Continuous Infusions of Cefazolin

The treatment guidelines for bone and joint infections are currently based on expert opinion, rather than clinical trials. There are several factors used in determining if an antibiotic is appropriate for this condition, including: good activity against the organism, good or excellent bone penetration and good patient tolerance. Cefazolin has those characteristics against methicillin-susceptible *S. aureus* and nonenterococcal streptococci. Continuous infusion of beta-lactam antimicrobials is the best way to take advantage of their pharmacodynamics, since their efficacy is time-dependent. Continuous infusion also avoids the need for repeated intermittent injections and is particularly advantageous for outpatient treatment. This study was done to evaluate the clinical efficacy, feasibility and safety of prolonged administration of continuous infusion cefazolin in patients with bone and joint infections.

This was a retrospective cohort study that included all the patients treated for bone and/or joint infections with continuous intravenous cefazolin for two weeks or longer, and who had two or more cefazolin serum concentrations determined. Cefazolin was administered through a central venous catheter starting with a loading dose of one gram infused over 10 minutes when the daily dose was ≤ 4 g or of two grams when the daily dose was greater than four grams. Immediately following the loading dose a continuous infusion of 60 to 80 mg/kg/day was dissolved in 50 ml of 5% dextrose, and administered over a 12 hours period twice daily via an infusion pump. All patients received combined antibiotic therapy. Patients were discharged to home parenteral antimicrobial therapy when the treatment duration exceeded three weeks and the infection was seen to be resolving. At home a visiting nurse administered the twice daily infusion with either a constant-infusion pump or an elastomeric infusion device. Serum cefazolin levels were monitored at least twice in each patient with a target serum level of 40 to 70 mg/l. The daily cefazolin dose was increased or decreased by 20 to 25% based on those levels. Patients were assessed for follow-up at six weeks, three months, six months and twelve months, and assessed for relapse, reinfection or death.

One hundred consecutive patients hospitalized between February 2005 and May 2007 were included in the study. The mean patient age was 56 years, 44% of patients had a joint arthroplasty infection and 34% had chronic osteomyelitis. *Staphylococcus aureus* was the predominant organism in 56% of patients, followed by gram-positive anaerobic bacteria (*Propionibacterium*). Cefazolin doses were adjusted in 47 patients, between the first and second serum sampling for 32 patients, and after the second sampling for 15 patients. Two patients developed cefazolin-related adverse effects, one with *C. difficile* infection and one with confusion. The median serum cefazolin concentration was 63 mcg/ml on days 2 to 10, and 57 mcg/ml on days 11 to 21. Bone cefazolin levels were obtained in eight patients revealing a median bone concentration of 13.5 mcg/g (range 3.5 to 29 mcg/g). At a mean follow-up time of 25 months, five patients with *S. aureus* infection relapsed. There was one patient death that was considered infection and treatment related. Overall, 93% of the evaluable patients were considered to have been cured (53 patients) or probably cured (29 patients).

Effective treatment of bone and joint infections requires identification of the pathogen, surgical intervention and prolonged antimicrobial therapy. Cefazolin has good activity against many gram-positive cocci responsible for bone and joint infections, has a low incidence of adverse effects and is inexpensive. Prolonged treatment of bone and joint infections with a continuous intravenous infusion of cefazolin is feasible, effective, well-tolerated and safe.

**Voriconazole Dosing in Children**

Voriconazole (Vfend™) is a broad-spectrum antifungal agent with activity against *Aspergillus spp.*, *Candida krusei*, *Candida glabrata* and other less common fungal organisms such as *Scedosporium spp.* and *Fusarium spp.* The recommended dosing regimen in adults consists of two intravenous loading doses of 6 mg/kg 12 hour apart, followed by 3 to 4 mg/kg twice daily. When given orally to adults, the two loading doses are 400 mg given twelve hours apart, followed by 200 mg twice daily. Oral doses are halved in patients weighing less than 40 kg. In Europe, voriconazole is licensed for pediatric use in patients between 2 and 12 years old, with a recommended dose of 7 mg/kg twice daily intravenously and 200 mg twice daily for the oral suspension, without a loading dose. Voriconazole is heptically metabolized by CYP450 isoenzymes so that its pharmacokinetics is nonlinear. At present, the optimum dosing regimen for children is unclear. This report describes the...
results of a population pharmacokinetic analysis characterizing the interrelationships between voriconazole plasma concentrations and potential covariates in children.

Data from three open-label pediatric studies with a total of 82 patients aged 2 to 12 years were used for the analysis. These three studies investigated the pharmacokinetics, safety and tolerability of oral and/or intravenous voriconazole examining a range of dosage regimens, including single and multiple doses. The analysis considered other factors that might influence voriconazole pharmacokinetics including, demographic factors, biochemistry, concomitant medications, underlying disease states and other factors. The formal population pharmacokinetic analysis of the combined plasma samples was carried out by applying the nonlinear mixed-effect modeling approach utilizing the NONMEM (version V, level 1.1).

The patient’s average body weight was 22.8 kg (range, 10.8 to 54.9 kg) with an average baseline alanine aminotransferase (ALT) level of 40.7 IU/L (range, 7 to 242 IU/L) and an average alkaline phosphatase level of 136 IU/L (range, 46 to 309 IU/L). There were 31 patients with leukemia, 39 with bone marrow transplantation and 57 patients had mucositis. The final pharmacokinetic model described voriconazole elimination by a Michaelis-Menten process and distribution by a two-compartment model. There was also a statistically significant influence from the CYP2C19 genotype on voriconazole clearance.

As a result, dosage regimens of 7 mg/kg twice daily intravenously or 200 mg twice daily orally irrespective of body weight, is recommended for this pediatric population. At these doses, the pediatric area-under-the-curve (AUC) exhibited the least overall difference from the adult AUC, obtained with recommended doses. Loading doses or individual dosage adjustments are not considered necessary in administering voriconazole to children.


Safety of Caspofungin in Patients Less than Three Months of Age

Candida infections are a major concern in neonatal intensive care units, especially for infants with very low birth weights (LBW). Late-onset sepsis develops in approximately 20% of critically ill neonates and LBW infants with Candida species accounting for at least 10% of these infections. Many antifungal agents are associated with increasing fungal resistance, considerable toxicity or limited spectrums of activity. The echinocandin antifungal agent, caspofungin (Cancidas™) may be useful in these situations. Data for children 3 to 24 months of age who receive caspofungin at 50 mg/M² show pharmacokinetic results similar to those seen in children 2 to 11 years old. However, the appropriate dose for neonates is not clearly defined. This prospective study evaluated the safety, tolerability and plasma levels of caspofungin in patients less than 3 months of age given 25 mg/M² daily.

This was a multicenter, open-label, noncomparative study conducted from July through October 2006 at eight sites. Eligible patients were less than three months of age, weighed at least 500 g and had a documented or highly suspected invasive Candida infection. Documented Candida infection was defined as the presence of at least one positive Candida species from blood or another normally sterile site, which had been obtained within four days of study entry. Patients received either a single dose, or a once daily dose of 25 mg/M² of caspofungin for at least 4 days and up to 28 days. All patients were required to receive an intravenous amphotericin formulation at the time of study entry, and to remain on the amphotericin for the duration of caspofungin therapy. Monotherapy with caspofungin was not permitted. For the patients receiving multiple dose caspofungin, blood for sampling was collected before the first dose of caspofungin, and at one hour and 24 hours after the infusion on day one and day four. These peak and trough plasma levels were then compared to the levels seen in adult patients who received multiple 50 mg/M² of caspofungin.

Twelve patients were enrolled in the multiple dose study and six were enrolled in the single dose study. The majority of patients or 72% had a gestational age of ≤ 36 weeks at birth. Their body surface area ranged from 0.0758 to 0.236 M² (mean, 0.1529 M²). The mean duration of caspofungin therapy in the multidose study patients was 8.7 days. On day one and day four, the peak caspofungin concentrations were similar to those for adults receiving 50 mg daily doses, 8.2 mcg/ml and 10.9 mcg/ml, respectively. The mean trough levels of caspofungin were slightly elevated in the neonates compared to adults, 1.8 mcg/ml and 2.4 mcg/ml, respectively. Compared to children 2 to 11 years of age, adolescents of 12 to 17 years and young children of 3 to 24 months of age who received 50 mg/M² per day, the caspofungin peak concentrations in neonates/infants were somewhat reduced on days one and four. Conversely, trough concentrations in the neonates/infants at doses of 25 mg/M² were somewhat increased on both day one and day four, relative to trough concentrations achieved in older pediatric patients receiving 50 mg/ M² daily of caspofungin. One or more clinical adverse events were reported in 94.4% or 17 of 18 patients during caspofungin therapy or in the 14-day follow-up. The most common adverse events were pyrexia, hyperventilation and hypertension. None of the adverse clinical events were considered to be related to caspofungin therapy.

This was the first prospective study of caspofungin in neonates and very young infants. Although, the number of patients studied
was small, it shows that a dose of caspofungin of 25 mg/M² daily provided plasma concentrations fairly similar to those observed in adults receiving 50 mg per day, and was generally well tolerated.


Safety and Dosing of Caspofungin in Older Infants and Toddlers

Incidence rates of Candida and Aspergillus infection are increasing in children with hematological malignancies, congenital immune deficiencies and other childhood medical conditions that require aggressive immunosuppressive or antibacterial therapy. Blood stream infections with Candida (often C. parapsilosis) are also occurring at increasing rates in other hospitalized children. The pharmacokinetics of caspofungin have been evaluated in children and adolescents 2 to 17 years of age and a dosing regimen using a body surface area approach of 50 mg/M² daily (maximum of 70 mg) has been established for this age group. The recommended dosing regimen for patients ≤ 3 months of age is given above. An open-label study to evaluate the safety, tolerability and pharmacokinetics of the same dosing regimen as two year old children was conducted in infants and toddlers 3 to 24 months of age.

Patients between the ages of 3 and 24 months with leukemia, lymphoma, bone marrow or peripheral stem cell transplantation, aplastic anemia and neutropenia, at least one recorded fever and two or more infectious episodes, were eligible for study inclusion. All patients received caspofungin at 50 mg/M² once daily as a one-hour infusion with a daily maximum of 70 mg. Caspofungin was administered daily until the patients recovered from neutropenia. Plasma samples for caspofungin levels were collected on days one and four.

Nine patients were enrolled in the study and their ages ranged from 10 to 22 months. The patient weights ranged from 9.4 to 11.9 kg and most patients had severe neutropenia (absolute neutrophil count (ANC) < 100 cells/mm³).

On day four, the mean area under the curve from 0 to 24 hours was 130.3 mcg-hr/ml, the peak concentration was 17.2 mcg/ml and the trough concentration was 1.6 mcg/ml. The geometric mean ratios (GMR) for these parameters in infants/toddlers relative to adults were 1.26, 1.83 and 0.81, respectively. Relative to children (2 to 11 years of age), the day four GMRs were 1.13, 1.10 and 1.12, respectively. The mean elimination phase half-life in infants/toddlers (8.8 h) was reduced relative to adults (13.0 h), but similar to that in children (8.2 h). Clinical adverse events occurred in seven patients, but none were considered drug related. Three patients had possible drug related laboratory adverse events including (increases in aspartate aminotransferase, alanine aminotransferase or glucose levels).

Caspofungin at 50 mg/M² daily was well tolerated in infants and toddlers; the AUC and peak caspofungin serum levels were generally comparable to those in adults receiving 50 mg daily.


Maximizing Posaconazole Absorption

Posaconazole (Noxafil™) is an extended-spectrum triazole antifungal agent with potent activity against many clinically important yeasts and molds, including Aspergillus and zygomycetes. In the United States posaconazole is approved for the prophylaxis of invasive Aspergillus and Candida infections in immunocompromised patients, and for the treatment of oropharyngeal candidiasis. In the European Union, posaconazole is approved for the treatment of refractory invasive fungal infections. The pharmacokinetics of posaconazole has been well studied in various groups of patients and normal volunteers. It is well absorbed after oral administration, has a large volume of distribution, and has dose-proportional pharmacokinetics for doses up to 800 mg/day. Posaconazole has a half-life of approximately 35 hours, and its maximum concentration is achieved in about three to five hours after administration. In healthy volunteers, administration of posaconazole oral suspension with a high-fat meal, low-fat meal or a liquid nutritional supplement increases the mean area under the concentration-time curve (AUC) by four fold, 2.6 fold and 2.6 fold, respectively, compared with the AUCs achieved with administration in the fasting state. Under fasting conditions, administration of the total daily dose as divided doses increased the level of exposure to posaconazole, compared with that achieved by the use of a single dose. Although much is known about the pharmacokinetics of posaconazole, less is known about its pharmacokinetics in seriously ill patients with gastric absorption difficulties, such as those seen in patients with graft versus host disease or patients with gastrointestinal motility disorders. The purpose of this study was to evaluate the pharmacokinetics of posaconazole in healthy volunteers under well-controlled conditions, that simulate the various clinical scenarios that may be encountered in patients who require posaconazole therapy. Specifically, the study evaluated the effects of gastric pH, the posaconazole dosing frequency and prandial state, the timing of food consumption relative to the time of posaconazole administration and gastric motility on the absorption of posaconazole.

This was a four-part, randomized, open-label, crossover study with 49 healthy subjects between the ages of 18 and 55 years and a body
mass index between 20 and 30 kg/M^2. In part one, a single 400 mg dose of posaconazole was administered alone in the fasting state, or with an acidic carbonated beverage (ginger ale, 12 ounces), or a 40 mg dose of esomeprazole for two days before posaconazole administration, or with the carbonated beverage and esomeprazole while fasting. In part two, posaconazole (400 mg twice daily and 200 mg four times daily) was administered for seven days with and without a nutritional supplement (Boost™). Subjects were fasted for the entire duration of each seven day treatment period, although nonfat snacks, such as apples, oranges and/or gelatin desserts were permitted. In part three, a single 400 mg dose of posaconazole was administered while the subjects were fasting, and five minutes before, in the middle of and 20 minutes after a high fat (50 g) meal. In part four, a single 400 mg dose of posaconazole and the nutritional supplement were administered alone or with 10 mg of metoclopramide (Reglan™) three times daily on the day before and the day of posaconazole administration or a single dose of loperamide (Imodium™) 4 mg.

Compared with the results of posaconazole alone, administration with an acidic beverage increased the posaconazole maximum concentration (C_{max}) and AUC by 92% and 70%, respectively, whereas a higher gastric pH with esomeprazole decreased the posaconazole C_{max} and AUC by 46% and 32%, respectively. Compared to the results obtained with posaconazole alone, posaconazole at 400 mg or 200 mg plus the nutritional supplement increased the posaconazole C_{max} and AUC by 65% and 66%, respectively and by up to 137% and 161%, respectively. Administration before a high-fat meal increased the C_{max} and AUC by 96% and 111%, respectively, while administration during and after the meal increased the C_{max} and AUC by up to 339% and 387%, respectively. Increasing gastric motility decreased the C_{max} and AUC by 21% and 19%, respectively. In contrast, administration of posaconazole at 400 mg with the nutritional supplement under conditions of reduced gastric motility (loperamide) had an insignificant effect.

Posaconazole absorption is affected by the consumption of an acidic beverage, gastric pH, prandial state and the time of dose administration relative to the time of a meal. Strategies to maximize posaconazole exposure in patients with absorption difficulties include administration with or after a high-fat meal, with any meal or nutritional supplement, with an acidic beverage or in divided doses and the avoidance of proton pump inhibitors.


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