MAJOR ARTICLE

Fatal Interaction between Clarithromycin and Colchicine in Patients with Renal Insufficiency: A Retrospective Study

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Background. Clarithromycin is frequently used to treat community-acquired pneumonia in elderly persons. Like erythromycin, it may interact with other drugs by interfering with metabolism by cytochrome P450 enzymes and with the P-glycoprotein transporter system. Colchicine, used for treatment of acute gout and for prophylaxis, may cause bone marrow toxicity. It is metabolized by CYP3A4 and is transported by P-glycoprotein. Initial case reports suggested potentially fatal interactions between clarithromycin and colchicine.

Methods. A retrospective study was conducted with 116 patients who were prescribed clarithromycin and colchicine during the same clinical admission. Case-control comparisons were made between patients who received concomitant therapy with the 2 drugs and patients who received sequential therapy. We assessed the clinical presentations and outcomes of the 2 patient groups and analyzed the risk factors associated with fatal outcomes.

Results. Nine (10.2%) of the 88 patients who received the 2 drugs concomitantly died. Only 1 (3.6%) of the 28 patients who received the drugs sequentially died. Multivariate analysis of the 88 patients who received concomitant therapy showed that longer overlapped therapy (relative risk [RR], 2.16; 95% confidence interval [CI], 1.41–3.31; $P \leqslant .01$), the presence of baseline renal impairment (RR, 9.1; 95% CI, 1.75–47.06; $P < .001$), and the development of pancytopenia (RR, 23.4; 95% CI, 4.48–122.7; $P < .001$) were independently associated with death.

Conclusions. Clarithromycin increases the risk of fatal colchicine toxicity, especially for patients with renal insufficiency. Since there are other drugs for treatment of pneumonia and gout, these 2 drugs should not be coprescribed, because of the risk of fatality.

Acute community-acquired pneumonia is one of the most common medical conditions requiring hospitalization for patients aged >65 years, with an annual incidence of 25–44 cases per 1000 noninstitutionalized patients and 33–114 cases per 1000 long-term care institutionalized residents [1]. Clarithromycin is a commonly prescribed antibiotic that is often used in combination with β-lactams for treatment of pneumonia [2]. Elderly patients with pneumonia frequently have major underlying medical illnesses, such as hypertension, ischemic heart disease, congestive heart failure, chronic renal insufficiency, and hyperuricemia. Many of them developed acute gout during hospitalization as a result of a variety of precipitating factors, such as dehydration, diuretics, and sepsis. Colchicine has often been prescribed as a rapidly effective and inexpensive treatment for gout. We previously described 2 patients who developed fatal drug interactions, characterized by marrow hypoplasia, after concomitant therapy with clarithromycin and colchicine [3]. Review of the literature suggested a possible interaction between clarithromycin and colchicine at the cellular level that involved cytochrome P450 metabolism and P-glycoprotein transportation. Such interactions affect the oral bioavailability, metabolism, and excretion of colchicine. Therefore, a retrospective

Received 3 February 2005; accepted 16 March 2005; electronically published 23 June 2005.

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Clinical Infectious Diseases 2005; 41:291–300

1058-4838/2005/4103-0003$15.00

study was undertaken to define the incidence and risk factors for adverse outcomes in patients who were treated with these 2 agents during hospitalization.

PATIENTS AND METHODS

This study was conducted in a 1300-bed tertiary care teaching hospital that has a computer system at the pharmacy that records daily prescriptions for all hospitalized patients. The clinical management system (CMS) was installed and put into full use in September 1997. Patient data, including hospital identification numbers, the durations of hospitalization, and the dates of prescription of colchicine and macrolides, as well as other drugs, can be retrieved from this database. All patients who were prescribed macrolides and colchicine were recruited for this study. Their clinical records and laboratory investigation results were retrieved for detailed analysis. A patient's demographic characteristics and underlying diseases, the diagnosis at admission, the dosage of macrolides and colchicine, the dates of administration, the indication for colchicine, adverse effects, laboratory findings during hospitalization, and outcomes were recorded. The prescriptions of all recruited patients were scrutinized for drugs known to cause pancytopenia and any drugs known to produce potentially fatal drug interactions with macrolides and colchicine, such as ciprofloxacin, doxycycline, isoniazid, protease inhibitors, azole antifungals, diclofenac, imatinib, propofol, quinidine, and verapamil. Results of microbiological examinations for community- and hospital-acquired sepsis were retrieved and reviewed. Case-control comparisons were made between patients who received concomitant therapy with colchicine and macrolides and patients who did not. Among the patients who received concomitant therapy, we then compared those who died within 28 days after hospital admission with those who survived, and we compared those who developed pancytopenia with those who did not. Concomitant therapy was defined as the receipt of clarithromycin and colchicine with a period of overlap, whereas sequential therapy was defined as simply the receipt of clarithromycin and colchicine during the same admission. For the clinical presentation and investigation findings, fever was defined as a body temperature of >38°C, renal insufficiency was defined as a creatinine level of >140 μmol/L, and diarrhea was defined as bowel opening at a frequency of $\geq$3 times daily. In addition, baseline alanine transaminase (ALT) levels that were $\geq$2 times the upper limit of normal (>80 U/L) were recorded. Pancytopenia was defined as a neutrophil count of $<2.0 \times 10^9$ cells/L, a hemoglobin level of <12 g/dL for women and <14g/dL for men, and a platelet count of $<150 \times 10^9$ platelets/L. Adverse outcomes included development of pancytopenia, death, or both. The premorbid status of each patient was quantitatively assessed using the Charlson index [4]. The Charlson index contains 19 categories of comorbidity that are defined using *International Classification of Diseases, Ninth Edition, Clinical Modification* diagnosis codes. The overall comorbidity score reflects the cumulative likelihood of mortality within 1 year.

We compared the clinical characteristics, investigation results, and adverse outcomes of these patients by Fisher's exact test, for categorical variables, and Student's *t* test, for continuous variables. A 2-tailed *P* value of <.05 was considered statistically significant. For nonparametric variables, the Mann-Whitney *U* test was used. Statistically significant risk factors identified on univariate analysis were further analyzed by linear regression to identify independent risk factors associated with

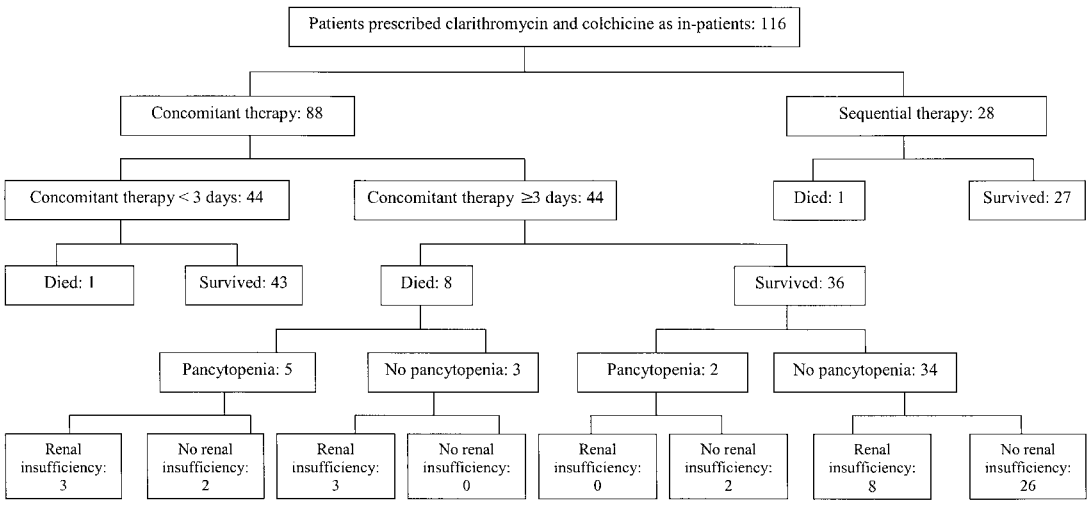

Figure 1. Flow chart showing the outcomes for patients who received clarithromycin and colchicine therapy and the relationship between outcomes and renal insufficiency.

poor outcomes, in terms of pancytopenia and death. All statistical analyses were performed using statistical software (SPSS version 11.0; SPSS)

RESULTS

Between 1 February 1997 and 30 September 2004, 116 of 201,340 patients admitted to the medical wards were prescribed clarithromycin and colchicine during the same admission (figure 1). No other macrolides were prescribed for this cohort of patients. All colchicine prescriptions were for treatment purposes only. Eighty-eight patients (75.9%) had concomitant administration of these 2 drugs (hereafter, "the concomitant group"), whereas 28 patients received the 2 drugs sequentially (hereafter, "the sequential group"). The mean length of stay ($\pm$SD) for the concomitant group was 9.7 $\pm$ 16.4 days, compared with 9.1 $\pm$ 7.7 days for the sequential group ($P = .8$). The mean duration of colchicine therapy ($\pm$SD) for the concomitant group was 3.95 $\pm$ 4.6 days, compared with 2.8 $\pm$ 1.4 days for the sequential group ($P = .2$). The mean duration of the clarithromycin therapy ($\pm$SD) for the concomitant group was 5.5 $\pm$ 2.7 days, compared with 4.3 $\pm$ 2.3 days for the sequential group, with a statistically significant difference ($P = .04$). The baseline characteristics of the 116 patients and their outcomes are shown in figure 1.

The concomitant group had an overall mortality rate of 10.2% (9 of 88 patients), whereas the mortality rate among the sequential group was 3.6% (1 of 28 patients) (table 1). The demographic characteristics, clinical profiles, baseline investigative findings, and outcomes were not statistically different between the 2 groups. In the concomitant group, 9 patients (11.39%) developed pancytopenia (table 2). Comparison by univariate analysis showed that significantly more patients who developed pancytopenia had an ALT level $\geq$2 times the upper limit of normal ($P = .01$) than did patients without pancytopenia and that patients who developed pancytopenia had a significantly higher median total dose of colchicine ($P < .01$), higher median number of days of concomitant therapy ($P < .01$), and higher mortality rate ($P < .001$). Multivariate analysis showed that only a higher total dose of colchicine (relative risk [RR], 1.89; 95% CI, 1.23–2.89; $P = .04$) was independently associated with pancytopenia. Comparison by univariate analysis of the nonsurvivors and survivors within the concomitant group (table 3) showed that significantly more nonsurvivors had baseline renal impairment ($P < .01$) and developed pancytopenia during hospitalization ($P < .001$) and that nonsurvivors had a higher median total colchicine dose ($P < .001$) and a higher median number of days of overlapped therapy ($P < .001$). Multivariate analysis showed that longer overlapped therapy (RR, 2.16; 95% CI, 1.41–3.31; $P < .01$), the presence of baseline renal impairment (RR, 9.1; 95% CI, 1.75–47.06; $P < .001$), and the development of pancytopenia during hospitalization (RR, 23.4; 95% CI, 4.48–122.7; $P < .001$) were independently associated with death.

The clinical profiles of all patients with pancytopenia were tabulated in table 4. Their ages ranged from 55 to 92 years, with a ratio of men to women of 1:1. Eleven patients were admitted for community-acquired pneumonia, and 1 was admitted for acute gastroenteritis. The number of days of con-

Table 1. Comparison of patients who received concomitant therapy with clarithromycin and colchicine with patients who received sequential therapy.

Variable	Concomitant therapy group ($n = 88$)	Sequential therapy group ($n = 28$)	P
Age, mean years $\pm$ SD	73.9 $\pm$ 14.55	78.21 $\pm$ 11.15	.08
Ratio of men to women	1.26	0.65	.19
Fever at presentation[a]	55 (62.5)	11 (39.29)	.05
Baseline renal impairment[b]	29 (33)	8 (28.6)	.82
Baseline ALT level $\geq 2 \times$ ULN	0 (0)	4 (14.29)	.57
Diarrhea during hospitalization[d]	37 (42.05)	11 (39.29)	.83
Pancytopenia during hospitalization[e]	9 (10.2)	0 (0)	.11
Total dose of colchicine, median mg (IQR)	3.0 (1.63–4.5)	3.5 (2.63–5)	.08
Charlson index score, median (IQR)	1 (0–2)	2 (1–3.75)	.06
Death	9 (10.2)	1 (3.6)	.45

NOTE. Data are no. (%) of patients, unless otherwise indicated. ALT, alanine transaminase; IQR, interquartile range; ULN, upper limit of normal.

[a] Fever was defined as a body temperature of >38°C.

[b] Baseline renal impairment was defined as a creatinine level of >140 μmol/L.

[d] Diarrhea was defined as bowel opening at a frequency of $\geq$3 times daily.

[e] Pancytopenia was defined as a neutrophil count of $<2.0 \times 10^9$ cells/L, a hemoglobin level of <12 g/dL, and a platelet count of $<150 \times 10^9$ platelets/L.

Table 2. Comparison of patients in the concomitant-therapy group who developed pancytopenia with those who did not.

Analysis, variable	Patients with pancytopenia[a] (n = 9)	Patients without pancytopenia[a] (n = 79)	RR (95% CI) of developing pancytopenia	P
Univariate analysis				
Age, mean years ± SD	74.89 ± 10.22	74.54 ± 15.12	…	.95
Ratio of men to women	0.29	0.88	…	.29
Fever at presentation[b]	8 (88.89)	47 (59.49)	…	.08
Baseline renal impairment[c]	3 (33.3)	26 (32.91)	…	1
Baseline ALT level ⩾2 × ULN	6 (66.67)	3 (33.33)	…	.01
Diarrhea during hospitalization[d]	4 (44.4)	33 (41.77)	…	1
Administration of drugs with potential to cause pancytopenia	0 (0)	4 (5.1)	…	1
Total colchicine dose, median mg (IQR)	6 (3.5–9.8)	3 (1.5–4.5)	…	<.01
Duration of colchicine regimen, median days (IQR)	4 (2.5–7)	3 (2–4)	…	.06
Duration of clarithromycin regimen, median days (IQR)	3 (7–10)	5 (3–7)	…	.31
Length of overlapped clarithromycin and colchicine therapy, median days (IQR)	5 (2.5–7)	2 (0–3)	…	<.01
Charlson index score, median (IQR)	4 (0.5–4.5)	1 (0–2)	…	.11
Death	5 (55.6)	4 (5.06)	…	<.001
Multivariate analysis				
Median total colchicine dose	…	…	1.89 (1.23–2.89)	.04

NOTE. Data are no. (%) of patients, unless otherwise indicated. ALT, alanine transaminase; IQR, interquartile range; RR, relative risk; ULN, upper limit of normal.

[a] Pancytopenia was defined as a neutrophil count of $<2.0 \times 10^9$ cells/L, a hemoglobin level of <12 g/dL, and a platelet count of $<150 \times 10^9$ platelets/L.

[b] Fever was defined as a body temperature of >38°C.

[c] Baseline renal impairment was defined as a creatinine level of >140 μmol/L.

[d] Diarrhea was defined as bowel opening at a frequency of ⩾3 times daily.

comitant administration of clarithromycin and colchicine ranged from 1 to 10 days, with a median of 3 days. For the 7 patients with pancytopenia, the hematological abnormalities were most severe at 9–18 days (median, 10 days) after the first dose of concomitant administration. The terminal event for 7 patients was pneumonia, but 2 of those patients had acute renal failure with preexisting chronic renal failure (i.e., "acute-on-chronic renal failure"), 1 had congestive heart failure, and 1 had multiple organ failure. Biopsy of a bone marrow specimen obtained from 1 of the patients who died showed moderately hypocellular marrow with left-shifted granulopoieisis and no abnormal infiltration. Postmortem examination of another patient showed agranulocytosis and massive hepatic necrosis. None of these 9 patients were given other drugs that have the potential to cause pancytopenia either by themselves or through drug-drug interactions. Microbiological findings are summarized in table 5.

DISCUSSION

Macrolides have long been known to be a substrate, in addition to being a reversible inhibitor, of the cytochrome P450 enzyme CYP3A4 [5–7]. Recently, they have also been found to be important inhibitors of the P-glycoprotein transporter system [8–11]. These properties lead to important effects of drug interactions due to either increased macrolide levels or increased levels of other concomitantly administered drugs as a result of competition for the same pathway of metabolism or excretion. A recent report described the development of serious cardiac arrhythmias associated with concomitant use of erythromycin and various inhibitors of CYP3A4 [12]. In addition, potentially fatal drug interactions with drugs such as clozapine, disopyramide, and cisapride that are the result of their decreased metabolism due to inhibition of CYP3A4 by macrolides, are also commonly reported in the literature [13–15]. Colchicine, an effective and commonly prescribed drug for the treatment of gout and familial Mediterranean fever, is metabolized via the enzyme CYP3A4, in addition to being a substrate of the P-glycoprotein [16–18]. Despite the expected drug interactions between macrolides and colchicine, only 4 cases of serious interaction were found in our review of the literature (table 6) [19–22]. Except for 1 case of deliberate ingestion of a megadose of colchicine (40 mg bolus) in a suicide attempt [22], the

patients received a maintenance dosage of colchicine (range, 1–1.5 mg/day) for treatment of familial Mediterranean fever [19–21]. It is noteworthy that those 3 patients had chronic renal insufficiency. All 3 of them developed features of colchicine toxicity, manifesting as gastrointestinal symptoms (abdominal pain, vomiting, and diarrhea), fever, and pancytopenia, shortly after concomitant administration of macrolides (median time to presentation, 8 days; range, 7–19 days) for management of a variety of conditions. The duration of concomitant therapy ranged from 4 to 14 days (median, 7 days). In a patient who died as a result of multiorgan failure, bone marrow examination revealed the presence of bone marrow hypocellularity [20]. The colchicine level was markedly elevated in at least 1 of the patients (22 ng/mL) [21].

In our retrospective study, comparison was made between patients who received concomitant therapy and patients who received sequential therapy (table 1). Despite the fact that a higher percentage of patients in the concomitant group than in the sequential group developed pancytopenia (10.2% vs. 0%) and that there was a higher mortality rate in the concomitant group than in the sequential group (10.2% vs. 3.6%), the differences were not statistically significant. One possible reason is the relatively small sample size, which is a limitation of the study. We therefore compared the patients in the concomitant group who developed pancytopenia with those who did not and also compared the survivors and the nonsurvivors in the concomitant group. Longer overlapped therapy, baseline renal impairment, and development of pancytopenia were independently associated with mortality. This confirmed the findings of the case reports mentioned above. In contrast to the patients described in the literature, 11 of our 12 patients who had adverse outcomes were admitted for community-acquired pneumonia and were initially prescribed macrolide therapy (table 4 and figure 1). During their hospital stay, these patients developed acute gouty attack secondary to various conditions and, in addition, were administered colchicine. Bone marrow examination for 2 of the patients with pancytopenia revealed hypocellular marrow, similar to the findings for the cases described previously. Despite the fact that none of these patients had their serum colchicine levels measured, the clinical features and disease progressions were, in retrospect, strongly suggestive of colchicine toxicity [23–25]. Yet none of the physicians in charge of the aforementioned patients suspected this condition while the patients were being cared for in the hospital. It was

Table 3. Comparison between patients in the concomitant-therapy group who survived and those who died.

Analysis, variable	Nonsurvivors (n = 9)	Survivors (n = 79)	RR (95% CI) of death	P
Univariate analysis				
Age, mean years ± SD	78.56 ± 11.53	74.13 ± 14.94	…	.39
Ratio of men to women	1.25	0.76	…	.5
Fever at presentation[a]	8 (88.89)	47 (59.5)	…	.15
Baseline renal impairment[b]	7 (77.78)	22 (27.85)	…	<.01
Baseline ALT level ⩾2 × ULN	3 (33.33)	22 (27.85)	…	.71
Diarrhea during hospitalization[c]	5 (55.56)	32 (40.5)	…	.48
Pancytopenia during hospitalization[d]	5 (55.56)	4 (5.1)	…	<.001
Administration of drugs with potential fatal interaction with macrolides and/or colchicine	0 (0)	4 (5.06)	…	1
Total colchicine dose, median mg (IQR)	6 (4.75–7.25)	3 (1.5–4.5)	…	.001
Duration of colchicine regimen, median days (IQR)	4 (3–6)	3 (2–4)	…	.13
Duration of clarithromycin regimen, median days (IQR)	7 (3–10)	5 (3–7)	…	.19
Length of overlapped clarithromycin and colchicine therapy, median days (IQR)	6 (4–7)	2 (1–3)	…	<.001
Charlson index score, median (IQR)	2.0 (0.5–4)	1 (0–2)	…	.12
Multivariate analysis				
Median length of overlapped clarithromycin and colchicine therapy	…	…	2.16 (1.41–3.31)	<.01
Baseline renal impairment[b]	…	…	9.1 (1.75–47.06)	<.001
Pancytopenia during hospitalization[d]	…	…	23.4 (4.48–122.7)	<.001

NOTE. Data are no. (%) of patients, unless otherwise specified. ALT, alanine transaminase; IQR, interquartile range; RR, relative risk; ULN, upper limit of normal.

[a] Fever was defined as a body temperature of >38°C.

[b] Baseline renal impairment was defined as a creatinine level of >140 μmol/L.

[c] Diarrhea was defined as bowel opening at a frequency of ⩾3 times daily.

[d] Pancytopenia was defined as a neutrophil count of $<2.0 \times 10^9$ cells/L, a hemoglobin level of <12 g/dL, and a platelet count of $<150 \times 10^9$ platelets/L.

Table 4. Clinical profile of the 12 patients who had adverse outcomes due to interaction between clarithromycin and colchicine.

Patient[a]	Age in years, sex	Underlying disease or condition	Diagnosis at admission to hospital	Oral clarithromycin dosage	Complications during hospitalization	Oral colchicine dosage	Duration of concomitant therapy, days	Time from day 1 of concomitant therapy to CBP nadir, days	Colchcine adverse effects	Outcome
1	74, M	DM nephropathy, hyperlipidemia	CHF, pneumonia	250 mg b.i.d. for 3 days	AOC renal failure, gout	0.5 mg t.i.d. for 3 days	3	12	Nausea and vomiting, pancytopenia	AOC renal failure, pneumonia; patient died
2	81, M	BPH, DM nephropathy, HT, left cataract, prior MI	CHF, pneumonia	250 mg b.i.d. for 5 days	Gout	0.5 mg t.i.d. for 3 days	4	11	Pancytopenia	CHF, pneumonia; patient died
3	68, M	DVT, gout, HT, prior PTB	Pneumonia	500 mg b.i.d. for 10 days	Gout	0.5 mg t.i.d. for 8 days	7	10	Diarrhea, nausea and vomiting, pancytopenia	Pneumonia; patient died; finding of hypocellular bone marrow
4	88, F	HT, IHD	Pneumonia	500 mg b.i.d. for 14 days	Gout, hepatic dysfunction	0.5 mg t.i.d. for 3 days	3	9	Pancytopenia	Patient readmitted 6 days after discharge for pneumonia; patient died
5	55, F	DM nephropathy,[b] Turner syndrome	Gastroenteritis, pneumonia	250 mg b.i.d. for 3 days	Gout	0.5 mg b.i.d. for 3 days	3	10	Nausea and vomiting, pancytopenia	Aspiration pneumonia; patient died; finding of hypocellular bone marrow
6	80, M	HT	Pneumonia	500 mg b.i.d. for 7 days	Gout	0.5 mg b.i.d. for 10 days	4	10	Diarrhea, pancytopenia	Pneumonia resolved
7	70, M	AAA, gastric ulcer, gout, HT	Pneumonia	500 mg b.i.d. for 10 days	Gout	0.5 mg b.i.d. for 20 days	10	18	Diarrhea, nausea and vomiting, pancytopenia	Pneumonia resolved
8	82, F	None	Pneumonia	500 mg b.i.d. for 5 days	Gout, ischio-rectal abscess, respiratory failure	0.5 mg t.i.d. for 4 days	0	NA	Diarrhea, nausea and vomiting	Pneumonia; patient died
9	87, F	CHF, COAD, CRF, HT	Pneumonia	500 mg b.i.d. for 8 days	Gout	0.5 mg t.i.d. for 3 days	3	NA	Diarrhea, dyspnea, fluid retention	CHF; patient died
10	78, F	CRF, hypothyroidism, OA knees	Pneumonia	500 mg b.i.d. for 10 days	Gout	0.5 mg t.i.d. for 4 days	5	NA	Diarrhea	Patient readmitted 2 days after discharge with diarrhea, dehydration, and multiorgan failure; patient died
11	92, M	Cervical spondylolitheisis, CRF, HT, IHD	Pneumonia	500 mg b.i.d. for 7 days	Gout	0.5 mg t.i.d. for 3 days	3	NA	Abdominal pain, diarrhea, dyspnea	AOC renal failure; patient died
12	84, F	DM nephropathy, IHD, prior MI	Pneumonia	250 mg b.i.d. for 3 days	Gout	0.5 mg t.i.d. for 1 day	1	NA	Fluid retention	AOC renal failure; patient died

NOTE. AAA, abdominal aortic aneurysm; AOC renal failure, acute renal failure in a patient with chronic renal failure (i.e., "acute-on-chronic renal failure"); BPH, benign prostatic hypertrophy; CBP, complete blood picture; CHF, congestive heart failure; COAD, chronic obstructive airway disease; CRF, chronic renal failure; DM, diabetes mellitus; DVT, deep venous thrombosis; HT, hypertension; IHD, ischemic heart disease; MI, myocardial infarction; NA, not applicable; OA, osteoarthritis; PTB, pulmonary tuberculosis.

[a] Patients 3 and 5 were reported by Cheng et al. [3].

[b] Patient received continuous abdominal peritoneal dialysis.

recently reported that the adjusted rate of sudden death from cardiac causes was 5 times as high (incidence rate ratio, 5.35; 95% CI, 1.72–16.64; $P = .004$) among those who used CYP3A inhibitors and erythromycin concurrently than among those who did not [12]. However, our study demonstrated that, in patients who received concomitant therapy with colchicine and clarithromycin and who developed pancytopenia, the risk of death was increased 25-fold (RR, 25; 95% CI, 5.19–125.3; $P < .001$).

The metabolism and deposition of colchicine have been reviewed extensively [26–28]. In brief, after absorption from the small bowel, the drug underwent substantial presystemic metabolism, leading to a bioavailablity of only 25%–50%. Thirty percent of the absorbed colchicine was distributed to tissues, including the gastrointestinal tract, muscle, heart, and spleen, and to WBCs [29]. Colchicine was particularly concentrated in WBCs, which might have led to subsequent marrow suppression in the case of overdose. Twenty percent of the colchicine was excreted in the urine as unchanged drug, whereas the other 50% was metabolized by the cytochrome P450 system—mainly involving the CYP3A4 system in the liver—by deacetylation, demethylation, and glucuronidation [30]. Clarithromycin and other macrolides could potentially alter the absorption, metabolism, and excretion of colchicine via different mechanisms [31–37]. Clarithromycin can increase oral bioavailability by increasing the absorption and presystemic metabolism of colchicine through inhibition of the P-glycoprotein in the enterocytes. It can decrease hepatic metabolism and clearance of colchicine by acting as a slow reversible inhibitor of the cytochrome P450 system in the liver. In addition, clarithromycin could impair the excretion of colchicine via the hepatic metabolism and renal excretion—again, by interfering with the P-glycoprotein. Under normal circumstances, the excretion of colchicine in the urine could increase to compensate for reduced liver metabolism in patients with liver disease or to counteract the effects of the administration of drugs that interact with the cytochrome P450 system [38]. However, this mechanism would be hampered if the patients already had concomitant renal insufficiency, leading to an accumulation of colchicine and the subsequent fatal outcomes. Colchicine toxicity can be divided into 3 sequential stages [39]. The first stage occurs during the first 24 h after ingestion and is dominated by the aforementioned gastrointestinal symptoms. The second stage (24–72 h after ingestion) is dominated by multiorgan failure. This includes bone marrow failure, renal failure, adult respiratory distress syndrome, arrhythmias, disseminated intravascular coagulation, and neuromuscular disturbances. Recovery of bone marrow, with rebound leukocytosis; resolution of organ system derangement; and development of alopecia characterize the third phase, if the patient survives the toxicity. Treatment is mainly supportive, with daily subcutaneous in-

Table 5. Summary of the microbiological findings.

Clinical test, type of organism	No. of isolates
Blood culture	
Coagulase-negative staphylococci	1
Escherichia coli	1
Methicillin-susceptible *Staphylococci aureus*	1
Proteus vulgaris	1
Streptococcus agalactiae	1
Respiratory culture	
Acinetobacter baumanii	1
Acinetobacter species	1
Candida albicans	6
Candida species	3
Coagulase-negative staphylococci	2
Enterobacter species	2
Enterococcus species	1
Haemophilis influenzae	1
Klebsiella species	2
Methicillin-resistant *S. aureus*	3
Mycobacterium tuberculosis	3
Pseudomonas aeruginosa	2
Pseudomonas species	2
Stenotrophomonas maltophilia	1
Streptococcus pneumoniae	1
Urine culture	
C. albicans	2
Candida glabrata	3
Candida species	5
Enterobacter species	1
Enterococcus species	1
E. coli	7
Proteus species	2
S. agalactiae	1
Trichosporon species	1
Stool culture	
Clostridium difficile	1
Enterococcus gallinarum	1
Miscellaneous cultures[a]	
A. baumanii	1
C. albicans	3
Candida species	2
Citrobacter freundii	1
Coagulase-negative staphylococci	6
Enterobacter species	1
Enterococcus species	3
E. coli	1
Flavobacterium species	1
Klebsiella species	2
S. agalactiae	1
Immunofluorescence tests for respiratory viruses	
Influenza A	1

[a] Wound swab specimen, catheter tip, and joint or other normally sterile body fluid.

Table 6. Clinical profile of patients reported in the literature who had an adverse outcome due to the interaction between colchicine and clarithromycin, erythromycin, or josamycin.

Patient	Age in years, sex	Underlying disease or condition	Indication for colchicine	Interacting drug, dosage	Indication for interacting drug	Colchicine dosage	Duration of overlapping therapy, days	Symptoms presented[a]	Major complications	Colchicine level	Outcome, remarks
1	29, F	Amyloidosis of kidneys, liver, and GI; CRF[b]	Familial Mediterranean fever	Oral erythromycin, 2 g/day for 14 days	Acute bronchitis	1 mg/day	14	Diffuse abdominal pain, fever, recurrent diarrhea and vomiting, myalgia, lower-limb parasthesia (16)	Alopecia, convulsion, hypoglycemia, liver impairment, pancytopenia, paralytic ileus, psychosis	Elevated (22 ng/mL)	Patient recovered with supportive treatment; colchicine therapy permanently stopped
2	41, M	Chronic alcoholism, chronic bronchitis, gout	Suicide attempt	Oral josamycin, 10 g bolus	Suicide attempt	40 mg bolus (~0.55 mg/kg)	1	Vomiting (1)	Acute renal failure, cardiogenic shock, DIC, leucocytosis, liver impairment, metabolic acidosis	Elevated (12.22 ng/mL)	Colchicine level remained elevated for 3 days; patient died from multiorgan failure
3	67, M	ESRF[c]	AA amyloidosis	Oral clarithromycin, 1 g/day for 4 days	Acute URI	1 mg/day	4	Fever, diarrhea, myalgia, abdominal pain (4)	Liver impairment, pancytopenia	NA	Patient died from multiorgan failure; bone marrow was hypocellular
4	76, M	CRF, HT	Familial Mediterranean fever	Oral clarithromycin, 1 g/day for 7 days	*Helicobacter pylori*–associated gastritis	1.5 mg/day	7	Fever, abdominal pain, bloody diarrhea, vomiting (4)	Alopecia, liver and renal impairment, metabolic acidosis pancytopenia	NA	Patient recovered with supportive treatment; colchicine therapy was resumed after acute episode

NOTE. AA, amyloid A; CRF, chronic renal failure; DIC, disseminated intravascular coagulation; ESRF, end-stage renal failure; GI, gastrointestinal tract; HT, hypertension; NA, not applicable; URI, upper respiratory infection.

[a] The number in parentheses indicates the number of days after initiation of the second drug that clinical presentation of the patients

[b] Patient received hemodialysis.

[c] Patient received continuous abdominal peritoneal dialysis.

jections of granulocyte-colony stimulating factor (G-CSF) during severe leukopenia. Anecdotal experience with the use of colchicine-specific Fab fragments for treatment of severe colchicine toxicity has also been reported, but these antibodies are not readily available [40].

In our cohort, 6 of 10 patients died as a result of pneumonia, and 5 of them developed pancytopenia. G-CSF (300 μg) was administered subcutaneously to 1 of the 5 patients with pancytopenia. The other 4 patients reportedly died as a result of acute chronic renal failure (2 patients), congestive heart failure (1 patient), and multiorgan failure (1 patient). These deaths could be explained by the direct toxic effect of colchicine on the various organs, including the liver, kidney, and bone marrow, especially for patients who had chronic renal insufficiency before hospital admission. In our hospital, clarithromycin is the most commonly prescribed macrolide, because it has better gastrointestinal tolerance than erythromycin and because it was introduced earlier into the local market than azithromycin was. In conclusion, clarithromycin and colchicine should not be prescribed concomitantly, especially for patients who have chronic renal insufficiency. It is important to alert the pharmacy service to intervene on dual prescriptions. Other strong inhibitors of CYP3A4 should similarly be avoided. If a macrolide must be prescribed with colchicine, azithromycin should be considered, because it is mainly excreted unchanged in the bile and has no effect on cytochrome P450 metabolism and the P-glycoprotein transporter system [41, 42].

Acknowledgments

Potential conflicts of interest. All authors: no conflicts.

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