



Colchicine and macrolides: a cohort study of the risk of adverse outcomes associated with concomitant exposure

Malinda S. Tan¹ · Ainhua Gomez-Lumbreras¹ · Lorenzo Villa-Zapata² · Daniel C. Malone¹

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Abstract

Colchicine is increasingly used as the number of potential indications expands. However, it also has a narrow therapeutic index that is associated with bothersome to severe side effects. When concomitantly use with medications inhibiting its metabolism, higher plasma levels will result and increase likelihood of colchicine toxicity. We conducted a cohort study using electronic health records comparing encounters with colchicine plus a macrolide and colchicine with an antibiotic non-macrolide. We assessed the relationship between the two groups using adjusted multivariate logistic regression models and the risk of rhabdomyolysis, pancytopenia, muscular weakness, heart failure, acute hepatic failure and death. 12670 patients on colchicine plus an antibiotic non-macrolide were compared to 2199 patients exposed to colchicine plus a macrolide. Patients exposed to colchicine and a macrolide were majority men ($n = 1329$, 60.4%) and white ($n = 1485$, 67.5%) in their late sixties (mean age in years 68.4, SD 15.6). Heart failure was more frequent in the colchicine plus a macrolide cohort ($n = 402$, 18.3%) vs the colchicine non-macrolide one ($n = 1153$, 9.1%) ($p < 0.0001$) and also had a higher mortality rate [(85 (3.87%) vs 289 (2.28%), $p < 0.0001$ macrolides vs non-macrolides cohorts, respectively)]. When the sample was limited to individuals exposed to either clarithromycin or erythromycin and colchicine, the adjusted OR for acute hepatic failure was 2.47 (95% CI 1.04–5.91) and 2.06 for death (95% CI 1.07–3.97). There is a significant increase in the risk of hepatic failure and mortality when colchicine is concomitantly administered with a macrolide. Colchicine should not be used concomitantly with these antibiotics or should be temporarily discontinued to avoid toxic levels of colchicine.

Keywords Colchicine · Macrolides · Drug interactions · Cytochrome P-450 CYP3A inhibitors · Drug-related side effects and adverse reactions · Risk

Introduction

Colchicine, an alkaloid that has been used for centuries, and now primarily prescribed for gout and Familial Mediterranean fever, has experienced a resurgence in use. Over the last two decades, colchicine has been studied for treatment of vasculitis, Behçet disease, pericarditis, coronary artery disease, and COVID-19 [1–4]. Colchicine has a narrow therapeutic index and the most frequent side effects are gastrointestinal (abdominal pain, diarrhea, vomits), though severe and life-threatening reactions such as rhabdomyolysis and pancytopenia can occur [5–7]. Cases of severe neurotoxicity due to colchicine have also been described [8, 9]. Colchicine's toxicity makes challenging to dose when used in patients with renal impairment or when concomitantly prescribed with drugs that can increase its plasma levels [9]. Elevated levels of colchicine can be fatal [10, 11].

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

Malinda S. Tan
m4linda90@gmail.com

Ainhua Gomez-Lumbreras
ainhoa.gomez-lumbreras@pharm.utah.edu

Lorenzo Villa-Zapata
villazapata_la@mercer.edu

¹ Department of Pharmacotherapy, College of Pharmacy, University of Utah, 30 South 2000 East, Salt Lake City, UT 84112, USA

² Department of Pharmacy Practice, College of Pharmacy, Mercer University, Atlanta, GA, USA

Colchicine's metabolic pathway is through the cytochrome P450 and is a substrate for cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp) [12]. Pharmacokinetic studies on colchicine and CYP3A4 inhibitors have shown an increase in colchicine plasma levels [13, 14]. CYP3A4 inhibitor medications can increase colchicine plasma levels, resulting in a higher frequency and severity of colchicine's side effects. Case reports have documented neutropenia, neuropathy, myopathy and death in the presence of this drug–drug interaction (DDI) [15–18]. Among the drugs inhibiting the CYP3A4 macrolides, such as clarithromycin and erythromycin, have been described as acting not only inhibiting the CYP3A4 isoform but also inhibiting the P-gp [12]. Clarithromycin has been used concomitantly with colchicine in 50% of the cases and in 72% in two Japanese studies analyzing colchicine concomitant medications and, in 32% in a French study [19, 20]. While case reports have documented consequences of co-administration of colchicine and medications that inhibit its metabolism, few studies exist that examine the use of colchicine across the cohort of patients taking the medication with an interacting medication. Therefore, the purpose of this study was to examine if concomitant use of colchicine with macrolides increases colchicine-associated adverse events and severe clinical consequences.

Methods

Study design

This study was a retrospective cohort study of patients receiving colchicine and macrolide antibiotics or non-macrolides ones. The study was conducted using an electronic health records (EHR) system across multiple institutions with encounters. To account for indication bias, we compared encounters where colchicine was prescribed with a macrolide to encounters where colchicine was concomitantly use with a non-interacting systemic antibiotic. Additional details are provided below.

Study source

The source of data for this study came from the CERNER Health Facts database (<https://sc-ctsi.org/resources/cerner-health-facts>). This database contains de-identified EHR patient data from participating medical institutions across the US, including more than 300 million encounters. Patient information on patient demographic, medical diagnosis codified with the International Classification of Diseases (ICD) 9th and 10th versions, insurance status and drug prescription were also collected. Data from January 2002 to December 2018 were used in this analysis.

Study population

The following inclusion and exclusion criteria were used to select observations for this study. Inclusion criteria included: patients ≥ 18 years old; at least one encounter with exposure to colchicine; and receipt of either a non-macrolides and macrolide antibiotics. Exclusion criteria included: individuals < 18 years old; encounters with any non-macrolide but CYP3A4/P-gp inhibitors medications (see Appendix A in supplemental materials).

Exposures

Colchicine + non-macrolide antibiotic exposure: individuals with a colchicine and a non-macrolide antibiotic prescription in the same encounter (please see Appendix B of the Supplemental Material).

Colchicine + macrolide exposure: individuals with a colchicine prescription and at least one of the following macrolides: azithromycin, clarithromycin or erythromycin at the same encounter. Formulations that were administered via an oral, intramuscular or intravenous route were of interest. Other formulations including otic, ophthalmic or topic applications or other external preparations were excluded.

Potential confounders

The Charlson comorbidity index score was calculated for both groups to account for comorbidities [21].

Outcomes

Adverse events resulting from colchicine toxicity were identified by ICD 9th edition and 10th edition codes (see Supplementary Material Appendix C). Generally, these conditions include: rhabdomyolysis; pancytopenia; muscular weakness; heart failure; or acute hepatic failure. In an effort to identify those possible cases of rhabdomyolysis not identified by diagnosis codes, an outcome for laboratory creatine kinase (CK) values corresponding to rhabdomyolysis (over 5 times the upper normal limit i.e. ≥ 1500 UI/L) was also identified [22].

Statistical analysis

Descriptive statistics were used to describe patient demographics (age, sex and race), comorbidities (Charlson comorbidity index), and primary outcomes. The relationship between DDI exposure and outcomes was assessed using both unadjusted and adjusted multivariable logistic regression models. The adjusted model controlled for age, sex,

race, and Charlson comorbidity index. Both clarithromycin and erythromycin have been known to strongly bind and inhibit CYP 3A4/P-gp, while azithromycin has been shown to interfere poorly with cytochrome P450 [23]. Therefore, we performed a sub-analysis of the colchicine and macrolide exposure consisting of only those encounters with colchicine and clarithromycin or erythromycin (strong CYP3A4 inhibitor exposure).

Ethics

The study is using only de-identified data. Confidentiality of patient records has been maintained at all times. All study reports will contain aggregate data only and will not identify individual patients or physicians. Ethic approval from the IRB from the University of Utah was obtained.

Results

A total of 12670 patients were exposed to colchicine and a non-macrolide antibiotic (controls), and a total of 2199 patients were exposed to colchicine and a macrolide (DDI exposure). There were more men than women in both cohorts [7855 (62%) in the colchicine + non-macrolide antibiotic and 1329 (60%) in the colchicine + macrolides], and the majority of patients in each group were Caucasian [8757 (69%) and 1485 (68%), colchicine + non-macrolides and colchicine + macrolides, respectively]. Patients in the colchicine + non-macrolide antibiotic group were younger [63.1 (SD = 16.8) vs 68.4 (SD = 15.6) years of age, p 0.47] (see

Table 1). More than half of the patients in both groups had a Charlson comorbidity index under 3 [9636; (76%) colchicine + non-macrolide; 1409 (64%) colchicine + macrolides, $p < 0.001$]. Those in the colchicine + macrolides group had higher Charlson scores [9.6% with 5 or more Charlson index scored vs 5% in the colchicine + non-macrolide antibiotic] (p value < 0.001).

The most frequent adverse event in both cohorts was heart failure [1153 (9.1%) in colchicine + non-macrolide antibiotic and 402 (18.3%) in the colchicine + macrolides, $p < 0.001$], followed by pancytopenia [638 (5.0%) and 103 (4.7%) colchicine + non-macrolide antibiotic and colchicine + macrolide respectively, $p = 0.48$] (see Table 2). The colchicine + macrolide cohort had a significantly higher death rate than the colchicine + non-macrolide antibiotic group [85 (3.87%) vs 289 (2.28%) respectively, $p < 0.001$].

A logistic regression analysis accounting for age, sex, race and Charlson comorbidity index found a nearly eight-fold higher risk of rhabdomyolysis (determined by CK laboratory value) with the concomitant use of colchicine and any macrolide, including azithromycin [OR_{adj} 7.88 (95% CI 1.29–48.01)]. However, when the diagnosis of rhabdomyolysis by ICD code was used, no statistically significant difference in risk was observed [OR_{adj} 1.00 (95% CI 0.61–1.65)] (see Table 3). The risk for rhabdomyolysis using laboratory CK values to define the condition found even higher risk for patients prescribed colchicine plus a strong inhibitor of CYP3A4 (clarithromycin or erythromycin) [OR_{adj} = 22.58 (95% CI 1.84–277.39)].

Among other outcomes, an increased risk of heart failure was observed for individuals exposed to colchicine

Table 1 Cohort demographics

Total patients by one encounter	Exposure to colchicine + non-macrolide antibiotic <i>n</i> = 12670	Exposure to colchicine + macrolide <i>n</i> = 2199	<i>p</i>
Age (mean, SD)	66.4 (15.8)	68.4 (15.6)	0.470
Sex (<i>n</i> , %)			
Female	4813 (38.0)	870 (39.5)	0.316
Male	7855 (62.0)	1329 (60.4)	
Unknown	2 (0.0)	0 (0.0)	
Race (<i>n</i> , %)			
African American	2802 (22.1)	519 (23.6)	0.539
Asian	314 (2.5)	54 (2.4)	
Caucasian	8757 (69.1)	1485 (67.5)	
Other	535 (4.2)	99 (4.5)	
Unknown	262 (2.1)	42 (1.9)	
Charlson comorbidity index			
0	4999 (39.4)	641 (29.1)	<0.001
1–2	4640 (36.6)	768 (34.9)	
3–4	2393 (18.9)	578 (26.3)	
≥5	638 (5.0)	212 (9.6)	

Table 2 Frequency of adverse events

	Exposure to colchicine + non-macrolide antibiotics <i>n</i> = 12670 (100%)	Exposure to colchicine + macrolides <i>n</i> = 2199 (100%)	<i>p</i>
Rhabdomyolysis by lab CK value (CK > 1500UI/L)	2 (0.0)	3 (0.1)	0.03
Rhabdomyolysis by diagnosis	96 (0.7)	19 (0.8)	0.60
Pancytopenia	638 (5.0)	103 (4.7)	0.48
Muscle weakness	44 (0.3)	8 (0.3)	0.90
Heart failure	1153 (9.1)	402 (18.3)	<0.0001
Acute hepatic failure	92 (0.7)	21 (0.9)	0.25
Expired	289 (2.28)	85 (3.87)	<0.0001

Lab laboratory, *CK* creatine kinase

Table 3 Results from adjusted multivariate regression models for overall and subgroup

Outcomes	OR _{adj} (95% CI) for colchicine and any macrolides	OR _{adj} (95% CI) for colchicine and clarithromycin/erythromycin
Rhabdomyolysis by laboratory CK values > 1500 UI/L	7.88 (1.29–48.01)	22.58 (1.84–277.39)
Rhabdomyolysis by diagnosis	1.00 (0.61–1.65)	1.02 (0.25–4.2)
Pancytopenia	0.74 (0.59–0.92)	1.13 (0.67–1.92)
Muscle weakness	0.81 (0.38–1.73)	~
Heart failure	1.67 (1.45–1.93)	1.06 (0.67–1.67)
Acute hepatic failure	0.98 (0.61–1.6)	2.47 (1.04–5.91)
Expired	1.46 (1.14–1.88)	2.06 (1.07–3.97)

~ there were zero observations for clarithromycin/erythromycin group

plus any macrolide [OR_{adj} 1.67 (95% CI 1.45–1.93)]. However, there was not a statistically significant increase in the risk of a diagnosis of heart failure when clarithromycin or erythromycin combined with colchicine was compared to colchicine + non-macrolide antibiotic [OR_{adj} 1.06 (95% CI 0.67–1.67)]. On the other hand, the odds of having acute hepatic failure were higher with concomitant exposure to colchicine and a macrolide strong inhibitor of CYP3A4 [OR_{adj} 2.47 (95% CI 1.04–5.91)], and the odds of death were twofold higher for this group [OR_{adj} 2.06 (95% CI 1.07–3.97)] (see Table 3). For the other outcomes of interest, there was no observed increase in risk for either muscle weakness or pancytopenia with the concomitant exposure either to colchicine and any macrolide or colchicine and clarithromycin/erythromycin.

As only 5 patients showed CK values over 1500 IU/L, these cases were manually reviewed, with two having been diagnosed with “Drug induce myopathy” and “Rhabdomyolysis”, one having suffered a car accident, one having had septic shock, and one without a diagnosis that could relate these high CK values to a suspected drug interaction or drug induce myopathy (Appendix D of the Supplemental Material).

Discussion

Our analysis examined clinically meaningful severe adverse events when colchicine and a macrolide are administered concomitantly, with the results indicating a higher mortality rate in individuals exposed to this interaction compared to those not exposed. The studied cohorts were generally composed of men in their sixties, a cohort that aligns well with the onset of gout, a primary indication for colchicine [5].

Individuals receiving colchicine and a macrolide concomitantly had higher rates of heart failure but similar rates of pancytopenia, muscular weakness, and acute hepatic failure compared to patients receiving colchicine and other antibiotics. The risk of acute hepatic failure was much higher when colchicine was used concomitantly with clarithromycin or erythromycin. Case reports have been published describing pancytopenia, hepatic failure and rhabdomyolysis as adverse outcomes when colchicine was used concomitantly with clarithromycin [15–17]. In a chart review of hospitalized patients treated with colchicine, among the 37 fatal cases, 17 had a CYP3A4 inhibitor

drugs mentioned, including one individual with exposure to a macrolide [24]. An analysis of the FDA Adverse Event Reporting System (FAERS) found 58 reports mentioning colchicine and clarithromycin, including 13 (22%) reports of death [25]. A retrospective study reported that nine (10.2%) of the 88 patients who received clarithromycin and colchicine had expired [26]. In our analysis only accounting for strong CYP3A4 inhibitor macrolide (clarithromycin and erythromycin) heart failure was not associated with the concomitant exposure while hepatic failure and death were related agreeing with the above described. Colchicine has recently been studied for several cardiovascular diseases though its use has not been that extended to heart failure in routine clinical practice and may explain the higher incidence of heart failure in this study [27]. However, a recent clinical trial did not find any likelihood for death or hospital stay due to heart failure in patients on colchicine with stable heart failure [28].

Pancytopenia has been reported as a side effect of colchicine due to colchicine interfering with the production of neutrophils, leading to fatal outcomes [29–31]. It is a rare adverse event and our analysis found that compared to those exposed to colchicine and non-macrolide antibiotic, patients exposed to colchicine plus a macrolide had lower odds of experience pancytopenia [OR_{adj} 0.74 (95% CI 0.59–0.92) and OR_{adj} 1.13 (95% CI 0.67–1.92), all macrolides and only those strong CYP3A4 inhibitors respectively]. This finding also contradicts that of a retrospective study, which showed an elevated risk of pancytopenia [26]. A major difference between previous studies and our analysis is that most of the individuals we evaluated were hospitalized and may have been more closely monitored for changes in white blood cells.

Despite the availability of large health databases to study and evaluate DDIs, most information on DDIs continues to be based on preclinical pharmacokinetics studies and safety data recorded during clinical trials before marketing authorization [32]. Pharmacokinetic data are theoretically useful, they do not provide evidence for clinically significant adverse outcomes. After marketing, observational studies may be useful in detecting potential DDIs and assessing the clinical consequences of concomitant exposure [19, 33]. The research conducted prior to approval does not necessarily provide clinicians information regarding the risk of DDI or how to best manage them. Also, elderly are exposed to polypharmacy and have an increased risk for adverse events rate due to DDI [34–36].

A concerning issue with the colchicine and drug interactions is the confusing and/or inaccurate information on the interaction. There is inconsistency in the seriousness of this interaction across DDI websites, where concomitant exposure to colchicine and CYP3A4 inhibitors are classified as “major contraindication” or “serious interaction”

[37–41]. However, these terms may fail to reflect the seriousness of harm and prevent exposure to these medications as demonstrated by this analysis. Additionally, many drug information sources do not mention colchicine dose adjustment in patients with decreased renal function, as included in product labeling. These websites also have limited information on alternatives to macrolides (See Appendix E of the Supplemental Material for the review of the DDI checkers websites).

Colchicine has been used available for many years, but new indications for its use continue to emerge. In 2020, during the COVID19 outbreak, colchicine was studied as a therapeutic drug for COVID-19 infected patients [42–44]. The COLCORONA trial conducted in Canada showed a reduction in the composite, death and hospitalization outcomes for those community-treated COVID-19 patients with colchicine against placebo, though no analysis or mention of antibiotics such as macrolides for COVID-19 treatment was made [42]. The use of macrolides has been studied in patients with COVID-19 pneumonia, though the clinical trials did not contemplate the concomitant use of colchicine and did not specifically mention this as an exclusion criterion [45–47].

Our study has limitations that should be considered when interpreting the results. The administered dose of colchicine was not evaluated in our analysis due to the lack of information. Patients with renal failure are at increased risk of colchicine toxicity and the colchicine dose should have been adjusted thus, one limitation was that we did not attempt to include measures of kidney function due to the lack of this data being routinely available for all observations [48]. One retrospective study comparing patients concomitantly prescribed colchicine and clarithromycin and patients sequentially prescribed these drugs showed a higher risk of pancytopenia in those with renal impairment [26]. To account for comorbidities, we used the Charlson comorbidity index, but this risk adjustment tool does not include kidney failure as a risk factor [49]. Another limitation is that we did not attempt to control for the duration of exposure to both medications. The amount of concomitant exposure may be an important factor in evaluating potential toxicity. Another limitation is the information on other concomitant medications patients may have been received that would increase the risk for AE. We did not attempt to examine potential confounding by other medications. This study also used the diagnosis of conditions as an outcome of interest. We do not have longitudinal data that would permitted us to evaluate if these diagnoses are incident conditions or conditions that were long-standing before the receipt of colchicine and an interacting medication. An inherent limitation when using EHR is missing data. We identified only 5 patients with CK values over 1500 IU/L. This may be an underrepresentation of what actually occurred. Also, when manually reviewing

these patients, two had alternative explanations for these high CK values, including severe trauma and sepsis [50].

In conclusion, this analysis demonstrates the increased risk of colchicine toxicity when colchicine is concomitantly administered with a macrolide. Due to its narrow therapeutic index, colchicine toxicity may contribute to increased risk of mortality among hospitalized patients. When possible, the combination of colchicine and clarithromycin or erythromycin should be avoided.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s00296-022-05201-5>.

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Author contributions MST participated in developing the study protocol and research design, analyzed data, and contributed to interpretation of data. She also reviewed and edited the manuscript. AGL has participated developing the study protocol and research design, interpretation of data and drafted the manuscript. LVZ participated in developing the research design and interpretation of results. He has reviewed and edited the manuscript. DCM led the conception of the work, supervised the study and drafted the study protocol and research design, guided the analysis of data, provided interpretation as well as reviewed and edited the final manuscript. All co-authors agree to be accountable for all aspects of the work, taking full responsibility for the integrity and accuracy of all aspects. All authors approved the version to be published.

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Data availability The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Conflict of interests All the authors declare no conflicts of interest.

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