

Risk Factors for Arthralgias or Myalgias Associated with Quinupristin-Dalfopristin Therapy

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Study Objective. To evaluate risk factors for the development of arthralgias or myalgias associated with quinupristin-dalfopristin.

Design. Retrospective chart review and case-control analysis.

Setting. An 850-bed tertiary care medical center.

Patients. All adult and pediatric patients who had received quinupristin-dalfopristin through either a compassionate-use protocol (February 1996–October 1999) or in the year after quinupristin-dalfopristin was added to the hospital formulary (November 1999–October 2000) were included in this study. Case patients were those who developed arthralgias or myalgias while receiving quinupristin-dalfopristin therapy; control patients were those who received quinupristin-dalfopristin but did not develop arthralgias or myalgias.

Intervention. Medical records, pharmacy dispensing information, and microbiology data were reviewed by a physician and a pharmacist, both of whom specialized in infectious diseases. Presence or absence of arthralgias or myalgias was the primary outcome assessed.

Measurements and Main Results. Quinupristin-dalfopristin was administered to 68 patients during the period defined by the study. Arthralgias and myalgias could not be assessed in 18 of the 68 patients because they were sedated and paralyzed, or they were young children who could not communicate the presence of pain. Univariate analysis demonstrated that significant risk factors for arthralgias or myalgias associated with quinupristin-dalfopristin were female sex, chronic liver disease, receipt of liver transplant, elevated bilirubin level at baseline, major surgery, and receipt of either mycophenolate or cyclosporine. Multivariate analysis demonstrated a strong association with chronic liver disease, receipt of liver transplant, elevated bilirubin level at baseline, and receipt of either cyclosporine or mycophenolate. Of 50 evaluable patients receiving quinupristin-dalfopristin, 25 had pain that may have been associated with this antimicrobial agent.

Conclusion. The mechanism for development of arthralgias or myalgias associated with quinupristin-dalfopristin remains unknown, but these adverse events are more likely to occur in patients with chronic liver disease and those who have received a liver transplant or are receiving cyclosporine or mycophenolate.

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Quinupristin-dalfopristin is a streptogramin agent with a broad spectrum of activity against many resistant gram-positive organisms, such as

vancomycin-resistant *Enterococcus faecium* and methicillin-resistant *Staphylococcus aureus*.^{1–3} During initial treatment trials with quinupristin-

dalfopristin, arthralgias or myalgias were not reported in some studies^{4, 5} and were reported in approximately 10% of patients in others.⁶⁻⁸ However, several subsequent reports demonstrated a rate of occurrence of these adverse effects of 33-47%.⁹⁻¹¹

In our medical center it appeared that a significant proportion of patients receiving quinupristin-dalfopristin experienced arthralgias or myalgias, and often required therapy with intravenous analgesics or discontinuation of quinupristin-dalfopristin. We reviewed our experience to assess the proportion of patients who developed these adverse effects and to determine if specific underlying illnesses or concurrent drugs contributed to their occurrence.

Methods

Setting and Patients

The University of Michigan Hospitals and Health Centers comprise an 850-bed tertiary care center with solid organ and bone marrow transplant services. All adult and pediatric patients who had received quinupristin-dalfopristin either through a compassionate-use protocol (February 1996-October 1999) or in the year after quinupristin-dalfopristin was added to the hospital formulary (November 1999-October 2000) were included in our study. Case patients were those who developed arthralgias or myalgias while receiving quinupristin-dalfopristin; control patients were those who received quinupristin-dalfopristin but did not develop arthralgias or myalgias. Only patients with complete medical records were assessed. Approval from the institutional review board was obtained for this retrospective chart review.

Data Collection

Medical records, pharmacy dispensing information, and microbiology data were reviewed. The dates, dosages, and durations of

quinupristin-dalfopristin therapy were noted. Relevant clinical information, concomitant drugs, and laboratory data were recorded. Medical conditions of particular interest were chronic liver or kidney disease, hematologic malignancies, receipt of a solid organ or bone marrow transplant, dialysis, hospital stay in intensive care unit, mechanical ventilation, and recent surgery. Concurrent drugs were reviewed for potential drug interactions. Dosages of concurrent drugs metabolized by cytochrome P450 (CYP) 3A4 were recorded.

Charts were reviewed by a physician and a pharmacist, both of whom specialized in infectious diseases. Presence or absence of arthralgias or myalgias was the primary outcome assessed. Presence of pain was ascertained from progress notes of medical and nursing staff; patients had to have communicated to health care personnel that they experienced muscle or joint pain. Arthralgias or myalgias were considered associated with quinupristin-dalfopristin if they were temporally related to quinupristin-dalfopristin therapy and no other cause was identified.

Statistical Analysis

Potential risk factors for arthralgias or myalgias during quinupristin-dalfopristin therapy were identified by means of univariate analysis. Either the χ^2 or the two-tailed Fisher's exact test was used for categorical variables. Continuous variables were compared using the Student *t* test or the Mann-Whitney *U* test. Variables that were significant in the univariate analysis were further tested by logistic regression using the forward conditional method; a *p* value less than 0.05 was considered statistically significant. Statistical analysis was performed using SAS 6.0 and Statview 5.0.1 (SAS Institute, Cary, NC).

Results

Complete medical records were available for 68 patients; of those, the occurrence of arthralgias and myalgias could not be assessed in 18 (26.5%) because the patients were intubated, sedated, and paralyzed, or they were young children who could not communicate the presence of pain. Mean age of the 50 evaluable patients was 48.4 \pm 14.4 years; only two were younger than 18 years. Two children received quinupristin-dalfopristin; one, an infant, was treated on three separate occasions, for a total of 57 days of therapy. Because he was only 3 months old at the start of

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Table 1. Univariate Analysis Results of Patients with and without Arthralgias or Myalgias Associated with Quinupristin-Dalfopristin Therapy

Variable	No. of Patients with Arthralgias or Myalgias (n=25)	No. of Patients without Arthralgias or Myalgias (n=25)	p Value	Odds Ratio (95% confidence interval)
Age, yrs (mean \pm SD)	49.3 \pm 13.7	47.4 \pm 15.3	0.71	2.1 (0.6–9.5)
M/F	10/15	17/8	0.047	3.2 (1.0–10.1)
Duration of quinupristin-dalfopristin therapy, days (mean \pm SD)	15.9 \pm 10.8	12.8 \pm 14.2	0.57	1.8 (0.5–6.8)
Medical history				
Chronic liver disease	13	4	0.01	7.9 (1.8–35.2)
Liver transplantation	9	2	0.02	6.5 (1.2–34.0)
Other major surgery	19	10	0.01	4.8 (1.4–16.1)
Chronic renal failure	10	8	0.56	1.4 (0.4–4.5)
Dialysis	13	9	0.25	1.9 (0.6–6.0)
Bone marrow transplantation	3	7	0.16	0.4 (0.1–1.6)
Hematologic malignancy	5	9	0.21	0.4 (0.1–1.6)
Had hospital stay in intensive care unit	15	9	0.09	2.7 (1.9–8.4)
Elevated levels at baseline				
Aspartate and alanine aminotransferases	6	2	0.07	4.6 (0.8–26.5)
Alkaline phosphatase	5	4	0.06	1.5 (0.3–6.3)
Bilirubin	12	5	0.03	3.7 (1.0–13.0)
Elevated levels during therapy				
Aspartate and alanine aminotransferases	6	2	0.07	2.6 (1.7–9.3)
Alkaline phosphatase	9	3	0.35	2.1 (0.4–9.9)
Bilirubin	14	10	0.23	2.1 (0.6–7.0)
Mechanical ventilation required	12	9	0.39	1.6 (0.5–5.1)
Concomitant drug therapy				
Mycophenolate	10	3	0.04	4.4 (1.0–18.6)
Cyclosporine	10	4	0.05	3.5 (1.9–13.3)
Tacrolimus	5	6	0.73	0.8 (0.2–3.0)
Fluconazole	15	13	0.57	1.4 (0.5–4.3)
Omeprazole	11	9	0.56	1.4 (0.5–4.4)
Corticosteroids	14	10	0.26	1.9 (0.6–5.9)
Conjugated estrogens	5	3	0.44	1.8 (0.4–8.7)

therapy, it was impossible to discern whether he experienced arthralgias or myalgias during therapy. The second child received quinupristin-dalfopristin for 20 days. Although 5 years old, this child was noncommunicative. Thus, both pediatric patients were placed in the unassessable group.

Twenty-five (50%) of the 50 patients experienced arthralgias or myalgias. We could not determine from the medical records of most patients whether the symptoms were primarily muscular or articular; complaints were generally of diffuse aching and pain that was not localized to joints or muscle groups. All patients were given quinupristin-dalfopristin 7.5 mg/kg as an intravenous infusion every 8 hours. The dosage for two adult patients was decreased later to 5 mg/kg every 8 hours in an effort to reduce their arthralgias and myalgias.

Onset of symptoms occurred an average of 3.1

\pm 2 days (range 1–5 days) after therapy was started. For the 13 patients who completed therapy despite having arthralgias or myalgias, these symptoms resolved a mean of 4.2 \pm 2 days after quinupristin-dalfopristin was stopped. Symptoms improved in the two patients whose quinupristin-dalfopristin dosage had been decreased, and two patients refused further infusions because of the severity of their symptoms. Of the 25 patients who developed arthralgias or myalgias, 12 died as a result of underlying disease processes; of the 25 who had no arthralgias or myalgias, nine died.

Univariate analysis showed the following significant risk factors for arthralgias or myalgias associated with quinupristin-dalfopristin: female sex, chronic liver disease, receipt of liver transplant, major surgery, elevated bilirubin level at baseline, and receipt of either mycophenolate and cyclosporine (Table 1). A multivariate

Table 2. Multivariate Analysis Results of Patients with and without Arthralgias or Myalgias Associated with Quinupristin-Dalfopristin Therapy

Risk Factor	No. of Patients with Arthralgias or Myalgias (n=25)	No. of Patients without Arthralgias or Myalgias (n=25)	p Value	Odds Ratio (95% confidence interval)
Chronic liver disease	13	4	0.03	10.4 (3.5–21.2)
Liver transplantation	9	2	0.04	8.8 (1.4–28.4)
Elevated bilirubin level at baseline	9	5	0.01	9.6 (3.9–12.3)
Mycophenolate	9	2	0.03	3.2 (2.3–41.1)
Cyclosporine	10	4	0.04	3.8 (1.6–14.6)

logistic regression model demonstrated that chronic liver disease, receipt of liver transplant, elevated bilirubin level at baseline, and receipt of either mycophenolate or cyclosporine remained independently associated with development of myalgias and arthralgias during quinupristin-dalfopristin therapy (Table 2).

Discussion

Quinupristin is converted to two conjugated metabolites and dalfopristin to one nonconjugated metabolite.² We were concerned that some patients could exhibit higher plasma concentrations of quinupristin, dalfopristin, or their metabolites. Because the frequency of arthralgias and myalgias may be higher in these patient populations, we felt it important to look for this possible association. Although single-dose (7.5 mg/kg) studies¹² suggest that age, sex, and obesity appear to have no clinically significant effects on the pharmacokinetics of quinupristin-dalfopristin, limited pharmacokinetic data suggest that plasma concentrations of quinupristin and dalfopristin may be slightly impaired in patients with severe chronic renal failure.¹² However, no accumulation of the parent drugs or their metabolites was evident in patients with end-stage renal disease who received an infusion of quinupristin-dalfopristin 7.5 mg/kg twice/day.

In patients with cirrhosis, mean values for area under the curve (AUC) of quinupristin and dalfopristin in combination with their respective metabolites were approximately 2.8 and 1.5 times higher than in healthy volunteers. Also, patients with high bilirubin levels (> 3 times normal) have experienced a marked increase in exposure to quinupristin metabolites (up to a 4-fold increase in AUC) because of delayed elimination of the drug.¹²

Quinupristin-dalfopristin does not significantly inhibit the human CYP isoenzymes 1A2, 2A6,

2C9, 2C19, 2D6, or 2E1.¹² However, although quinupristin-dalfopristin is not metabolized by CYP3A4, it inhibits the biotransformation rate of specific CYP3A4 substrates, such as nifedipine, midazolam, terfenadine, and cyclosporine. Thus, concurrent drugs chosen for evaluation in this study were primarily known or suspected substrates, inhibitors, and inducers of this enzyme.

We also evaluated drugs such as digoxin that are substrates, inhibitors, or inducers of P-glycoprotein, and commonly used agents that interact (through other CYP pathways) with numerous drugs. Of these other agents, the most commonly administered were digoxin and omeprazole. Administration of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors was monitored specifically because of their metabolism by the CYP pathway and the arthralgias and myalgias observed with elevated plasma concentrations of these agents. No patients in our study received these agents.

Myalgias or arthralgias were significant adverse events among patients receiving quinupristin-dalfopristin at our medical center. The 50% occurrence rate is higher than that observed in other reports, which noted these symptoms in 0–10% of patients receiving quinupristin-dalfopristin,^{4–8} but is similar to that noted in other series.^{9–11} In one report, 47% of 32 patients experienced arthralgias or myalgias related to quinupristin-dalfopristin, and 60% of the group with these adverse effects had received a liver transplant, versus 36% of those without symptoms.⁹ Perhaps because of the small number of patients studied, significant risk factors for development of arthralgias or myalgias (e.g., chronic liver disease, receipt of liver transplant, or elevated bilirubin level) could not be established.

A study with a group of patients similar to our

population, most of whom had received a liver transplant, reported a 33% frequency of arthralgias or myalgias. The results also showed that the frequency was dose related and did not occur in patients who had received a lower dosage of 5 mg/kg every 8 hours.¹¹ Another study noted a 36% frequency of arthralgias or myalgias associated with quinupristin-dalfopristin in 56 patients with cancer, most of whom had leukemia.¹⁰ None of these studies assessed the effects of concomitant drugs on development of arthralgias or myalgias.

The etiology of arthralgias or myalgias related to quinupristin-dalfopristin remains unknown. We found a strong association between the occurrence of arthralgias or myalgias and liver disease or liver transplantation. It is tempting to speculate that these effects could be related to increased levels of quinupristin-dalfopristin or its metabolites that accumulate with hepatic dysfunction. Decreasing the dosage might diminish the risk for development of arthralgias or myalgias.¹¹ Symptoms improved quickly in the two patients whose dosage was decreased in our study.

We anticipated that inhibitors or competitors of the metabolism of quinupristin-dalfopristin or its metabolites by CYP3A4 might result in elevated drug concentrations of quinupristin-dalfopristin or its metabolites. However, only two drugs—mycophenolate and cyclosporine—were associated with arthralgias or myalgias, and mycophenolate is not metabolized through the CYP3A4 route. Mycophenolate is metabolized completely to mycophenolic acid (the active form of mycophenolate), which subsequently is metabolized to mycophenolic acid glucuronide by hepatic glucuronosyl transferase.¹³

Although theoretical, competition for metabolism by hepatic glucuronosyl transferase could result in altered concentrations of quinupristin or dalfopristin; however, no data support such an interaction. Despite the similarity in routes of metabolism of cyclosporine and tacrolimus, we found no association between tacrolimus therapy and development of arthralgias or myalgias. Our data suggest that inhibition of metabolism by CYP3A4 leading to accumulation of quinupristin-dalfopristin metabolites is probably not the primary mechanism of development of arthralgias or myalgias.

Physicians' notes for several of our patients made no mention of pain, whereas nurses' notes clearly reported pain with movement. In these

instances, the primary team caring for the patient did not associate the pain noted by the nurses with quinupristin-dalfopristin. Caregivers should be aware that quinupristin-dalfopristin causes arthralgias and myalgias, and that these adverse effects appear to be more common in patients who have underlying hepatic disease or are receiving cyclosporine or mycophenolate.

Conclusion

Of 50 evaluable patients receiving quinupristin-dalfopristin, 25 experienced pain that may have been associated with this antimicrobial agent. Multivariate and univariate analysis demonstrated a strong association between pain and quinupristin-dalfopristin therapy in patients with chronic liver disease, receipt of a liver transplant, elevated bilirubin level at baseline, and receipt of either cyclosporine or mycophenolate. The mechanism of development of arthralgias or myalgias associated with quinupristin-dalfopristin remains unknown, but these adverse effects are more likely to occur in patients with chronic liver disease and those who have undergone liver transplantation or are receiving cyclosporine or mycophenolate.

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