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

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Published Case Reports of Colchicine Drug Interactions

The following table present the details of the case reports describing colchicine drug-drug interactions. See footnotes (a through f) of first section of Table (Antiarrhythmics) for general explanations for all sections of the table.

Antiarrhythmics – Amiodarone

Patient [Ref][a]	Colchicine Dose	Amiodarone Dose	Onset,[b] Presenting Symptoms	Laboratory and Other Findings[c]	Risk Factors[d]	Resolution[e]	DIPS Rating[f]
74 M [1]	1 mg/day	200 mg/day	Colchicine stopped after first dose due to severe diarrhea, several days later: colonic perforation	GFR 34 mL/min, SCr increased from 2.4 to 5.2 before colon perforation	Renal impairment; diclofenac and prednisone increased risk of colon perforation?	Surgical repair of colon perforation	Doubtful[g]
65 F [2]	1 mg/day	200 mg/day, 5 days per week	2 weeks after starting colchicine for pericarditis she complained of myalgia and muscle weakness	CK 5780 IU/L, Aldolase 3700 IU/L, renal function and liver enzymes normal	None noted.	Colchicine stopped, and Sx improved rapidly; CK and aldolase decreased markedly; patient died from cardiac arrhythmia	Possible
69 F [3]	1.2 mg/day	1200 mg/day	After starting colchicine for pericarditis, nausea, vomiting, diarrhea, progressing to multiorgan failure and cardiogenic shock	Estimated CrCl 74 mL/min; serum colchicine still high 65 hours after last dose of colchicine (3.3 ng/mL)	Mild reduction in renal function; colchicine continued for 10 days despite clear evidence of colchicine toxicity	After developing multiorgan failure and cardiogenic shock, she died of cardiac arrest	Probable
68 M [3]	11.8 mg over 17 hours	1200 mg/day	None mentioned	Estimated CrCl 53mL/min before colchicine; rapidly developed acute renal failure, thrombocytopenia, and hypotension	Markedly excessive colchicine dose for a patient with renal impairment[h]	Died of cardiac arrest	Possible

a. Abbreviations used in tables: ALT Alanine Aminotransferase; AST Aspartate Aminotransferase; CK Creatinine Kinase; CYC Cyclosporine; DCd Discontinued; Dx Diagnosis; ED Emergency department; EMG Electromyography; GFR Glomerular filtration rate; SCr Serum Creatinine; Sx Symptoms; F Female, LD Lactate Dehydrogenase; LFT Liver function tests; M Male; NS Not stated; Sx Symptoms; WBC White Blood Cell Count

b. Onset of symptoms after second drug started (colchicine or interacting drug).

c. Laboratory results represent peak values during the adverse drug interaction.

d. Included here are disease states likely to increase the risk of colchicine toxicity, such as renal impairment or liver disease. Also included are other drugs that may have contributed to the reaction, and excessive doses of colchicine.

e. Resolution of adverse effects, including the measures taken to combat the reaction, and the patient outcome.

f. DIPS Rating: Drug Interaction Probability Scale (DIPS) as described in Horn, J.R., Hansten, P.D., Chan, L-N. Proposal for a New Tool to Evaluate Drug Interaction Cases. *Ann. Pharmacother*. **41**, 674-680 (2007).

g. The authors proposed that colchicine concentrations were elevated due to severe renal impairment and amiodarone, causing severe diarrhea leading to perforation of the colon which was more susceptible to perforation due to the prednisone and diclofenac therapy. Nonetheless, it is not known 1) whether the colonic perforation was caused by the diarrhea, or 2) whether the severe diarrhea would have occurred without the amiodarone therapy (given the renal failure which would have elevated the colchicine concentrations by itself).

h. The high colchicine dose given the renal impairment was probably the main cause of the colchicine toxicity, but the amiodarone likely contributed.

Azole Antifungals - Fluconazole

Patient [Ref]	Colchicine Dose	Fluconazole Dose	Onset, Presenting Symptoms	Laboratory and Other Findings	Risk Factors	Resolution	DIPS Rating
54 F [4]	1.2 mg/day	100 mg/day x 7 days	2 days after finishing the 7-day course of fluconazole she went to ED with marked lower limb weakness and bilateral ankle pain	CK 803 IU/L, SCr 11.2 mg/dL, Potassium 6.2 mmol/L, ALT 112 U/L, WBC 2830 cells/mL; EMG: consistent with colchicine myopathy	Severe renal impairment (SCr 11.2 mg/dL)[a]	Colchicine stopped; 10 days later her laboratory results returned to normal; weakness gradually improved	Probable

a. The fluconazole dose was only 100 mg/day, a dose that would be expected to have minimal effects on colchicine pharmacokinetics. But fluconazole is largely eliminated unchanged in the urine, and this patient's serum creatinine was 11.2 mg/dL. Her fluconazole serum concentrations, therefore, were probably much higher than they would be in a person with normal renal function. [Berl, T. et al. Pharmacokinetics of fluconazole in renal failure. *J. Am. Soc. Nephrol.* **6**, 242-247 (1995).]

Calcineurin Inhibitors: Cyclosporine (CYC)

Patient, [Ref]	Colchicine Dose	Cyclosporine Dose	Onset, Presenting Symptoms	Laboratory and Other Findings	Risk Factors	Resolution	DIPS Rating
57 F [5]	2 mg/d x 4 days	440 mg/day	12 days after colchicine started: myalgia, muscle weakness with full functional disability	CK 2344 U/L, LD 622 U/L, SCr 1.6 mg/dL	CYC dose increased. 320 to 440 mg/d 14 days before colchicine; renal transplant	CYC decreased to 280 mg/d; Sx and lab abnormalities resolved in 7 d	Possible
44 M [6]	1.2 mg/day	5mg/kg/day	~ 30 days after start of cyclosporine severe muscle weakness requiring intubation	CK 600 U/L, LFTs elevated (AST, ALT, bilirubin); EMG and muscle biopsy consistent with colchicine myopathy	Had CYC-induced nephrotoxicity; renal transplant; on clotrimazole (inhibits CYP3A4)	Improved over 1-2 months; still required a crutch to walk	Possible
55 M [7]	1.2 mg/day	100 mg/day	2 weeks after starting colchicine: diarrhea, GI distress, progressive muscle weakness	CK 2339 U/L, AST 393 U/L, ALT 233 U/L, LD 643 U/L; EMG: toxic myopathy	Chronic corticoids; renal transplant, renal impairment	Colchicine stopped, CK decreased, marked Sx improvement over 3 weeks	Probable
57 M [8]	1.2 mg/day	175 mg/day	8 weeks after starting colchicine he was admitted for progressive muscle weakness	CK normal; SCr stable at 2.1 mg/dL; Muscle biopsy: colchicine myopathy	Chronic corticoids; renal transplant	Colchicine stopped; within 2 weeks muscle strength improved	Probable
Four M age 26-41 [9]	1.0–2.0 mg/day	Started with dose of 3.0 mg/kg/day (all had low serum levels)	In "early stages" all 4 had diarrhea and other GI symptoms; one was hospitalized due to muscle weakness and myalgia	All 4 had increased LD; 3 had increased ALT and bilirubin; 2 had substantial increases in SCr	Chronic corticoids; renal transplant	CYC stopped during third week; all 4 patients had rapid resolution of symptoms and lab values returned to baseline	Possible[a]
48 M [10]	1 mg/d x 7 days	NS	7 days after starting colchicine: diarrhea, paralysis, rhabdomyolysis	CK 31,110 U/L, LD 8,330 U/L, SCr 2.8 mg/dL, WBC 1500/mm^3	Chronic corticoids, renal transplant	Sx resolved over 1 month; required cane to walk	Probable
48 F [11]	0.6 mg/day	NS	3 months after starting colchicine: progressive muscle weakness leading to inability to walk	CK 254 U/L, SCr 2.8 mg/dL, CYC 515 ng/dL (ref. 100-250 ng/dL); Muscle biopsy: colchicine myopathy; EMG: myotonia	Chronic corticoids, renal transplant, renal impairment, excessive CYC levels	Colchicine stopped, dose of CYC reduced, improved over 10 weeks, still needed cane to walk	Probable

Patient, [Ref]	Colchicine Dose	Cyclosporine Dose	Onset, Presenting Symptoms	Laboratory and Other Findings	Risk Factors	Resolution	DIPS Rating
48 M [11]	0.6 mg/day	NS	9 months after starting colchicine muscle weakness	CK 2100 U/L, SCr 3.3 mg/dL, CYC levels therapeutic	Chronic corticoids, renal transplant, renal impairment, excessive CYC levels	Colchicine stopped, weakness improved within weeks	Possible[a]
41 M [11]	0.6 mg/day	NS	About 16 months after starting colchicine muscle weakness	CK 319 U/L, CYC levels therapeutic, on hemodialysis	Chronic corticoids, renal transplant, renal impairment	Colchicine stopped, weakness improved within weeks	Possible[a]
70 M [12]	1.2 mg/day x 7 years	NS	2 months after CYC started, bedridden from extreme myalgia; also fatigue, anorexia, muscle weakness	CK 434 U/L, SCr 2 mg/dL; Muscle biopsy: colchicine myopathy	Chronic corticoids, renal transplant, renal impairment	Colchicine stopped, myalgia and weakness improved over 10 days; minimal pain at 1 month	Probable
39 F [13]	0.6 mg/day	NS	14 days after starting colchicine severe muscle weakness; colchicine started 1 week after renal allograft	CK not measured; EMG not measured; no muscle biopsy done; AST increased after colchicine started, decreased after colchicine stopped	CYC and corticoid dose increased before myopathy; chronic corticoids; renal transplant	CYC stopped; weakness better at 2 weeks, resolved by 4 weeks	Possible
70 M [14]	1 mg/day	NS	16 months after colchicine started developed muscle weakness	CK 425 U/L, SCr 2.2 mg/dL; EMG: myogenic syndrome; Muscle biopsy: colchicine myopathy	Reduced renal function; on chronic corticoids; renal transplant	Improved after colchicine stopped; time course NS	Possible[a]
55 M [14]	1 mg/day	NS	2 months after colchicine started developed myalgia	CK 1840 U/L, SCr 1.7 mg/dL	Reduced renal function; on chronic corticoids; renal transplant	Improved after colchicine stopped; time course NS	Possible[a]
49 F [14]	1 mg/day	NS	26 months after colchicine started she developed myalgia	EMG: myogenic syndrome; Muscle biopsy: colchicine myopathy; CK 1234 U/L, SCr 1.8 mg/dL	Reduced renal function; on chronic corticoids; renal transplant	Improved after colchicine stopped; time course NS	Possible[a]
56 M [14]	1 mg/day	NS	11 months after colchicine started he developed myalgia	CK 251 U/L, SCr 1.4 mg/dL; EMG: axonal neuropathy	Reduced renal function; chronic corticoids; renal transplant	Improved after colchicine stopped; time course NS	Possible[a]
67 M [14]	1 mg/day	NS	10 months after colchicine started he developed myalgia and muscle weakness	CK 1135 U/L, SCr 1.4 mg/dL; EMG: severe myopathy	Reduced renal function; on chronic corticoids; renal transplant	Improved after colchicine stopped; time course NS	Possible[a]
49 M [15]	2.4 mg/day x 3 days	250 mg/day	4 days after colchicine started he developed myalgia, muscle weakness	EMG: myopathy; CK 14,958 U/L, Creatinine 2.7 mg/dL, CYC levels high normal	Large dose of colchicine; renal transplant; mild renal impairment	Improved over a few weeks after colchicine stopped	Probable
53 M [16]	0.6 mg/day	350 mg/day	Onset NS; First myalgia, fatigue, malaise, followed by severe muscle weakness	CK > 3,000 U/L, Creatinine 2.9 mg/dL; serum CYC elevated; EMG: myopathy; Muscle biopsy: colchicine myopathy	Chronic corticoids; renal impairment; elevated serum CYC	Colchicine and CYC stopped; muscle weakness improved within 1 week	Probable
56 M [16]	0.6 mg/day	450 mg/day	6 weeks after starting cyclosporine: muscle weakness, fatigue, malaise	CK 449 U/L, Creatinine 1.9 mg/dL; Serum CYC elevated; EMG: myopathy; Muscle biopsy: colchicine myopathy	Chronic corticoids; renal impairment; elevated serum CYC	Colchicine stopped; muscle weakness resolved over a few weeks	Probable
57 F [16]	0.6 mg/day	120 mg/day	5 days after starting CYC she developed severe muscle weakness, paresthesias	CK 721 U/L, Creatinine 2.2 mg/dL; EMG: myopathy	Cardiac transplant 5 days earlier; renal failure; chronic corticoids	CYC stopped; weakness improved over 1 month	Possible

Patient, [Ref]	Colchicine Dose	Cyclosporine Dose	Onset, Presenting Symptoms	Laboratory and Other Findings	Risk Factors	Resolution	DIPS Rating
53 M [17]	1.5 mg/day	250 mg/day	Gradual onset of myalgia, muscle weakness, then severe weakness, diarrhea	CK 3003 U/L, Creatinine 3.4 mg/dL; EMG: normal; Muscle biopsy: necrotizing myopathy	Chronic corticoids; renal impairment	Colchicine stopped; Sx gone in several days	Probable
60 M [18]	1 mg/day	200 mg/day	Patient with Behçet disease on colchicine for 10 years and CYC for 6 years: muscle weakness progressed over 4 weeks; required wheelchair	CK 626 U/L, SCr 1.4 mg/dL, serum CYC in normal range; Muscle biopsy: colchicine myopathy (vacuoles)	Renal impairment	CYC stopped, colchicine dose reduced to 1 mg/day; 3 weeks later his muscle strength was normal and he could walk	Possible
72 M [19]	1 mg/day	NS	On chronic CYC; ~ 1 month after colchicine dose increased to 1 mg/d: severe muscle weakness, myalgia, lethargy	CK 766 U/L, Creatinine 1.2 mg/dL; EMG: severe myopathy	Chronic corticoids; renal transplant	Colchicine stopped; he was pain-free, able to walk by 3 weeks	Probable
47 F [20]	1.2 mg/day	200 mg/day	After many months of combined therapy, admitted with weakness, myalgia, fatigue of 7 days duration	CK normal, SCr 1.8 mg/dL, small elevation of liver enzymes (AST, ALT, LD), cyclosporine 451 ng/mL; EMG: myopathy; Muscle biopsy: vacuolar myopathy (colchicine)	Chronic corticoids; renal transplant; cyclosporine levels slightly elevated	Cyclosporine stopped for 5 days, then restarted at 100 mg/day but Sx worsened; Colchicine stopped, Sx disappeared, lab results normalized	Possible
62 Gender NS [21]	2 mg/day x 3 days; 1 mg/day QOD x 5 days; then 1 mg/day	125 mg/d	3 days after colchicine started diarrhea, followed by nausea, abdominal pain, myalgia, severe muscle weakness, fatigue, insomnia, confusion, adynamic ileus, arrhythmia	CK 2671 U/L, Creatinine 2.27 mg/dL, CrCl 23 mL/min, pancytopenia	On diltiazem (known to increase colchicine AUC); renal impairment	Colchicine stopped; gradual improvement over 2 to 3 weeks	Possible
47 M [22]	1 mg/day	200 mg/d	2 months after starting colchicine admitted with progressive muscle weakness becoming severe	CK 25,237 U/L, AST 225 U/L, SCr 6.2 mg/dL	On atorvastatin 20 mg/day (myopathy risk and some inhibition of P-gp); chronic corticoids; renal transplant	Atorvastatin stopped no improvement; then COL stopped and CK declined, normal in 3 weeks	Probable
60 M [23]	1 mg/day x 6 days	175 mg/d	3 days after starting colchicine, diarrhea, vomiting, myalgia, weakness, fever, dyspnea, supraventricular tachycardia, rhabdomyolysis, neutropenia	CK 1553 U/L, myoglobin 5188 ng/mL, Creatinine 7.9 mg/dL; elevated serum colchicine persisted days after stopping colchicine[b]	Severe renal impairment; On amiodarone (inhibits CYP3A4 and P-gp), but only after reaction had started	Colchicine stopped and Sx improved within 2-3 days; myalgia persisted, but he improved gradually over several weeks	Probable
66 M [24]	1.2 mg/day	150 mg/d	4 months after colchicine: muscle weakness and myalgia; after admission: dyspnea, rhabdomyolysis, oliguria	CK 33,580 U/L; Muscle biopsy: colchicine myopathy	Simvastatin dose doubled when colchicine started; simvastatin + CYC can cause myopathy; on other myotoxic drugs: corticoids, and propofol[c]	Died 5 days after admission from pneumonia and septic shock	Possible
34 M [25]	3 mg/day x 1 day; 2 mg/day x 2 days; then 1 mg/day x 6 days	340 mg/day	12 days after starting colchicine admitted to ICU with cough, dyspnea, hemoptysis, profuse diarrhea, rhabdomyolysis	CK 3206 U/L, Creatinine 2.4 mg/dL, Myoglobin 573 µg/L (ref. 28-72 µg/L); serum COL more than 4 x the reference range; still elevated almost a week after COL stopped[d]	Large dose of COL; on azithromycin (↑ colchicine AUC); on pravastatin (can cause myopathy); CYC ↑ pravastatin AUC; renal impairment, chronic corticoids	Colchicine stopped; 11 days later improvement in muscular and respiratory Sx; renal function stabilized	Possible

Patient, [Ref]	Colchicine Dose	Cyclosporine Dose	Onset, Presenting Symptoms	Laboratory and Other Findings	Risk Factors	Resolution	DIPS Rating
59 M [26]	3 mg/day	NS	5 days after starting colchicine developed abdominal pain, mucous diarrhea, myalgia; day 7 developed quadriparesis, alopecia on day 29	CK 12,116 U/L, Hemoglobin 8.2 g/dL, Creatinine 5.8 mg/dL; LFTs elevated, Serum colchicine still therapeutic 11 days after DCd	Large dose of colchicine; on atorvastatin (myopathy risk and some inhibition of P-gp); renal failure, chronic corticoids	Colchicine & atorvastatin DCd; CYC switched to tacrolimus; Recovered gradually over 3 months	Probable
57 F [27]	0.6 mg/day	100 mg/day	After starting colchicine: Day 5: abdominal pain, nausea, vomiting; Day 7: tingling and numbness in hands and feet; Day 21: to ED with worsening renal function, elevated CK, liver enzymes and myoglobin	CK: 2316 U/L, LD: 973 U/L, AST 227 U/L, Myoglobin 2151 ng/mL, SCr 1.97 mg/dL, ANC 1.0 x 10^3/µL; CYC levels: therapeutic range	On rosuvastatin 20 mg/day; chronic corticoids; renal transplant	Colchicine, rosuvastatin stopped on day 21; GI Sx improved in 2 days; normalization of CK, LD, AST, SCr, ANC occurred over 3 weeks	Probable
58 F [28]	7.8 mg over 3 days	NS	1 day after starting colchicine, severe diarrhea; 3 days after starting colchicine progressive weakness, hypotension; to ED with probable sepsis, alopecia	Pancytopenia, neutrophils had vacuoles (indicating COL toxicity), CYC concentration low	Excessive colchicine dose; renal impairment; chronic corticoids; renal transplant	Died 7 days after admission from pancytopenia and multiorgan failure	Possible[e]
46 M [29]	0.5 mg/day x 6 months	NS	Presented with nausea, lethargy, generalized aches, and 6 months of diarrhea; Exam showed muscle weakness	CK 523 U/L, SCr 2.9 mg/dL, cyclosporine trough level high normal; EMG: severe myopathy	Chronic corticoids; renal transplant	Rx: IV fluids, corticoids; CYC dose adjusted; incr. weakness until colchicine DCd 3 weeks later	Possible

a. Inadequate information provided on concurrent medications for detailed assessment of causality.
b. Serum colchicine after stopping colchicine: 36 hours = 7 ng/mL, 50 hours = 6.5 ng/mL, 74 hours = 5 ng/mL (reference 1 to 4 ng/mL).
c. Propofol may inhibit CYP3A4 [Hamoka, N et al. Clin Pharmacol Ther. **66**, 110-7 1999], and may also increase the risk of rhabdomyolysis [Hemphill S et al. *Br. J. Anaesth*. **122**, 448-59 (2019)]
d. Serum colchicine 24h after last dose = 13 ng/mL; after 153 hours = 2.7 ng/mL (reference range: 0.3-2.5 ng/mL).
e. Cyclosporine serum concentration 25 ng/mL (ref. 250-1000 ng/mL) so contribution of cyclosporine not clear.

Calcineurin Inhibitors: Tacrolimus

Patient, Ref.	Colchicine Dose	Tacrolimus Dose	Onset, Presenting Symptoms	Laboratory and Other Findings	Risk Factors	Resolution	DIPS Rating
62 M [30]	1.2 mg/day		A few days after starting colchicine: myalgia, malaise, fatigue	CK 9084 U/L, SCr 1.2 mg/dL, AST 4-fold increase	On nifedipine and vardenafil, both of which might modestly inhibit P-gp	Colchicine DCd, and CK declined to 5204 U/L in 3 days, AST normal in 2 mo	Probable

Calcium Channel Blockers - Verapamil

Patient, Ref.	Colchicine Dose	Verapamil Dose	Onset, Presenting Symptoms	Laboratory and Other Findings	Risk Factors	Resolution	DIPS Rating
83 M [31]	1 mg/day x 2 days (drops, self- dosed)	120 mg/day	Muscle weakness during 2 day course of colchicine; 4 days later hospitalized for flaccid tetraparesis	CK 1288 U/L, normal renal/hepatic function; EMG: lower motor neuron lesion; Muscle biopsy: one vacuole; excessive colchicine concentrations in serum and cerebrospinal fluid; colchicine half-life 272 hrs[a]	None observed. Given normal renal/hepatic function, and high serum colchicine, it is possible he took more colchicine drops than he reported	Follow-up about a month later found only partial recovery	Probable

a. The half-life was 8 times longer than expected in dose and age matched controls. The authors propose that the elevated cerebrospinal fluid colchicine concentrations were caused by P-gp inhibition by verapamil at the blood-brain barrier.

Enzyme Inducers

Patient, Ref.	Colchicine Dose	Enzyme Inducer Dose	Onset, Presenting Symptoms	Laboratory and Other Findings	Risk Factors	Resolution	DIPS Rating
Carbamazepine (CBZ)							
61 M [32]	1.2 mg/day x 6 days	Chronic CBZ Dose N.S.	Patient with hemorrhagic pericarditis failed to improve after 6 days of colchicine	Serum colchicine subtherapeutic (0.94 ng/mL) after 6 days of colchicine 1.2 mg/day	None reported	Carbamazepine and colchicine DCd; no more colchicine levels done	Probable
Rifampin							
54 M [33]	1.8 mg/day x 9 days, then 3.6 mg/day	Rifampin chronic use; Dose N.S.	Acute gout did not respond to 1.8 mg/day x 9 days; pain relief after increased to 3.6 mg/day	Serum colchicine 1 and 6 hours after 0.6 mg colchicine 1.4 ng/mL and 0.2 ng/mL (much lower than other patients	Chronic kidney disease (SCr 7.6 mg/dL	No described.	Probable

Grapefruit

Patient, Ref.	Colchicine Dose	Grapefruit Dose	Onset, Presenting Symptoms	Laboratory and Other Findings	Risk Factors	Resolution	DIPS Rating
8 W [34]	2 mg/day for 10 months	1 liter grapefruit juice/day for 2 months	After 2 months of daily grapefruit juice in large amounts, she was admitted with fever, severe abdominal pain, recurrent vomiting, sore throat; then CHF, arrhythmias, circulatory shock, pancytopenia; later developed atonia/weakness leading to falls	WBC 420 cells/mm^3, Platelets 27,000 /mm^3, SCr 1.1 mg/dL, elevated AST and ALT, Sodium 127 mEq/L	Large dose of colchicine, large amount of grapefruit juice	Admitted pediatric ICU, assisted ventilation, fresh frozen plasma, platelets and packed cells infusions, antibiotics; reversed completely after about 2 weeks	Possible[a]

a. The severe colchicine toxicity observed in this 8-year-old girl is not necessarily inconsistent with the negative results in a study of healthy subjects [Wason S, DiGiacinto JL, Davis MW. Effects of grapefruit and Seville oranges on the pharmacokinetic properties of colchicine in healthy subjects. *Clin. Ther*. **34**, 2161-73 (2012).] Perhaps ingestion of normal amounts of grapefruit juice has little effect on colchicine pharmacokinetics, but large amounts (such as 1 liter/day in an 8-year-old) have a greater effect on CYP3A4, and also a significant inhibitory effect on P-gp as well. The magnitude of pharmacokinetic drug interactions is usually dose-related, and the fact that grapefruit juice produces a small increase in digoxin serum concentration suggests that grapefruit may have some inhibitory effect on P-gp. Also, some people have lower P-gp activity due to genomic differences, and such people tend to have higher bioavailability to drugs that are substrates for P-gp such as digoxin. [Kurata, Y et al. Role of human *MDR1* gene polymorphism in bioavailability and interaction of digoxin, a substrate of P-glycoprotein. *Clin Pharmacol. Ther*. **72**, 209-19 (2002)] Accordingly, even if normal amounts of grapefruit juice have little effect on P-gp in most people, if a patient with genetically low P-gp activity ingests grapefruit juice, they would, in effect, have low activity of both CYP3A4 and P-gp. This would predispose them to grapefruit-induced elevations of colchicine serum concentrations.

HMG-CoA Reductase Inhibitors (Statins)

Patient, Ref.	Colchicine Dose	Statin Dose	Onset, Presenting Symptoms	Laboratory and Other Findings	Risk Factors	Resolution	DIPS Rating
Atorvastatin							
45 M [35]	1.5 mg/day	Atorvastatin 10 mg/day	2 weeks after atorvastatin started, muscle weakness, myalgia, fatigue, altered mentation	CK 9,035 U/L, SCr 8.1 mg/dL, dark urine, Myoglobin >3000 ng/mL; Dx: rhabdomyolysis	Nephrotic syndrome	Colchicine & atorvastatin stopped with some improvement but died of septic shock on day 18	Probable
43 M [36]	1.5 mg/day	Atorvastatin 10 mg/day	2 weeks after atorvastatin started, muscle weakness, myalgia	CK 608 U/L, SCr 1.4 mg/dL, estimated GFR 71.5 mL/min; EMG: myopathy	Renal amyloidosis with modest reduction in renal function	Colchicine & atorvastatin stopped; resolution over 2 weeks	Probable

Patient, Ref.	Colchicine Dose	Statin Dose	Onset, Presenting Symptoms	Laboratory and Other Findings	Risk Factors	Resolution	DIPS Rating
41 M [36]	1.0 mg/day	Atorvastatin 20 mg/day	20 days after atorvastatin started, muscle weakness, myalgia, dyspnea	CK 11,069 U/L, SCr 1.39 mg/dL, estimated GFR 74.5 mL/min, proteinuria 4g/day; EMG: myopathy	Renal amyloidosis with modest reduction in renal function	Colchicine & atorvastatin stopped; symptoms resolved in 1 week, labs resolved over 2 weeks	Probable
47 M [37]	1.0 mg/day	Atorvastatin 20 mg/day	2 months after starting colchicine admitted with progressive muscle weakness becoming severe	CK 25,237 U/L, AST 225 U/L, SCr 6.2; Dx: rhabdomyolysis	On cyclosporine (likely more responsible than atorvastatin for the myopathy); Chronic corticoids; Renal transplant	Atorvastatin stopped but CK continued to rise; then colchicine stopped and CK normalized within 3 weeks	Doubtful (Probable for CYC, see above)
66 F [38]	0.6 mg/day	Atorvastatin 80 mg/day	On chronic colchicine and atorvastatin; 3 weeks after sofosbuvir + ledipasvir started nausea, vomiting, diarrhea, abdominal pain; 1 week later myalgia, weakness	CK 7,979 U/L, AST 362 U/L, SCr 2.5 mg/dL estimated GFR 23 mL/min; EMG: myopathy; Dx: rhabdomyolysis	Chronic kidney disease, liver cirrhosis; Ledipasvir is a P-gp inhibitor which may have increased levels of both colchicine and atorvastatin	Atorvastatin stopped, gradual improvement; muscle weakness persisted for months	Possible
55 M [39]	Not stated	Atorvastatin dose NS	1 week after starting atorvastatin, severe, muscle weakness	CK 222,166 U/L; Dx: rhabdomyolysis	None stated	Colchicine & atorvastatin stopped with gradual resolution; colchicine later restarted without incident	Possible
41 M [40]	2 mg/day	Atorvastatin 10 mg/day	On chronic atorvastatin; 6 months after colchicine started developed rhabdomyolysis	CK 13,192 U/L, SCr 19 mg/dL	Large colchicine dose given; reduced renal function (renal amyloidosis); renal function gradually declined before rhabdomyolysis	Colchicine & atorvastatin stopped; patient started chronic hemodialysis and was not re-started on colchicine.	Possible
70 F [41]	0.6 mg/day	Atorvastatin 20 mg/day	6 days after starting colchicine and daptomycin developed increasing muscle weakness and myalgia	CK 4,860, SCr 1.04 mg/dL, eGFR 49 mL/min, AST 310, ALT 98	Daptomycin can cause myopathy; it was restarted without colchicine or	Colchicine, daptomycin and atorvastatin were stopped; 1 week later symptoms resolved and labs normal	Possible[a]
94 M [42]	0.5 mg/day	Atorvastatin 40 mg/day	On chronic atorvastatin; one month after colchicine started presented with tetraparesis and inability to walk	CK 1.563 U/L, SCr 1.6 mg/dL. Negative for autoimmune diseases and Ab anti HMG-CoA; EMG: myopathy; Muscle biopsy: sarcoplasmic vacuoles, no necrosis	Chronic kidney disease (baseline SCr 1.2 mg/dL)	Colchicine & atorvastatin stopped; CK normal after 5 days. SCr normalized in 1 week (1.23mg/dL). Residual leg weakness of for months	Probable
Fluvastatin							
70 M [43]	1.5 mg/day	Fluvastatin 80 mg/day	3 days after starting colchicine nausea, abdominal pain; 10 days after starting colchicine he had muscle weakness, severe myalgia, and rhabdomyolysis	CK 37,782 U/L; myoglobin in urine; myoglobinuric acute renal failure; one month prior to colchicine his SCr was 0.9 mg/dL and urea nitrogen was 38 mg/dL	None stated.	Colchicine and fluvastatin stopped; gradual improvement over 2-3 weeks	Possible
77 M [44]	1.0 mg/day	Fluvastatin 80 mg/day	14 days after starting colchicine nausea and abdominal pain, followed later by severe myalgia and muscle weakness	CK 2371 U/L, Myoglobin > 3000 ng/mL, SCr 1.74 mg/dL, estimated CrCl 41 mL/min; EMG: myopathy	Chronic renal failure; taking unspecified calcium channel blocker[b]	Colchicine and fluvastatin stopped; gradual improvement over 16 days	Possible

Patient, Ref.	Colchicine Dose	Statin Dose	Onset, Presenting Symptoms	Laboratory and Other Findings	Risk Factors	Resolution	DIPS Rating
Lovastatin							
74 M [45]	Not stated	Lovastatin (Dose NS)	About 14 days after starting lovastatin developed severe muscle weakness	CK 8370 U/L; EMG: myopathy	None observed; patient had normal renal function and was not on other medications	Colchicine and lovastatin were stopped; gradual improvement over weeks	Possible[b]
Pravastatin							
65 F [46]	1.5 mg/day	Pravastatin 20 mg/day	20 days after starting pravastatin: muscle weakness	CK 914 U/L; EMG: myopathy	None stated.	Colchicine and pravastatin were stopped; gradual improvement over 7 days[c]	Possible[d]
34 M [25]	Variable[e]	Pravastatin 20 mg/day	12 days after colchicine started: "muscle symptoms"	CK 3206 U/L, rhabdomyolysis with renal failure	Patient also on cyclosporine and azithromycin; both can increase colchicine AUC	Colchicine DCd; 11 days later improved muscular and respiratory Sx; renal function stabilized	Doubtful[f]
Rosuvastatin							
68 M [47]	0.5 mg/day	Rosuvastatin (Dose NS)	14 days after starting colchicine: muscle weakness (difficulty with gait and rising from a chair)	CK 2,200 U/L; EMG: myopathy; Muscle biopsy: vacuolar myopathy (suggesting colchicine effect)	Genotyping of P-gp showed much lower P-gp activity compared to 4 controls	Colchicine & rosuvastatin stopped; CK normal in 1 week; gradual symptom improvement	Probable
72 M [47]	Not stated	Rosuvastatin (Dose NS)	Had 3 rhabdomyolysis episodes of a 2-year period with weakness, myalgia, and reduced mobility	CK on 3 episodes: 4,021, 4,568 and 3212; Muscle biopsy: vacuolar myopathy (suggesting colchicine effect)	Genotyping of P-gp showed marginally lower P-gp activity compared to 4 controls		Possible[g]
49 M [48]	1.0 mg/day	Rosuvastatin 40 mg/day	On colchicine for 1 month; 10 days after starting rosuvastatin progressive muscle pain, severe muscle weakness; fatigue, dark urine; Dx: rhabdomyolysis	CK 21,000 U/L; SCr 5.2 mg/dL (2.5 mg/dL before rosuvastatin started); AST 645 U/L; ALT 689 U/L; LDH 930 U/L;	Chronic renal insufficiency (stage III); on amlodipine (weak CYP3A4/Pgp inhibitor);	Colchicine & rosuvastatin stopped; in 1 week SCr returned to baseline; muscle-related enzymes gradually normalized	Probable
Simvastatin							
70 M [49]	1.0 mg/day	Simvastatin (Dose NS)	14 days after starting colchicine, severe muscle weakness, no myalgia	CK 918 U/L, SCr 3.0 mg/dL	Chronic renal insufficiency	Colchicine & simvastatin stopped; resolution over 2 weeks	Probable
79 M [50]	0.6 mg/day x 4 days; 1.2 mg/day for 4 days	Simvastatin 40 mg/day	8 days after colchicine started, severe muscle weakness, dyspnea	CK 50,936 U/L (peak), SCr went from 4.3 to 6.5 mg/dL due to myoglobinuria; EMG: myopathy; Muscle biopsy: vacuolar myopathy (colchicine)	Chronic renal insufficiency	Colchicine stopped; resolution over 2 weeks	Probable
61 F [51]	1.2 mg/day	Simvastatin 80 mg/day	Muscle weakness 12 days after colchicine began, became severe over next 9 days, no myalgia	CK 6765 U/L, SCr 1.7 mg/dL; myoglobinuria	Simvastatin dose increased from 40 mg/day to 80 mg/day 1 week before myopathy; mild renal impairment	Colchicine & simvastatin DCd; resolved in 2 weeks; later simvastatin 80/day restarted w/ no myopathy	Possible
30 M [36]	1.5 mg/day	Simvastatin 20 mg/day	3 weeks after simvastatin started, developed muscle weakness, myalgia, cramps	CK 1232 U/L, SCr 1.28 mg/dL, estimated GFR 76.4 mL/min	Renal amyloidosis with modest renal impairment	Colchicine & simvastatin DCd; resolved in 2 weeks	Probable
66 M [24]	1.2 mg/day	Simvastatin 30 mg/day, then 60 mg/day	Increasing muscle weakness over 4 months after simvastatin dose increased from 30 to 60 mg/day;	CK 33,580 U/L	On cyclosporine and propofol, both of which may have contributed to myopathy; chronic corticoids	Colchicine & simvastatin were stopped, but he developed pneumonia and	Possible

			On admission severe muscle weakness, myalgia, dyspnea			septic shock and died 5 days later	
84 M [52]	1.0 mg/day x 3 days, then 0.5 mg/day	Simvastatin 40 mg/day	Over 3 weeks after starting colchicine, increased muscle weakness, myalgia, dysphagia	CK 2837 U/L, baseline eGFR: 37mL/min decreasing to 23mL/min during reaction; no myoglobinuria	Renal impairment; on amlodipine (modest inhibitor of P-gp); chronic corticoids	Colchicine & simvastatin stopped; resolution of CK by 3 weeks, and muscle weakness over 8 weeks	Possible
60 M [29]	1.5 mg/day x 6 weeks	Simvastatin (Dose NS)	3 weeks after starting colchicine: diarrhea, anorexia, muscle weakness causing falls	CK 1,912 U/L, SCr 5.9 mg/dL (had been about 2.6 mg/dL); EMG: acute myopathy; Muscle biopsy did not show vacuoles typical of colchicine	Stage 4 chronic kidney disease, colchicine dose too high for degree of renal impairment; On amlodipine (modest inhibitor of P-gp)	Colchicine, simvastatin, amlodipine stopped; still anuric, but improved after 3 hemodialysis sessions; resolved over 3 weeks	Possible
70 M [53]	0.5 to 1.0 mg/day	Simvastatin 40 mg/day	On simvastatin x 6 years, started on colchicine; later (time NS) progressive muscle weakness, severe myalgia; difficulty walking/climbing stairs; dyspnea	CK More than 100 times upper limit of normal; Myoglobin 21,896 µg/L; SCr 7.7 mg/dL; Muscle biopsy consistent with statin-induced myopathy	Renal impairment	Simvastatin stopped; hemofiltration started; normalization of renal function by 3 days, CK by 15 days	Possible
64 M [54]	1.2 mg/day	Simvastatin 80 mg/day	On chronic simvastatin and colchicine when clarithromycin started; after 3 weeks admitted with muscle pain, muscle weakness, and dark urine	CK 213,978 U/L (peak); SCr 8.0 mg/dL (baseline 4.8 mg/dL); AST 981 U/L; ALT 301 U/L;	On clarithromycin (1000 mg/day which increases AUC of both colchicine and simvastatin; severe renal impairment	Simvastatin, colchicine and clarithromycin DCd, but he developed cardiac & respiratory arrest and later died on day 117	Doubtful[h]

a.

b. If the calcium-channel blocker was diltiazem or verapamil, either one could have elevated colchicine serum concentrations.

c. Drug doses were not given, so it is difficult to evaluate the case. Also, one cannot rule out the possibility that the myopathy was due to lovastatin alone. Nonetheless, it is possible that there was additive myotoxicity of lovastatin and colchicine.

c. The colchicine was subsequently re-started at a lower dose of 1 mg/day without incident.

d. One cannot rule out that the myopathy was due to colchicine alone although she did not have renal impairment and colchicine-induced myopathy at that dose of colchicine would be unusual.

e. Twelve days before admission he took 3 mg/d x 1 day, 2 mg/d x 2 days, then 1 mg/day x 6 days.

f. The myotoxicity was much more likely to be due to the cyclosporine and azithromycin the patient was taking, both of which have been shown to increase colchicine serum concentrations. Also, cyclosporine increases pravastatin serum concentrations, [Yee, SW et al. Organic anion transporter polypeptide 1B1 polymorphism modulates the extent of drug-drug interaction and associated biomarker levels in healthy volunteers. *Clin. Transl. Sci.* 12, 388-399 (2019)] which would increase the risk of pravastatin myopathy.

g. One of the 3 episodes of rhabdomyolysis occurred with colchicine alone, so the role of a drug interaction was not clear. One retrospective study compared the risk of myopathy in patients receiving statins with or without concurrent colchicine, 28 patients took rosuvastatin with colchicine. [Kwon 2017] Two of the patients on rosuvastatin and colchicine developed myopathy (both took 1.2 mg/day colchicine) but too little information was provided to assess causality.

h. The patient was on chronic colchicine and high-dose simvastatin without muscle symptoms, so this reaction is unlikely to be due to a DDI between simvastatin and colchicine. Rhabdomyolysis only occurred after clarithromycin was started. The ability of clarithromycin to increase the serum concentrations of both colchicine and simvastatin was the likely cause.

Macrolides: Clarithromycin (Two case below. Our group previously published a table describing the other 20 cases. See table in Villa-Zapata,[48] and references 49-60 below. The Australian Adverse Drug Reactions Advisory Committee reported four cases of severe colchicine toxicity due to clarithromycin, three of which were fatal. Not enough detail was given to evaluate causality. (Topliss 2008)[61]

Patient, Ref.	Colchicine Dose	Clarithromycin Dose	Onset, Presenting Symptoms	Laboratory and Other Findings	Risk Factors	Resolution	DIPS Rating
85 F [62]	2 mg/day	1 g/day x 14 days	On clarithromycin for *H. pylori*; 4 days after adding colchicine platelet count reduced to half	Estimated GFR 28 mL/min; Platelet count: before colchicine 230 10^9/L; 4 days after colchicine 127x10^9/L; 6	Clearly excessive dose of colchicine given marked impairment of renal function	6 days after colchicine added to clarithromycin, she died of a cardiac arrest	Probable

				days after colchicine 32x10^9/L, and white cell count 0.8x10^9/L			
64 M [54] Lee	1.2 mg/day	1 g/day for 21 days	On chronic simvastatin and colchicine when clarithromycin started; after 3 weeks admitted with muscle pain, muscle weakness, and dark urine	CK 213,978 U/L (peak); SCr 8.0 mg/dL (baseline 4.8 mg/dL); AST 981 U/L; ALT 301 U/L;	On high-dose simvastatin (80 mg/day) severe renal impairment	Simvastatin, colchicine and clarithromycin DCd, but he developed cardiac & respiratory arrest and later died on day 117	Probable[a]

a. The reaction was likely due to a triple drug interaction, with clarithromycin increasing the serum concentrations of both colchicine and simvastatin. Colchicine serum concentrations were probably high due to the clarithromycin and the severe renal impairment. The simvastatin serum concentrations were probably high due to the large dose (80 mg/day) and the clarithromycin.

Macrolides: Erythromycin

Patient, Ref.	Colchicine Dose	Erythromycin Dose	Onset, Presenting Symptoms	Laboratory and Other Findings	Risk Factors	Resolution	DIPS Rating
29 F [63]	1 mg/day	2 g/day x 14 days	16 days after starting erythromycin admitted with diarrhea, vomiting, abdominal pain, dyspnea, fever, severe myalgia, paresthesias	SCr 10.4 mg/dL, liver enzymes markedly elevated; pancytopenia, serum colchicine about 10 times higher than upper end of reference range[a]	Renal and liver amyloidosis, on hemodialysis	Colchicine stopped, extra hemodialysis given, patient later developed seizures,[b] alopecia, hypoglycemia, bizarre behavior; hospitalized for 70 days[c]	Probable

a. Serum colchicine on admission was 22 ng/mL (reference range of 1-2.5 ng/mL). Colchicine levels 1 and 5 months before the current admission (when renal function was about the same) were 9.0 and 12.6 mg/dL respectively. This suggests that in patients on chronic hemodialysis, colchicine 1 mg/day may be excessive. The colchicine levels 1 and 5 months earlier also support the role of erythromycin as the precipitating cause of the colchicine toxicity, since the colchicine serum concentrations approximately doubled after two weeks on clarithromycin.

b. The seizures were treated with a phenobarbital drip, which inadvertently may have helped the patient eliminate the colchicine by inducing the CYP3A4 enzyme.

c. Despite "intensive hemodialysis" the colchicine toxicity was prolonged; one month after the last dose of colchicine the serum concentration was still 0.23 ng/dL. This demonstrates how difficult it is to treat colchicine toxicity in patients with severe renal impairment, since colchicine is not removed by hemodialysis. Her impaired liver function may have contributed as well.

Quinolines: Hydroxychloroquine

Patient, Ref.	Colchicine Dose	Quinoline Dose	Onset, Presenting Symptoms	Laboratory and Other Findings	Risk Factors	Resolution	DIPS Rating
66 F [64]	Not stated	Hydroxychloroquine 400 mg/day	4+ weeks after colchicine added, admitted with severe muscle weakness; not able to stand; no myalgia	CK 343 U/L; Normal: CBC, liver function tests, electrolytes, and urine analysis; Electron microscopy suggested myopathy due to both hydroxychloroquine and colchicine	She had mild muscle weakness before colchicine started	Both hydroxychloroquine and colchicine stopped; symptoms resolved by 8 weeks	Possible[a]

a. The colchicine dose was not stated, so it is not possible to rule out an excessive dose of colchicine as the cause of the myopathy.

Miscellaneous Drugs

Patient, Ref.	Colchicine Dose	Drug and Dose	Onset, Presenting Symptoms	Laboratory and Other Findings	Risk Factors	Resolution	DIPS Rating
Disulfiram							
44 M [65]	1 mg/day	Disulfiram 200 mg/day	12 hours after first dose of disulfiram, severe erythematous skin reaction, leukopenia, fever, tachycardia	Leukocyte count 3800/mcL, Hemoglobin 10.6 g/dL	None stated	Disulfiram stopped with continued colchicine; reaction resolved over 2 days	Doubtful[a]

Fibrates							
40 M [66]	1.5 mg/day	Gemfibrozil 1200 mg/day	On chronic colchicine, started on gemfibrozil; weeks later developed muscle pain, dark brown urine, fatigue, and anorexia	CK 3559 U/L, SCr 2.6 mg/dL, elevated LFT (ALT, AST, LD), Urine protein 5 g/day	Chronic hepatic and renal disease; Excessive colchicine dose given hepatic and renal impairment	All drugs discontinued; clinical and laboratory improvement by day 4; recovery by day 9; colchicine 1 mg/day started with no myopathy	Possible[b]
75 M [67]	Not stated	Bezafibrate 400 mg/day	14 days after colchicine started: severe diarrhea, tetraparesis and numbness of all 4 limbs	Elevated muscle enzymes; EMG: suggested neuromyopathy	Chronic renal failure	Bezafibrate & colchicine DCd and Sx resolved rapidly	Possible[c]
Nivolumab							
70 M [68]	1.8 mg/day 3 courses	Nivolumab 3 mg/kg every 2 weeks	None stated. Patient did not develop nausea, vomiting or diarrhea	After 8 weeks of colchicine platelet count decreased from 160,000/mm^3 to 125,000, and to 115,000 by 12 weeks; absolute neutrophil count 2200/mm^3	None described (renal and liver function tests all normal)	Colchicine stopped; thrombocytopenia resolved in about 1 month; neutrophils increased to 3200/mm^3	Possible
Sunitinib							
82 M [69]	4.8 mg/day x 7 days; 3.6 mg/day x 2 days; 0.6 mg x 1 day	Sunitinib 50 mg/day	Started sunitinib on day 7 of colchicine, on day 8 severe diarrhea, on day 10 admitted with shortness of breath and chest pain	Day 2 of admission fever, metabolic acidosis, hypokalemia, heart failure, thrombocytopenia, white cell abnormalities, anemia	Excessive dose of colchicine, particularly given renal impairment; patient also on diltiazem	Not discussed. (assume patient survived)	Doubtful[d]

a. Although the authors attributed the reaction to colchicine toxicity caused by disulfiram, it is unlikely that a single dose of a questionable P-gp inhibitor such as disulfiram would interact with colchicine, especially that quickly.

b. The relative roles of gemfibrozil and colchicine—alone or together—in the etiology of the rhabdomyolysis is not clear. Several factors should be considered: 1) The patient had modest impairment of renal function before the gemfibrozil, so the original dose of colchicine may have been excessive. 2) The addition of the gemfibrozil may have caused the rhabdomyolysis by itself, with no contribution from the colchicine. 3) Gemfibrozil-induced rhabdomyolysis may have reduced renal function from baseline resulting in elevated colchicine serum concentrations and worsening of the myotoxicity. 4) Perhaps the colchicine and gemfibrozil had an intrinsic additive effect in producing the myopathy.

c. Article was in Japanese, and not enough information was given in the English abstract for detailed assessment of causality.

d. The most likely cause of the colchicine toxicity was the clearly excessive dose of colchicine in the presence of renal impairment, and the diltiazem therapy, a drug known to increase colchicine serum concentrations. It is possible that sunitinib contributed to the colchicine toxicity by inhibiting P-gp, but this is speculative.

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