REVIEW ARTICLE

Colchicine Drug Interaction Errors and Misunderstandings: Recommendations for Improved Evidence-Based Management

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Abstract

Colchicine is useful for the prevention and treatment of gout and a variety of other disorders. It is a substrate for CYP3A4 and P-glycoprotein (P-gp), and concomitant administration with CYP3A4/P-gp inhibitors can cause life-threatening drug–drug interactions (DDIs) such as pancytopenia, multiorgan failure, and cardiac arrhythmias. Colchicine can also cause myotoxicity, and coadministration with other myotoxic drugs may increase the risk of myopathy and rhabdomyolysis. Many sources of DDI information including journal publications, product labels, and online sources have errors or misleading statements regarding which drugs interact with colchicine, as well as suboptimal recommendations for managing the DDIs to minimize patient harm. Furthermore, assessment of the clinical importance of specific colchicine DDIs can vary dramatically from one source to another. In this paper we provide an evidence-based evaluation of which drugs can be expected to interact with colchicine, and which drugs have been stated to interact with colchicine but are unlikely to do so. Based on these evaluations we suggest management options for reducing the risk of potentially severe adverse outcomes from colchicine DDIs. The common recommendation to reduce the dose of colchicine when given with CYP3A4/P-gp inhibitors is likely to result in colchicine toxicity in some patients and therapeutic failure in others. A comprehensive evaluation of the almost 100 reported cases of colchicine DDIs is included in table form in the electronic supplementary material. Colchicine is a valuable drug, but improvements in the information about colchicine DDIs are needed in order to minimize the risk of serious adverse outcomes.

1 Introduction

Colchicine has been a valuable drug in the prevention and treatment of gout for many centuries, and it is also approved for use in familial Mediterranean fever. Colchicine has a

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Key Points

Colchicine is a valuable drug for many indications, but it has a number of potentially serious drug interactions.

Most current sources of colchicine drug interaction information have errors of omission or commission regarding which drugs interact clinically with colchicine.

Adverse colchicine drug interactions can almost always be prevented through proper management and patient education.

variety of off-label uses, including pericarditis, various dermatologic disorders, Behçet's disease, and more recently it has been used to reduce cardiovascular events in patients with coronary artery disease [1–4]. Colchicine has also been tested in patients with COVID-19 in numerous clinical trials, but the results to date have been disappointing [5, 6].

Colchicine is still under investigation for treatment of long COVID [7], and it can be used to treat the pericarditis that can occur in COVID patients [8]. As the indications for colchicine increase beyond gout, it is logical to expect to see more adverse drug–drug interactions (DDIs) because more people will receive colchicine, and the prescribers may have little previous experience using the drug. In clinical trials of low-dose colchicine (0.5 mg/day) following myocardial infarction, few DDIs have been observed [2]. This lack of DDIs in low-dose colchicine trials is consistent with the case reports detailed in the electronic supplementary material (ESM), in which the vast majority of adverse colchicine DDIs involved colchicine doses > 0.5 mg. Nonetheless, it is likely that the risk of colchicine DDIs is lower in these clinical trials as opposed to the general clinical setting in which patients may receive higher colchicine doses and where patients are not as carefully screened for risk factors, concomitant therapy, and may not be carefully monitored for adverse outcomes [9]. Given that colchicine DDIs can result in serious or fatal outcomes, it is important that health care professionals (i) know which drugs can interact with colchicine, and (ii) understand how to manage such DDIs to minimize the risk of patient harm. The purpose of this paper is to provide that information, based on the evidence provided in the literature and the general principles of drug interaction management.

2 Colchicine Toxicity

Colchicine has a narrow therapeutic index and must be dosed carefully to minimize the risk of toxicity. Toxicity tends to occur when the serum colchicine concentration exceeds 3.0 μg/L [10]. While colchicine has been used safely in many patients for many centuries, colchicine toxicity can occur when patients develop excessive serum concentrations, often resulting from some combination of excessive dosing, drug interactions, and impaired renal or hepatic function [11]. Once serious colchicine toxicity occurs it can be very difficult to treat, especially if the toxicity damages the kidneys

and liver, which further impairs the ability of the person to eliminate colchicine. Even when the patient survives, elevated colchicine concentrations may persist for weeks after it is discontinued [12–14] resulting in continuing damage to tissues and organs. Colchicine is not dialysable, so dialysis does not shorten the process. Indeed, patients on maintenance hemodialysis appear to be at greater risk from colchicine DDIs [15–17]. Colchicine toxicity usually manifests as gastrointestinal, musculoskeletal, hematologic, and—with severe toxicity—cardiovascular. These are summarized in Table 1. Over 100 DDI cases of colchicine-related toxicity, many of them life-threatening or fatal, have been published in case reports, case series, and adverse reaction reporting systems [18, 19]. A detailed analysis of colchicine DDI cases published in the medical literature is provided in the online Supplemental Table (see ESM).

3 Colchicine Pharmacokinetics

Despite colchicine being used for many centuries, its pharmacokinetics have only been studied in the past few decades after suitable assay techniques were developed. Research is still being conducted, particularly on the effect of transporters on colchicine disposition.

3.1 Absorption

Colchicine is a lipid-soluble alkaloid and undergoes extensive first-pass metabolism resulting in an absolute bioavailability of approximately 30–50% [11, 20, 21]. Bioavailability can vary substantially from one patient to another, probably due to the numerous enzymes and transporters involved during absorption. In one study of healthy subjects, mean bioavailability was 45%, but it varied among subjects from 28 to 88% [22]. Colchicine is a substrate for CYP3A4 and P-gp in the intestine, and P-gp appears to transport colchicine back into the intestinal lumen. It has been proposed that colchicine may be a substrate for transporters such as MRP2 and OATP2B1 [23, 24] but their role remains to be established.

Table 1 Clinical findings of colchicine toxicity

Severity	Signs and symptoms
Mild	Gastrointestinal: diarrhea, nausea, vomiting, abdominal pain Miscellaneous: fatigue, lethargy, malaise, insomnia
Moderate	Neuromuscular: muscle pain, muscle weakness, paresthesias Hematologic: moderate neutropenia and/or moderate thrombocytopenia Respiratory: shortness of breath, cough Dermatologic: alopecia (usually late)
Severe/fatal	Neuromuscular: rhabdomyolysis, atonia, dark brown urine Hematologic: pancytopenia (infections, fever, bleeding) Multiorgan failure: renal failure, liver failure Cardiovascular: cardiac arrhythmias, cardiac failure, hypotension, cardiac arrest

3.2 Distribution

Colchicine is rapidly distributed, and the apparent volume of distribution of colchicine is large; it is usually about 5–10 L/kg but can range from 2 to 12 L/kg. The wide distribution and low (nanogram per milliliter) concentrations in the plasma are consistent with the failure of dialysis to effectively treat colchicine toxicity. Binding to serum protein is about 40%, again with high variability. Colchicine crosses the placenta and is distributed into breast milk [11, 21]. There are no reported DDIs based on changes in colchicine distribution.

3.3 Metabolism

Colchicine metabolism takes place primarily through demethylation by CYP3A4 in the intestine and liver. Other CYP isozymes and phase II metabolism do not appear to play a significant role in colchicine metabolism.

3.4 Elimination

The kidneys are important in the elimination of colchicine, but estimates of the percentage of total colchicine clearance by the kidneys have varied [21]. In 12 healthy subjects given colchicine 1 mg, 40–65% was recovered unchanged in the urine [25], but others have found lower percentages for renal elimination [21]. Biliary excretion also appears to be an important pathway of colchicine elimination, and P-gp appears to be involved in both the renal tubular secretion and the biliary excretion of colchicine [21, 26]. The half-life in healthy subjects is generally about 15–30 h [21, 22]. In one small study, total body clearance was about twice as high and area under the concentration–time curve (AUC) was about four times smaller for healthy subjects compared with elderly patients [22].

4 Mechanisms of Colchicine Drug Interactions

Colchicine can interact with other drugs by a variety of different mechanisms (see Table 2). For some colchicine DDIs, more than one mechanism is involved. For example, several drugs that cause myopathy also inhibit CYP3A4 and/or P-gp (e.g., amiodarone, cyclosporine, statins). Colchicine is rarely the perpetrator in DDIs with other drugs, and in this paper we address only colchicine as the victim drug in DDIs.

4.1 Inhibition of CYP3A4 and/or P-gp

Colchicine is a substrate for CYP3A4 in the intestine and liver, and undergoes considerable first-pass metabolism resulting in bioavailability of 30–50% [11, 21]. It is also a substrate for P-gp in the small intestine, liver, and kidneys [11, 23]. Colchicine undergoes enterohepatic circulation as parent drug and metabolites. Many drugs that produce combined CYP3A4/P-gp inhibition have been shown to increase colchicine serum concentrations and cause colchicine toxicity as we describe elsewhere in this paper.

Because it is well documented that combined CYP3A4/P-gp inhibitors increase colchicine AUC, drugs that inhibit either CYP3A4 or P-gp alone are also often assumed to be capable of increasing colchicine AUC. The vast majority of drugs that inhibit CYP3A4 also inhibit P-gp, so this is not an issue for most colchicine DDIs. It is not established, however, that inhibition of either CYP3A4 or P-gp alone is enough to cause clinically significant DDIs with colchicine. In fact, the available evidence, although limited, suggests otherwise. Drugs that primarily inhibit one or the other—such as voriconazole (CYP3A4 inhibitor) or propafenone (P-gp inhibitor)—have not had much effect on colchicine pharmacokinetics.

Voriconazole is classified by the US FDA as a 'strong' CYP3A4 inhibitor, and it can substantially increase the AUC of CYP3A4 substrates [27, 28]. Voriconazole may

Table 2 Sites of potential interaction with colchicine

Process	Mediated by	Drugs that may interact
Absorption	CYP3A4 and P-gp in wall of small intestine[a]	Inhibitors or inducers of CYP3A4 and P-gp in wall of small intestine
Hepatic metabolism	CYP3A4 and P-gp in liver	Inhibitors or inducers of CYP3A4 and P-gp in liver Hepatotoxic drugs (theoretically)
Biliary excretion	P-gp in liver	Inhibitors or inducers of P-gp in liver
Renal excretion	Glomerular filtration P-gp in kidney	Nephrotoxic drugs (theoretically) Inhibitors or inducers of P-gp in kidney
Myotoxicity	Possible additive effect with myotoxic effect of colchicine	Drugs that cause myopathy

[a]Colchicine undergoes enterohepatic circulation, it may be exposed to CYP3A4 and P-gp more than once

not inhibit P-gp, however, suggested by a lack of voriconazole on digoxin pharmacokinetics in healthy subjects [29]. A pharmaceutical company applying to the US Food and Drug Administration (FDA) for approval of their colchicine product performed a non-randomized, open-label, crossover study in 12 healthy subjects given colchicine 0.6 mg before and after voriconazole 200 mg twice daily for 5 days. Voriconazole did not affect colchicine pharmacokinetics [30].

On the other hand, propafenone inhibits P-gp but is not known to inhibit CYP3A4. A pharmaceutical company applying to the US FDA for approval of their colchicine product conducted a non-randomized, open label, crossover study in nine healthy male subjects who were given a single dose of colchicine 0.6 mg before and after propafenone 225 mg twice daily for 5 days. Propafenone did not appear to affect colchicine pharmacokinetics [30]. However, one cannot rule out that a larger daily dose of propafenone given for a longer period might interact with colchicine. It is also possible that P-gp inhibition without CYP3A4 inhibition has little effect on colchicine pharmacokinetics. A tentative conclusion from the studies of voriconazole and propafenone is that inhibition of both CYP3A4 and P-gp is needed in order to manifest clinically important effects on colchicine pharmacokinetics. Nonetheless, one cannot rule out that inhibition of either CYP3A4 or P-gp alone may be sufficient to interact with colchicine, especially in patients predisposed to colchicine toxicity such as those with renal or hepatic toxicity, or those with reduced activity of P-gp or CYP3A4 due to genetics.

4.2 Enzyme Inducers

Enzyme inducers such as rifampin, barbiturates, carbamazepine, efavirenz, lumacaftor, phenytoin, primidone, and St. John's wort increase CYP3A4/P-gp activity, and would be expected to reduce colchicine AUC. Case reports suggest that both rifampin and carbamazepine can substantially reduce colchicine concentrations [31, 32]. (See case report details in the online Supplemental Table in the ESM). Lesinurad appears to be a modest CYP3A4 inducer, and it produced modest reductions in colchicine AUC in healthy subjects [33]. Although the evidence for the effect of CYP3A43 inducers on colchicine is limited, it seems very likely that patients on enzyme inducers are at increased risk of subtherapeutic colchicine concentrations.

4.3 Additive Myotoxic Effects

Colchicine therapy alone has been associated with myopathy and rhabdomyolysis [34–40], and it is possible that additive myotoxic effects with other drugs can occur.

Myotoxicity has been reported in numerous patients receiving colchicine along with drugs that can independently lead to myotoxicity such as certain statins and cyclosporine. (See case report details in the online Supplemental Table, ESM.) Although it is thought that these reactions are due to additive myotoxic effects, it cannot yet be ruled out that pharmacokinetic DDIs may also occur, involving CYP3A4, P-gp, OATP [24] or MRP2 [23, 41]. Evidence to date suggests that not all statins pose the same risk when combined with colchicine, as discussed in Table 3. The signs and symptoms of myotoxicity in these cases often included muscle weakness and/or muscle pain, and sometimes darkened urine; myopathy is also often accompanied by nonspecific symptoms such as fatigue and malaise, and shortness of breath.

5 Risk Factors for Colchicine DDIs

The risk of adverse outcomes from colchicine DDIs can be influenced substantially by the dose and duration of colchicine therapy as well as kidney and liver function

5.1 Colchicine Dose and Duration

Epidemiological studies using low-dose colchicine have generally found little evidence of adverse consequences with colchicine and interacting medications [1–4]. This is consistent with the case reports described in the online Supplemental Table in which the majority of adverse DDIs reported involved colchicine doses >0.5 mg/day (see ESM). Nonetheless, the epidemiological studies were not designed to detect adverse DDIs and we cannot rule out that some at-risk patients had DDIs. At colchicine doses > 0.5 mg/day, as one would expect, the risk of colchicine adverse DDIs appears to increase as the colchicine dose is increased. The duration of colchicine use is also important. It is unusual to see significant colchicine toxicity until at least 3 or 4 days of concurrent use of colchicine and the interacting drug, although in rare cases it can occur after only a day or two of concurrent therapy [18]. The case reports in the online Supplemental Table also provide onset of adverse reaction information. A more typical onset of adverse effects from the colchicine DDI would be after 5 or 10 days of concurrent therapy, and in some cases (especially DDIs causing myopathy) it may take weeks or even months.

5.2 Renal Disease/Age

Renal impairment predisposes to colchicine toxicity [42]. In 21 patients with varying levels of kidney impairment, the three patients with low estimated glomerular filtration rate

Table 3 Management options for colchicine drug interactions

Drugs	Evidence for drug interaction (DDI)	ORCA class[a] and management options	Management if concurrent use needed
Antiarrhythmics			
Amiodarone	Amiodarone inhibits CYP3A4/P-gp and would be expected to ↑ colchicine AUC; [61] several case reports suggest that a DDI may occur[b]	**ORCA Class 2: Avoid if possible[c]** Use alternative: other than amiodarone and dronedarone, most other antiarrhythmics are not known to inhibit CYP3A4 and P-gp Or consider alternative to colchicine[d]	Reduce colchicine dose 50–75% Monitor for colchicine toxicity Advise patient about colchicine toxicity[e]
Dronedarone	Dronedarone inhibits CYP3A4/P-gp and theoretically would be expected to ↑ colchicine AUC [62, 63]	**ORCA Class 2: Avoid if possible[c]** Use alternative: other than amiodarone and dronedarone, most other antiarrhythmics are not known to inhibit CYP3A4 and P-gp Or consider alternative to colchicine[d]	Reduce colchicine dose 50–75% Monitor for colchicine toxicity Advise patient about colchicine toxicity[e]
Propafenone	Propafenone inhibits P-gp but has little effect on CYP3A4; no colchicine DDI was found in healthy subjects with propafenone 450 mg/d × 5 days [30, 56]	**ORCA Class 4: Low risk** Concurrent use need not be avoided, but some patients might have increased colchicine levels especially if they have low CYP3A4 activity due to other drugs or genetics	Normal monitoring for colchicine toxicity
Quinidine	Quinidine is a potent inhibitor of P-gp, but not CYP3A4 [64]; it is not known if P-gp inhibition alone affects colchicine pharmacokinetics, no clinical data are available	**ORCA Class 3: Assess risk; take action if needed** Concurrent use need not be avoided, but increased colchicine levels possible, especially in predisposed patients (e.g., on CYP3A4 inhibitors, severe renal or hepatic impairment)[c]	Monitor for altered colchicine effect if quinidine is started, stopped or changed in dosage Advise patient about colchicine toxicity[e]
Ranolazine	Ranolazine appears to be a modest inhibitor of CYP3A4 and P-gp [65–67]; it is not known if inhibition of CYP3A4 and P-gp is large enough for interaction	**ORCA Class 3: Assess risk; take action if needed** Concurrent use need not be avoided, but increased colchicine levels possible, especially in predisposed patients (e.g., on CYP3A4 inhibitors, severe renal or hepatic impairment)[c]	Monitor for altered colchicine effect if ranolazine is started, stopped or changed in dosage Advise patient about colchicine toxicity[e]
Azole antifungals			
Fluconazole	Fluconazole is a dose-dependent inhibitor of CYP3A4 that probably has little effect on P-gp [27, 68–70]; fluconazole 400 mg on day 1 and 200 mg on days 2–5 ↑ colchicine AUC by 40% in healthy subjects [56]; one case of colchicine toxicity with fluconazole in patient with renal failure[b]	**ORCA Class 3: Assess risk; take action if needed** Concurrent use need not be avoided, but increased risk with renal impairment[c,f] or if patient has low P-gp activity[g] Or consider alternative to fluconazole: voriconazole may be less likely to interact with colchicine (see below); terbinafine does not inhibit CYP3A4	**If no renal impairment or ↓ P-gp activity:** Monitor for colchicine toxicity particularly during start of fluconazole therapy Advise patient about colchicine toxicity[e] **With renal impairment or ↓ P-gp activity:** Reduce colchicine dose 50–75% Monitor for colchicine toxicity Advise patient about colchicine toxicity[e]
Itraconazole	Itraconazole inhibits CYP3A4/P-gp [27] and would be expected to ↑ colchicine AUC as does ketoconazole (see below)	**ORCA Class 2: Avoid if possible[c]** Consider stopping colchicine during short-term itraconazole Or use alternative. Fluconazole (see above) and voriconazole (see below) are less likely to interact; terbinafine does not inhibit CYP3A4 Or consider alternative to colchicine[d]	Reduce colchicine dose 50–75% Monitor for colchicine toxicity Advise patient about colchicine toxicity[e]

Table 3 (continued)

Drugs	Evidence for drug interaction (DDI)	ORCA class[a] and management options	Management if concurrent use needed
Ketoconazole	Ketoconazole inhibits CYP3A4/P-gp. A study in 24 healthy subjects found a mean 212% ↑ in colchicine AUC after ketoconazole 200 mg BID for 5 days; one subject had a 420% ↑ in AUC [25]	**ORCA Class 2: Avoid if possible[c]** Consider stopping colchicine during short-term ketoconazole Or use alternative. Fluconazole (see above) and voriconazole (see below) are less likely to interact; terbinafine does not inhibit CYP3A4 Or consider alternative to colchicine[d]	Reduce colchicine dose 50–75% Monitor for colchicine toxicity Advise patient about colchicine toxicity[e]
Voriconazole	Voriconazole is a strong CYP3A4 inhibitor, but appears to have little effect on P-gp [27–29]; a study in healthy subjects found no effect of voriconazole 200 mg BID for 5 days on colchicine AUC [30]	**ORCA Class 4: Low risk** Concurrent use need not be avoided, but some patients might have increased colchicine levels, especially if P-gp activity is low[g]	Normal monitoring for colchicine toxicity
Antivirals—protease inhibitors and adjuvants			
Atazanavir Cobicistat Darunavir[h] Fosamprenavir Indinavir Nelfinavir Ritonavir Saquinavir Telaprevir	These agents inhibit CYP3A4 and P-gp and would be expected to ↑ colchicine AUC; a study in 18 healthy subjects found a mean 296% ↑ in colchicine AUC after ritonavir 100 mg/day for 5 days; one subject had a 924% ↑ in colchicine AUC[i] [25, 45]	**ORCA Class 2: Avoid if possible[c]** Use alternative. For most patients it may be easier to avoid colchicine than the antiviral agent[d]. Stop colchicine before antiviral is started, and for 3–4 days after antiviral is stopped. If concurrent use is deemed necessary (which should very rarely be the case), see column to the right. Ritonavir + nirmatrelvir (Paxlovid) is normally given for 5 days, so stopping colchicine during Paxlovid therapy would usually be the best management	Reduce colchicine dose 50–75% Monitor for colchicine toxicity Advise patient about colchicine toxicity[e]
Tipranavir	Unlike many other protease inhibitors, tipranavir tends to ↑ P-gp activity, which might reduce colchicine AUC[i] [71]	**ORCA Class 3: Assess risk; take action if needed** Concurrent use need not be avoided, but some patients may have reduced colchicine concentrations; more data are needed	Monitor for altered colchicine effect if tipranavir is started, stopped, or changed in dosage; adjust colchicine dose as needed; note that the onset and offset of enzyme induction may occur slowly over 1–2 weeks
Antivirals—miscellaneous			
Boceprevir	Boceprevir inhibits CYP3A4 [72], but its effect on P-pg is not known. Effect on colchicine requires further study	**ORCA Class 3: Assess risk; take action if needed** Concurrent use need not be avoided, but some patients might have increased colchicine levels, especially if P-gp activity is low[g]	Monitor for altered colchicine effect if boceprevir is started, stopped or changed in dosage Advise patient about colchicine toxicity[e]
Letermovir	Letermovir inhibits CYP3A4 [73], but may not affect P-pg [74]. Effect on colchicine requires further study	**ORCA Class 3: Assess risk; take action if needed** Concurrent use need not be avoided, but some patients might have increased colchicine levels, especially if P-gp activity is low[g]	Monitor for altered colchicine effect if letermovir is started, stopped or changed in dosage Advise patient about colchicine toxicity[e]
Efavirenz Etravirine Nevirapine	These enzyme inducers are known to induce CYP3A4, and are likely to reduce colchicine serum concentrations	**ORCA Class 3: Assess risk; take action if needed** Concurrent use need not be avoided, but some patients may have reduced colchicine concentrations; more data are needed	Monitor for altered colchicine effect if these agents are started, stopped, or changed in dosage; adjust colchicine dose as needed; note that the onset and offset of enzyme induction may occur slowly over 1–2 weeks

Table 3 (continued)

Drugs	Evidence for drug interaction (DDI)	ORCA class[a] and management options	Management if concurrent use needed
Calcineurin inhibitors			
Cyclosporine	Cyclosporine inhibits CYP3A4 and P-gp; a study in 23 healthy subjects found a mean 259% ↑ in colchicine AUC after a single 100-mg dose of cyclosporine; one subject had a 512% ↑ [25, 45, 75]; possible additive myopathy[k], over 30 cases of colchicine–cyclosporine DDI reported[b]	**ORCA Class 2: Avoid if possible[e]** The risk would almost always outweigh the benefit Use alternative: If appropriate, tacrolimus appears less likely to interact with colchicine (see below); many other immunosuppressants are not known to inhibit CYP3A4 and P-gp Or consider alternative to colchicine[d]	Reduce colchicine dose 50–75% Monitor for colchicine toxicity, especially for signs of myopathy Advise patient about colchicine toxicity[e]
Tacrolimus	Tacrolimus inhibits P-gp somewhat, but may be only weak inhibitor of CYP3A4; Two small studies found increased colchicine AUC with tacrolimus, but less than with cyclosporine [16, 75]	**ORCA Class 3. Assess risk; take action if needed** Colchicine levels are likely to increase some-what, especially in predisposed patients (e.g., on CYP3A4 inhibitors, or with severe renal or hepatic impairment)[c] Consider alternative to tacrolimus or colchicine[d]	Monitor for altered colchicine effect if tacrolimus started, stopped, or changed in dosage Advise patient about colchicine toxicity[e]
Calcium-channel blockers (CCBs)			
Diltiazem	Diltiazem inhibits CYP3A4 and P-gp; in 20 healthy subjects, diltiazem 240 mg BID for 7 days ↑ colchi-cine AUC by 93%; one subject had a 339% increase [25, 45]; a patient on diltiazem developed fatal col-chicine toxicity, but causality was not established[b]	**ORCA Class 2: Avoid if possible[e]** Use alternative. If appropriate, use an alternative to diltiazem or verapamil; most other CCBs such as dihydropyridines appear to have little effect on CYP3A4 or P-gp Or consider alternative to colchicine[d]	Reduce colchicine dose 50–75% Monitor for colchicine toxicity, especially for signs of myopathy Advise patient about colchicine toxicity[e]
Verapamil	Verapamil inhibits CYP3A4 and P-gp; in 24 healthy subjects, verapamil 240 mg BID for 5 days ↑ colchi-cine AUC by 103%; one subject had a 217% increase [25, 45]; a patient on verapamil developed serious colchicine toxicity[b]	**ORCA Class 2: Avoid if possible[e]** Use alternative. If appropriate, use an alternative to verapamil or diltiazem; most other CCBs such as dihydropyridines appear to have little effect on CYP3A4 or P-gp Or consider alternative to colchicine[d]	Reduce colchicine dose 50–75% Monitor for colchicine toxicity, especially for signs of myopathy Advise patient about colchicine toxicity[e]
Enzyme inducers			
Carbamazepine (CBZ)	Carbamazepine induces CYP3A4 and P-gp, and would be expected to reduce colchicine AUC; case report of very low colchicine levels in patient on CBZ[b]	**ORCA Class 2: Avoid if possible** It may be difficult to achieve therapeutic colchicine levels in presence of CBZ Use alternative. If appropriate, use an alternative to the CBZ or colchicine[d]	Monitor for altered colchicine effect if CBZ is started, stopped, or changed in dosage; adjust colchicine dose as needed; note that the onset and offset of enzyme induction may occur slowly over 1–2 weeks
Rifampin	Rifampin induces CYP3A4 and P-gp, and would be expected to reduce colchicine AUC; case report of low colchicine levels in patient on rifampin[b]	**ORCA Class 2: Avoid if possible** It may be difficult to achieve therapeutic colchicine levels in presence of rifampin Use alternative. If appropriate, use an alternative to rifampin or colchicine[d]	Monitor for altered colchicine effect if CBZ is started, stopped, or changed in dosage; adjust colchicine dose as needed; note that the onset and offset of enzyme induction may occur slowly over 1–2 weeks

Table 3 (continued)

Drugs	Evidence for drug interaction (DDI)	ORCA class[a] and management options	Management if concurrent use needed
Barbiturates Bosentan Dabrafenib Lumacaftor Phenytoin Primidone Rifabutin Rifapentine St. John's wort Topiramate	These enzyme inducers are known to induce CYP3A4, and are likely to reduce colchicine serum concentrations	**ORCA Class 2: Avoid if possible** It may be difficult to achieve therapeutic colchicine levels in presence of these enzyme inducers Use alternative. If appropriate, use an alternative to the enzyme inducer or colchicine[d]	Monitor for altered colchicine effect if inducer is started, stopped, or changed in dosage; adjust colchicine dose as needed; note that the onset and offset of enzyme induction may occur slowly over 1–2 weeks
Foods			
Grapefruit	Grapefruit inhibits CYP3A4, but appears to be a weak P-gp inhibitor; a single case of life-threatening colchicine toxicity was reported in an 8-year-old girl[b] and in vitro evidence [76] suggest a DDI; but study in 21 healthy subjects given 240 mL grapefruit juice BID for 4 days found no effect on colchicine AUC [24]	**ORCA Class 3. Assess risk; take action if needed** Although evidence for an interaction is weak, it might occur in patients with low P-gp activity[g] It would be prudent to advise patents to drink juices other than grapefruit	If the patient drinks grapefruit juice, advise them to avoid ingesting more than 240 mL/day
Seville oranges	A study in 23 healthy subjects given 240 mL Seville orange juice BID for 4 days found a small decrease in colchicine AUC [24]	**ORCA Class 4. Low risk** Concurrent use need not be avoided, but a slight reduction in colchicine AUC may occur	Normal monitoring for colchicine toxicity
HMG-CoA reductase inhibitors			
Atorvastatin	A study in 24 healthy subjects found a mean 24% ↑ in colchicine AUC after atorvastatin 40 mg/day for 14 days [77]; due to weak P-gp inhibition by atorvastatin? 7 case reports of myopathy with combination[b]; additive myotoxicity? [58, 59]	**ORCA Class 3. Assess risk; take action if needed** Concurrent use need not be avoided, especially if the colchicine dose is 0.6 mg/day or less If colchicine dose is > 0.6 mg/day, myopathy risk may be increased in predisposed patients, (i.e. impaired renal function, elevated statin levels due to dose, DDIs, etc.)[c,m] Consider alternative: fluvastatin, pravastatin, and rosuvastatin may be less likely to interact	Monitor for colchicine toxicity, especially for signs of myopathy Advise patient to report evidence of myopathy (muscle weakness, myalgia, dark urine)
Fluvastatin	Not expected to affect colchicine AUC; isolated cases of rhabdomyolysis reported with combination, but causality was not established[b]; additive myotoxicity? [58, 59]	**ORCA Class 4: Low risk** Concurrent use need not be avoided; it is possible that the myopathy risk is increased in predisposed patients, but more data are needed[n]	Normal monitoring for colchicine toxicity, with emphasis on signs of myopathy (muscle weakness, myalgia, dark urine)
Lovastatin	Possible P-gp inhibitory effect of lovastatin? [78] Possible additive myotoxicity? [58, 59]. Isolated cases of myopathy[b]; lovastatin has similar pharmacokinetic properties as simvastatin (see below)	**ORCA Class 3: Assess risk; take action if needed** Concurrent use need not be avoided, especially if the colchicine dose is 0.6 mg/day or less If colchicine dose is > 0.6 mg/day, myopathy risk may be increased with renal impairment or elevated statin levels due to dose, DDIs, etc.)[c,m] Consider alternative: fluvastatin, pravastatin, and rosuvastatin may be less likely to interact	Monitor for colchicine toxicity, especially for signs of myopathy Advise patient to report evidence of myopathy (muscle weakness, myalgia, dark urine)

Table 3 (continued)

Drugs	Evidence for drug interaction (DDI)	ORCA class[a] and management options	Management if concurrent use needed
Pravastatin	Not expected to affect colchicine AUC; isolated cases of myopathy reported with combination, but causality was not established[b]; additive myotoxicity? [58, 59]	**ORCA Class 4: Low risk** Concurrent use need not be avoided; it is possible that the myopathy risk is increased in predisposed patients, but more data are needed[n]	Normal monitoring for colchicine toxicity, with emphasis on signs of myopathy (muscle weakness, myalgia, dark urine)
Rosuvastatin	Not expected to affect colchicine AUC; isolated cases of myopathy reported, but causality was not established[b]; additive myotoxicity? [58, 59] Combination has been used to treat COVID [79]	**ORCA Class 4: Low risk** Concurrent use need not be avoided; it is possible that the myopathy risk is increased in predisposed patients, but more data are needed[n]	Normal monitoring for colchicine toxicity, with emphasis on signs of myopathy (muscle weakness, myalgia, dark urine)
Simvastatin	Possible P-gp inhibitory effect of simvastatin? [80] Numerous case reports of myopathy reported with combination, usually in patients with preexisting renal impairment[b]; possible additive myotoxicity [58, 59]	**ORCA Class 3: Assess risk; take action if needed** Concurrent use need not be avoided, especially if the colchicine dose is 0.6 mg/day or less If colchicine dose is > 0.6 mg/day, myopathy risk may be increased with renal impairment or elevated statin levels due to dose, DDIs, etc.[c,m] Consider alternative: fluvastatin, pravastatin, and rosuvastatin may be less likely to interact	Monitor for colchicine toxicity, especially for signs of myopathy Advise patient to report evidence of myopathy (muscle weakness, myalgia, dark urine)
Macrolide antibiotics			
Azithromycin	A study in 21 healthy subjects found a mean 57% ↑ in colchicine AUC after azithromycin 500 mg on day 1, then 250 mg/day for 4 days; one subject had a 241% increase [25, 45]; azithromycin is a modest P-gp inhibitor	**ORCA Class 3. Assess risk; take action if needed** Colchicine levels are likely to increase somewhat, especially in predisposed patients (e.g., on CYP3A4 inhibitors, or with severe renal or hepatic impairment)[c] Consider alternative to antibiotic or colchicine[d]	Monitor for altered colchicine effect if azithromycin is started, stopped or changed in dosage Advise patient about colchicine toxicity[e]
Clarithromycin	A study in 23 healthy subjects found a mean 282% ↑ in colchicine AUC after clarithromycin 500 mg/day for 7 days; one subject had a 852% ↑; clarithromycin inhibits both CYP3A4 and P-gp; fatalities reported in case series [19], among >2 dozen case reports,[b] and ADR reporting systems [18, 81]	**ORCA Class 1. Avoid combination** The risk would almost always outweigh the benefit Consider stopping colchicine during clarithromycin therapy Or use alternative to clarithromycin; azithromycin has a smaller effect on colchicine (see above); many other antibiotics have little effect on CYP3A4 or P-gp	It should not be necessary to use colchicine and clarithromycin together. If it is absolutely necessary: Reduce colchicine dose by 75% Monitor for colchicine toxicity Advise patient about colchicine toxicity[e]
Erythromycin	Erythromycin inhibits CYP3A4 but may inhibit P-gp less than clarithromycin; isolated DDI case reports[b]	**ORCA Class 2: Avoid if possible[c]** Consider stopping colchicine during erythromycin therapy Or use alternative. Consider an alternative to erythromycin; azithromycin has a smaller effect on colchicine (see above); many other antibiotics have little effect on CYP3A4 or P-gp	Reduce colchicine dose 50–75% Monitor for colchicine toxicity, especially for signs of myopathy Advise patient about colchicine toxicity[e]

Table 3 (continued)

Drugs	Evidence for drug interaction (DDI)	ORCA class[a] and management options	Management if concurrent use needed
Miscellaneous CYP3A4 inhibitors			
Aprepitant Ceritinib Conivaptan Crizotinib Fedratinib Idelalisib Imatinib Lapatinib Lomitapide Lefamulin Mifapristone Nefazodone Quinupristin Ribociclib Telithromycin	All of these drugs inhibit CYP3A4 and many are also known to inhibit P-gp; no information is available on the effect of these drugs on colchicine AUC, but interactions should be considered possible until proven otherwise	**ORCA Class 2: Avoid if possible[c]** Use alternative. If appropriate, us an alternative to the CYP3A4 inhibitor that does not inhibit CYP3A4[d] Or consider alternative to colchicine[d]	Reduce colchicine dose 50–75% Monitor for altered colchicine response if CYP3A4 inhibitor started, stopped, or changed in dosage Advise patient about colchicine toxicity[d]
Quinolines			
Chloroquine	Chloroquine alone can cause myopathy [82], so additive myotoxicity with colchicine is possible; no supporting clinical data	**ORCA Class 4. Low risk** Concurrent use need not be avoided; it is possible that the myopathy risk is increased in predisposed patients, but more data are needed	Normal monitoring for colchicine toxicity, with emphasis on signs of myopathy
Hydroxychloroquine (HQ)	HQ alone can cause myopathy; additive myotoxicity possible and single case of myopathy reported[b]; HQ might inhibit P-gp, but no PK studies with colchicine; HQ has been used with colchicine to treat various disorders [83–85]	**ORCA Class 4. Low risk** Concurrent use need not be avoided; it is possible that the myopathy risk is increased in predisposed patients, but more data are needed	Normal monitoring for colchicine toxicity, with emphasis on signs of myopathy
Other drugs			
Digoxin	Digoxin is purported to cause myopathy when combined with colchicine [25, 55] but supporting evidence is lacking; the fact that digoxin is a P-gp substrate is not proof that it inhibits P-gp	**ORCA Class 4. Low risk** Concurrent use need not be avoided	Normal monitoring for colchicine toxicity
Disulfiram	Evidence that disulfiram inhibits P-gp or CYP3A4 is weak [86, 87]; single case report of DDI with colchicine, but causal relationship doubtful[b]	**ORCA Class 4. Low risk** Concurrent use need not be avoided	Normal monitoring for colchicine toxicity
Fibrates	Fenofibrate and gemfibrozil known to cause myopathy, with or without statins [88]; additive myotoxic effect with colchicine? Evidence that fenofibrate inhibits P-gp is weak [89]; one case of myopathy with gemfibrozil + colchicine[b]	**ORCA Class 3: Assess risk; take action if needed** Concurrent use need not be avoided; it is possible that the myopathy risk is increased in predisposed patients, but more data are needed. Risk may be increased if patient is also taking a statin	Monitor for colchicine toxicity, especially for signs of myopathy Advise patient to report evidence of myopathy (muscle weakness, myalgia, dark urine)
Lesinurad	Lesinurad may be a modest CYP3A4 inducer [90]; PK study in healthy subjects found modest ↓ in colchicine AUC, but lesinurad dose was high (400–600 mg/day) [33]	**ORCA Class 3: Assess risk; take action if needed** Concurrent use need not be avoided, but some patients may have reduced colchicine concentrations; more data are needed	Monitor for altered colchicine effect if lesinurad is started, stopped, or changed in dosage. Adjust colchicine dose as needed

Table 3 (continued)

Drugs	Evidence for drug interaction (DDI)	ORCA class[a] and management options	Management if concurrent use needed
Nivolumab	Thrombocytopenia reported in a patient on nivolumab and colchicine[b]; nivolumab may inhibit CYP3A4 by upregulating cytokines [91] but an effect on colchicine is speculative	**ORCA Class 3: Assess risk; take action if needed** This DDI is largely theoretical, and concurrent use need not be avoided, some patients might have increased colchicine AUC, but more data are needed to establish a causal effect	Monitor for altered colchicine effect if nivolumab is started, stopped, or changed in dosage. Adjust colchicine dose as needed
Sunitinib	Colchicine toxicity reported in a patient on sunitinib[b], but the colchicine toxicity was more likely due to the excessive dose of colchicine, and the effect of concurrent diltiazem (see above)	**ORCA Class 4: Low risk** Concurrent use need not be avoided	Normal monitoring for colchicine toxicity

ADRs adverse drug reactions, *AUC* area under the concentration–time curve, *BID* twice daily, *DDIs* drug–drug interactions, *P-gp* P-glycoprotein, *PK* pharmacokinetics, ↑ indicates increase, ↓ indicates decrease

[a]ORCA: OpeRational ClassificAtion of drug interactions [92]: Class 1 = Avoid combination; Class 2 = Avoid combination unless benefit outweighs risk; Class 3 = Assess risk and take action if needed; Class 4 = Low risk: no special precautions; Class 5 = No interaction

[b]Case report details, including evaluation of causality, are presented in Online Resource (see ESM)

[c]Drug interactions that result in elevated colchicine plasma concentrations tend to be more dangerous in patients with renal impairment. Consider patients with significant renal impairment (e.g., creatinine clearance [CrCl] < 60 mL/min) to be at somewhat higher risk, and patients with severe renal disease (e.g., CrCl < 30 mL/min) at much higher risk of colchicine toxicity from drug interactions. For all drug interactions listed as 'Class 2', consider them contraindicated in patients with severe renal disease. The effect of liver disease is more theoretical, but assume ORCA class 2 DDIs are contraindicated if patient has a Child-Pugh score of C

[d]If colchicine is being used for acute gout, consider using alternative gout therapy. If colchicine is being used chronically for gout prophylaxis, consider the risk of colchicine toxicity vs the expected benefit of gout prevention. If colchicine is being used for familial Mediterranean fever, cardiovascular disease, dermatologic disorders, Covid-19, or other disorders, it may be more difficult to find alternatives for colchicine. For some disorders such as pericarditis, colchicine may be deemed necessary

[e]Patient should report colchicine toxicity such as severe diarrhea, protracted vomiting, muscle weakness, muscle pain, dark urine, fever or other signs of infection, unusual bleeding or bruising, severe fatigue

[f]Fluconazole and colchicine are both eliminated renally, so patients with severe renal impairment will have increased serum concentrations of both drugs. And since the ability of fluconazole to inhibit CYP3A4 is related to serum concentrations, there will be increased CYP3A4 inhibition

[g]Based on available evidence, drugs that inhibit CYP3A4 but not P-gp have little effect on colchicine AUC. But the risk of a DDI with colchicine would theoretically be increased if CYP3A4 inhibitors are given to patients with low P-gp activity due to other drugs or genetics

[h]Darunavir inhibits CYP3A4, but may induce P-gp somewhat. Theoretically, this might mitigate any increase in colchicine serum concentrations

[i]Long-term ritonavir therapy can result in enzyme induction [93], so it is not clear if these results apply to patients on chronic ritonavir

[j]Tipranavir is generally given with ritonavir, but the result (CYP3A4 inhibition with P-gp induction) does not seem likely to increase colchicine serum concentrations based on study of tipranavir/ritonavir with other CYP3A4/P-gp substrates [71]

[k]Both colchicine and cyclosporine can cause myopathy, and all case reports of colchicine–cyclosporine DDI had evidence of myopathy (e.g., some combination of muscle pain, muscle weakness, dark urine)

[l]The lack of effect of grapefruit juice in the healthy subject study is consistent with the theory that inhibition of both CYP3A4 and P-gp is necessary for a DDI with colchicine. It is possible that the huge amount of grapefruit juice ingested by the 8-year-old girl (1 L/day for 2 months) was enough to inhibit P-gp. It is also possible that the grapefruit juice used in the healthy subject study did not contain sufficient quantities of the CYP3A4-inhibiting phytochemicals to affect colchicine pharmacokinetics. Different types of grapefruit are known to contain differing amounts of CYP3A4-inhibiting compounds [94, 95]

[m]Atorvastatin, lovastatin, and simvastatin are all metabolized by CYP3A4, so patients on CYP3A4 inhibitors are likely to be at increased risk

[n]Ptavastatin, pravastatin, and rosuvastatin are all substrates for OATP transporters, so patients on OATP inhibitors may be at increased risk

(eGFR) (mean eGFR = 25) had 51% higher colchicine AUC compared with six patients with normal GFR (mean eGFR = 110). In patients on hemodialysis three times a week with eGFR = 0, colchicine AUC was more than 5-fold higher than those with normal GFR [16]. Another study found a colchicine half-life to be four times higher in patients with renal insufficiency compared with those with normal kidney function [26]. A study of colchicine pharmacokinetics found total body clearance of colchicine about twice as high in younger subjects as in elderly patients with a mean creatinine clearance (CrCl) of 46 mL/min [22]. Elderly patients may also be at higher risk of colchicine toxicity due to polypharmacy. Renal impairment may also increase the risk of colchicine DDIs by increasing the serum concentration of the drug interacting with colchicine. For example, fluconazole displays dose-dependent inhibition of CYP3A4, and undergoes renal elimination, so patients with severe renal dysfunction would tend to have higher concentrations of fluconazole [43]. This would lead to increased CYP3A4 inhibition, as well as compromised renal elimination of colchicine, a combination that may have led to colchicine toxicity [44].

In many case reports of colchicine toxicity due to DDIs described in the online Supplemental Table (see ESM), renal impairment appeared to be a predisposing factor. It is not possible to precisely determine the degree of increased risk of colchicine DDIs at given levels of renal impairment, but a consensus statement on the use of colchicine used an eGFR of < 30 mL/min as the point where colchicine concentrations can start to increase substantially [10]. Based on the available data, we might estimate that the renal elimination of colchicine starts to be compromised somewhere around an eGFR of 60 mL/min and becomes a serious problem as one approaches an eGFR of 30 mL/min.

5.3 Liver Disease

As with many drugs, the effect of liver disease on colchicine elimination is not well characterized. There are many types of liver disease with different etiologies, and varying effects on drug metabolism and elimination. Moreover, there is no agreed upon measurement of liver function, unlike eGFR for kidney function, to quantify the likely reduction in colchicine elimination in patients with liver disease. One consensus statement on the use of colchicine in liver disease used a Child-Pugh score of C as the point where the half-life of colchicine starts to increase substantially [10], and, in the absence of definitive data, reduction in colchicine dose at this level of hepatic impairment appears to be a reasonable guideline. Nonetheless, patients with lesser degrees of hepatic malfunction may have some reduction in colchicine clearance, thus increasing the risk of colchicine DDIs to some degree.

5.4 Transporter Polymorphisms

Given that colchicine is a substrate for P-gp, it would be expected that those with polymorphisms resulting in low P-gp activity may be at increased risk for adverse colchicine DDIs. For example, drugs that primarily inhibit CYP3A4 and appear to have little effect on colchicine (e.g., voriconazole) might have a greater effect in patients with low P-gp activity due to genomics or other drugs. Little is currently known regarding the effect of transporters other than P-gp on colchicine pharmacokinetics, so it may be useful to study the effect of polymorphisms in MRP2 or OATPs on colchicine disposition.

5.5 Dose/Duration of Perpetrator Drug

The magnitude of perpetrator drug inhibition or induction on drug metabolizing enzymes and transporters can be affected by the dose of the drug and the duration of perpetrator drug therapy.

6 Management Options

Given the potentially life-threatening outcomes of colchicine drug interactions and the difficulty of treating severe colchicine toxicity once it occurs, it is imperative to avoid putting patients at risk. There are essentially three ways to reduce the risk of adverse outcomes from colchicine DDIs: (i) avoid using the interacting drug while the patient is on colchicine, (ii) avoid using colchicine during administration of the interacting drug, or (iii) give colchicine and the interacting drug, but reduce the colchicine dose. We now consider these three approaches.

6.1 Avoid Using the Interacting Drug

If the patient on colchicine has severe renal or hepatic impairment, it is particularly important to avoid the use of CYP3A4/P-gp inhibitors. But even when the patient does not have significant renal or hepatic disease, avoiding the interacting drug is likely to be the preferred option when it is feasible. For example, it is difficult to imagine a scenario in which it would be necessary to give clarithromycin to a patient on colchicine, a combination that has produced numerous fatalities [18]. If another antibiotic is suitable, it would almost always be preferable to use it in place of the clarithromycin (most antibiotics do not inhibit CYP3A4 and P-gp). A similar argument could be made for calcium channel blockers, where diltiazem and verapamil inhibit CYP3A4 and P-gp, but most of the other calcium-channel blockers do not. Other calcium-channel blockers may or

may not be appropriate to use in place of diltiazem or vera-pamil in any given patient, but if they are, an interaction with colchicine could be easily avoided. Table 3 presents non-interacting alternatives for many of the drugs that can interact with colchicine.

6.2 Stopping Colchicine During Use of the Interacting Drug

If the interacting drug is clinically necessary, stopping colchicine during the use of the interacting drug may be appropriate, especially if the interacting drug is used for a limited time (such as an antibiotic). Whether this is a viable option would also depend on the indication for colchicine. If colchicine is being used for gout, short-term alternatives to colchicine may be available. If colchicine is used for familial Mediterranean fever or for cardiovascular disorders such as pericarditis or post-myocardial infarction, stopping colchicine may or may not be the best option.

6.3 Reduce Colchicine Dose When Precipitant Drug is Started

If concurrent use of colchicine with the interacting drug cannot be avoided—which should rarely be the case—one could consider prophylactic colchicine dosage reductions. Theoretically, reducing the colchicine dose when the precipitant drug is added would offset the pharmacokinetic interaction and maintain colchicine serum concentrations in the therapeutic range, as has been recommended in the labeling for some colchicine products [25] and in published

articles [45, 46]. In practice, however, because the magnitude of these DDIs is so variable from one person to another, a 'one size fits all' a priori colchicine dosage reduction is likely to be excessive for some people (resulting in subtherapeutic colchicine concentrations) and insufficient for others (leading to colchicine toxicity). Accordingly, colchicine dosage reduction is best considered a last resort, and only when both colchicine and the interacting drug must be used together. Consider the interaction with ritonavir, where the mean increase in colchicine AUC following ritonavir was 296%, but the range was 54–924% as shown in Fig. 1 [25, 45]. Despite this marked variability, the colchicine labeling for Colcrys states that if colchicine and ritonavir are used together, the colchicine dose should be reduced by 50% [25]. (One possible source of ritonavir's highly variable effect on colchicine is that ritonavir affects transporters in addition to P-gp, and affects CYP isozymes in addition to CYP3A4, but this hypothesis requires confirmation.)

The marked variability seen in healthy subjects is likely to be even greater in patients, who may be taking various other medications, may have varying degrees of renal or hepatic impairment, and may have other disorders that affect colchicine pharmacokinetics. Moreover, the much larger numbers in the patient population will virtually guarantee that some patients will have pharmacogenomic differences that will predispose them to colchicine toxicity (e.g., low P-gp activity). Finally, the pharmacokinetic studies conducted in healthy subjects (shown in Fig. 1) involved single, small doses of colchicine, unlike what is usually the case for patients receiving colchicine therapeutically. In patients who develop serious colchicine toxicity from a DDI, multiorgan

Fig. 1 The high variability of changes in colchicine AUC in 18–24 healthy subjects given a single dose of colchicine 0.6 mg with and without pretreatment with various drugs. The bars represent the subject with the smallest increase and the subject with the largest increase for each interacting drug. Adapted from data presented in references [25, 45, 47]
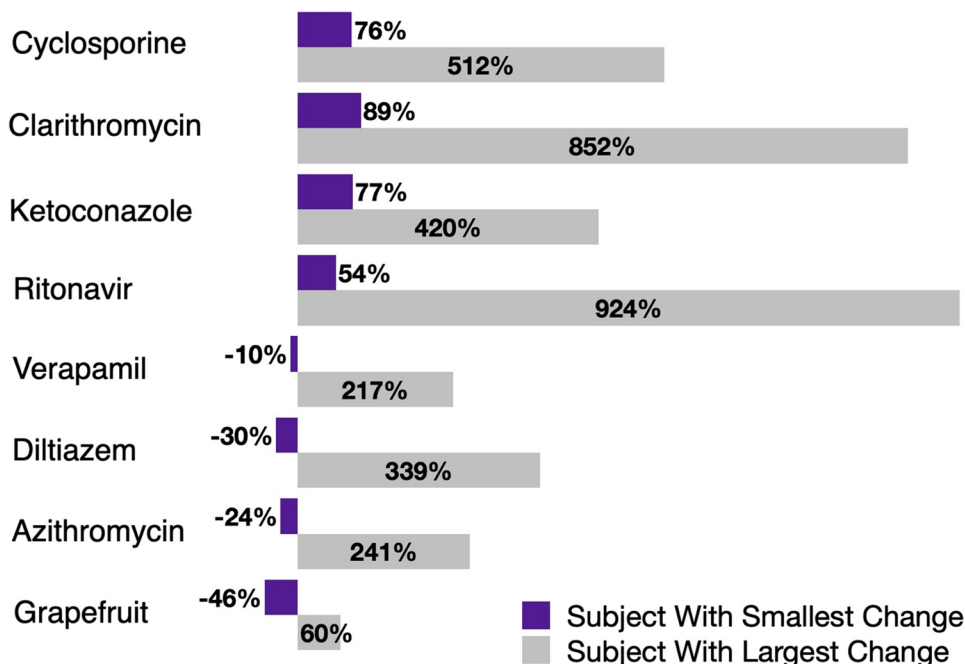
failure can occur with marked reduction in kidney function; this in turn can worsen the colchicine toxicity. None of these problems would occur with single-dose studies in healthy subjects. For all of these reasons, one cannot use the single-dose studies in healthy subjects to predict whether a small or marked increase in colchicine plasma concentrations will occur in any given patient.

Figure 2 represents a hypothetical estimate of what might be expected to happen if we follow the rule of thumb recommendations for avoiding colchicine toxicity when patients receive CYP3A4/P-gp inhibitors with colchicine. These are hypothetical scenarios but they are entirely plausible given the evidence of high intersubject variability in the magnitude of colchicine DDIs as shown in Fig. 1. In Fig. 2, 'a' represents the starting conditions in a group of patients, and to simplify the discussion let us assume that they all have therapeutic colchicine serum concentrations. Next is 'b', which represents what may happen if a CYP3A4/PGP inhibitor is added, but the DDI is ignored; here some patients are likely to develop colchicine toxicity and some may die. Next is 'c', in which we adopt the colchicine dosage reduction recommendations, but—due to the large variability—some patients become subtherapeutic, and others develop colchicine toxicity. Finally, 'd' represents what may happen if we lowered the colchicine dose sufficiently to avoid all colchicine toxicity, resulting in an unacceptable number of patients with subtherapeutic colchicine levels.

Whether or not it is appropriate to prophylactically adjust the dose of an object drug when starting a precipitant drug depends on the drugs involved in the interaction. For some drugs, such as warfarin, if one adjusts the warfarin dose when adding a CYP2C9-inhibiting drug, at least one can monitor the INR to determine if the warfarin dosage adjustment was too large or too small. For colchicine, however, serum concentrations are not routinely available at this time, and life-threatening colchicine toxicity (e.g., pancytopenia, multi-organ failure, rhabdomyolysis) can begin after only a few days of administration of the interacting drug (see case reports in the online Supplemental Table, ESM). There is no specific remedy, and once the kidney and liver start to fail, colchicine may persist for weeks until the patient dies or (usually very slowly) recovers [48–50]. Dialysis is not effective in colchicine poisoning, but in one case the patient was successfully treated with kidney replacement therapy and plasmapheresis [51]. It is not known if giving an enzyme inducer such as rifampin would help eliminate colchicine, but it is an intriguing possibility given that rifampin probably increases colchicine elimination [31]. Rifampin has been used in poisonings with other drugs to increase elimination [52], but the efficacy and safety of using rifampin for colchicine toxicity is not established. The use of activated charcoal (and possibly other binding agents) may be worth trying, since colchicine undergoes enterohepatic circulation, although this has not been studied [11].

A summary of suggested management options for colchicine DDIs with CYP3A4/P-gp inhibitors is presented in Fig. 3.

Fig. 2 Hypothetical predicted outcomes for various ways of managing the addition of CYP3A4/P-gp inhibitors to colchicine. **a** Before interacting drug added, **b** interacting drug added with no change in colchicine dose, **c** colchicine dosage reduction method, **d** reducing colchicine dosage enough to avoid all colchicine toxicity
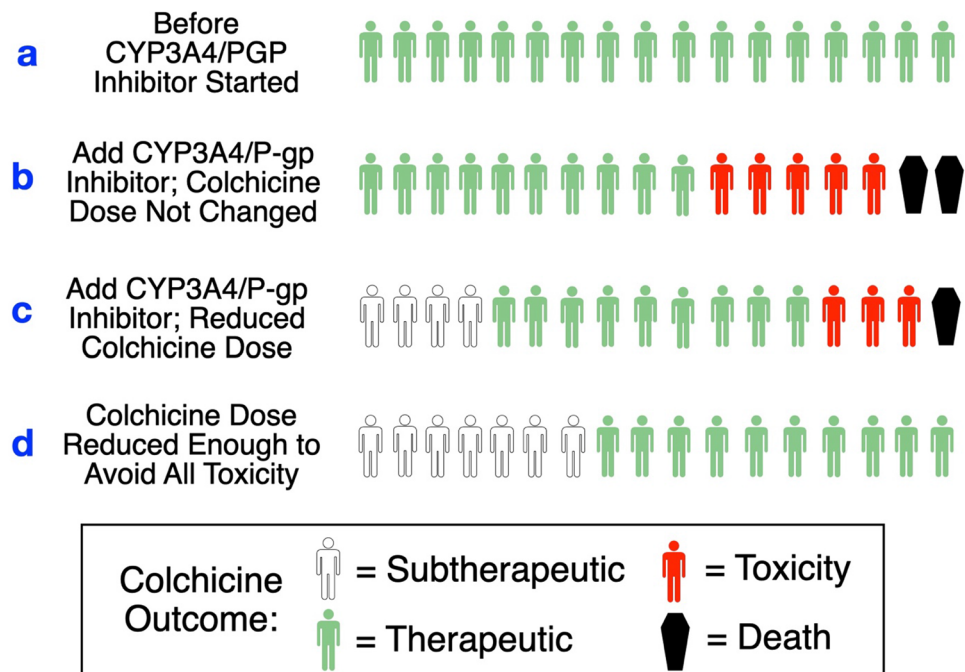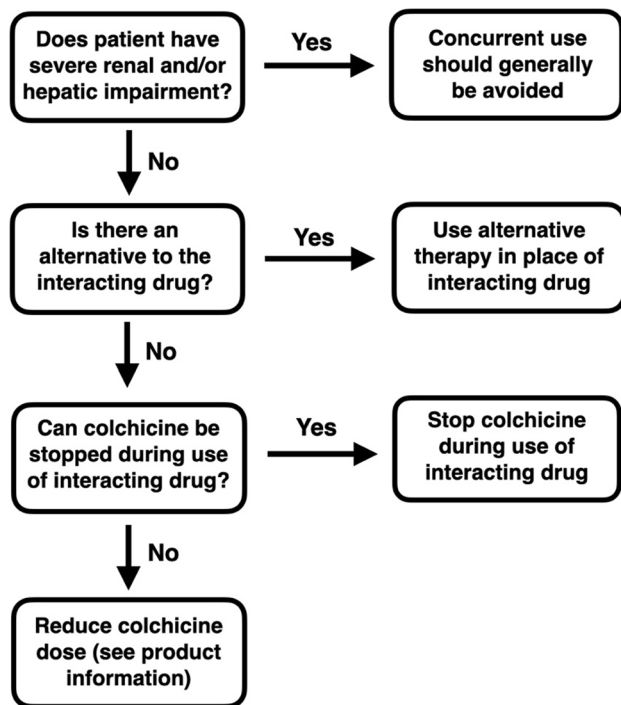
Fig. 3 Management option algorithm for minimizing the risk of colchicine drug–drug interactions

6.4 Patient Education

If concomitant use of colchicine with interacting drugs is necessary, it is crucial to advise the patient to be alert for evidence of colchicine toxicity. There are three primary types of toxicity for which the patient should be vigilant:

- Gastrointestinal toxicity: severe diarrhea (often with some combination of nausea, vomiting, or abdominal pain)
- Neuromuscular toxicity: muscle weakness, myalgia, dark or brown urine
- Hematologic toxicity (pancytopenia): fever, other signs of infection, excessive or unusual bleeding

Mild to moderate diarrhea is common when colchicine serum concentrations are elevated, but if the diarrhea is severe or prolonged, the patient should contact their prescriber. Regarding signs and symptoms of myopathy, some have proposed a 'classic triad' of myalgia, muscle weakness, and 'tea-colored urine' [53]. However, muscle weakness often occurs without myalgia, and sometimes the reverse is true (see cases in the online Supplemental Table, ESM). Darkened urine from myoglobinuria is usually a late sign of myotoxicity, and often occurs after the muscle weakness and/or myalgia has become so severe that the patient has already sought medical care. Moreover, using the term

'tea-colored urine' is problematic given that tea can have many different colors from dark brown to very light, so it would be better to say 'dark' or 'brown' urine. Darkened urine is a particularly ominous sign, because the excessive myoglobinuria may lead to acute kidney injury, thus prolonging the colchicine toxicity.

Colchicine toxicity can produce many other signs and symptoms, but they are either relatively nonspecific (fatigue, lethargy, malaise, insomnia), or they occur relatively infrequently (shortness of breath, cough, cardiac arrhythmias), or they tend to occur late in the course of colchicine toxicity (alopecia). Accordingly, it is probably best to concentrate the patient education on the more specific and common signs and symptoms as described above.

7 Drugs That May Interact with Colchicine

Colchicine DDIs have been extensively studied, and include pharmacokinetic studies, case reports, and case series. See Table 3 for a summary of these DDIs as well as management recommendations. Details of all case reports mentioned in Table 3, including supporting references, can be found in the online Supplemental Table (see ESM).

8 Misleading Colchicine Drug Interaction Information

Colchicine DDI information for health professionals is available from a variety of sources. The medical literature provides numerous pharmacokinetic studies, case reports, epidemiological studies, and reviews on colchicine DDIs, resulting in many conflicting recommendations. There are also numerous inconsistencies in the prescribing information for the various colchicine products, as well as in online DDI checking software and in clinical decision support systems [3, 10, 25, 30, 45, 46, 54–57]. The result is a jumble of confusion, with errors of omission, errors of commission, conflicting statements, and vague pronouncements as summarized in Table 4.

A striking example is the variability in recommendations for using concurrent colchicine and statins. Some have claimed that combining colchicine and statins does not cause adverse DDIs [46, 54] while others urge that the combinations be avoided [55]. A thorough assessment of the data by Wiggins et al. fell between these extremes and provided nuanced and useful guidelines [58], and a systematic review of the colchicine-statin DDI thoroughly assessed the data and concluded that the DDIs can be serious, and mitigation strategies are necessary to avoid patient harm [59]. While the data suggest that most people

Table 4 Misleading statements in published literature, product information, online sources [3, 10, 25, 30, 45, 46, 54–57]

Type of problem	Examples
Recommending colchicine dosage adjustments instead of avoiding combinations	For the reasons detailed in the previous sections, if the drug interaction with colchicine is important enough to warrant a dose reduction, it is usually safer to avoid the combination entirely if possible
Errors of omission	Virtually all sources have incomplete lists of drugs likely to interact with colchicine (e.g., CYP3A4/P-gp inhibitors, enzyme inducers)
Errors of commission	Many sources list drugs as interacting with colchicine that are unlikely to affect colchicine AUC or toxicity (for explanations, see Table 3). Errors include: Voriconazole as increasing colchicine AUC Tipranavir as increasing colchicine AUC Digoxin as a "potentially significant drug interaction," a 'serious' DDI, and as contraindicated
Errors regarding effects of drugs on enzymes and transporters[a]	Voriconazole as a P-gp inhibitor Clarithromycin as a 'moderate' 3A4 inhibitor Fluconazole as a strong P-gp inhibitor Cobicistat as a 'mild' CYP3A4 inhibitor Erythromycin as a 'mild' CYP3A4 inhibitor Amiodarone as a 'mild' P-gp inhibitor; no mention of 3A4 Diltiazem and verapamil as 'mild' P-gp inhibitors, with no mention of 3A4 Ritonavir as a 'moderate' inhibitor of CYP3A4 and P-gp Quinidine as a 'mild' P-gp inhibitor Cyclosporine as a 'moderate' CYP3A4 inhibitor, but no mention of P-gp
Excessive reliance on purported magnitude of inhibitory potency on CYP3A4 and P-gp (strong, moderate, mild)	The desire to have set guidelines is understandable, but these categories of inhibitors provide general recommendations. Clinical consequences may vary based on a host of other factors, only some of which have been characterized in clinical studies. There is a large overlap in the magnitude of effect of 'moderate' and 'strong' inhibitors in PK studies[b]
Failure to consider dose of inhibitor	Fluconazole and grapefruit both inhibit CYP3A4, but the magnitude of inhibition is dose-related. Small doses usually have little effect, while large doses may have a strong inhibitory effect on CYP3A4[c]
Vague statements	Some sources list HIV medications (ritonavir) under moderate P-gp inhibitors. This is misleading because: (1) Some HIV medications are enzyme inducers and would be expected to *reduce* colchicine concentrations (e.g., tipranavir, efavirenz, etravirine, nevirapine), and (2) Many HIV medications other than ritonavir also inhibit CYP3A4/P-gp, but they are not listed as interacting with colchicine

Excessive reliance on data from epidemiological studies that were not designed to assess colchicine DDIs	Epidemiological studies of colchicine for coronary artery disease
	  Used low doses of colchicine (usually 0.5 mg/day)
	  Patients were screened for risk factors (renal disease, drugs, etc.)
	  Often relied on self-reporting of ADRs by patient
	  Laboratory confirmation of DDIs may or may not have been done
	 Epidemiologic studies for colchicine DDIs (e.g., Kwon statin study)
	  Unlikely to detect rare DDIs due to inadequate power
	  Statins were lumped together to obtain results

ADRs adverse drug reactions, *AUC* area under the concentration–time curve, *DDIs* drug–drug interactions, *P-gp* P-glycoprotein, *PK* pharmacokinetics

[a]Errors partly result from relying on in vitro or animal studies without human in vivo data

[b]For example, as seen in Fig. 1, the 'moderate' CYP3A4 inhibitor diltiazem produced a 339% increase in colchicine AUC in one healthy subject, while the 'strong' CYP3A4 inhibitor ritonavir produced a 54% increase in colchicine AUC in another subject

[c]Other factors may also contribute to the variability in fluconazole effect on colchicine, such as low P-gp activity (due to genetics or drugs) or serious renal impairment (increasing concentrations of both fluconazole and colchicine)

using concurrent statins and low-dose colchicine do not develop myopathy, reasonable precautions are warranted as discussed in Table 3.

In addition to improving the information on colchicine DDIs, it may be necessary to raise awareness in health care professionals on how serious these DDIs can be. In one study, over 90% of the alerts for colchicine with strong CYP3A4 inhibitors flagged in clinical decision support systems were overridden by prescribers [60]. It seems likely that more than 10% of these patients were at risk, and these results suggest a lack of awareness regarding the potentially life-threatening nature of colchicine DDIs.

9 Conclusion

Colchicine is a useful drug for a wide range of disorders and is usually safe when used in appropriate doses given the patient's renal function. Numerous drugs are capable of causing colchicine toxicity, however, and given that colchicine toxicity is potentially fatal and difficult to treat, it is imperative that every effort be made to avoid placing patients at risk from these drug interactions. Currently available information on colchicine DDIs can be confusing and inconsistent, and in this paper we have tried to present recommendations based on the empirical evidence. Enough is known about colchicine drug interactions so that virtually every case of colchicine toxicity could have been prevented had the appropriate precautions been taken.

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Declarations

Conflict of interest Philip Hansten and John Horn receive royalties from books published on drug–drug interactions. There was no support from any organization for the submitted work. None of the authors have a financial relationship with any organizations that might have an interest in the submitted work in the previous 3 years, and have no other relationships or activities that could appear to have influenced the submitted work.

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