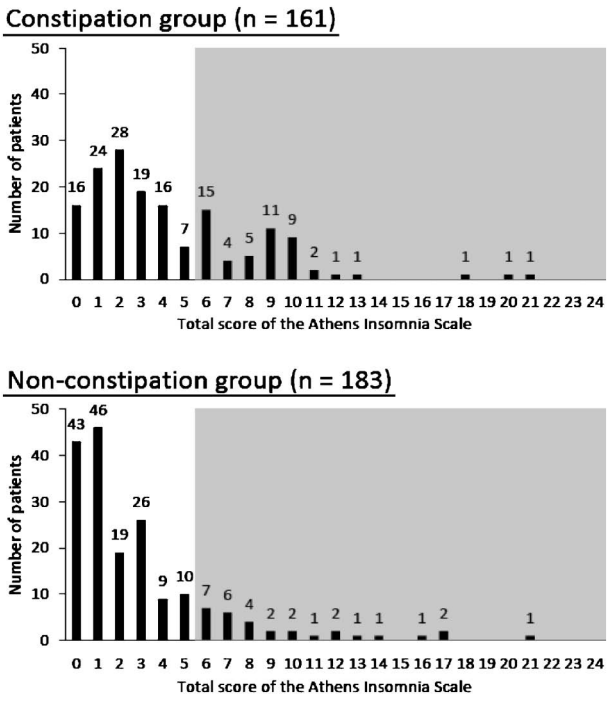

Fig. 2. Bar Graph of the Number of Patients per Total Score of Athens Insomnia Scale in Constipation and Non-constipation Groups

The numbers on top of the bars represent counts of patients per score of Athens Insomnia Scale.

Table 1. Comparison of Patient Backgrounds between Constipation and Non-constipation Groups

Patient backgrounds	Overall (n=344)	Constipation group (n=161)	Non-constipation group (n=183)	p value
Age (years)	70.5 (19–94)	73 (19–91)	67 (23–94)	<0.001[c]
Gender (male/female)	174/170	67/94	107/76	0.002[a]
Number of used drugs (excluding laxatives)	5 (0–27)	6 (0–21)	4 (0–27)	<0.001[c]
History of allergy or adverse drug reactions	65	26	39	0.222[a]
History of gastrointestinal resection	27	15	12	0.342[a]
Body mass index (kg/m^2)	23.4 (12.4–53.3)	23.4 (12.4–53.3)	23.6 (15.3–42.1)	0.082[c]
Athens Insomnia Scale	2 (0–21)	3 (0–21)	2 (0–21)	<0.001[c]
Underlying diseases				
Hypertension	192	86	106	0.401[a]
Diabetes mellitus	116	56	60	0.696[a]
Hyperlipidemia	93	42	51	0.710[a]
Hypothyroidism	12	9	3	0.046[a]
Cerebrovascular disease	40	23	17	0.149[a]
Bronchial asthma	26	9	17	0.195[a]
Chronic obstructive pulmonary disease	17	12	5	0.044[a]
Renal failure	15	6	9	0.589[a]
Heart failure	52	24	28	0.919[a]
Liver disease	38	14	24	0.192[a]
Ischemic heart disease	115	62	53	0.061[a]
Gastroduodenal ulcer	8	4	4	>0.999[b]
Gastric cancer	10	5	5	>0.999[b]
Colon cancer	10	7	3	0.199[b]
Liver cancer	8	4	4	>0.999[b]
Lung cancer	5	0	5	0.063[b]
Depression	15	9	6	0.295[a]
Anemia	15	9	6	0.295[a]

Age, number of used drugs, body mass index, and Athens Insomnia Scale indicate medians (ranges). Other data indicate number of patients. Statistical analyses were applied to (a) χ^2-test, (b) Fisher's exact test, (c) Mann-Whitney test.

use of hypnotics (OR, 2.33; 95% CI, 1.30–4.16; p=0.004) were significantly related to constipation.

Types of Hypnotics The types of hypnotics taken are shown in Table 4. There were no significant differences in the proportion of constipation among individual drugs, but benzodiazepines showed a tendency to increase the proportion than non-benzodiazepines. In the examination of the number of hypnotics taken, of the 109 patients who were taking one kind of hypnotic, 69 (63.3%) were classified into the constipation group. As for patients taking more than two kinds, 18 of 28 (64.3%) were classified into the constipation group. The proportion of constipation with the regular and occasional use of hypnotics was 70 of 110 (63.6%) and 17 of 27 (63.0%), respectively. No difference was detected in the number of hypnotics taken and frequency of hypnotic use.

DISCUSSION

Our previous studies on the relationship between constipation and drugs showed that hypnotics were significantly related to constipation;[12,13] however, sleep conditions were not taken into consideration. The aim of the present study was to determine whether there is a relationship between hypnotics and constipation, with considering potential confounding factors such as sleep disorders. Our data indicated a significant relationship between hypnotics and constipation.

Previous reports[7–9] have shown that constipation can be induced by most central nervous system drugs, including hypnotics; for example, antidepressants are known as drugs causing constipation, while not much is known about hypnotics.

One possible mechanism of constipation caused by

Table 2. Comparison of Taken Drugs between Constipation and Non-constipation Groups

Drugs	Overall (n=344)	Constipation group (n=161)	Non-constipation group (n=183)	p value
Calcium channel blockers (CCBs)	139	65	74	0.990[a]
Angiotensin converting enzyme inhibitors	22	11	11	0.756[a]
Angiotensin II receptor blockers	100	41	59	0.167[a]
α-Blockers	18	11	7	0.211[a]
β-Blockers	40	16	24	0.359[a]
Diuretics	65	38	27	0.036[a]
Coronary vasodilators excluding CCBs	70	42	28	0.013[a]
HMG-CoA reductase inhibitors	82	42	40	0.358[a]
Bezafibrates	7	3	4	$>$0.999[b]
Anticoagulants (warfarin)	17	8	9	0.983[a]
Antiplatelet drugs	42	22	20	0.439[a]
Antiarrhythmic drugs	18	8	10	0.837[a]
Digitalis	12	5	7	0.717[a]
Urate-lowering drugs	30	17	13	0.257[a]
Thyroid hormones	12	9	3	0.046[a]
Prostaglandin analogues	19	11	8	0.319[a]
NSAIDs including low-dose aspirin	123	68	55	0.019[a]
Histamine-2 receptor antagonists	73	39	34	0.201[a]
Proton pump inhibitors	44	27	17	0.038[a]
Antipsychotics	16	9	7	0.438[a]
Antidepressants	19	15	4	0.004[a]
Antianxiety drugs	56	33	23	0.047[a]
Hypnotics	137	87	50	$<$0.001[a]
Antiepileptics	7	5	2	0.259[b]
Antiparkinson drugs	7	5	2	0.259[b]
Muscle relaxants	13	8	5	0.278[a]
Hypoglycemic drugs	50	28	22	0.159[a]
α-Glucosidase inhibitors	22	13	9	0.232[a]
β-Adrenoceptor agonists	6	3	3	$>$0.999[b]
Xanthines (theophylline)	16	7	9	0.802[a]
Steroids	7	3	4	$>$0.999[b]
Antiallergic drugs	23	13	10	0.334[a]
Iron preparations	5	4	1	0.190[b]
Hemostatics	5	2	3	$>$0.999[b]
Antibiotics	12	5	7	0.717[a]
Osteoporosis drugs	28	18	10	0.053[a]
Anticancer drugs	6	2	4	0.689[b]
Anticholinergics for neurogenic bladder	9	6	3	0.314[b]

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

hypnotics is based on anticholinergic and myorelaxant effects. The pharmacological actions of hypnotics are similar to those of anti-anxiety drugs, while their anticholinergic effects are weaker than those of antidepressants; however, our data showed that only hypnotics were significantly 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 constipation.

Comparison of the constipation group and non-constipation groups showed differences in the types of drugs taken, with significant effects of diuretics, coronary vasodilators, thyroid hormones, NSAIDs, proton pump inhibitors, antidepressants, and anti-anxie-

ty drugs, which are already known to cause constipation. Antidepressant-induced constipation is well-known, but we were not able to show the significance of the relationship with multivariable analysis. Recently, new antidepressants, such as selective serotonin reuptake inhibitors, which exhibit fewer adverse reactions than tricyclic antidepressants,[21] have been

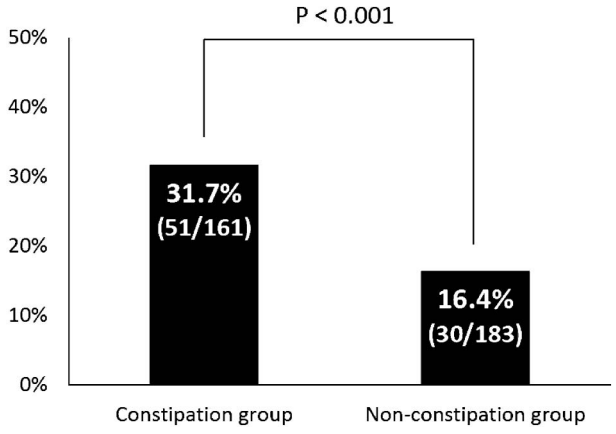

Fig. 3. Proportion of the Total Athens Insomnia Scale Score of 6 or More in Constipation and Non-constipation Groups
Statistical analysis used χ^2-test.

Table 3. Multiple Logistic Regression Analysis for the Risk Factors Related to Constipation

Factors	Odds ratio	95%CI	*p* value
Age	1.03	1.01–1.04	0.007
Female gender	1.96	1.21–3.18	0.006
Number of used drugs	0.97	0.89–1.06	0.522
Athens Insomnia Scale	1.10	1.02–1.18	0.010
Hypothyroidism	2.54	0.22–29.71	0.458
Chronic obstructive pulmonary disease	3.01	0.94–9.65	0.064
Use of diuretics	1.27	0.67–2.41	0.457
Use of coronary vasodilators	1.95	0.97–3.93	0.061
Use of thyroid hormones	1.28	0.11–15.32	0.844
Use of NSAIDs including low-dose aspirin	1.03	0.53–2.01	0.920
Use of proton pump inhibitors	1.48	0.71–3.12	0.299
Use of antidepressants	2.72	0.80–9.20	0.109
Use of antianxiety drugs	0.88	0.41–1.88	0.745
Use of hypnotics	2.33	1.30–4.16	0.004

CI: denotes confidence interval, NSAIDs: non-steroidal anti-inflammatory drugs.

Table 4. Types of Hypnotics and Proportion of Constipation

Classification		Duration of action		Generic name	
Non-benzodiazepines	34/62 (54.8%)	Ultra short-acting type	63/99 (63.6%)	Zolpidem tartrate	24/43 (55.8%)
				Zopiclone	10/19 (52.6%)
				Triazolam	29/37 (78.4%)
Benzodiazepines	71/106 (67.0%)	Short-acting type	25/40 (62.5%)	Brotizolam	21/35 (60.0%)
				Lormetazepam	1/2 (50.0%)
				Rilmazafone hydrochloride	3/3 (100%)
		Intermediate-acting type	17/24 (70.8%)	Estazolam	2/2 (100%)
				Flunitrazepam	8/13 (61.5%)
				Nitrazepam	7/9 (77.8%)
		Long-acting type	0/5 (0.0%)	Quazepam	0/5 (0.0%)
Barbiturates	0/1 (0.0%)	Intermediate-acting type	0/1 (0.0%)	Pentobarbital calcium	0/1 (0.0%)

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

prescribed for many patients.[22] Other drugs possibly cause constipation but may not have a significant association because of limited and inconsistent views about the constipating drugs in a few previous reports.[10,11] Also, while the frequencies of adverse drug reactions ordinarily rise with an increase in the number of drugs taken,[23,24] drug-induced constipation may be little influenced by the number of drugs and more by certain drugs, such as hypnotics.

Other than the drugs used, the other significant factors related to constipation were age, gender, and AIS score. Constipation in older adults is widely considered to be a common problem due to a decline in bowel movement. Females suffer from constipation more than males according to epidemiological studies.[1–3] With respect to the sleep disorders, the relationship to constipation was uncertain. In this study, the sleep conditions between constipation and non-constipation groups were significantly different, as shown in Figs. 2 and 3. When our data were analyzed by multivariable analysis, the relationship became clear as an independent risk factor of constipation. These results support the view that constipation can result from sleep disorders.[14–17]

As strategies to prevent constipation, we note sleep conditions and the use of hypnotics. First, in regard to the sleep conditions, cognitive behavioral therapy, such as sleep hygiene, sleep restriction, stimulus control, and cognitive therapy, is effective in the treatment of insomnia.[25–27] This non-pharmacologic therapy can lead to the prevention of constipation over and above the improvement of insomnia. Second, in regard to the use of hypnotics, non-benzodiazepines may have a relatively lower risk of causing constipation than benzodiazepines, which may be tolerated by patients with constipation. Furthermore, ramelteon, a selective melatonin receptor agonist,[28,29] has little affinity for other receptors, including acetylcholine, and therefore may be useful from the viewpoint of avoiding constipation.

Our study has some limitations. Diet and exercise,[8,9] known to be related to constipation, were not considered in this study, and their inclusion may provide better analytical precision. Also, more study needs to be done on the administration of several types of drugs as the number of such patients in this study was too small to reach any conclusions; for example, opioids are also considered to have a significant relationship with constipation.

In conclusion, constipation was related to age, female gender, sleep conditions, and use of hypnotics in our subjects. The present study provides evidence that the drugs with the strongest relationship with constipation are hypnotics. Therefore, the administration of hypnotics may be undesirable for patients who should avoid occurrence of constipation such as ileus patients. Care should be taken to prevent hypnotics-induced constipation.

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