Relationship Between Constipation and Medication

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Abstract: Constipation is very common and can be caused by adverse drug reactions as a result of many drugs. While the adverse effects of several medications such as opioids and anticholinergic agents are well established and well known, other commonly prescribed drugs, such as hypnotics, are less well understood. This review presents the results of an analysis of the relationship between constipation and drugs.

Keywords: constipation, adverse drug reaction, opioid, anticholinergic agent, hypnotic.

Introduction

Constipation is one of the most common gastrointestinal complaints [1–10], and is associated with adverse implications for patients’ quality of life and economic costs [11–15]. Most epidemiological studies have reported prevalence rates between 14–30% in the general population [5–11]. These high rates make constipation a major public health issue.

In recent years, the relationship of constipation to cardiovascular disease and chronic kidney disease, independently of known risk factors, has been clarified [16–18]. Although commonly assumed to be benign, constipation was found to have an increased risk of poorer survival in a large population-based cohort study [19], so importance of the management of constipation is being recognized.

Generally, constipation occurs more frequently in older adults and females [1–10]. Secondary constipation is induced by diseases such as diabetes mellitus and hypothyroidism [1–7, 10]. Constipation is also an adverse effect of many drugs [1–7, 10, 20–23]. Adverse effects and the inappropriate use of drugs may be the principal causes of constipation [24–26], but little is known about the relative risks of individual drugs.

In this review, we present the results of an analysis of the relationship between constipation and drugs, including our own studies.

Relationship between constipation and medication in consideration of patient backgrounds

The causes of constipation are multi factorial and also commonly encountered as adverse drug reactions. Common medications implicated in the development of constipation are presented in Table 1 [1–7, 10, 20–23]. Opioid-induced constipation is the most prevalent and persistent adverse reaction [27–29], with some estimates being as high as 40–81% in patients receiving opioids [30, 31]. The cause of opioid-induced
constipation is the action of opioids on their receptors in the gastrointestinal tract. Anticholinergic agents such as tricyclic antidepressants and antipsychotics that possess high affinity for muscarinic cholinergic receptor are also known to cause constipation [32, 33].

Opioid-induced constipation appears obviously frequently [30, 31], but the relative risks of individual drugs other than opioids in the development of constipation are limited. Therefore we analyzed the relationship between constipation and drugs in consideration of patient backgrounds [21]. To clarify the relationship between constipation and various drugs, we investigated the defecation frequency and use of laxatives in 251 patients. The subjects were internal medicine and cardiovascular disease patients who were not using opioids. They were divided into a constipation group (n=73) and a non-constipation group (n=178) according to their defecation intervals and use of laxatives. The constipation group reported defecation intervals equal to or more than 3 days and/or the use of laxatives, and the non-constipation group reported both defecation intervals of less than 3 days and the non-use of laxatives. A comparison of the patient backgrounds of the two groups revealed significant differences in age, gender, number of drugs taken regularly, colon cancer, use of non-steroidal anti-inflammatory drugs (NSAIDs), and use of hypnotics, antidepressants, anti-anxiety drugs, and iron preparations. Multiple logistic regression analysis using these nine factors as autonomous variables showed that female gender (odds ratio [OR]: 2.01, 95% confidence interval [CI]: 1.06−3.81, \(P=0.033\)) and use of hypnotics (OR: 3.98, 95% CI: 1.40−11.28, \(P=0.010\)) were significantly related to constipation. An examination of the types of hypnotics showed a higher proportion of constipation in patients who took benzodiazepines rather than non-benzodiazepines such as zolpidem tartrate and zopiclone.

It has been reported that sleep disorders are associated with gastrointestinal symptoms [34–36], and epidemiological surveys have suggested a relationship between sleep disorder and abnormal defecation, including constipation [35, 36]. In our previous study, hypnotics were strongly related to constipation, but it was not clear whether this was due to the clinical condition of sleep disorder or an adverse effect of the hypnotics. Therefore we analyzed the relationship between constipation and drugs by considering the patients’ background, including sleep conditions [22], by investigating self-reported bowel habits, use of laxatives, and the sleep conditions in 344 patients.

The subjects were mostly internal medicine and cardiovascular disease patients, and only one patient was using opioids. Bowel habits were classified into five groups: “Normal”, “Constipation”, “Occasional constipation”, “Diarrhea”, and “Constipation and diarrhea”. Patients who reported “Diarrhea” and “Constipation and diarrhea” were excluded from the study. The sleep conditions were evaluated by the Athens Insomnia Scale (AIS), a self-administered psychometric instrument consisting of eight items. 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) [37, 38].

### Table 1. Medications associated with constipation

| Medication Type                        |
|----------------------------------------|
| Opioids                                |
| Nonsteroidal anti-inflammatory agents  |
| Tricyclic antidepressants              |
| Antiparkinsonian drugs                 |
| Antipsychotics                         |
| Antispasmodics                         |
| Antihistamines                         |
| Anticonvulsants                        |
| Hypnotics                              |
| Calcium channel blockers               |
| Diuretics                              |
| Centrally acting antihypertensive drugs|
| Antiarrhythmics                        |
| Beta-adrenoceptor antagonist           |
| Bile acid sequestrants                 |
| Aluminum or calcium containing antacids|
| Iron supplements                       |
| Calcium supplements                    |
| Bismuth                                |
| Lithium                                |
| Vinca alkaloids                        |
| Alkylating agents                      |
| Sympathomimetics                       |
| Monoamine oxidase inhibitors           |
| Bisphosphonates                        |
| 5-hydroxytryptamine 3 receptor antagonists |
The patients were then divided into a constipation group (n=161) and a non-constipation group (n=183). 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. 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, nonsteroidal anti-inflammatory agents, proton pump inhibitors, antidepressants, anti-anxiety drugs, and hypnotics. Multiple logistic regression analysis using these fourteen factors as autonomous variables showed that age (OR: 1.03, 95% 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. Examination of the types of hypnotics showed a higher proportion of constipation in patients who took benzodiazepines rather than non-benzodiazepines.

Previous reports have shown that constipation can be induced by most central nervous system drugs [1–7, 10, 20]. For example, antidepressants and antipsychotics are known as drugs that cause constipation, while not much is known about hypnotics. Psychiatric patients and opioid users were not included in our studies, so it may be that the hypnotics were extracted from commonly used drugs.

One possible mechanism of constipation caused by 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. One explanation of why our data showed that hypnotics were significantly related to constipation 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, benzodiazepines showed a higher tendency to increase the proportion of constipation than non-benzodiazepines, which have lower myorelaxant effects [39]. Thus it seems that the pharmacological action of hypnotics affects the occurrence of constipation.

Risk factors for the development of constipation in the hospital setting

Constipation is a common problem and more frequently occurs in hospitalized patients [40–42]. The prevalence in hospitalized patients aged over 65 years is estimated at 50% [41], and one third of hospitalized older patients need a laxative at least once every 3 days [42]. Constipation occurs much more frequently in critically ill patients, and its incidence has been reported to be 70–83% [43, 44]. Constipation may also be associated with prolonged intensive care unit (ICU) stay, increased infection rates, and increased ICU mortality [45, 46].

Factors known to increase the risk of constipation are age, diet, being bedridden, and drugs [40, 47–51]. However, there is limited data on the degree of influence of the various factors in the development of constipation, and little is known about the relative risks among individual drugs in the hospital setting. Therefore we performed a study on the factors affecting the development of constipation in hospitalized patients [23] by investigating laxative administration during hospitalization in 165 patients who were not laxative users on admission. The subjects, who were admitted to the internal medicine ward or cardiovascular disease ward, were divided into constipation (n=35) and non-constipation (n=130) groups according to the administration of laxatives. Newly administrated drugs were surveyed retrospectively from the day of laxative administration in the constipation group and from the day of discharge in the non-constipation group. Comparison of the patient backgrounds in the two groups revealed significant differences in the activities of daily living (dependence), length of fasting, rest level on admission (bed rest), cerebrovascular disease, and administration of hypnotics. Multiple logistic regression analysis using these five factors as autonomous variables showed that administration of hypnotics (OR, 2.79; 95% CI, 1.10–7.06; P = 0.031) was significantly related to laxative use. Examination of the types of hypnotics revealed a higher proportion of constipation in patients who had been injected with a drug such as midazolam. Benzo-
diazepines also showed a higher tendency to increase the proportion than non-benzodiazepines.

Our data indicated a causal relation between hypnotics and the use of laxatives. A few reports have shown that the constipating drugs in hospital settings are muscle relaxants in the elderly and sedatives in ICU patients [46, 50]. The pharmacological actions of these drugs are similar to those of hypnotics. In fact, the development of constipation in hospitalized patients is caused by multiple factors and therefore does not result from a single factor. A comparison of the constipation and non-constipation groups showed significant differences in the patient backgrounds of activities of daily living, days of fasting, rest level, and cerebrovascular disease, which are already known to cause constipation. Taking these factors into consideration, it is suggested that hypnotics may contribute strongly to the development of constipation.

Conclusion

This review summarized the relationship between constipation and medication. Adverse drug reactions as the causes of constipation are commonly encountered. Thus, the administration of constipating drugs may be undesirable for patients who should avoid the occurrence of constipation, such as ileus patients [52]. In the real world, the prescription of many anticholinergics is highly prevalent, despite these drugs being undesirable in older patients [24, 25, 53–56]. Care should be taken to prevent drug-induced constipation.

Results from our previous studies showed that the drugs that are related to constipation are hypnotics. This evidence is being recognized slightly [50, 57]. However, new types of ramelteon (a selective melatonin receptor agonist) and suvorexant (an orexin receptor antagonist) were not used in our studies [58, 59]. More study needs to be done on the new hypnotics, which have little affinity for other receptors, including acetylcholine and few myorelaxant effects, and therefore might have a low risk for the development of constipation.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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便秘と服用薬剤の関連性

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要 旨：便秘は、非常に一般的であり、多くの薬剤の有害反応によって引き起こされる。オピオイドや抗コリン剤などの薬剤の有害作用に関する知識と認識は確立されているが、睡眠剤などの一般的に処方されている薬剤についてはあまりよく理解されていない。本総説では、便秘と薬剤との関連性を分析した結果を提示する。

キーワード：便秘, 薬物有害反応, オピオイド, 抗コリン剤, 睡眠剤。