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# Evidence of Clinically Meaningful Drug–Drug Interaction With Concomitant Use of Colchicine and Clarithromycin

**Lorenzo Villa Zapata**[1], **Philip D. Hansten**[2], **John R. Horn**[3], **Richard D. Boyce**[4], **Sheila Gephart**[5], **Vignesh Subbian**[6], **Andrew Romero**[7], **Daniel C. Malone**[8]

[1]Skaggs School of Pharmacy and Pharmaceutical Sciences, Center for Pharmaceutical Outcomes Research, University of Colorado, Aurora, CO, USA

[2]School of Pharmacy, University of Washington, Seattle, WA, USA

[3]Department of Pharmacy Practice, School of Pharmacy and Associate Director, Pharmacy Services UW Medicine, University of Washington, Seattle, WA, USA

[4]Department of Biomedical Informatics, School of Medicine, University of Pittsburgh, Pittsburgh, PA, USA

[5]Community and Health Systems Science, College of Nursing, The University of Arizona, Tucson, AZ, USA

[6]Department of Biomedical Engineering and Department of Systems and Industrial Engineering, College of Engineering, The University of Arizona, Tucson, AZ, USA

[7]Department of Pharmacy, Banner University Medical Center, Tucson, AZ, USA

[8]Department of Pharmacotherapy, College of Pharmacy, University of Utah, Salt Lake City, Utah, USA

## Abstract

**Introduction—**Colchicine is currently approved for the treatment of gout and familial Mediterranean fever, among other conditions. Clarithromycin, a strong inhibitor of CYP3A4 and P-glycoprotein, dramatically increases colchicine's half-life, augmenting the risk of a life-threatening adverse reaction when used inadvertently with colchicine.

**Objectives—**The aim of this study was to examine the evidence and clinical implications of concomitant use of colchicine and clarithromycin.

Daniel C. Malone, dan.malone@utah.edu.

**Conflict of interest** All authors have completed the ADIS uniform disclosure. There was no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years, and no other relationships or activities that could appear to have influenced the submitted work.

**Ethical approval** None.

**Disclaimer** The authors affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Data availability

Reports of colchicine–clarithromycin drug interactions in FAERS can be publicly accessed via: https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-public-dashboard

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**Methods—**Case reports of colchicine–clarithromycin co-administration were searched using the FDA's Adverse Event Reporting System (FAERS) database. PubMed, EMBASE, and Web of Science electronic databases were also searched from January 2005 through November 2019 for articles reporting colchicine–clarithromycin concomitant use. Individual reports were reviewed to identify consequences of coadministration, dose, days to onset of interaction, symptoms, evidence of renal disease, time to resolution of symptoms, and Drug Interaction Probability Scale (DIPS) rating.

**Results—**The FAERS search identified 58 reported cases, nearly 53% of which were from patients aged between 65 and 85 years. Of 30 reported deaths, 11 occurred in males, and 19 in females. Other frequent complications reported in FAERS included diarrhea (31%), pancytopenia (22%), bone marrow failure (14%), and vomiting (14%). From published literature, we identified 20 case reports of concomitant exposure, 19 of which were rated 'probable' and one 'possible' according to DIPS rating. Of these cases, four 'probable' patients expired. The documented onset of colchicine toxicity occurred within 5 days of starting clarithromycin, and death within 2 weeks of concomitant exposure.

**Conclusion—**Clinical manifestations of colchicine–clarithromycin interaction may resemble other systemic diseases and may be life threatening. Understanding this clinically meaningful interaction can help clinicians avoid unsafe medication combinations.

## 1 Introduction

Colchicine is an alkaloid extracted from autumn crocus (*Colchicum autumnale*), and its use dates back over 4000 years. Based on historical records attributed to Byzantine physician Alexander of Tralles, it was used as a specific treatment for gout [1]. Nowadays, the therapeutic use of colchicine has been well documented in gout and familial Mediterranean fever (FMF) [2]. However, it has also been used to treat other conditions such as Behçet's disease (BD), pericarditis, coronary artery disease, and other inflammatory and fibrotic conditions [3]. The mechanism of action of colchicine is multifactorial. Colchicine's most studied therapeutic mechanism is binding to subunits of the cytoskeletal protein tubulin to prevent microtubule polymerization [4, 5]. This inhibition prevents/inhibits a number of critical cellular functions including intracellular vesicle transport, cell division, cell migration, and secretion of chemokines and cytokines [6]. Colchicine has shown the ability to inhibit neutrophil adhesion and mobility in crystal-induced neutrophil activation by selective inhibition of tyrosine phosphorylation as well as induction of COX-1 and COX-2 gene expression [6, 7]. Furthermore, colchicine interferes with neutrophil adhesion and recruitment to inflamed tissues following monosodium urate crystal stimulation [8, 9].

Colchicine has a narrow therapeutic window, and adverse reactions with its use are common [10]. Up to 20% of patients taking colchicine have reported gastrointestinal symptoms, such as abdominal pain, diarrhea, nausea, and vomiting, which are often mild, temporary, and reversible upon lowering the dose. However, even at therapeutic doses, serious adverse reactions have been reported, including leukopenia, granulocytopenia, thrombocytopenia, pancytopenia, and aplastic anemia [11].

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Colchicine undergoes considerable pre-systemic metabolism and therefore its bioavailability is around 50%. Thirty percent of available colchicine is distributed to the gastrointestinal tract, muscles, heart, spleen, and white blood cells [10]. Particularly noteworthy is colchicine's affinity for hematopoietic stem cells when used in higher doses or as result of a drug–drug interaction [3]. In patients with normal physiological functioning, up to 20% of the administered colchicine dose is eliminated unchanged in the urine, and approximately 50% of the absorbed drug is metabolized, mainly involving the CYP3A4 system [12]. According to the present understanding of colchicine metabolism, medications that inhibit CYP3A4 increase the potential for colchicine toxicity [10, 11]. Fatal consequences have been reported with concomitant use of strong CYP3A4 inhibitors (e.g., clarithromycin, itraconazole, ketoconazole, and some protease inhibitors) [11]. Colchicine is also a substrate for p-glycoprotein (PGP). Because almost all drugs that inhibit CYP3A4 also inhibit PGP, elevated colchicine concentrations are to be expected with co-administration of CYP3A4 inhibitors. In most of the cases, the interaction occurs with colchicine serum concentrations within therapeutic range. Current recommendations suggests that clinicians should avoid prescribing colchicine with interacting medications and reduce the dose of colchicine in patients who are elderly and/or who have renal or hepatic impairment [13].

Many case reports of drug interactions with colchicine involve clarithromycin, a bacteriostatic antimicrobial used for the treatment of upper and lower respiratory infections, *Helicobacter pylori* infection, mycobacterial infections, and other infections. It is metabolized in the liver by CYP3A4 enzymes to the active 14-hydroxy form and six other molecules. Up to 40% of an oral dose of clarithromycin is excreted in the urine either unchanged or as the active metabolite. In patients with moderate to severe renal impairment (i.e., creatinine clearance < 30 mL/min), the dose should be reduced [14, 15].

Clarithromycin interacts with colchicine, increasing its oral bioavailability by increasing absorption through inhibition of the PGP in the enterocytes [16]. It also decreases the hepatic metabolism and clearance of colchicine by acting as a slow reversible inhibitor of CYP3A4 in the liver. In addition, clarithromycin could delay the elimination of colchicine via hepatic metabolism and renal excretion by interfering with the P-glycoprotein [16]. These actions can lead to adverse drug reactions due to increased levels of other concomitantly administered drugs resulting from competition for the similar route of metabolism or from excretion interference. Given the potential for toxicity with this combination, the aim of this study was to examine the evidence and clinical implications related with the concomitant use of colchicine and clarithromycin.

## 2 Methods

### 2.1 Identification of Relevant Case Reports

Several sources of potential case reports were searched for information regarding drug interaction between colchicine and clarithromycin. First, the US Food and Drug Administration's Adverse Event Reporting System (FAERS) database, designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products, was accessed. It includes global adverse event reports, medication error reports, and product quality complaints resulting in adverse events that were submitted to FDA. The

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FAERS database was searched using the FAERS Public Dashboard, where ‘search by product’ was utilized using the medication names ‘colchicine’ and ‘clarithromycin’. The next step was to select under ‘cases by reaction’ using the terms ‘drug interaction’, ‘adverse drug reaction’, and ‘adverse reaction’. Under ‘suspect product active ingredients’, it was necessary to specify the colchicine–clarithromycin pair to narrow the search. Reports evaluated were available up to November 2019.

As is widely known, FAERS does not provide sufficient information to permit assessment of causality but steps were taken to minimize misclassification errors. Reported cases arise from multiple sources and it was necessary to eliminate duplicate observations. The evaluation of duplicates was conducted by evaluating each reported case to all other reported cases by comparing reason for use, reaction reported (i.e., clinical symptoms), clinical outcomes (i.e., died), patient gender, event date reported versus latest FDA received date, patient age, report sender (i.e., pharmaceutical company), concomitant medications (when available), country where the event occurred, and if the case was reported in the literature.

In addition, PubMed, EMBASE, and Web of Science electronic literature databases were searched using ‘colchicine’, ‘clarithromycin’, ‘drug-drug interaction’, ‘interaction’, and ‘case reports’ as search terms, considering reports published within the time frame of January 2005 to August 2019. Reports were required to include both medications; no language restrictions were included in search criteria. Individual literature reports were initially reviewed by a clinical pharmacist (PDH) with over 40 years of experience in drug interaction research to identify attributes of interest for case reports, including dosage of medications involved, days to onset of the interaction, signs and symptoms, evidence of renal disease, time to resolution of symptoms (offset), and Drug Interaction Probability Scale (DIPS) rating. A second clinical pharmacist also evaluated each report and evaluated use of concomitant medications. Frequencies expressed as percentages were used to summarize gender, age, country of origin of the report, diagnosis, and clinical implications due to drug–drug interaction. Range of doses, onset, and offset were considered to summarize information from case reports.

### 2.2 Assessment of Drug–Drug Interaction Case Report Validity

DIPS was utilized to assess the probability of a causal relationship between a potential drug interaction and an observed event [17]. This scale was developed to provide a guide to evaluating drug interaction causation in a specific patient and is intended to be used to assist practitioners and researchers in the assessment of drug interaction-induced adverse outcomes. The scale includes a series of ten questions to estimate the potential drug interaction. The total score is used to estimate the probability that the interaction is causally related to the patient event. Probability is assigned as doubtful, possible, probable, or highly probable. Affirmative responses increase the probability that the observed event was caused by an interaction and negative responses reduce the probability. Questions that cannot be answered due to lack of information or applicability are not considered in the evaluation.

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# 3 Results

In FAERS, a search combining the terms ‘drug interaction’, ‘adverse drug reaction’, and ‘adverse reaction’, and medication names along with a timeframe from 1997 to November 2019 identified 58 cases, with 3% (2 cases) reported as occurring in the US. For 36% of reports, it was not possible to establish the country of origin. The mean age for all reported cases was 71 ± 14 years, with 28 (48%) of cases occurring in females. Thirty-one (53%) of these reports were in patients between 65 and 85 years of age; 28% ($n$ = 16) of patients were between 18 and 64 years of age; 14% ($n$ = 8) of patients were older than 85 years of age; and three reports did not specify age.

FAERS reports most commonly involved patients with a diagnosis of gout ($n$ = 36, 62%), followed by FMF ($n$ = 3, 5%), BD ($n$ = 3, 5%), and amyloidosis ($n$ = 1, 2%). A total of 30 patients died (11 male, 19 female). Twenty-two of the deceased patients received the combination of the two agents for concomitant gout and pneumonia; three patients were diagnosed with gout and *H. pylori* infection; and one had amyloidosis or upper respiratory infections. Other reported symptoms included diarrhea ($n$ = 18, 31%), pancytopenia ($n$ = 13, 22%), bone marrow failure ($n$ = 8, 14%), vomiting ($n$ = 8, 14%), thrombocytopenia ($n$ = 4, 7%), rhabdomyolysis ($n$ = 3, 5%), and renal failure ($n$ = 3, 5%).

From the published literature, we identified a total of 20 case reports of exposure to colchicine and clarithromycin. Nineteen were rated ‘probable’ and one was rated as ‘possible’ using DIPS. Details on these reports are presented in Table 1. Among these 20 cases, four patients (20%) were reported to have died. The documented onset of colchicine toxicity was fairly rapid, within 5 days of starting clarithromycin (range 1–14 days), and for the patients who died, death occurred within 2 weeks after concomitant exposure.

## 3.1 Patient Risk Factors

While some patients may be exposed to the combination and not suffer serious consequences, we sought to identify potential risk factors that may potentiate the interaction. Further details on potential risk factors are presented in the following sections.

**3.1.1 Medication Intensity—**Among the published case reports of colchicine toxicity after exposure to clarithromycin, the average colchicine dose was 1.4 mg/day (range 0.5–4.0 mg/day), with 7 of the 20 patients receiving 1.0 mg/day or less. Thus, it appears that the interaction can occur with ‘normal’ colchicine doses. Severe adverse outcomes have occurred in patients taking colchicine for gout as well as for FMF. Some patients with FMF received higher doses of colchicine, perhaps resulting in greater risk of toxicity [2]. Theoretically, parenteral administration of colchicine would reduce the magnitude of the interaction because this route of administration bypasses intestinal CYP3A4 and P-glycoprotein. For clarithromycin, 15 of the 20 case reports indicated an average dose of 1.0 g per day, a dose sufficient to inhibit CYP3A4 and PGP. One published case report of long-term, low-dose clarithromycin (200 mg/day) did not appear to result in colchicine toxicity [18].

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**3.1.2 Pharmacogenomics and Patient Age—**The effect of pharmacogenomics on this drug–drug interaction have not been well studied. Theoretically, genetic variations in CYP3A4 or PGP activity could alter the magnitude of the interaction.

**3.1.3 Renal Function—**Renal impairment may increase the risk of colchicine toxicity. Renal disease was present in 8 of the 20 published case reports where renal function was mentioned (see Table 1). Also, a retrospective case series showed that 29 of 88 patients (33%) receiving clarithromycin and colchicine had renal impairment, defined as creatinine level > 140 μmol/L, which contributes to the manifestation of this drug–drug interaction [16]. The degree to which renal impairment increases the risk of this interaction has not been well established. Mild to moderate renal disease may not have large effects on colchicine pharmacokinetics. One study of three patients with low estimated glomerular filtration rate (GFR) (14, 27, and 36 mL/min) documented only modest increases in colchicine AUC (area under the curve) compared with patients with normal GFR [19]. It should be noted that serious adverse outcomes can occur in the absence of renal impairment, as was the case for eight patients with FMF [20, 21]. Decline in renal function with age may increase the risk [16], but the average age in the case reports was 54 years (range 23–76 years).

It is important to note that colchicine is not removed by dialysis. A rapid-acting enzyme inducer such as rifampin theoretically could increase colchicine elimination if given early enough (i.e., before renal/hepatic failure). Enzyme induction from rifampicin can begin after 2 days, but maximum induction usually takes 1–2 weeks [22]. However, no data are available to support the use of rifampin for colchicine toxicity. Colchicine-specific antibodies (Fab fragments) have been used successfully to treat colchicine toxicity, but this treatment is not widely available [23].

**3.1.4 Concomitant Medications—**In the FAERS dataset, two (3%) patients were receiving other CYP3A4 inhibitors for the treatment chronic conditions; one (2%) was receiving statins (rosuvastatin or simvastatin); and one (2%) was receiving calcium channel antagonists (verapamil or diltiazem).

**Enzyme Inducers:** Patients on inducers of CYP3A4 and/or PGP are likely to have low colchicine concentrations, and theoretically would be less likely to develop colchicine toxicity. Such inducers may also reduce clarithromycin concentrations, further reducing the risk of colchicine toxicity (e.g., oxcarbazepine, phenobarbital, doxorubicin). No reported cases from either the literature or FAERS mentioned patients taking these medications.

**Statins:** Since myopathy is one of the adverse outcomes of this drug–drug interaction, concurrent statin therapy would theoretically increase the risk of muscle damage. Also, atorvastatin, lovastatin, and simvastatin are metabolized by CYP3A4 and clarithromycin would likely increase their concentrations. Other medications known to cause myopathy would also be expected to increase the risk of rhabdomyolysis in patients receiving concomitant colchicine and clarithromycin. As stated above, one (2%) of 58 FAERS cases was also on a statin and one (2%) was receiving verapamil or diltiazem.

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## 4 Discussion

There is strong evidence that clarithromycin can cause serious toxicity when administered concurrently with colchicine based on (1) interactive properties of the drugs, (2) pharmacokinetics studies in healthy subjects, (3) 20 case reports, the majority ($n = 19$) with a 'probable' DIPS rating, (4) fatalities in a case series dependent on overlap of the two drugs, (5) and most important, 30 fatalities involving concomitant exposure reported in the FAERS database [24]. These findings are not unique, but the magnitude of harm is much larger than previously reported. In a retrospective case–control study of 88 patients with renal impairment who received colchicine and clarithromycin concurrently, nine patients were reported to have expired. Of the half of the 88 patients who had more than a 2-day overlap of the two drugs, 18% died; of the other half who had 1–2 days of overlap, 3% died [16]. Although this is a retrospective study involving relatively few patients, it is consistent with other data about this interaction.

Interactions between colchicine and products that inhibit CYP3A4 and PGP such as clarithromycin may lead to an increase of serum and tissue colchicine concentrations, thus triggering the occurrence of an adverse event, resulting in toxicity and potentially death.

In this paper, we document how clarithromycin added to colchicine has resulted in fatal and near fatal colchicine toxicity (see Table 1). As with other serious drug interactions, the published reports likely represent only a small portion of the actual adverse drug interactions from concurrent colchicine and clarithromycin. Indeed, the fact that FAERS received reports of 58 patients with serious or fatal adverse drug reactions related to the concurrent use of colchicine and clarithromycin is further evidence that this interaction can be dangerous. FAERS is a commonly used source for spontaneously reported adverse events; it can be accessed publicly allowing researchers and/or pharmacovigilance specialists to explore this data source; however, due to a lack of curator from the FDA, it is necessary to carefully review each report to avoid the inclusion of duplicates when conducting pharmacoepidemiologic or pharmacovigilance studies.

The interaction between colchicine and clarithromycin occurs not only by concomitant use of multiple doses, but also single doses. In a study of 23 healthy subjects given a single 0.6-mg dose of colchicine with and without clarithromycin 250 mg twice a day for 7 days, clarithromycin produced a 282% (range 89–852) increase in colchicine AUC [13]. The magnitude of these increases would be expected to cause serious toxicity in patients taking colchicine chronically, especially those at the higher end of the range. It is difficult to extrapolate the results of a single dose study of healthy subjects with normal renal and hepatic function taking no other medications to the complex situation of patients taking the drugs chronically. Almost certainly, the variability in magnitude of the interaction would be even greater in an actual clinical situation.

Other medications that strongly inhibit CYP3A4 and PGP might result in similar consequences. For instance, the combination of cyclosporine and colchicine is dangerous because cyclosporine inhibits CYP3A4 and PGP, and like colchicine, is associated with myopathy and rhabdomyolysis [25]. Medications associated with myopathy may increase

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the risk of this adverse outcome when combined with colchicine. For instance, clinical interactions have been reported in patients treated concomitantly with HMG-CoA reductase inhibitors. The manifestation of this interaction is often muscle weakness or cramps. It is necessary to be attentive to patient complaints because symptoms could start months after the start of concomitant use. Patients with renal dysfunction are prone to present these symptoms [26].

Awareness of this particular drug interaction by prescribers is unknown. However, based on the results presented here, it would be prudent to avoid prescribing patients both medications concurrently. The two common online reference databases of drug information (MICROMEDEX and Lexicomp) stated that concurrent use of clarithromycin and colchicine is contraindicated because it may result in increased colchicine plasma concentrations and increase the risk of toxicity and suggested considering antibiotic alternatives to clarithromycin.

### 4.1 Management Options

The toxicity produced by colchicine can be generally divided into three sequential stages. The first stage occurs within 24 h and is related to gastrointestinal symptoms. After 24 h (second stage), symptoms involve multiple organ failure and may place patients experiencing the following symptoms at a higher risk of death: bone marrow deficiency caused by myeloproliferative disorders (e.g., pancytopenia); renal insufficiency; arrhythmias; disseminated intravascular coagulation; and neuromuscular disturbances. If patients survive the second stage, the last stage, or recovery, is characterized by a rebound of blood dyscrasias and alopecia [10]. Treatment of the interaction is mainly supportive, focusing on recovering from leukopenia using granulocyte-colony-stimulating factors.

Colchicine toxicity usually occurs soon after starting clarithromycin such that laboratory monitoring is not useful. If colchicine toxicity is suspected, clinicians should monitor white blood cells, creatine kinase, renal function, and liver function. Symptom monitoring should include the identification of the symptoms described above; pancytopenia through the presence of fever; other signs of infection and bleeding; rhabdomyolysis with muscle pain, muscle weakness and dark urine; and gastrointestinal toxicity with diarrhea, nausea, vomiting, and abdominal pain.

Replacing colchicine generally would not be an option because there are few alternatives for the drug (e.g., glucocorticoids, NSAIDs). Pausing colchicine while taking clarithromycin may be appropriate, considering that the use of clarithromycin is related to acute conditions. Clinicians should also consider using another antibiotic, though erythromycin and telithromycin are not recommended alternatives because they inhibit CYP3A4 and may inhibit PGP. One case of serious erythromycin-induced colchicine toxicity has been reported (DIPS: ‘probable’) [27]. Azithromycin does not inhibit CYP3A4, but may be a modest inhibitor of PGP; a pharmacokinetic study of 21 subjects found a small (57%) increase in colchicine AUC [13]. Thus, azithromycin appears to be much safer than clarithromycin in patients receiving colchicine. Ciprofloxacin should be avoided, as it inhibits CYP3A4. Other drugs that inhibit both CYP3A4 and PGP include amiodarone, cobicistat, conivaptan, crizotinib, cyclosporine, diltiazem, dronedarone, indinavir, itraconazole, ketoconazole,

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lapatinib, mifepristone, nelfinavir, posaconazole, ritonavir, saquinavir, simeprevir, tamoxifen, telaprevir, telithromycin, verapamil, and voxilaprevir [28].

## 5 Conclusion

While colchicine toxicity is relatively uncommon, coadministration with clarithromycin can result in fatal consequences. Clinical manifestations of the colchicine–clarithromycin interaction may resemble many other systemic diseases. Understanding this clinically meaningful interaction can help to improve the efficacy of each treatment while reducing the threat of adverse reactions, toxicity, and death.

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**Key Points**

Clarithromycin interacts with colchicine, increasing its oral bioavailability and decreasing hepatic metabolism and clearance of colchicine by acting as an inhibitor of CYP3A4 and p-glycoprotein. These actions can lead to life-threatening adverse drug reactions due to increased levels of colchicine.

The FDA Adverse Event Reporting System (FAERS) received reports of 58 serious cases with 30 fatal outcomes, possibly due to adverse drug reactions from concurrent use of colchicine and clarithromycin. This is further evidence that this interaction is life-threatening and co-administration of clarithromycin and colchicine should be avoided.

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**Table 1**

Literature case reports of colchicine-clarithromycin interaction

| Patient, gender and [reference] | Diagnosis for use of colchicine | Dose of colchicine (mg/d) | Dose of clarithromycin (gram/d) | Onset (days)[a] | Reported signs and symptoms | Renal disease | CK (U/L) | Time to resolution of symptoms | DIPS rating[b] |
|---|---|---|---|---|---|---|---|---|---|
| 67, M [29] | FMF | 1.0 | 1.0 | 4 | AP, DI, FV, MF, MG, PC | Yes | No data | Expired | Probable |
| 76, M [30] | FMF | 1.5 | 1.0 | 3 | AC, AP, DI, FV, PC | Yes | No data | 10 days | Probable |
| 68, M [31] | Gout | 1.5–2.0 | 1.0 | 3 | DI, HF, RF, PC | No | No data | Expiredy 13 days post-admission | Probable |
| 55, F [31] | Gout | 1.5 | 0.5 | < 2 | FV, PC | Yes | No data | Expired 12 days post-admission | Probable |
| 23, F [32] | FMF | 1.0 | 1.0 | 6 | AP, DI, FV, NU, PC, VM | Yes | No data | 26 days | Probable |
| 61, M [32] | Gout | 1.0 | 1.0 | 6 | DI, NU, VM | Yes | No data | 12 days | Probable |
| 73, M [33] | Gout | 0.5 | NS | 7 | FT, MW | Yes | 1396 | 14 days | Probable[c] |
| 48, M [34] | Gout | 0.6 | 1.0 | 3 | MG | Yes | 22,996 | 5 days | Probable |
| 52, M [35] | Hyperuricemia | 1.0[d] | 1.0 | 5 | AP, DI, PC, MF, VM | No data | No data | Expired 3 days post-admission | Probable |
| 59, M [36] | Behçet's syndrome | 1.2 | 1.0 | 9 | FV, MG, MW | No | 766 | 14 days | Probable |
| 43, M [20] | FMF | 1.5 | NS | 9 | DI, MG, VM, MW | No | 31,000 | 6 days | Probable |
| 52, F [20] | FMF | 1.5 | NS | 3 | DI, MG, MW, PT | No | 2805 | 10 days | Probable |
| 61, F [21] | FMF | 2.0 | 1.0 | 1 | AP, DI, MG, PC, PN | No | 400 | 3 days | Probable |
| 36, F [21] | FMF | 1.5 | 1.0 | NS | AP, DI, MG, VM | No | 3624 | NS | Probable |
| 71, F [21] | FMF | 1.5 | 1.0 | NS | AP, DI, MG | No | 1036 | NS | Probable |
| 41, F [21] | FMF | 2.5 | 1.0 | NS | AP, DI, MG | No | Elevated | NS | Probable |
| 24, F [21] | FMF | 2.5 | 1.0 | NS | AP, DI, VM, MW | No | Elevated | NS | Probable |
| 69, F [21] | FMF | 2.0 | 1.0 | ~ 4 | AP, DI, MG, MW, VM | No | 6277 | 6 weeks | Probable |
| 40, M [37] | FMF | 1.0 | 1.0 | ~ 7 | AP, DI, MG, MW | Yes | 9035 | 3 days | Probable |
| 78, M [38] | Gout | 4.0 | NS | ~ 14 | MG | No data | 2660 | Months | Possible[e] |

*AC* acidosis, *AP* abdominal pain, *CK* creatine kinase, *DI* diarrhea, *F* female, *FMF* familial Mediterranean fever, *FT* fatigue, *FV* fever, *HF* hepatic failure, *M* male, *MF* multi-organ failure, *MG* myalgia, *MW* muscular weakness, *NS* not stated, *NU* nausea, *PC* pancytopenia, *PN* pain, *PT* paresthesia, *RF* renal failure, *VM* vomiting

[a] Onset of symptoms after starting second drug (colchicine or clarithromycin)

[b] DIPS = Drug Interaction Probability Scale (See Ref. 17)

[c] Patient started on simvastatin 20 mg/day 3 months before reaction, but muscle biopsy suggested colchicine toxicity

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[d] Patient had taken extra colchicine before the reaction

[e] Patient's colchicine dose was increased from 1 mg/d to 4 mg/d around same time clarithromycin started