Prescription of Colchicine with Other Dangerous Concomitant Medications: A Nation-Wide Survey Using the Japanese Claims Database

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INTRODUCTION

The anti-inflammatory agent colchicine may cause toxic effects such as rhabdomyolysis, pancytopenia, and acute respiratory distress syndrome in cases of overdose and when patients have renal or liver impairment. Colchicine is a substrate for CYP3A4 and P-glycoprotein (P-gp), drug–drug interactions are important factors that cause fatal colchicine-related side effects. Thus, we conducted a nation-wide survey to determine the status of inappropriate colchicine prescriptions in Japan. Patients prescribed the regular use of colchicine from April 2014 to March 2017 were identified using the Japanese large health insurance claims database. As the primary endpoint, we evaluated the concomitant prescription proportions of strong CYP3A4 and/or P-gp inhibitors classified as “contraindications for co-administration” with colchicine in patients with renal or liver impairment. We defined these cases as “inappropriate colchicine prescriptions.” Additionally, factors affecting inappropriate colchicine prescriptions were analyzed. Among the 3302 enrolled patients, 43 (1.30%) were inappropriately prescribed colchicine. Of these 43 patients, 11 had baseline renal and/or liver impairment. By multiple regression analysis, the primary diseases “gout” and “Behçet’s disease” were extracted as independent factors for inappropriate colchicine prescriptions with odds ratios of 0.40 (95% confidence interval: 0.19–0.84) and 4.93 (95% confidence interval: 2.12–11.5), respectively. We found that approximately 1% of patients had important colchicine interactions. Particularly, Behçet’s disease was a risk factor for inappropriate prescriptions, with approximately 25% of patients showing renal and/or liver impairment (classified as “contraindications for co-administration”). These findings may be useful for medical professionals who prescribe colchicine therapy.

Key words colchicine; CYP; drug–drug interaction; insurance claim; P-glycoprotein

MATERIALS AND METHODS

Data Sources This epidemiological study was conducted using the database of Japanese health insurance claims including medical institutions and pharmacies, named the “JMDC claims database” constructed by the JMDC, Inc. (Tokyo, Japan). The database comprised data from approximately 5.6 million insured persons, representing approximately 5% of the population in Japan. Patients aged < 75 years and mainly working-class people and their families were included.

Study Population and Data Collection Patients pre-
scribed the regular use of colchicine from April 2014 to March 2017 were included. Patients prescribed occasional use of colchicine were excluded because it is difficult to calculate the prescription period for these patients. The occasional use of colchicine prescriptions were detected based on the “occasional use flag” in the JMDC claims database. Colchicine was identified using the Anatomical Therapeutic Chemical (ATC) system, code M04AC01. Additionally, we investigated the proportions of concomitant administration with the following medications classified as “contraindications for co-administration,” based on the colchicine package insert and label, in patients with renal or liver impairment: clarithromycin (ATC code: A02BD, A02BD07, J01FA09), cyclosporine (ATC code: L04AD01, S01XA18), itraconazole (ATC code: J02AC02), and antiviral agents [telaprevir (ATC code: J05AE11) and cobicistat (ATC code: J05AR14, J05AR15)]. Although the antiviral agents atazanavir, indinavir, nelfinavir, ritonavir, saquinavir, darunavir, and telithromycin are classified as contraindications for co-administration with colchicine, they were not evaluated in this study because anti-human immunodeficiency virus agents were not included in the JMDC claims database, and telithromycin was discontinued in December 2005 in Japan. If the prescription period overlapped, the case was defined as “concomitant use.” If a single patient was given multiple colchicine prescriptions, only the first administration was included in the analysis.

The primary diseases for which colchicine was prescribed were identified from the diagnostic fields using the International Classification of Diseases, Tenth Revision (ICD-10) codes. We classified these primary diseases as gout (ICD-10 code: M100, M101, M104, M109), familial Mediterranean fever (ICD-10 code: E850), pericarditis (ICD-10 code: I010, I300, I301, I309, I311, I318, I319, M321, M359), Behçet’s disease (ICD-10 code: M352), and others. We also extracted renal impairment (ICD-10 code: N180, N188, N189, N289) and liver impairment (ICD-10 code: B181, B182, K703, K709, K729, K746, K769, T864) as baseline concurrent diseases from 1 year prior to colchicine prescription. The baseline was defined as the day of the first colchicine prescription during the study period.

Moreover, demographic data such as age, sex, inpatient or outpatient status, clinical departments and institutions that prescribed colchicine and concomitant medications, daily dose, and duration of administration were collected. Clinical departments and institutions were identified based on text codes and institution IDs. The five clinical departments with the highest frequency of prescriptions were extracted. The durations of administration were calculated as the total number of prescription days from April 2010 to March 2017. A period of more than 7 d between administration was considered the end of the administration.

The reasons for selecting these variables were: (1) primary diseases, daily dose, and duration of administration of colchicine: the recommended daily dose and duration of administration of colchicine differed between primary diseases. This may be related to inappropriate prescriptions; (2) clinical departments: a previous research reported that inappropriate prescriptions of nonsteroidal anti-inflammatory drugs are related to the clinical departments who prescribe them; (3) baseline concurrent diseases: in patients with renal and liver impairment, clinicians that prescribe colchicine may avoid concomitant use of strong CYP3A4 and/or P-gp inhibitors; (4) age and sex: prevalence of complications such as chronic kidney disease varies with age and sex; (5) inpatient or outpatient status: inpatients may be easier to grasp concomitant medications than outpatients by clinicians.

**Outcomes** As the primary endpoint, the prescription proportions of concomitant use of clarithromycin, cyclosporine, itraconazole, and antiviral agents (telaprevir and cobicistat) were evaluated. We defined the concomitant use of these agents as “inappropriate colchicine prescriptions,” as they are classified as contraindications for co-administration with colchicine in patients with renal or liver impairment. Thus, the proportions of patients with renal or liver impairment were also calculated. As the secondary endpoint, factors affecting inappropriate colchicine prescription were analyzed using a logistic regression model. Demographic factors were also examined to determine their relationship. In addition, among patients who received inappropriate colchicine prescriptions, we evaluated the proportions at which colchicine and concomitant medications were prescribed by different clinical departments and institutions, such as when colchicine was prescribed by an internal medicine department, whereas clarithromycin was prescribed by another department. Moreover, in these patients, we compared the timing of first prescription between colchicine and each concomitant medication. In other words, these patients were categorized as: (1) addition of colchicine in patients already receiving CYP3A4 and/or P-gp inhibitors, (2) received colchicine and CYP3A4 and/or P-gp inhibitors prescriptions at the same time, (3) addition of CYP3A4 and/or P-gp inhibitors in patients already receiving colchicine.

Furthermore, to investigate the detailed characteristics of the patients, we compared the duration of administration of colchicine in each primary disease.

**Data Analyses** Categorical variables were compared by a Pearson’s chi-square or Fisher’s exact test. In a 2 × 2 contingency table, if more than 20% of cells had expected frequencies less than 5, a Fisher’s exact test was employed. We confirmed that all continuous variables had non-normal distributions by performing the Shapiro–Wilk test. Thus, continuous variables were compared by a Mann–Whitney U test.

To analyze the factors affecting inappropriate colchicine prescription, multiple logistic regression analyses using a stepwise approach were conducted. The potential risk factors were applied in this analysis based on univariate analysis (p < 0.1). If correlations were observed between potential risk factors extracted from the univariate analysis, only one factor was selected based on clinical importance and applied to the multivariate analysis. Correlations were evaluated using Cramer’s V, correlation ratio, Pearson’s and Spearman’s correlation coefficients. The cutoff value was defined as a correlation coefficient > 0.3.

A significant difference was defined as a p value ≤ 0.05. JMP 14® software (SAS Institute, Inc., Cary, NC, U.S.A.) was used for all statistical analyses.

**Ethics** The institutional review board of the Faculty of Pharmaceutical Sciences of Hokkaido University reviewed this study. The institutional review board waived the requirement for informed consent because the JMDC claims database is anonymized.
RESULTS

Proportions of Inappropriate Colchicine Prescriptions and Patient Characteristics  As shown in Fig. 1, we initially identified 4596 patients who had been prescribed colchicine between April 2014 and March 2017; of these patients, 1294 were excluded because they received occasional use of colchicine prescriptions. Ultimately, a total of 3302 patients were enrolled. Among them, 43 (1.30%) were prescribed inappropriately. Table 1 shows the details of inappropriate prescription because of concomitant medications (n = 43), which included clarithromycin (n = 31), cyclosporine (n = 11), and itraconazole (n = 2). No patients were prescribed antiviral agents. One patient was concomitantly administered cyclosporine and itraconazole. Additionally, 11 (25.6%) and 14 (32.6%) patients received prescriptions from different clinical departments and institutions, respectively.

The durations of administration of colchicine (median, interquartile range [range]) were longer for primary diseases in the order of Behçet’s disease (152.5, 52–381 [2–2398] days) > familial Mediterranean fever (103, 42–232 [7–1530] days) > pericarditis (23.5, 10–77 [3–692] days) > other diseases (14, 6–54 [1–1735] days) > gout (7, 5–14 [1–2610] days). Minimum durations of “1 day” were considered as colchicine administration on the day of prescription.

Table 2 shows a comparison of characteristics between patients in the inappropriate colchicine prescription group and others. Patients who received inappropriate colchicine prescriptions differed significantly from those who did not receive these prescriptions with respect to sex, primary diseases of gout and Behçet’s disease, other clinical departments, daily dose, and duration of colchicine administration. In both groups, gout was the most common primary disease for which colchicine was prescribed. In the inappropriate prescriptions group, 3 (6.98%) and 9 (20.9%) patients had renal and hepatic impairment, respectively. Among them, 1 patient had both diseases, and 11 patients (25.6%) had baseline concurrent diseases. Moreover, in each concomitant medication, more than half of patients were prescribed these medications before receiving colchicine prescriptions (i.e., addition of colchicine in patients already receiving CYP3A4 and/or P-gp inhibitors).

Factors Affecting Inappropriate Colchicine Prescriptions

Table 3 shows the factors affecting inappropriate colchicine prescription. Primary disease (familial Mediterranean fever) and clinical departments (urology) were excluded because no patients in these groups were inappropriately prescribed colchicine. Based on the results of univariate analysis of p < 0.1, sex (male), primary diseases (gout, Behçet’s disease, and other diseases), other clinical departments, daily dose, and duration of colchicine administration were extracted as factors for the multiple logistic regression analysis. Among these factors, strong correlations were observed for the primary diseases, gout and other diseases (correlation coefficient, 0.87 as calculated by Cramer’s V). As gout is the most typical disease associated with colchicine prescription, we excluded “other diseases” from multiple logistic regression analysis. As a result, primary diseases (gout and Behçet’s disease) for which colchicine was prescribed were extracted as independent factors associated with inappropriate prescription. The odds ratios for these groups were 0.40 (95% confidence interval (CI): 0.19–0.84) and 4.93 (95% CI: 2.12–11.5), respectively.

DISCUSSION

This study evaluated the prescription of colchicine with dangerous concomitant medications such as strong CYP3A4 and/or P-gp inhibitors. Based on the package insert and label,14,15 strong CYP3A4 and/or P-gp inhibitors with the concomitant use of clarithromycin, cyclosporine, itraconazole, and antiviral agents (telaprevir and cobicistat) were defined as “inappropriate colchicine prescriptions.” Combinations such as clarithromycin and cyclosporine have previously been reported to significantly increase colchicine concentrations.24

The resulting proportion of inappropriate colchicine prescriptions was 1.30% (Fig. 1; 43 of 3302). Among them, 11 patients (25.6%) had baseline renal and/or hepatic impairment (Table 2) and were classified as “contraindications for co-administration” and considered the most at-risk group.14,15 These combinations may cause fatal outcomes and should be avoided.5–9 Clarithromycin was the most common inappropriate...
ate concomitant medication (Table 1; n = 31) and was prescribed by internal medicine (n = 16) and otorhinolaryngology (n = 8). Clarithromycin is widely used to treat acute bacterial rhinosinusitis, strep throat, pneumonia, skin infections, and *Helicobacter pylori* infection.25–29) The proportions of differences in clinical departments and medical institutions between the prescription of colchicine and its concomitant medications were 25.6 and 32.6%, respectively. Although there were no comparable data, these proportions were not considered significantly high. Thus, other factors are likely affected by inappropriate colchicine prescriptions. In addition, more than half of patients were prescribed strong CYP3A4 and/or P-gp inhibitors before colchicine prescriptions (i.e., addition of colchicine in patients already receiving CYP3A4 and/or P-gp inhibitors). This result suggests that attention to drug–drug interactions is needed especially when colchicine is newly prescribed.

Primary diseases for which colchicine was prescribed were extracted as independent factors affecting inappropriate colchicine prescriptions (Table 3). Considering the odds ratios of 0.40 (95% CI: 0.19–0.84) and 4.93 (95% CI: 2.12–11.5), respectively, gout decreases the risk of inappropriate colchicine prescriptions, whereas Behçet’s disease increases the risk. Colchicine is most commonly prescribed for gout, which is consistent with our results (Table 2). Thus, clinicians prescribing colchicine for gout likely also recognize its interactions. Indeed, a recent review and guidelines of gout treatment also alerted physicians of the drug–drug interactions of colchicine.16,30,31) In contrast, although colchicine is recommended for the treatment of Behçet’s disease involving mucocutaneous and joint lesions, no warnings have been given in the guidelines regarding its drug–drug interactions.2,32,33) Moreover, the duration of administration of colchicine was longest for Behçet’s disease and shortest for gout. Thus, patients with Behçet’s disease have a higher chance of receiving dangerous concomitant medications than patients with gout. In addition, cyclosporine is recommended for Behçet’s disease if lesions involve the eye, acute deep vein thrombosis, or the nervous system.2) In the inappropriate prescription group, 5 of 8 patients with Behçet’s disease were concomitantly administered cyclosporine in this study (data not shown). Although colchicine is typically prescribed at relatively low doses (1–1.5 mg/daily) for Behçet’s disease,39) fatal side effects can still occur.
particularly in patients with renal or liver impairment.\textsuperscript{7,10} Generally, cyclosporine is prescribed as a switch from colchicine therapy in Behçet’s disease, but our results showed that colchicine was added to cyclosporine in 6 of 11 patients (Table 1). The reasons for this are currently unclear. Thus, as described, it is considered that various reasons may have accounted for this result. On the other hand, no patients received inappropriate colchicine prescriptions among patients with familial Mediterranean fever (Table 2). The reason for this is that the denominator was as small as 34 patients. Considering that the duration of administration of colchicine was the second longest, it should not be concluded that patients with familial Mediterranean fever are at a low risk of receiving inappropriate colchicine prescription.

Table 2. Comparison of Patient Characteristics between Inappropriate Colchicine Prescription Group and Others

| Description                                      | Inappropriate colchicine prescription group (n = 43) | Other colchicine prescriptions group (n = 3259) | p-Value |
|--------------------------------------------------|-----------------------------------------------------|------------------------------------------------|--------|
| Age (years), median (IQR) [range]                | 49 (37–54) [4–67]                                   | 48 (41–56) [3–74]                                   | 0.616<sup>1</sup> |
| Sex (male), n (%)                                 | 34 (79.1)                                           | 2951 (90.5)                                        | 0.019<sup>9,10</sup> |
| Visit to medical facility at beginning of colchicine, n (%) | 3 (6.98)                                            | 132 (4.05)                                         | 0.256<sup>1</sup> |
| In-patients                                      |                                                     |                                                  |        |
| Out-patients                                     | 40 (93.0)                                           | 3127 (95.9)                                        |        |
| Primary disease, n (%)                           | 32 (74.4)                                           | 2961 (90.9)                                        | <0.001<sup>11</sup> |
| Gout                                             |                                                     |                                                  |        |
| Familial Mediterranean fever                     | 0 (0.00)                                            | 34 (1.04)                                          | 1.000<sup>12</sup> |
| Pericarditis                                     | 1 (2.33)                                            | 37 (1.14)                                          | 0.394<sup>11</sup> |
| Behçet’s disease                                 | 8 (18.6)                                            | 108 (3.31)                                         | <0.001<sup>11</sup> |
| Other diseases                                   | 6 (14.0)                                            | 235 (7.21)                                         | 0.127<sup>11</sup> |
| Baseline renal impairment, n (%)                 | 3 (6.98)                                            | 358 (11.0)                                         | 0.620<sup>11</sup> |
| Baseline hepatic impairment, n (%)               | 9 (20.9)                                            | 715 (21.9)                                         | 0.874<sup>11</sup> |
| Clinical department of prescription of colchicine, n (%) |                                                     |                                                  |        |
| Internal medicine                                | 23 (53.5)                                           | 2005 (61.5)                                        | 0.282<sup>11</sup> |
| Orthopedic surgery                               | 8 (18.6)                                            | 528 (16.2)                                         | 0.671<sup>11</sup> |
| General surgery                                  | 2 (4.65)                                            | 232 (7.12)                                         | 0.766<sup>11</sup> |
| Gastroenterology                                 | 1 (2.33)                                            | 123 (3.77)                                         | 1.000<sup>11</sup> |
| Urology                                          | 0 (0.00)                                            | 33 (1.01)                                          | 1.000<sup>11</sup> |
| Other departments                                 | 9 (20.9)                                            | 338 (10.4)                                         | 0.040<sup>11</sup> |
| Daily dose of colchicine (mg), median (IQR) [range] | 1 (0.5–1.5) [0.2–5]                                | 1.5 (1–2) [0.4–3]                                 | 0.008<sup>11</sup> |
| Durations of colchicine (days), median (IQR) [range] | 10 (5–56) [1–2317]                                 | 7 (5–14) [1–2610]                                 | 0.041<sup>11</sup> |

IQR: interquartile range. a) Chi-squared test, b) Fisher’s exact test, c) Mann–Whitney U test. *p-Values ≤ 0.05 were considered statistically significant. d) Overlap in primary diseases.

Table 3. Factors Affecting Inappropriate Colchicine Prescriptions

| Characteristic                                      | OR      | 95% CI     | p-Value | OR      | 95% CI     | p-Value |
|-----------------------------------------------------|---------|------------|---------|---------|------------|---------|
| Age (years)                                         | 0.98    | 0.96–1.01  | 0.201   | 0.40    | 0.19–0.84  | 0.016<sup>9</sup> |
| Sex (male)                                          | 0.39    | 0.19–0.83  | 0.014<sup>9</sup> | 0.40    | 0.19–0.84  | 0.016<sup>9</sup> |
| Visit to medical facility at beginning of colchicine | 1.78    | 0.54–5.82  | 0.342   | 4.93    | 2.12–11.5  | <0.001<sup>9</sup> |
| In-patients                                         |         |            |         |         |            |         |
| Primary disease                                     |         |            |         |         |            |         |
| Gout                                                | 0.29    | 0.15–0.59  | 0.001<sup>9</sup> | 0.40    | 0.19–0.84  | 0.016<sup>9</sup> |
| Pericarditis                                        | 2.07    | 0.28–15.5  | 0.477   |         |            |         |
| Behçet’s disease                                    | 6.67    | 3.02–14.7  | <0.001<sup>9</sup> | 4.93    | 2.12–11.5  | <0.001<sup>9</sup> |
| Other diseases                                      | 2.09    | 0.87–4.99  | 0.099<sup>9</sup> |         |            |         |
| Baseline renal impairment                           | 0.61    | 0.19–1.98  | 0.408   |         |            |         |
| Baseline hepatic impairment                         | 0.94    | 0.45–1.97  | 0.874   |         |            |         |
| Clinical departments of colchicine prescription     |         |            |         |         |            |         |
| Internal medicine                                   | 0.72    | 0.39–1.32  | 0.284   |         |            |         |
| Orthopedic surgery                                  | 1.18    | 0.55–2.56  | 0.671   |         |            |         |
| General surgery                                     | 0.64    | 0.15–2.65  | 0.534   |         |            |         |
| Gastroenterology                                    | 0.61    | 0.08–4.45  | 0.623   |         |            |         |
| Other departments                                   | 2.29    | 1.09–4.81  | 0.029<sup>9</sup> |         |            |         |
| Daily dose of colchicine (mg)                       | 0.65    | 0.44–0.96  | 0.030<sup>9</sup> |         |            |         |
| Durations of colchicine (days)                      | 1.001   | 1.000–1.002| <0.001<sup>9</sup> |         |            |         |

OR: odds ratio, 95% CI: 95% confidence interval. a) p-Values ≤ 0.1 were included in the multiple logistic regression analysis. *p-Values ≤ 0.05 were considered statistically significant. Primary diseases of gout and other diseases had the strong correlations (correlation coefficient was 0.87 calculated by Cramer’s V). Thus, primary disease of other diseases was excluded from multiple logistic regression analysis.
Our study has several limitations. First, the concomitant medications were evaluated to detect overlap in the prescription periods. In addition, the durations of colchicine administration were calculated as the total number of prescription days. However, actual use could not be evaluated. Second, we could not evaluate patients who were prescribed occasional use of colchicine owing to the following reasons: (1) it was difficult to calculate the administration period for patients who were prescribed occasional use and (2) as described above, the primary endpoint of “the prescription proportions of concomitant use” was evaluated based on the overlapping prescription period. For example, if a strong CYP3A4 inhibitor was evaluated as concomitant use, the required number of patients for an 10-fold higher than the number of factors included in the analysis would be needed to determine inappropriate colchicine prescriptions in these patients.

This epidemiological study is the first nation-wide survey to investigate the status of inappropriate colchicine prescription. Our findings will be useful to clinicians and pharmacists. Specifically, when prescribing and dispensing colchicine, clinicians and pharmacists should be aware of drug–drug interactions because approximately 1% of patients were found to have important colchicine interactions. Particularly, those with Behçet’s disease were at a high risk. In addition, underlying diseases should be noticed in these patients because 25.6% had baseline renal and/or hepatic impairment (classified as “contraindications for co-administration”).

Conflict of Interest  The authors declare no conflict of interest.

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