Journal of Clinical Pharmacology and Therapeutics

ISSN: 2766-8347

Research Article

Clinical Pharmacology of Caspofungin in Infants and Children

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Abstract

Caspofungin (Cancidas®) is an echinocandin and inhibits 1,3-β-D-glucan synthesis which is an essential component of the fungal cell wall and is required for cellular integrity. Caspofungin exhibits fungicidal and fungistatic activities against *Candida* and *Aspergillus* species, respectively. Caspofungin is largely eliminated by N-acetylation, catalyzed by CYP3A4, and inhibition of this enzyme causes marked increase of Caspofungin plasma concentration. The dose of Caspofungin is: 25, 50, or 70 mg/m^2 once-daily for infants aged <3 months, and for children aged up to 11 or up to 17 years, respectively, and is administered by intravenous infusion. Proliferation of Candida and Aspergillus species is inhibited by caspofungin, the Minimum Effective Concentration (MEC) is 0.5 μg/ml, the plasma caspofungin concentration is about 11 and 2 μg/ml 1 and 24 hours after a standard dose to pediatric patients, thus trough caspofungin concentration is >MEC and decays slowly from plasma. Caspofungin induces alteration of hematic parameters, nephrotoxicity, fever, vomiting, diarrhea, rash, hypotension, and chills. Caspofungin interacts with drugs and the interaction may be synergistic or antagonistic. This antibiotic does not penetrate into the cerebral fluid, whereas it crosses the placenta in significant amount and causes malformation in the foetus. Fungal resistance to caspofungin may be caused by mutation of fungal genome or/and alteration of the fungal cell wall and caspofungin consumption induces resistance. The aim of this study is to review the published data on caspofungin-dosing, efficacy, safety, effects, metabolism, pharmacokinetics, drug-interactions, adverse-effects, treatment, Prophylaxis, infants and children, placenta-transfer, fungal-resistance, infants, and children.

Keywords: Caspofungin; Pharmacokinetics; Metabolism; Treatment; Prophylaxis; Fungal-resistance

Introduction

Caspofungin mechanism of action

Caspofungin (Cancidas®) is an echinocandin and inhibits 1,3-β-D-glucan synthesis which is an essential component of the fungal cell wall and is required for cellular integrity [1].

Antifungal activity of caspofungin

Caspofungin is a cyclic lipopeptide with a hexadepsipeptide nucleus and exhibits fungicidal activity against *Candida* species and fungistatic against *Aspergillus* species and cause morphological changes to the filaments. Caspofungin does not appear to have clinical useful activity against dimorphic fungi such as *Histoplasma capsulatum* and have no clinical activity against *Candida neoformans*, *Trichosporon* species, *Fusarium* species, or agents of mucormycosis [1].

Catabolism of caspofungin

Catabolism of caspofungin is largely due by hydrolysis catalyzed by N-acetylation and caspofungin is excreted in the urine and faeces. Mild and moderate hepatic insufficiency increases the AUC of caspofungin by 55 and 76%, respectively [1].

Therapeutic use of caspofungin

Caspofungin is approved for the treatment of invasive candidiasis and as salvage therapy for patients with invasive aspergillosis who fail or are intolerant of approved drugs, such as amphotericin B formulations or voriconazole. Caspofungin is also approved for treatment of oesophageal, oropharyngeal, invasive candidiasis, and for treatment of persistently febrile neutropenic in patients with suspected fungal infections. Caspofungin is one of the few antifungal agents which are approved for treatment of these diseases in infants [1]. Adverse-effects caused by caspofungin are: thrombophlebitis, hypercalcemia, hypokalaemia, elevated hepatic transaminase activities, hyperbilirubinemia, diarrhea, rash, hypotension, and chills. Dexamethasone, phenytoin, carbamazepine, nevirapine, and rifampin induce caspofungin total body clearance lowering its serum concentration. Caspofungin is incompatible with: acyclovir, cefazolin, ceftriaxone, clindamycin, furosemide, heparin, and piperacillin/tazobactam (NEOFAX®) (Figure 1).

Literature search

The literature search was performed electronically using PubMed database as search engine and the cut-off point was the 23rd of November 2020. The following key words were used: "caspofungin

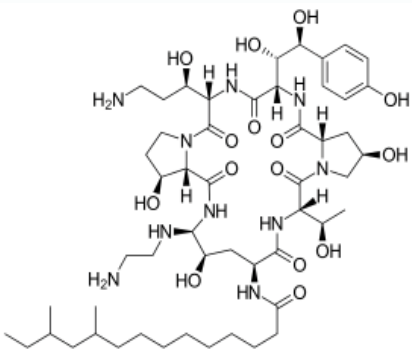

Figure 1: Molecular structure of caspofungin (molecular weight=1093 grams/mole).

Citation: Pacifici GM. Clinical Pharmacology of Caspofungin in Infants and Children. J Clin Pharmacol Ther. 2020;1(1):1006.

Publisher Name: Medtext Publications LLC

Manuscript compiled: Dec 31st, 2020

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efficacy, safety effects, infants, children", "caspofungin metabolism", "caspofungin pharmacokinetics infants, children", "caspofungin drug interactions", "caspofungin toxicity infants, children", "caspofungin treatment infants, children", "caspofungin prophylaxis infants, children", "Antifungal use during pregnancy", and "caspofungin bacterial-resistance". In addition, the books: The pharmacological basis of therapeutics, Neonatal formulary, NEOFAX®, and The British National Formulary for Children were consulted. The manuscript is written according to the "Instructions for authors".

Results

Administration schedules of caspofungin to infants and children

Treatment of infants (Neonatal Formulary, NEOFAX®)

Infants aged <3 months. Give: 25 mg/m^2 of body area (approximately 2 mg/kg) once-daily administered by intravenous infusion.

Treatment of children (The British national formulary for children)

Children aged 3 months to 11 months. Give: 50 mg/m^2 once-daily administered by intravenous infusion.

Children aged 1 year to 17 years. Give: 70 mg/m^2 once-daily administered by intravenous infusion (maximum per dose =70 mg) for the first day; then 50 mg/m^2 once-daily (maximum per dose =70 mg); increase the dose to 70 mg/m^2 once-daily (maximum per dose =70 mg); this dose may be used if the lower dose is tolerated but produce inadequate response.

Efficacy, safety, and effects of caspofungin in infants and children and general considerations

Invasive candidiasis in extremely preterm infants is the second most common cause of infectious disease-related death. Birth weight is strongly related to the incidence of invasive candidiasis (1% of infants with birth-weight of 1,000 grams to 1,500 grams *versus* up to 12% of infants with birth-weight of 401 grams to 750 grams). The morbidity-and mortality-rates of infants with invasive candidiasis are high [2]. Caspofungin was found efficacy and safe in neonates with birth-weight of 530 grams to 5,600 grams with candidaemia due to *Candida parapsilosis*, *Candida albicans*, *Candida tropicalis*, and treatment duration was 6 days to 30 days [3]. Caspofungin, administered at a dose of 50 mg/m^2 to immune compromised and seriously ill infants and children, was associated with little clinically significant toxicity compared to other antifungal agents such as azoles and amphotericin B [4]. Caspofungin was administered to 49 infants and children, aged 3 months to 17 years, with invasive candida and aspergillosis infections, was well tolerated in subjects aged 6 months to 17 years and the efficacy was observed in most subjects [5]. Caspofungin was administered to 20 children with invasive fungal infections, and following 147 days of follow-up, this treatment was found successful in 71.4% and only limited adverse-effects were noted [6]. Therapeutic concentration of caspofungin (2 μg/ml) significantly decreased the metabolism of Candida albicans and Candida parapsilosis (P-value ≤ 0.001) of 25% (biofilm of 48 hours) to 50% (biofilm of 2 hours) independently of the biofilm maturation age and caspofungin is a good candidate for the prevention of candidiasis [7]. Caspofungin increases the survival of infected *Galleria mellonella* larvae, and this is due to the antifungal properties of caspofungin and also to the ability of caspofungin to prime the insect's immune response [8]. Caspofungin increased the chitin and β-1,3-glucan on the surface of the majority of candida species with the exception of *Candida glabrata* and *Candida parapsilosis*. This increase in inner cell wall polysaccharides is correlated with reduced uptake by macrophages, and caspofungin causes a decrease in production of TNFα [9]. Letscher-Bru and Herbrecht [10], enrolled 128 patients with candidiasis; the primary endpoint was the outcome at 14 days after the end of treatment. Resolution of symptoms was observed in 34 of 46 patients (80.4%) following a caspofungin dose of 50 mg once-daily, and 25 of 28 patients (89.3%) treated with caspofungin at a dose of 70 mg once-daily, whereas treatment with amphotericin B cured only 63.0% patients; the results are showed in Table 1. This table shows that the effect of caspofungin is dose dependent and caspofungin is more effective than amphotericin B in curing candidiasis.

Effect of caspofungin on fungal metabolism

Susceptibility to caspofungin was studied with serum concentration from 0.008 μg/ml to 8 μg/ml in *Aspergillus fumigatus*, *Aspergillus flavus*, and terreus isolates. The Minimum Effective Concentration (MEC) and the metabolic activity were assessed. A significant reduction in metabolic activity was demonstrated at MEC concentration ranging from 0.25 μg/ml to 0.5 μg/ml for all Aspergillus organisms and was more pronounced in Aspergillus flavus. Assessment of metabolic activity may provide useful quantitative endpoints for *in-vitro* studies of caspofungin against Aspergillus species [11]. Table 2 shows the metabolic activities detected at MEC of caspofungin for three Aspergillus species.

Metabolism of caspofungin

Caspofungin is largely eliminated by N-acetylation, catalyzed by CYP3A4, and inhibition of this enzyme causes marked increase of caspofungin serum concentration. Caspofungin is an inhibitor of CYP3A4 and the inhibition by caspofungin causes 76% decrease in the metabolism of cytarabine. Rifampin, nevirapine, efavirenz, carbamazepine, dexamethasone and phenytoin, induce the metabolism of caspofungin. Caspofungin is a substrate and inhibitor of the organic anion transport B1, and rifampin inhibits the penetration of into body tissue cells *via* P1 transporter [12].

Pharmacokinetics of caspofungin in infants

The pharmacokinetics of caspofungin was studied in 18 newborn infants and infants, aged <3 months. Caspofungin was administered at a dose of 25 mg/m^2 once-daily, 6 subjects received a single dose of caspofungin and 12 subjects received multiple doses. The median postnatal age was 3.5 days (range, 1 to 7) and the range of body-weigh was ≤ 1 and >2.5 kg in 6 subjects who received a single dose of caspofungin. In 12 subjects who received multiple doses of caspofungin, the median postnatal age was 4.0 days (range, 2 to 11) and the body-weigh ranged from 1 to >5 kg. Subjects had oesophageal, oropharyngeal or invasive candidiasis [13]. Table 3 summarizes the plasma concentration of caspofungin according to the type of candidiasis. This table shows that caspofungin plasma concentration is independent by the type of candidiasis and it is lower at 24 hours than 1 hour following administration indicating that caspofungin decays slowly from plasma.

Pharmacokinetics of caspofungin in children

Yang et al. [14], evaluated the population pharmacokinetics of caspofungin in 48 children aged 2 to 12 years. The mean + SD of the age, body-weight, and body surface area were: 6.1 ± 2.7, 22.8 ± 8.7, and 0.84 ± 0.22 (range, 0.54 to 1.4), respectively. Children, suffering

Table 1: Efficacy of Caspofungin in curing oropharyngeal and oesophageal candidiasis. The figure are the number of patients cured and the (percentage), by Letscher-Bru and Herbrecht [10].

	Favourable responses (%)			
	*Caspofungin dose			*Amphotericin B dose
	35 mg/kg	50 mg/kg	70 mg/kg	0.5 mg/kg
Oesophageal candidiasis (N=128)	ND	34 of 46 (73.9%)	25 of 28 (89.3%)	34 of 54 (63.0%)
Oropharyngeal or oesophageal candidiasis				
Oropharyngeal only (N=52)	11 of 13 (84.6%)	13 of 14 (92.8%)	12 of 13 (92.3%)	8 of 12 (66.7%)
Oesophageal (N=86)	14 of 21 (66.7%)	18 of 20 (90.0%)	17 of 22 (72.3%)	14 of 23 (60.9%)
Oesophageal candidiasis (N=175)	ND	66 of 81 ()	ND	80 of 94 ()

*Doses were administered once-daily; ND=not determined

Table 2: Median metabolic activities (percentage of drug-free control) detected at the MEC, the MMC, and 8 µg/ml of Caspofungin for three Aspergillus agents[a], by Antachopoulos et al. [11]

Species and (No of strains)	Median and (range)				No isolates with paradoxical increase	% Metabolism at 8 µg/ml, median and (range)
	MEC (µg/ml)	% metabolism at MEC	MMC (µg/ml)	% metabolism at MEC		
Aspergillus fumigatus [9]	0.5 (0.25-0.5)	42 (56 – 73)	0.75 (0.5-2.0)	28 (16 - 46)	5 of 9	51 (18 -77)[c]
Aspergillus terreus [12]	0.5 (0.25-0.5)	53 (25 – 79)	1.0 (0.5-4.0)	38 (22 - 67)	6 of 12	57 (23 -85)[c]
Aspergillus flavus [8]	0.5 (0.25-0.5)	25 (12 – 32)[b]	2.0 (0.5-8.0)	17 (9 - 21)	1 of 8	20 (7 - 29)

MEC: Minimum Effective Concentration; MMC: Minimum Metabolic Activity Concentration

[a]The value for the MEC, MMC, and the number of isolates demonstrating a paradoxical increase in metabolic activity at higher concentrations are also presented. [b]P-value <0.01 compared to the corresponding percent metabolic activity of *Aspergillus fumigatus* or *Aspergillus terreus*. [c]P-value < 0.001 compared to the percent metabolism at the MMC.

Table 3: Caspofungin plasma concentration in 18 newborn infants and infants. Figures are the geometric mean and the 95% confidence interval, by Sáez-Llorens et al. [13]

Disease, number of subjects, and caspofungin plasma concentration (µg/ml)			
Oesophageal/oropharyngeal candidiasis	N	Geometrical mean	95% confidence interval
Day 1			
Caspofungin concentration 1 hour after dosing	18	8.2	6.8 - 10.0
Caspofungin concentration 24 hours after dosing	18	1.8	1.4 - 2.4
Day 4			
Caspofungin concentration 1 hour after dosing	12	11.1	8.8 - 13.9
Caspofungin concentration 24 hours after dosing	11	2.4	1.8 - 3.4
Invasive candidiasis			
Caspofungin concentration 1 hour after dosing	12	10.9	8.2 - 14.6
Caspofungin concentration 24 hours after dosing	11	2.3	1.6 - 3.5

from candidiasis, received a caspofungin loading dose of 70 mg/m^2 followed by a maintenance dose of 50 mg/m^2 once-daily. The dose was based on the body surface area and also on the body-weight and was 49.7 + 7.2 mg/m^2 (range, 36.0 to 81.0) and 2.0 + 0.42 mg/kg (range, 1.0 to 3.6), respectively. Table 4 summarizes the pharmacokinetic parameters of caspofungin. This table confirms that the adjustment of caspofungin dosing-regimen based on the body surface is the most appropriate in pediatric patients. In addition, the bootstrap analysis revealed that the median parameter estimates were within the 95% confidence interval, indicating that the final model had good predictive performance and could determine the estimates of population pharmacokinetic parameters.

Li et al. [15], described the pharmacokinetics of caspofungin in 125 pediatric patients, aged 3 months to 17 years, with new-onset fever and neutropenia or with Candida or Aspergillus infections. Caspofungin was administered at the dose of 50 mg/m^2 once-daily and in some subjects the dose was given at 70 mg/m^2. Table 5 shows $AUC_{0\text{-}24\ hours}$, concentration of caspofungin and both are grouped on the base of children age. Table 6 shows the pharmacokinetic parameters which are clustered on the base favourable effects and Table 7 shows these parameters which are associated with diseases. Body-weight and disease status are the only covariates which affect caspofungin pharmacokinetic parameters. A reduction of 10 kg of body-weight is associated with only 7% increase in caspofungin concentration 1 hour after dosing thus, no dose adjustment is required for beyond the dosing-regimen which is based on the body surface area, and the disease status is a significant co-variate for $AUC_{0\text{-}24\ hours}$. Comparison of children with fungemia to those with persistent fever and neutropenia, children with new-onset fever and neutropenia had modest but significant reduction in $AUC_{0\text{-}24\ hours}$ (25%; P-value=0.004) and the concentration measured at 24 hours after dosing (decreased of 36%; P-value <0.001). Acyclovir, vancomycin and dexamethasone are associated with reduction of the caspofungin concentrations measured at 1 and 24 hours after administration. Dexamethasone (a cytochrome P-450 inducer) is associated with a statistically significant reduction (44%) of caspofungin concentration measured at 24 hours

Table 4: Population pharmacokinetic parameters of caspofungin and bootstrap results, by Yang et al. [14]

	From full data set		Bootstrap median
	Final estimate	%RSE	(95% Confidence interval)
Total body clearance (L/h)	0.165	4.4	0.161 (0.137 - 0.174)
Central distribution volume (L)	1.73	8.2	1.910 (0.069 - 0.739)
Inter-compartmental TBC (L/h)	0.351	47.6	0.169 (0.069 - 0.739)
Peripheral distribution volume (L)	0.943	22.3	1.500 (0.611 - 3.520)
BSA-TBC	1.3	13.8	1.420 (1.025 - 1.865)
BSA-central distribution volume	1.5	13.5	1.380 (0.970 - 1.955)
Inter-individual variability (%)			
Total body clearance	0.242	21	0.237 (0.144 - 0.299)
Inter-compartmental TBC	1.616	90	1.086 (0.188 - 2.500)
Central distribution volume	0.766	71.6	0.828 (0.286 - 1.979)
Residual variability (%)			
---	0.196	19.6	0.184 (0.153 – 0.204)

TBC: Total Body Clearance; BSA: Body Surface Area; %RSE: % Relative Standard Error

Table 5: Comparison of time-averaged pharmacokinetic parameters (days 3 to 14) in pediatric patients who received 50 mg/m^2 once-daily of caspofungin. Figures are the geometric mean and the 95% confidence interval, by Li et al. [15]

Parameter[a]	Number of children	Geometric mean (95% confidence interval)
Caspofungin $AUC_{0\text{-}24\ hours}$ (μg*h/ml)		
Overall	67	144 (134 - 156)
Young children	10	143 (117 - 174)
Older children	35	146 (131 - 163)
Adolescents	22	143 (125 - 163)
Caspofungin plasma concentration 1 hour after dosing (μg/ml)		
Overall	94	16.6 (15.4 - 18.0)
Young children	10	18.4 (14.5 - 23.4)
Older children	55	17.2 (15.5 - 19.0)
Adolescents	29	15.1 (13.1 - 17.4)
Caspofungin plasma concentration 24 hours after dosing(μg/ml)		
Overall	97	2.5 (2.3 - 2.8)
Young children	10	1.9 (1.4 - 2.6)
Older children	57	2.4 (2.1 - 2.7)
Adolescents	30	3.0 (2.5 - 3.2)

[a]Overall values averaged across all age groups (age as categorical variable); young children are aged 3 to 24 months, older children are aged 2 to 11 years, adolescents are aged 12 to 17 years.

after dosing. Odds ratios are estimated for the association between logarithmic-transformed pharmacokinetic parameters and treatment outcome or adverse-effects. No pharmacokinetic parameters or hybrid parameters (AUC/MIC) was significantly correlated with treatment outcome or adverse-effects in the setting of similar response levels, which suggests that caspofungin concentrations fall within the therapeutic interval. A decrease of elimination half-life was observed in younger children, and such a decrease is related to increased plasma clearance, decreased distribution volume, or both. These results support that caspofungin, given at a dose of 50 mg/m^2 is appropriate (after a loading dose of 70 mg/m^2) in children aged 3 months to 17 years.

Interaction *in-vitro* or *in-vivo* of caspofungin with drugs in humans

Synergistic interactions: Caspofungin has a synergistic interaction with posaconazole and itraconazole in-vitro and increases the antifungal activity in Aspergillus fumigatus [16]. Caspofungin and posaconazole induces synergistic effect in Candida albicans *in vitro* and *in vivo* [17], increases the concentration of cyclosporine [18], increases the plasma levels of cyclosporine and induces renal damage [19], increases the phenotypical effect of cefepime and amoxicillin on Candida albicans biofilm growth (*in vitro*) and induces the tolerance of these drugs [20]. Rifampin induces the metabolism of caspofungin *in vivo* [21]. Caspofungin inhibits the metabolism of immunosuppressive agents and increases their plasma concentration in solid organ transplant recipients [22], and induces limited adverse-effects in children [23]. Other adverse effects are: thrombophlebitis, hypercalcemia, hypokalaemia, elevated hepatic transaminase activities, hyperbilirubinemia, diarrhoea, rash, hypotension, and chills (NEOFAX®).

Antagonistic interactions: Caspofungin and itraconazole are substrates of CYP3A4 and caspofungin inhibits the metabolism of itraconazole *in vitro* [24]. Caspofungin is a potent inhibitor of voriconazole *in vivo* [25]. Miconazole is a potent inhibitor of caspofungin metabolism *in vitro* [26] and *in vivo* [18]. Caspofungin inhibits the metabolism of fluoroquinolones *in vivo* and this drug combination should be avoided [27]. Calcineurin inhibitors and sirolimus inhibit the metabolism of caspofungin *in vitro* [28].

Caspofungin induces toxicity *in vitro* and adverse-effects in infants and children

Caspofungin incubated with HepG2/C3A cells induces toxicity in these cells [29]. Caspofungin empirical therapy induces fever in children [30], caspofungin treatment induces electrolyte abnormalities in infants which appear similar to those observed in children and in adults [31]. Caspofungin-related serious adverse-effects may require discontinuation of therapy but this is quite uncommon [32]. High-dose of caspofungin induces adverse-effects in children with haematological malignancies and hematopoietic stem cell transplantation [33] and induces short-term and long-term adverse-effects in children [34]. Falagas et al. [35], compared the adverse-effects of caspofungin to those induced by amphotericin B. Both drugs induced nephrotoxicity, hypokalaemia, and fever but these occur less frequently following caspofungin than amphotericin B [35]. Caspofungin induces: fever, nausea, vomiting, and phlebitis, eosinophilia, protein increased alkaline phosphatase, hypokalaemia and hypercalcemia [36].

Treatment with caspofungin in infants and children

Caspofungin treatments was initiated in seven preterm infants with 23 and 24 weeks of postmenstrual age and were suffering from systemic fungal infection, and caspofungin successfully cured fungemia [37]. Invasive fungal infection causes morbidity and mortality and is a major concern for most neonatal care units word-wild and caspofungin successfully cured invasive candidiasis in preterm infants [38]. Candida infection is a source of significant mortality and morbidity in neonates and treatment strategies continue to change with the introduction of new antifungal agents. Among new antifungal drugs, caspofungin occupies an important role in treatment of candidiasis in infants [39]. Candidiasis is relatively frequent in neonates and may cause abscesses and caspofungin cured abscesses caused by Candida species [40]. Mycosis often occurs in infants and children, they may become resistant to azoles and caspofungin is an appropriate drug to treat mycosis [41]. The caspofungin maintenance dose should not be reduced in child-Pug score if this classification is driven by hypalbuminaemia as it results in significantly lower exposure. A higher maintenance dose of 70 mg results in target attainment of >90% in these children with a fungal MIC up to 0.125 μg/ml [42]. The treatment of invasive candidiasis is complicated by disseminate disease and caspofungin is an appropriate antifungal agent to treat invasive candidiasis in infants and children [43].Caspofungin is well tolerated in pediatric patients with febrile neutropenia requiring empirical antifungal treatment, or with fungal infections [44]. Caspofungin is used in pediatric patients and it displays favourable safety and tolerance and has useful antifungal efficiency in severely immune-compromised pediatric patients [45]. The prevalence of invasive fungal infections becomes to be a major problem in immunocompromised children and neonates. Caspofungin is approved for use in infant's aged ≥ 3 months and is an appropriate antifungal agent to treat candidiasis in immunocompromised infants and children [46]. Caspofungin may be an effective therapeutic option when treating candidaemia in children after extensive cardio-surgical procedures [47]. Compared to other antifungal agents, caspofungin has the best safety profile; tolerability causes low drug-interactions making caspofungin an interesting and extremely valuable new antifungal agent that broadens the available therapeutic armamentarium for the treatment of systemic fungal

Table 6: potential for caspofungin pharmacokinetic parameters to predict favourable treatment outcome in pediatric patients, by Li et al. [15]

Child group and pharmacokinetic parameters[a]	Number of children		Odds ratio
	Favourable outcome	Total	(95% confidence interval)
Empirical therapy			
Caspofungin $AUC_{0\text{-}24\ hours}$ (µg*h/ml)	5	16	0.18 (0.00 – 38.4)
Caspofungin concentration 1 hour after dosing	14	38	0.66(0.09 – 4.8)
Caspofungin concentration 24 hours after dosing	15	40	1.2 (0.28 – 5.4)
Invasive aspergillosis			
Caspofungin $AUC_{0\text{-}24\ hours}$ (µg*h/ml)	1	2	ND
Caspofungin concentration 1 hour after dosing	5	8	0.08 (0.00 – 9.0)
Caspofungin concentration 24 hours after dosing	5	8	0.01 (0.00 – 12.2)
Invasive candidiasis			
Caspofungin $AUC_{0\text{-}24\ hours}$ (µg*h/ml)	23	26	5.4 (0.07 – 400)
$AUC_{0\text{-}24\ hours}$/MIC (h)	21	24	0.47 (0.10 – 2.3)
Caspofungin concentration 1 hour after dosing Caspofungin	23	28	9.5 (0.27 – 2.3)
Caspofungin concentration 1 hour after dosing Caspofungin/MIC	21	25	0.99 (0.31 – 3.1)
Caspofungin concentration 24 hours after dosing	24	29	1.7 (0.19 – 14.4)
Caspofungin concentration 24 hours after dosing/MIC	21	25	0.94 (0.34 – 2.5)
Invasive candidiasis with a favourable microbiological response			
Caspofungin $AUC_{0\text{-}24\ hours}$ (µg*h/ml)	24	26	4.2 (0.03 – 645)
$AUC_{0\text{-}24\ hours}$/MIC (h)	22	24	0.48 (0.07 – 3.1)
Caspofungin concentration 1 hour after dosing	25	27	0.38 (0.01 – 22.8)
Caspofungin concentration 1 hour after dosing/MIC	23	25	0.28 (0.02 – 3.44)
Caspofungin concentration 24 hours after dosing	26	28	9.0 (0.11 – 3.4)
Caspofungin concentration 24 hours after dosing/MIC	23	25	0.72 (0.17 – 3.05)

[a]Time average (day 3 and greater); [b]Fold change in odds (probability of a favourable outcome/probability of an un favourable outcome) per unit increase (on the log scale) in parameter; ND = not determined due to small number of children.

Table 7: Potential for caspofungin pharmacokinetic parameters to predict occurrence of selected clinical adverse-effects and/or laboratory abnormalities, by Li et al. [15]

Type of clinical adverse-effects and/or Laboratory abnormalities[a]	Number of children		Odds ratio	*P-value[b]
	With event	Total	(95% confidence interval)	
Caspofungin $AUC_{0\text{-}24\ hours}$ (µg*h/ml)				
ALT >2.5 times upper normal limit	5	66	0.08 (0.00 – 9.3)	0.294
ALT >5 times upper normal limit	5	66	0.26 (0.01 - 6.1)	0.399
ALT >2.5 times baseline	9	66	1.0 (0.04 – 27.2)	0.987
AST 2.5 times upper normal limit	6	66	2.3 (0.07 – 80.6)	0.64
AST 2.5 times baseline	11	66	0.56 (0.04 -8.8)	0.678
Potassium< 2.5 mEq	3	68	1.6 (0.03 – 94.4)	0.82
Fever[c]	6	69	5.94 (0.07 – 488)	0.428
Headache[c]	2	69	1.67 (0.00 - > 999)	0.891
Caspofungin concentration 1 hour after dosing				
ALT >2.5 times upper normal limit	9	9	0.50 (0.07 – 3.8)	0.501
ALT >5 times upper normal limit	7	7	1.9 (0.17 – 20.2)	0.609
ALT >2.5 times baseline	20	20	1.6 (0.35 – 7.7)	0.536
AST >2.5 times upper normal limit	10	10	0.71 (0.10 – 7.7)	0.736
AST >2.5 times baseline	17	17	0.88 (0.18 – 4.3)	0.878
Potassium < 2.5 mEq	4	4	0.29 (0.02 – 4.3)	0.37
Fever[c]	14	14	4.4 (0.62 – 31.7)	0.137
Headache[c]	5	5	0.36 (0.02 – 5.3)	0.46
Caspofungin concentration 24 hours after dosing				
ALT >2.5 times upper normal limit	9	99	1.7 (0.37 – 7.6)	0.499
ALT >5 times upper normal limit	6	99	0.78 (0.16 – 3.9)	0.76
ALT >2.5 times baseline[d]	20	99	---	---
Persistence fever and neutropenia	10	39	36.3 (2.3 – 575)	0.011
Invasive aspergillosis	4	8	1.2 (0.10 – 14.88)	0.88
Invasive candidiasis	2	28	535 (0.21 - > 999)	0.117
New fever	4	24	0.40 (0.06 – 2.5)	0.331
AST >2.5 times upper normal limit	10	99	2.3 (0.49 – 11.0)	0.286
AST >2.5 times baseline	18	99	1.6 (0.51 – 4.9)	0.431
Potassium< 2.5 mEq	5	101	2.7 (0.36 – 21.1)	0.332
Fever[c]	17	102	3.1 (0.78 – 12.3)	0.107
Headache[c]	5	102	3.4 (0.28 – 42.3)	0.333

[a]Time averaged (day 3 or later); *The odd ratios (95% confidence interval) and the P-values are based on the model that included disease indication and the log-transformed phar17macokinetic parameter without their interaction term; [c]Rated possibly, probable, or definitely drug related by the investigator; [d]Statistical significant (P-value=0.027). The relation between pharmacokinetic parameters and occurrence of an ALT level >2.5 times the baseline level with an odds ratio of 36.3 (95% confidence interval=2.3-575) and P-value=0.011 for pediatric patients empirically treated for suspected fungal infection but not for pediatric patients with other disease indications.

infections [48].

Treatment of meningitis with caspofungin

In literature there are only three reports on the treatment of meningitis with caspofungin. Caspofungin has low capacity to penetrate into the meninges, even when they are inflamed, and does not appear to be a suitable agent to treat meningitis caused by fungi [49]. Jans et al. [50], reported a case of neonatal cerebrospinal fluid shunt-associated *Candida meningitis*. When caspofungin was injected into the cerebrospinal fluid, its concentration was adequate even in presence of a high systemic fungal infection and the addition of intravenous caspofungin was beneficial. Wilson et al. [51], enrolled 204 pediatric and adult patients of whom 57 patients had infections in the central nervous system. Twenty-seven, of these 57 patients, had unedified the infective agents causing infections and caspofungin cured meningitis or encephalitis in some patients.

Prophylaxis with caspofungin in children

Prophylaxis with caspofungin causes significantly lower incidence of adverse-effects than that performed with fluconazole in children, adolescents, and young adults with acute myeloid leukaemia. Caspofungin is an appropriate agent for the prophylaxis for invasive fungal infection [52]. There is a strong argument for the use of caspofungin prophylaxis in high-risk children because of the significant mortality-rate associated with invasive fungal infection. The choice of antifungal agents to carry out prophylaxis should be guided by risk stratification, knowledge of local fungal epidemiology, the efficacy and the tolerability profile of available agents [53]. Prophylactic caspofungin and liposomal amphotericin B have similar efficacy in pediatric patients who received allogenic hematopoietic stem cell transplantation [54]. Large clinical trials with anidulafungin, caspofungin, and micafungin demonstrate excellent clinical and microbiological efficacy for prophylaxis of invasive candidiasis. Therefore, the echinocandins rapidly became established in guidelines and clinical practice as primary treatment options for moderately to severely ill children with invasive candidiasis [55].

Use of antifungals during human pregnancy

Antifungal prescription remains a challenge in pregnant women because of uncertainties regarding foetal toxicity and altered maternal pharmacokinetic parameters that may affect efficacy or maternal and foetal toxicity. Recent data have also provided additional safety data on itraconazole, and lipidic derivatives of amphotericin B. Regarding newer antifungal drugs, including posaconazole and echinocandins, clinical data are critically needed before considering prescription in pregnancy [56]. Oral fluconazole or itraconazole may increase the risk of birth defects. Nonetheless, the risk of congenital heart defects and limb defects after fluconazole exposure and eye defects after itraconazole exposure should be cautiously investigated [57]. At present, very little data exist regarding the safety of systemic antifungal in pregnancy and treatment is restricted to topical therapy because of the negligible systemic exposition [58]. Amphotericin B remains the drug of choice for the treatment of systemic fungal infections during pregnancy but its use should be judicious. There are serious risks of foetal malformations associated with the use of griseofulvin, ketoconazole, voriconazole, flucytosine and potassium iodide and these drugs are contraindicated in pregnancy. There are insufficient data regarding the use of caspofungin in pregnancy [59]. Fluconazole exhibits dose-dependent teratogenic effects; however, it appears to be safe at lower doses (150 mg daily). Ketoconazole, flucytosine, and griseofulvin have been shown to be teratogenic and/or embryotoxic in animals. Iodides have been associated with congenital goiter and should not be used during pregnancy [60].

Mechanisms of caspofungin resistance

Bacterial-resistance to caspofungin may be caused by alteration of fungal genome or by phenotypic changes such as the modification of the bacterial cell wall being the target site of caspofungin. Tolerant mutants possess cell walls with elevated chitin and show down regulation of genes involved in cell wall biosynthesis, namely, FKS, located outside Ch5, and CHT2, located on Ch5, irrespective of Ch5 ploidy. Also irrespective of Ch5 ploidy, the CNB1 and MID1 genes on Ch5, which are involved in the calcineurin signaling pathway, were expressed at the diploid level. Thus, multiple mechanisms can affect the relative expression of the aforementioned genes, controlling them in similar ways. The mechanism of resistance involves amino acid changes in hot-spot regions of FKS subunits of glucan synthase, which decrease the sensitivity of the enzyme to drug. Cellular stress response pathways lead to drug adaptation, which promotes the formation of resistant fks strains. Clinical factors promoting echinocandin-resistance include empiric therapy, prophylaxis, gastrointestinal reservoirs, and intra-abdominal [61]. Whole genome sequencing identified a mutation in the drug target, FKS2, accompanying a major resistance increase, and 8 additional non-synonymous mutations. The FKS2-T1987C mutation was sufficient for echinocandin-resistance, and associated with a fitness cost that was mitigated with further evolution. A CDC6-A511G (K171E) mutation acquired before FKS2-T1987C (S663P), conferred a small resistance increase. Elevated dosage of CDC55, which acquired a C463T (P155S) mutation after FKS2-T1987C (S663P), ameliorated fitness. Genetic or pharmacological compromise of Hsp90 or calcineurin function reduced basal tolerance and resistance. Hsp90 and calcineurin are required for caspofungin-dependent FKS2 induction, providing a mechanism governing echinocandin-resistance. Resistance of clinical isolates of Candida albicans to caspofungin is slowly emerging and is linked to mutations in short conserved regions in the FKS1 gene. The most prominent changes occurred at the serine 645 position in FKS1p with substitutions of proline, tyrosine, and phenylalanine. An allele-specific real-time PCR molecular-beacon assay was developed for rapid identification of drug resistance by targeting FKS1 mutations. Mutations altering serine 645 were reliably identified in both heterozygous and homozygous states. The molecular-beacon assay was used to evaluate two large collections of spontaneous mutants from separate strains of Candida albicans with resistance (MICs>16 μg/ml) to caspofungin with the goal of understanding the relationship between FKS1 mutations and echinocandin-resistance. Of 85 resistant isolates recovered, all were identified with mutations in FKS1; 93% showed changes at Ser645, with 62% displaying a characteristic S645P substitution expressed as either a homozygous or a heterozygous mutation in FKS1. Two other prominent amino acid substitutions, S645Y and S645F, were found at frequencies of 22% and 8%, respectively. Three new mutations were also identified: T1922C, G1932T, and C1934G, encoding F641S, L644F, and S645C substitutions, respectively. One strain had the double amino acid substitution L644F and S645C. Allele-specific probes were combined in a multiplex assay for reliable screening of known FKS1 mutations. These data support the importance of FKS1p substitutions in echinocandin-resistance and demonstrate the feasibility of applying molecular screening for routine resistance assessment [62]. Consumption of caspofungin induces resistance [63,64].

Discussion

Caspofungin (Cancidas®) is an echinocandin and inhibits 1,3-β-D-glucan synthesis, which is an essential component of the fungal cell wall and is required for cellular integrity. Caspofungin is a cyclic lipopeptide with a hexadepsipeptide nucleus, exhibits fungicidal and fungistatic activities against Candida and Aspergillus species, respectively. Caspofungin is approved for the treatment of invasive candidiasis, as salvage therapy for patients with invasive aspergillosis who fail or are intolerant to amphotericin B formulations or voriconazole, for both oesophageal, oropharyngeal candidiasis, invasive candidiasis, and for treatment of persistently febrile neutropenic patients with suspected fungal infections and is one of the few antifungal agents which is approved for treatment in infants and children [1]. Adverse-effects caused by caspofungin are: thrombophlebitis, hypercalcemia, hypokalaemia, elevated hepatic transaminase activities, hyperbilirubinemia, diarrhoea, rash, hypotension, and chills (NEOFAX®). The dose of caspofungin is: 25 mg/m^2 once-daily for infants aged <3 months (Neonatal formulary) 50, or 70 mg/m^2 once-daily, for children aged up to 11 or up to 17 years, respectively (The British National Formulary for Children) and is administered by intravenous infusion to infants and children. The morbidity- and mortality-rates of preterm infants with invasive candidiasis are high [2]. Caspofungin is found efficacy and safe in neonates with candidaemia [3], is associated with little clinically significant toxicity compared to other antifungal agents such as azoles and amphotericin B [4], is well tolerated in subjects aged 6 months to 17 years and is efficacy in most subjects [5]. Caspofungin (2 μg/ml) significantly decreased the metabolism of *Candida* and *Aspergillus* species and is used for the prevention of candidiasis [7]. Letscher-Bru and Herbrecht. [10] enrolled patients with candidiasis and the resolution of symptoms was observed in 80.4% patients following a caspofungin dose of 50 mg once-daily and in 89.3% patients treated with caspofungin at a dose of 70 mg once-daily, whereas treatment with amphotericin B cured only 63.0% patients. These results suggest that the effect of caspofungin is dose dependent and caspofungin is more effective than amphotericin B in curing candidiasis. Caspofungin is largely eliminated by N-acetylation, catalyzed by CYP3A4, and inhibition of this enzyme causes marked increase of caspofungin serum concentration. Caspofungin accumulates into tissue cells being transported by the organic anion transport B1 [12]. Antachopoulos et al. [11], measured the minimum effective concentration to inhibit the proliferation of three species of *Aspergillus*, resulted to be 0.5 μg/ml, and this concentration is 4-fold lower than the trough concentration of caspofungin [13] suggesting that after a standard dose, caspofungin is an effective against *Aspergillus* species. Yang et al. [14], assessed the caspofungin pharmacokinetics in pediatric patients after a loading dose of 70 mg/m^2 followed by a maintenance dose of 50 mg/m^2 and this dosing-regimen is appropriate. The bootstrap analysis revealed that the median parameter estimates were within the 95% confidence interval, indicating that this dosing-regimen has good predictive performance and could determine the estimates of population pharmacokinetic parameters. Li et al. [15], described the pharmacokinetics of caspofungin in 125 pediatric patients, aged 3 months to 17 years, with new-onset fever and neutropenia or with Candida or Aspergillus infections. Caspofungin was administered at the dose of 50 mg/m^2 once-daily and in some subjects it was given at 70 mg/m^2. Caspofungin AUC0-24 hours and concentrations measured at 1 and 24 hours did not differed in young, older, and adolescents and caspofungin produced more favourable outcome in invasive candidiasis than invasive aspergillosis. These authors also observed that caspofungin induces little adverse-effects both at 1 and 24 hours after dosing. Caspofungin interact with several drugs and the interactions may be synergistic or antagonistic. This drug induced alterations of blood parameters [33], fever diarrhoea, vomiting [30], and high dose of caspofungin induces nephrotoxicity [34], these-adverse effect are blander than those induced by amphotericin B, but may require treatment discontinuation [32]. Treatment with caspofungin successfully treated candidaemia in preterm infants reducing the mortality-rate [38,40] and this drug is also appropriate to treat fungemia in children [39]. Compared to other antifungal agents, caspofungin has the best safety profile, tolerability with very low potential drug-interactions, and broadens the available therapeutic drugs for the treatment of systemic fungal infections [48]. Caspofungin penetrates poorly into the cerebrospinal fluid and is not a suitable agent to treat fungemia of the central nervous system [49]. Prophylaxis with caspofungin caused significantly lower incidence of adverse-effects than those caused by fluconazole in pediatric patients and caspofungin is an appropriate agent for the antifungal prophylaxis [52] even in high-risk children [53]. Echinocandins such as anidulafungin, caspofungin, and micafungin demonstrate their excellent clinical and microbiological efficacy in the prophylaxis of invasive candidiasis [55]. Little is known about the use of antifungal during pregnancy, but it is possible to conclude that echinocandins and azoles induce toxicity in the foetus and should not be used in pregnancy. Amphotericin B is the only antifungal drug which it's used in pregnancy, but its use should be judicious. As regards caspofungin, its use in pregnancy is for topical applications only because of its absorption causes limited systemic exposure. Bacterial-resistance to caspofungin has be reported by various authors and the resistance may be due to fungal genomic alteration or/and by phenotypic modification, such as that of the bacterial cell wall, which is the target site of caspofungin. In addition, the consumption of caspofungin induces bacterial resistance [64-67].

In conclusion, Caspofungin (Cancidas®) is an echinocandin and inhibits 1,3-β-D-glucan synthesis, which is an essential component of the fungal cell wall and is required for cellular integrity. Caspofungin is a cyclic lipopeptide with a hexadepsipeptide nucleus and exhibits fungicidal activity against Candida species and fungistatic against Aspergillus species. The dose of caspofungin is: 25, 50, or 70 mg/m^2 once-daily for infants aged <3 months, and for children aged up to 11 or up to 17 years, respectively, and is administered by intravenous infusion to infants and children. Caspofungin has been found to be effective in treating fungal infusion and is safer than fluconazole and amphotericin B. Caspofungin at a concentration of 2 μg/ml decreased the metabolism of Candida parapsilosis and induced death in Aspergillosis species. Caspofungin is largely eliminated by N-acetylation, catalyzed by CYP3A4, and is actively transported into the tissue cells by the organic anion transporter B1. Optimal dosing-regimen of caspofungin consists in a loading dose of 70 mg/m^2 following by a maintenance dose of 50 mg/m^2 given once-daily in both infants and children. Caspofungin interacts with drugs and the interaction may be synergistic or antagonistic. This antibiotic induces alterations of blood parameters, fever, diarrhoea, thrombophlebitis, hypercalcemia, hypokalaemia, elevated hepatic transaminase activities, hyperbilirubinemia, diarrhoea, rash, hypotension, and chills and high doses induce nephrotoxicity which may require interruption of treatment, and should not be administered during pregnancy because it induces foetal toxicity. Prophylaxis with caspofungin has been recommended in order to prevent infants and children from fungal infection. Some fungi may become resistant to caspofungin

and the resistance is due to alteration of fungal genome (genetic-resistance) and phenotypic-resistance such as the modification of the fungal cell wall which is the target site of caspofungin. In addition, caspofungin consumption induces fungal-resistance.

Conflict of interests

The authors declare no conflicts of financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employments, gifts, and honoraria.

This article is a review and drugs have not been administered to men or animals.

Acknowledgment

The author thanks Dr. Patrizia Ciucci and Dr. Francesco Varricchio, of the Medical Library of the University of Pisa, for retrieving the scientific literature.

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