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Successful administration of quinupristin/dalfopristin in the outpatient setting

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Intravenous administration of quinupristin/dalfopristin outside the hospital setting has not been reported previously. We describe 37 outpatients receiving quinupristin/dalfopristin iv for infections including osteomyelitis, bacteraemia, abscesses and cellulitis. The most frequent aetiological pathogens found were *Enterococcus faecium*, *Staphylococcus aureus* and coagulase-negative staphylococci. Patients received an average of 9 days therapy as inpatients and 22 days as outpatients. Quinupristin/dalfopristin was administered using various access devices, most commonly peripherally inserted central catheters and tunnelled central catheters. The bacteriological and clinical success rates were both 89.2%. Five patients were readmitted to hospital; one patient developed catheter-related bacteraemia. The most frequently reported non-venous adverse events were nausea (18.9% of patients), myalgia (18.9%) and arthralgia (13.5%). Sixteen patients experienced venous access-related events, most commonly infusion pain, oedema and phlebitis. In this group of patients, for those who had difficult-to-treat infections, intravenous quinupristin/dalfopristin therapy was generally effective and safe outside the hospital setting.

Introduction

More than 20 years ago, clinicians began to administer iv antimicrobial therapy outside the hospital setting. This approach is now standard in the USA for medically stable patients who require a prolonged course of antibiotics.[1] Although patients' medical conditions have become more complex in recent years, with additional challenges posed by the increasing prevalence of resistant bacterial pathogens, early hospital discharge remains not only economically desirable, but also generally preferred by the patient given the associated benefits to quality of life.

Emergence of multiple-drug resistance among Gram-positive pathogens has encouraged the development of new antibiotics. Quinupristin/dalfopristin (Synercid, Aventis Pharmaceuticals, Bridgewater, NJ, USA) is a 30:70 mixture of quinupristin (a group B streptogramin) and dalfopristin (a group A streptogramin), which acts by inhibiting bacterial protein synthesis of most Gram-positive organisms.[2,3] Group A streptogramins block an early stage of protein elongation and group B streptogramins cause premature detachment of incomplete polypeptide chains later in protein synthesis. Quinupristin and dalfopristin act synergically to give up to a 100-fold increase in activity compared with either component alone.[4]

Phase I studies of quinupristin/dalfopristin demonstrated that peripheral venous administration is associated with venous irritation and inflammation. These observations were confirmed in Phase III studies.[5] In contrast, administration of quinupristin/dalfopristin via central venous access is well tolerated by hospitalized patients. However, iv administration of quinupristin/dalfopristin on an outpatient basis has not been described previously. This study reviews our experience with quinupristin/dalfopristin outside the hospital setting and pays special attention to venous access-related events. Data for the first 21 of the

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37 patients in this study have been published in abstract form,[6] and data for the remaining 16 patients were presented in a separate abstract.[7]

Materials and methods

Patients were identified by a review of study records at the Cleveland Clinic Foundation (Cleveland, OH, USA), the Springfield Clinic (Springfield, IL, USA) and the Bethesda Memorial Hospital (Boynton Beach, FL, USA). Each centre had participated in clinical trials of quinupristin/dalfopristin for either emergency use or the assessment of efficacy and safety in the Phase III programme.[8–10] Patients participating in these trials had provided written informed consent, and the trials were conducted in accordance with the guidelines of the respective institutions.

Principal investigators at the three sites identified 37 patients who had continued to receive quinupristin/dalfopristin therapy after hospital discharge (Cleveland, $n = 11$; Springfield, $n = 14$; Boynton Beach, $n = 12$). Hospital, outpatient and home care records were reviewed to obtain efficacy and safety data in these patients, with particular reference to venous access-related events. All patients were evaluated with an algorithm for clinical efficacy responses, and clinical response was defined as cure, improvement or failure. Bacteriological response was defined as eradication (negative post-therapy cultures of the infected site), presumed eradication (post-therapy cultures unobtainable, no residual signs or symptoms of infection) or persistence (positive post-therapy cultures).

Results

Patient demographics and treatment regimens

Demographic data for the 37 patients are shown in Table I. In every case, treatment was initiated in hospital and continued on an outpatient basis for a mean of 22.2 additional days (Table I). In total, 343 days of quinupristin/dalfopristin therapy were administered to hospital inpatients and 821 days to outpatients. Patients were treated at home, in extended care facilities or, when short-term skilled nursing care, rehabilitative therapy and close medical supervision was necessary, in subacute facilities. Patients received 1 h infusions of 7.5 mg/kg bodyweight quinupristin/dalfopristin every 8 or 12 h, for a duration judged appropriate by the investigator. Three patients received concomitant antibiotic therapy, two with ampicillin and one with ticarcillin/clavulanic acid. Three patients had antibiotic allergies, two to vancomycin and one to penicillin.

Indications and pathogens

The most common indications for treatment were osteomyelitis and bacteraemia (Table I); three patients had

Table I. Patient demographic data, indications and pathogens isolated

Parameter	
Age (years)	
mean ± S.D.	57.4 ± 16.5
range	20–86
Gender [*n* (%)]	
male	17 (45.9)
female	20 (54.1)
Duration of therapy (days)	
hospital	
mean ± S.D.	9.3 ± 6.4
range	2–26
outpatient	
mean ± S.D.	22.2 ± 19.1
range	1–84
mean total duration	31.4
Type of outpatient care [*n* (%)]	
home	27 (73.0)
subacute facility	6 (16.2)
extended care facility	4 (10.8)
Treatment regimen [*n* (%)]	
every 8 h	26 (70.3)
every 12 h	11 (29.7)
Indications for treatment [*n* (%)][a]	
osteomyelitis	12 (32.4)
bacteraemia	6 (16.2)
abscess	5 (13.5)
cellulitis	4 (10.8)
wound infection	3 (8.1)
peritonitis	3 (8.1)
empyema	2 (5.4)
septic arthritis/bursitis	2 (5.4)
pneumonia	1 (2.7)
sinusitis	1 (2.7)
urinary tract infection	1 (2.7)
Pathogen isolated [*n* (%)][b]	
vancomycin-resistant *E. faecium*	13 (35.1)
methicillin-resistant *S. aureus*	9 (24.3)
coagulase-negative staphylococci	9 (24.3)
methicillin-susceptible *S. aureus*	5 (13.5)
Streptococcus spp.	5 (13.5)
vancomycin-susceptible *Enterococcus* spp.	4 (10.8)
other[c]	6 (16.2)

[a]Three patients had more than one indication.
[b]Fourteen patients had two or more isolates; one patient was culture-negative.
[c]One patient each with *Propionibacterium acnes*, *Peptostreptococcus* spp., *Candida* spp., *Xanthomonas maltophilia*, *Pseudomonas aeruginosa* and *Proteus* spp. Patients concomitantly infected with one of the latter three pathogens received another parenteral antibiotic during all or part of the course of therapy with quinupristin/dalfopristin.

Table II. Summary of bacteriological and clinical outcome

Bacteriological outcome	No. of patients[a] (%)	Clinical outcome	No. of patients[a] (%)
Overall success rate	33 (89.2)	overall success rate	33 (89.2)
eradication	7 (18.9)	cure	31 (83.8)
presumed eradication	26 (70.3)	improvement	2 (5.4)
Persistence	4 (10.8)	failure	1 (2.7)
		unable to evaluate[b]	3 (8.1)

[a]Total number of patients = 37.
[b]The clinical outcome could not be assessed for three patients who died of their underlying illnesses; two had persistent infection at the time of death from other causes.

more than one indication. The most common pathogens isolated from these patients were vancomycin-resistant *Enterococcus faecium* (VREF), *Staphylococcus aureus* and coagulase-negative staphylococci (Table I). In 14 patients (37.8%), more than one pathogen was isolated. Over half of the isolates were resistant to vancomycin or methicillin.

Efficacy

Following quinupristin/dalfopristin outpatient therapy, the bacteriological success rate (eradication and presumed eradication) was 89.2% and the clinical success rate (cure and improvement) was 89.2% (Table II).

Three patients (8.1%) died of their underlying disease; all had non-bacteraemic VREF infection in the setting of relapsed leukaemia. Infection was eradicated before death in one of the three patients, who had a urinary tract infection with VREF and coagulase-negative *Staphylococcus* spp., and was readmitted after 5 days into a subacute unit because of neutropenic fever. The second patient, who was chronically thrombocytopenic, was given 5 days of quinupristin/dalfopristin therapy in a subacute facility before she died of a massive gastrointestinal bleed. Cultures revealed persistent VREF in a thigh abscess 5 days before she died. The third patient died after requesting withdrawal of all therapies. She had persistent VREF infection of a total hip arthrodesis and was not a candidate for further surgery. Quinupristin/dalfopristin was administered for 48 days in an extended care facility before her death.

Five patients were readmitted to hospital after commencing outpatient therapy; details are given in Table III. One patient was readmitted because of relapse of infection 5 days after completion of quinupristin/dalfopristin therapy; the rest were readmitted during the course of therapy for reasons unrelated to their underlying infections.

Safety

Nineteen patients (51.4%) experienced a total of 32 non-venous clinical adverse events. The most common events were myalgia (seven patients; 18.9%), nausea (seven patients; 18.9%), arthralgia (five), diarrhoea (three), headache (two) and vomiting (two). Chest pain, gastrointestinal bleeding, dry nose, intertrigo, pancreatitis and restlessness were each reported by one patient. The quinupristin/dalfopristin dosage was reduced in three patients because of myalgia, and in one patient because of nausea. No patients died at home and no patients stopped therapy because of arthralgias or myalgias, although one person required intensive encouragement to convince her to complete therapy. Abnormal laboratory results were obtained for five patients (13.5%), including anaemia (three patients), azotaemia and elevated transaminases (one patient each).

Venous access was gained with seven different types of access device, the most commonly used being peripherally inserted central catheters (PICCs) and tunnelled catheters (Table IV). Twenty-one of the 37 patients did not report any venous access-related adverse events. Sixteen patients (43.2%) experienced a total of 18 adverse events related to venous access after hospital discharge, most commonly pain with drug infusion, local oedema, and phlebitis (Table IV). One patient was readmitted for treatment of a venous access-related event, namely central catheter-related bacteraemia, but treatment continued successfully following removal of the infected PICC and its replacement by a central venous line. Two patients required treatment with urokinase because of sluggish flow. Among patients with heparin locks, two experienced painful drug infusions; they received symptomatic therapy with oral acetominophen or ibuprofen. Two patients with PICCs who experienced phlebitis or swelling of the arm were successfully treated by applying warm packs to the arm. Parenteral antibiotic treatment was discontinued prematurely in one patient with a PICC who experienced infusion pain; therapy was completed with oral penicillin. Venous access for another patient was changed from a PICC to a heparin lock for the final day of therapy because of phlebitis and arm swelling.

Discussion

The options for treating Gram-positive infections are becoming increasingly limited as a result of the rising

Table III. Details of patients requiring readmission ($n = 5$)

Days of inpatient Q/D therapy	Days of outpatient Q/D therapy	Bacteriological outcome	Brief clinical comments
9	24	persistence	readmitted with recurrent MRSA bacteraemia/empyema, 5 days after completing course of therapy
13	12	eradication	readmitted with central catheter-related bacteraemia; PICC removed, central venous line placed; treatment continued successfully
12	5	eradication	leukaemia patient, readmitted with neutropenic fever; died
14	29	presumed eradication	liver transplant recipient, readmitted with elevated liver enzymes
26	1	presumed eradication	readmitted with chest pain, judged unrelated to quinupristin/dalfopristin treatment

MRSA, methicillin-resistant *S. aureus*; PICC, peripherally inserted central catheter; Q/D, quinupristin/dalfopristin.

incidence of resistance to methicillin, vancomycin and teicoplanin among such pathogens. Vancomycin has been the treatment of choice for methicillin-resistant *S. aureus* (MRSA); therefore, the emergence of vancomycin-resistant strains is a cause for great concern.[11,12] To address the challenges of infections due to resistant Gram-positive pathogens, agents such as streptogramins (quinupristin/dalfopristin), oxazolidinones (linezolid), ketolides (telithromycin) and cyclic lipopeptide antibiotics (daptomycin) have been developed.

Quinupristin/dalfopristin is highly active *in vitro* against most isolates of *S. aureus*, *Staphylococcus epidermidis*, *Streptococcus pneumoniae*, *Streptococcus agalactiae*, *Streptococcus pyogenes* and *E. faecium.*[13] The drug shows a post-antibiotic effect (10 h) comparable to that of macrolides such as erythromycin and roxithromycin (9 h).[14] Over 5000 patients and healthy volunteers have received quinupristin/dalfopristin in worldwide multicentre clinical trials and emergency-use programmes in eight countries. Quinupristin/dalfopristin has been shown to be effective in treating complicated skin and skin structure infections,[15,16] nosocomial pneumonia,[10] bacteraemia,[9,17] and various infections caused by VREF[8,18] or MRSA.[19,20]

The findings of the present study show that quinupristin/dalfopristin was effective and generally well tolerated in the outpatient setting. The bacteriological and clinical success rates were high (both 89.2%) and most patients (86.5%) completed therapy without readmission to hospital. All three patients who died had leukaemia in relapse, and their deaths were not related to the infection undergoing treatment. If the patients who died with leukaemia are excluded from the denominator for the clinical response group, the success rate was 97.1% (33/34 patients).

The characteristics of the quinupristin and dalfopristin molecules necessitate certain considerations in preparation and administration of the antibiotic.[5] Lyophilized quinupristin/dalfopristin powder contains no antibacterial preservative; the diluted quinupristin/dalfopristin solution is stable for 54 h if stored in a refrigerator or 5 h at room temperature. Because of the drug's incompatibility with heparin or saline solutions, iv lines should be flushed with 5% dextrose in water. Most patients will receive quinupristin/dalfopristin through a central venous catheter, in which case the drug is diluted in 100 mL of 5% dextrose in water. When a peripheral venous catheter is used, the volume of diluent should be increased to at least 250 mL. One hour is required for each infusion. Quinupristin/dalfopristin is metabolized via the P450 pathway, so drugs that are P450 3A4 substrates (cyclosporin A, midazolam, nifedipine, terfenadine, etc.) should be used with caution and monitored when co-administered.

The most frequent non-venous adverse events reported during the present study were myalgia, nausea and arthralgia, all of which have been described previously in association with quinupristin/dalfopristin therapy.[5,21] In

Table IV. Venous access-related adverse events reported during the study

	Venous access device				
	PICC	tunnelled catheter[a]	heparin lock[b]	CVC	other[c]
Number of patients (%)	18 (48.6)	9 (24.3)	3 (8.1)	4 (10.8)	3 (8.1)
mean duration of outpatient use (days)	22.7	26.7	6.3	6.0	43.0
Number of adverse events (events/10 000 days of outpatient use)					
pain	1 (24.4)	1 (41.7)	2 (1052.6)	0	0
swelling/oedema	4 (97.8)	0	0	0	0
phlebitis	3 (73.3)	0	0	0	0
clots	1 (24.4)	1 (41.7)	0	0	0
infection[d]	1 (24.4)	0	0	0	0
other	1 (24.4)	2 (83.3)	1 (526.3)	0	0
total	11 (268.9)	4 (166.7)	3 (1578.9)	0	0

CVC, central venous catheter; PICC, peripherally inserted central catheter.
[a]Two patients also used PICC.
[b]One patient required five heparin locks in 15 days of therapy; another required six heparin locks in 7 days of therapy.
[c]Two subcutaneous ports, one haemodialysis catheter.
[d]One patient with a PICC was readmitted with central catheter-related bacteraemia.

comparative studies among hospitalized patients, the frequency of nausea as a drug-related adverse event was significantly lower in patients treated with quinupristin/dalfopristin (4.6% of 1099 patients) than in patients treated with comparator drugs (7.2% of 1094 patients), which included ceftriaxone, erythromycin, vancomycin, cefazolin and oxacillin.[5] In the emergency-use programmes, 4.2% of 998 patients receiving quinupristin/dalfopristin experienced nausea.[5] It is not clear why nausea occurred more commonly among outpatients than among the patients treated in hospital, although surveillance for this symptom was passive.

Arthralgia and myalgia occurred more frequently in the emergency-use studies (13.0% of 1199 patients) than in the comparative studies (1.3% of 1099 patients). Arthralgia and myalgia led to discontinuation of treatment in 3.0% of emergency-use patients.[5] The risk of development of arthralgia or myalgia was highest at treatment day 5 or 6, after which it decreased progressively.[21] To date, all arthralgia and myalgia events have been reversible upon treatment discontinuation, without chronic sequelae.[5] Dose reduction and a variety of analgesics, including non-steroidal anti-inflammatory drugs and narcotics, have been used to relieve symptoms of myalgia and arthralgia. In the present study, all patients had demonstrated tolerance of quinupristin/dalfopristin before hospital discharge. The rates of arthralgia and myalgia (18.9 and 13.5%, respectively) were somewhat higher than in the emergency-use and comparative studies, but no patients discontinued quinupristin/dalfopristin therapy due to non-venous clinical or laboratory adverse events. In four patients the quinupristin/dalfopristin dosage was reduced because of myalgia or nausea, and in each case the treatment was continued to a successful outcome.

In comparative trials, a high proportion (75%) of patients who received quinupristin/dalfopristin by the peripheral venous route experienced local adverse events, including inflammation, pain, oedema and infusion site reactions.[5] The frequency of local adverse events was also high (55%) in comparator groups receiving antibiotics by this route. Administration of quinupristin/dalfopristin by a central venous route has therefore been recommended to avoid local venous problems.[5] In the present study, administration of quinupristin/dalfopristin outside the hospital setting using various access devices was generally well tolerated. The most commonly reported problems were pain, phlebitis and oedema, but only one patient discontinued treatment prematurely. Remedial action, such as lysis of clots or the application of warm packs to reduce phlebitis or swelling, was performed on an outpatient basis. One patient with a PICC was readmitted with catheter-related bacteraemia, representing one case in 409 days of PICC use outside the hospital setting (24 per 10 000 catheter days). This compares with published rates of 11 cases per 10 000 catheter days for PICCs used in hospital,[22] and two to three per 10 000 catheter days for PICCs used for home therapy.[23,24] The difference in rates may be explained by the relatively limited number of days of therapy via PICCs in this review. The overall rate of bacteraemia in the patients treated at home was 12 per 10 000 catheter days (one case in 821 days of outpatient therapy).

The use of PICC and central venous catheters has been shown to reduce the risk of phlebitis when compared with short peripheral intravenous catheters.[25,26] PICCs are in-

creasingly favoured over other vascular access devices.[22,26] The characteristics and advantages of different types of device have been summarized by Graham *et al*.[27] In the present study, the PICC was the most commonly used access device. Three cases of phlebitis occurred among our 18 outpatients using PICCs (16.7%), compared with an incidence of 10% reported by Tice *et al*.[26] and 14% reported by Graham *et al*.[27] Comparisons between settings and studies may be difficult, however, because an inverse correlation has been reported between the incidence of phlebitis and the level of experience of the staff placing the catheters.[26] Moreover, some PICCs may be placed by radiologists, who tend to use 5–7 French sizes (F), whereas clinicians who insert PICCs at the bedside generally place smaller catheters of 3–4 F diameter. Thus, factors other than the type of device and the drug administered can affect the occurrence of adverse venous events. The numbers of patients using other devices in the present study were small, so no significant comparisons could be made between the incidence of central venous access-related problems with different devices. The single episode of clotted PICC (5.5%) in this study compares favourably with the 20% incidence noted in the early years of PICC use.[27]

Outpatient iv antimicrobial therapy is now considered appropriate for clinically stable patients who require prolonged courses of treatment.[27–29] Home treatment offers potentially improved patient convenience and substantial cost savings by releasing hospital facilities for other needs.[29,30] It has been suggested that central venous catheters can be used more successfully on an outpatient basis than in hospital, with lower rates of infection and fewer device-related problems.[24,27] This difference might reflect the relative lack of experience with the devices among hospital staff, a generally healthier population of patients at home, less exposure to nosocomial pathogens or closer attention to catheter care by patients who were carefully instructed in management. Guidelines for appropriate antibiotic selection and monitoring of patients treated with parenteral anti-infective therapy in outpatient settings have been published by the Practice Guidelines Committee of the Infectious Diseases Society of America.[1] The guidelines indicate that the use and monitoring of specific antibiotics must be individualized, depending on the type of agent and its adverse event profile. We recommend weekly monitoring of the complete blood count and hepatic function during outpatient courses of quinupristin/dalfopristin therapy.

In summary, previous studies have indicated the advantages of administering quinupristin/dalfopristin using central rather than peripheral venous access. In this study we examined the feasibility of quinupristin/dalfopristin therapy using PICC and other venous access devices in an outpatient setting. We conclude that, for carefully selected patients, outpatient therapy with quinupristin/dalfopristin can be safe and effective and may offer considerable advantages in terms of cost and patient well-being. However, as with any antimicrobial therapy, careful monitoring is necessary for early detection of access-related events or clinical deterioration.

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