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TREATING HEART FAILURE IN AFRICAN AMERICANS: FOCUS ON BIDIL®

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Heart failure (HF) is a progressive syndrome characterized by dyspnea, fatigue, and fluid overload. It affects about 6 million Americans and over half of this population dies within a few years of being diagnosed.[1] African Americans (AA) usually present with HF at a younger age, are affected approximately twice as often as other ethnic groups and are more likely to die from HF. Despite the success of conventional treatment options, including angiotensin converting enzyme (ACE) inhibitors and β-blockers, morbidity and mortality from HF remains high, especially in AA.

The hallmark of this syndrome is left ventricular dysfunction (LVD), which leads to decreased cardiac output (CO). A reduction in forward flow of blood activates a number of systemic and local compensatory responses. Ventricular dilation and hypertrophy occur in an attempt to increase diastolic filling capacity and increase CO. In addition to mechanical stretch, neuro-hormonal adaptive mechanisms also contribute to heart failure. These are mainly mediated by the sympathetic nervous system (SNS) and the renin-angiotensin-aldosterone system (RAAS).[1]

Heart failure is typically treated with ACE inhibitors, but in African Americans the RAAS appears to play a less significant role, thus ACE inhibitors and other drugs that modulate the RAAS may be less effective than in other populations.[2] Some studies have suggested a lower response in African Americans to ACE inhibitors,[3,5] whereas others have not.[6] African Americans due seem to exhibit lower levels of nitric oxide in their coronary and peripheral vasculature. This observation suggests that African Americans may be more responsive to nitric oxide replacement than other races.[7]

The combination of hydralazine and nitrates was used to mange CHF before the advent of ACE inhibitors and angiotensin receptor blockers (ARBs). Presently, the combination is reserved for patients intolerant of more conventional pharmacologic agents. BiDil®, a fixed dose combination of hydralazine and isosorbide dinitrate (Hyd-ISDN), has been developed by NitroMed for the treatment of African Americans with HF. The drug was approved by the FDA in June 2005 and the 37.5/20 mg (hydralazine/ISDN) strength used in the African American Heart Failure Trial (A-HeFT) trial was made available for prescription in July 2005.[9] This article will examine the efficacy and safety of Hyd-ISDN and explore its role in clinical practice.

Pharmacology and Pharmacokinetics

Hydralazine is a peripheral, direct-acting

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Table 1. Clinical trials of hydralazine/isosorbide dinitrate combination therapy in patients with HF.[1]

	N	Design	Study drug/ dose	Comparator	Results	Conclusions
V-HeFT I (1986)[11]	630	RDB	Hyd-ISDN 300/160 mg	Prazosin 20 mg/placebo	Mortality in AA = 9.7% in Hyd-ISDN group and 17.3% in placebo group (p=0.04). Whites 16.9% vs 18.8% in placebo	Hyd-ISDN showed significant mortality benefit among black patients, indicating possible NO deficiency in this population.
V-HeFT II (1991)[12]	789	RDB	Enalapril 20 mg	Hyd-ISDN 300/160 mg	Annual mortality rate was not different in black patients treated with enalapril (12.8%) compared to those treated with Hyd-ISDN (12.9%). White patients treated with enalapril showed decrease in mortality (11%) compared to those treated with Hyd-ISDN (14.9% - p=0.02)	Compared with hyd-ISDN, white population experienced survival benefit with enalapril, but AA experienced similar mortality with enalapril and Hyd-ISDN, indicating a greater response to Hyd-ISDN, lesser response to ACE inhibition, or both.
Exner et al. (2001)[6]	1996	Cohort	Enalapril 20mg	Placebo	Black patients randomized to enalapril had more hospitalizations than white patients (p=0.001). Black patients randomized to placebo had similar rates of hospitalization compared to whites (p=0.06). Mortality was similar in both racial groups regardless of treatment.	Enalapril therapy seems to be associated with decrease in the risk of hospitalization among white patients with LVD but not in black patients.
A-HeFT (2005)[3]	1050	RDB	Hyd-ISDN 37.5/20mg three times daily titrated to 2 tablets three times daily	Placebo	43% reduction in all-cause mortality (p=0.01) in Hyd-ISDN group compared with placebo in addition to standard HF therapies. First hospitalization rate due to HF decreased 33% in the Hyd-ISDN group compared to placebo (p = 0.001)	Mortality reduction is consistent with the existence of another mechanism which controls HF progression besides neurohormonal mediators

RDB denotes a randomized, double-blind trial design. NO denotes nitric oxide.

vasodilator, which induces relaxation of arteriolar muscles resulting in afterload reduction. Hydralazine's onset of action following oral administration is 20-30 minutes; bioavailability is 30-50% in fast acetylators and food reportedly enhances its absorption.[8] Hydralazine is about 90% protein bound and metabolized by hepatic acetylation. It is excreted renally with a 1.75-hour elimination half-life in HF patients with normal renal function, and 14% is excreted as unchanged drug. Renal impairment prolongs the half-life and results in higher hydralazine plasma concentrations.[8] Dosage adjustment is indicated when creatinine clearance is below 50 ml/min.

ISDN is converted to nitric oxide, which stimulates synthesis of cyclic guanosine monophosphate (cGMP). cGMP reduces intracellar calcium concentrations resulting in vasodilatation via relaxation of smooth muscle cells and a decrease in preload. The oral bioavailability of ISDN is approximately 58% and absorption is reduced if taken with food. Its onset of action is about 15 minutes following oral administration with a duration of action of four to six hours.[8] The drug is extensively metabolized hepatically to active metabolites, such as the 5-

Table 2. Adverse effects associated with hydralazine and ISDN.[1,8]

	Cardiovascular	Gastrointestinal	Dermatologic	Misc
Hydralazine	Tachycardia Angina Hypotension (rare)	Constipation Anorexia Nausea, vomiting, diarrhea	Rash (rare)	Lupus-like syndrome (dose-related) Headache
ISDN	Tachycardia Flushing Postural hypotension	Nausea Vomiting Bowel incontinence	Rash (rare)	Headache (common) Cold sweat Syncope (rare)

mononitrate and 2-mononitrate. Half-lives for parent drug and metabolites are 4 hours and 5 hours, respectively. Elimination is virtually completely via metabolism and no dosage adjustment is necessary in the setting of renal impairment.

Growing evidence suggests that nitric oxide plays a pivotal role in the pathophysiology of CHF and cardiac remodeling, and impaired availability of nitric oxide occurs in various models of HF.[3] ISDN serves as a nitric oxide donor and hydralazine acts as an antioxidant which prevents the breakdown of nitric oxide by inhibiting the formation of reactive oxygen radicals, including superoxide.[10] Theoretically, this tandem process should be useful considering that excess superoxide reacts directly with nitric oxide and disrupts its signaling capacity while producing other toxic, reactive species in the process.

Clinical Trials

Some studies have demonstrated a racial difference in response to ACE inhibitors.[4,5] Exner et al. compared the response of enalapril in blacks and whites with HF and found that enalapril was associated with a significant decrease in hospitalization in caucasians with LVD but not in AAs.[6] (Table 1)

The Vasodilator-Heart Failure Trial (V-HeFT) demonstrated that the combination of hyd-ISDN decreased mortality in patients with HF.[11] (Table 1) The first V-HeFT I study was conducted between 1980 and 1985 with 450 white male patients and 180 African American male patients who were randomized to hyd-ISDN 300/160 mg daily, prazosin 20mg daily or placebo. There was a significant decrease in mortality in the group of patients treated with hyd-ISDN compared to no change in the prezosin or placebo-treated groups. However, overall, in V-HeFT-II, patients randomized to enalapril experienced greater survival compared with hyd-ISDN.[12] Retrospective analyses of the V-HeFT data have suggested that Caucasians respond best to inhibition of the renin-angiotensin system, whereas Afircan Americans are more responsive to nitric oxide replacement. Nevertheless, in the wake of V-HeFT-II and subsequent studies with ACE inhibitors, Hyd-ISDN became an alternative for patients unable to tolerate ACE inhibitor therapy.

The A-HeFT trial was a phase III confirmatory study of a fixed-dose combination of hydralazine and isosorbide dinitrate.[3] It demonstrated that when administered with conventional HF therapies like β-blockers, angiotensin receptor blockers (ARBs), ACE inhibitors, spironolactone, diuretics or digoxin, hyd-ISDN decreases morbidity and mortality in African Americans with HF. The study was a randomized, double blind, placebo-controlled trial with 1050 self-identified AAs men and women with decreased ejection fraction, left ventricular hypertrophy, and class NYHA III and IV HF. Treatment included either hyd-ISDN or placebo in addition to background therapy for HF. The dose was 37.5 mg hydralazine and 20 mg ISDN as one tablet administered three times daily, titrated up to two tablets three times daily (225/120 mg daily) as tolerated.[3] The primary endpoint was a composite of weighted values for any-cause death, first hospitalization for HF during the 18-month follow-up period, and change in quality of life after 6 months as assessed by the Minnesota Living with Heart Failure questionnaire.[3] The study was originally designed to continue until early 2005 but was halted prematurely in July 2004 due to significant survival benefit observed in the treatment group compared to placebo.

Safety and Toxicity

The most common adverse events among patients treated with BiDil® in A-HeFT were headache (47.5%) and dizziness (29.3%) which occurred significantly more frequently in the group given hyd-

ISDN. HF exacerbations were more frequent and severe in the placebo group. The trial data did not address whether or not these side effects were dose-related. Hydralazine can cause a clinical syndrome similar to systemic lupus erythematosus (SLE). In patients who develop symptoms suggestive of SLE, monitoring of complete blood counts and ANA titers is warranted. Table 2 lists other side effects encountered with hydralazine and ISDN.

Dosing and Monitoring

BiDil® should be initiated at 1 tablet (37.5 mg hydralazine/20 mg ISDN) three times daily and titrated up to 2 tablets three times daily (225/120 mg daily).[3] There are no recommended dosage adjustments in patients with renal or hepatic impairment.

Cost

The cost for a 180-count bottle (2 tablets three times daily) of BiDil® is $324 ($1.80/tablet). However, BiDil® will be made available by NitroMed under a novel pricing structure. NitroMed has announced that patients without insurance whose incomes are up to 3 times the poverty level, will be able to acquire BiDil® free of charge. For those without insurance, the cost will be approximately $25/month. Thus, most patients should be able to access the medication at a reasonable cost.

Summary

Based on the theory that the progression of HF may involve both neurohormonal pathways and the nitroso-redox balance in the cardiovascular system, the hyd-ISDN combination therapy appears to be an effective agent for the treatment of patients self-identified as blacks with NYHA class III or IV HF when used in conjunction with their current HF therapies. Considering that there is still controversy about whether or not a racial difference in response to conventional therapies exists, there is a need to conduct studies in other populations of patients. For now, BiDil® is a welcomed addition to the pharmacological repertoire with the potential to further reduce mortality in African Americans with HF.

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TYGACIL™: A NEW BROAD-SPECTRUM ANTIBIOTIC

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The emergence of resistant bacteria to a variety of antibiotics is a major concern to healthcare. In 1995, the Center for Disease Control and Prevention (CDC), recognizing the importance of such resistance, created a national campaign to reduce antibiotic resistance through promotion of appropriate antibiotic use.[1] Appropriate antibiotic use consists of proper prescribing, targeting therapy toward specific pathogens, and utilizing suitable antibiotic regimens for an appropriate duration. Simply stated, antibiotic use contributes to resistance, but widespread misuse breads resistance.

The antibiotic era is threatened by high levels of resistance among key pathogens, inadequate supplies of novel antibiotics, and reduction in the number of drug companies engaged in antibiotic development.[2] Fifty percent of pneumococcal strains in the US express resistance to penicillin, 50% of all *Staphylococcus aureus* are methicillin resistant (MRSA), 30% of enterococci are vancomycin resistant (VRE), and 20% of *Pseudomonas aeruginosa* are resistant to fluoroquinolones.[2] Exacerbating the problem, in 2002, of 89 new drugs approved, not one was an antibiotic.[3] As of July 2004, only 5 antibiotics were in development, compared to over 500 total agents in the pipeline. Agents approved in recent years have major limitations. For example, daptomycin only covers gram-positive organisms and a few anaerobes, while the broad-spectrum antibiotic, ertapenem, is inactive against MRSA and less active than other carbapenems against *P. aeruginosa*.

Tigecycline, or Tygacil™, is a broad-spectrum glycylcycline antibiotic that has activity against gram-positive, gram-negative, anaerobic, and atypical bacteria.[4] Its activity encompasses resistant pathogens as well. Tigecycline, a structural analog to tetracycline, overpowers the two types of resistance mechanisms that engender resistance to tetracycline: drug efflux and ribosomal modifications.[5] Tigecycline is marketed by Wyeth, and is approved for the treatment of complicated intra-abdominal infections (cIAI) and complicated skin and skin structure infections (cSSSI).[14] This article will summarize the pharmacokinetic, safety, and in vitro data, and examine clinical trials of tigecycline.

Pharmacology and Pharmacokinetics

Tigecycline's mechanism of action is similar to that of macrolides and aminoglycosides. It invades bacteria though passive or active pathways and reversibly binds to the 30S subunit of the ribosome. This blocks the entry of transfer RNA into the A site, which prevents protein synthesis and bacterial growth.[5] Tigecycline is considered bacteriostatic.[14]

Pharmacokinetic data were evaluated in three groups of men 18- to 50-years-old.[6] The 3 groups contained 8 subjects each; 6 received tigecycline and 2 received placebo. The first group received ascending single intravenous (IV) doses of tigecycline, from 12.5 mg to 300 mg, infused over 1 or 4 hours. Half of this group received tigecycline in the fed state, while the others received the antibiotic in the fasting state. The second group received 25, 50, 75 and 100 mg doses of tigecycline as 1 hour infusions, every 12 hours for 9 days. The last group received a 100 mg loading dose, followed by 9 doses of 50 mg of tigecycline every 12 hours for 5 days. Results from this study concluded that tigecycline's serum concentration did not differ in the fed or fasting state. Dose-proportional Cmax, or the peak serum concentration, values ranged from 0.11 to 2.8 μg/ml and the corresponding AUCs, or the amount of drug in the body over time, were 0.75 to 17.8 μgh/ml. Mean clearance (CL) was not significantly different among doses, ranging from 0.2 – 0.3 L/h/kg. The mean half-life was 40 to 60 hours and the mean Vd was larger than 8 L/kg. Vd relates the amount of drug in the body to the plasma concentration. Tigecycline's large Vd indicates extensive tissue distribution with steady-state levels occurring in 7 days. Tigecycline is excreted in bile, but approximately 15% of tigecycline is excreted as unchanged drug. No major metabolites of tigecycline have been identified. Pooled pharmacokinetic parameters from the tigecycline's prescribing information are shown in Table 1.

Cmax and AUC were slightly higher in patients with renal impairment (CrCl < 30 ml/min)

Table 1. Pharmacokinetic Parameters of Tigecycline.[14]

	Single Dose, 100 mg (N=224)	Multiple Dose,[a] 50 mg q12h (N=103)
Cmax (μg/mL)[b]	1.45	0.87
Cmax (μg/mL)[c]	0.90	0.63
AUC (μg·h/mL)	5.19	--
AUC0-24h (μg·h/mL)	--	4.70
Cmin (μg/mL)	--	0.13
t½ (h)	27.1	42.4
CL (L/h)	21.8	23.8
CLr (mL/min)	38.0	51.0
Vss (L)	568	639

[a]100 mg initially, followed by 50 mg every 12 hours. [b] 30-minute infusion, [c] 60-minute infusion. Cmax= maximum serum concentration. Cmin= minimum serum concentration. AUC= area under the concentration-time curve which represents total drug exposure. t½ = half-life. CL= clearance. CLr= renal clearance. Vss= volume of distribution at steady state.

and patients with end-stage renal disease on hemodialysis.[7] Tigecycline is not significantly removed by hemodialysis and dosage adjustments for renal impairment are not necessary at this time. No dosage adjustment is recommended in patients with mild to moderate hepatic impairment, but in patients with severe hepatic impairment, the maintenance dose of tigecycline should be decreased 50% to 25 mg every 12 hours.[14]

Tigecycline was evaluated in patients of differing age, race, and gender. Although women and men aged > 75 years had the highest AUC values, all pharmacokinetic parameters studied were not significantly different.

In vitro studies indicate that tigecycline demonstrates a post-antibiotic effect (PAE). After a single dose of tigecycline, the PAE was 8.9 hours for *Streptococcus pneumonia* and 4.9 hours for *E. coli*.[8] Such data suggests the potential for tigecycline to exert an antibacterial effect at sub-MIC concentrations.

Resistance

The primary mechanisms of tetracycline resistance, and possibly tigecycline resistance, involve ribosomal modification and an active efflux. Tigecycline's higher binding affinity to ribosomes and its ability to go unrecognized by efflux pumps, allows tigecycline to overcome resistance at this time.[4] Although attempts have been made to induce resistance in laboratory settings, no resistant isolates have been observed.[9] Therefore, clinically relevant resistant strains are not expected to develop quickly, though longitudinal surveillance will be necessary to confirm this assumption.[5]

Spectrum of Activity

Tigecycline has in vitro activity against gram-positive, gram-negative, anaerobic and atypical organisms, including resistant strains. **Table 2** identifies minimum concentrations (MIC) required to inhibit 50% and 90% of isolates (MIC50 and MIC90) along with MIC ranges. Early breakpoints for susceptibility to tigecycline are as follows: isolates with MICs $\leq$ 2 ug/ml are considered susceptible, and isolates with MICs $\geq$ 8 ug/ml are considered resistant.[4]

Tigecycline is active against most gram-positive aerobes, including methicillin-susceptible *S. aureus* (MSSA), methicillin-resistant *S. aureus* (MRSA), penicillin-resistant *S. pneumoniae* (PRSP), *E. faecalis* and *E. faecium*.[5] Gram-negative coverage includes *E. coli, Haemophilus influenzae, Klebsiella pneumoniae, Moraxella catarrhalis, Neisseria, Salmonella,* and *Shigella.* Atypical coverage includes *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*; no activity is noted against *Mycobacterium avium*. Tigecycline has no activity against *Proteus mirabilis* or *Pseudomonas aeruginosa*.[4] Even though in vitro data provides valuable information, evaluation of tigecycline in the clinical setting is imperative in defining its role in therapy.

To date, only two phase II clinical trials have evaluated tigecycline in active infections. Postier et al. compared two doses of tigecycline in cSSSI.[10] A total of 160 patients were randomized to receive tigecycline 25 or 50 mg IV doses, every 12 hours for 7 to 14 days. The primary outcome was the clinically observed cure rate among clinically evaluable (CE) patients at the test-of-cure visit, within 3 weeks of initiation of therapy. Secondary endpoints were the clinical cure rate at the end of treatment and bacterial response in the microbiologically evaluable (ME) patients. Organisms cultured to determine bacterial response were MRSA, MSSA, *S. pyogenes, E. coli, E. faecalis, and E. faecium*. CE patients were required to receive 7 to 14 days of therapy, complete a test-of-cure visit, and not receive concomitant antibiotics. In 109 CE patients, clinical cure rates were 74% for the 50 mg tigecycline dose and 67% for the 25 mg dose. Bacteriologic response was 70% and 56%, respectively (**Table 3**).

Murray et al.[11] evaluated tigecycline in patients with complicated intra-abdominal infections.

Table 2. In vitro activity of tigecycline against clinical isolates obtained from 1997–2004.[5]

Organisms	Isolates (#)	MIC (mg/L) Range	50%	90%
Gram-positive aerobic pathogens				
Staphylococcus aureus				
Methicillin-susceptible	160	0.03–0.25	0.12	0.12
Methicillin-resistant	170	0.03–2	0.12	0.25
Community-acquired methicillin-resistant	10	0.12–0.25	0.12	0.25
Glycopeptide-intermediate	19	0.06–1	0.12	0.25
Staphylococcus epidermidis				
Methicillin-susceptible	159	0.03–2	0.12	0.5
Methicillin-resistant	155	0.03–1	0.12	0.5
Streptococcus pneumoniae				
Penicillin-susceptible	176	≤0.03–0.12	≤0.03	0.06
Penicillin-intermediate	305	≤0.03–0.03	≤0.03	0.06
Penicillin-resistant	270	≤0.03–0.25	≤0.03	0.06
Enterococcus faecalis				
Vancomycin-susceptible	159	0.03–0.25	0.06	0.12
Vancomycin-resistant	147	≤0.016–0.5	0.06	0.12
Enterococcus faecium				
Vancomycin-susceptible	171	≤0.03–0.25	0.06	0.12
Vancomycin-resistant	155	≤0.03–0.25	≤0.03	0.12

Table 2 Continued.

Gram-negative aerobic pathogens				
Citrobacter freundii	160	≤0.06–8	0.25	0.5
Enterobacter aerogenes	161	≤0.06–4	0.25	1
Enterobacter cloacae	160	0.25–8	0.5	0.5
Escherichia coli				
Non-ESBL producing	208	0.06–1	0.12	0.5
ESBL producing	170	0.06–4	0.25	0.5
Klebsiella pneumoniae				
Non-ESBL	180	0.25–4	0.5	1
ESBL producing	171	0.12–4	0.5	2
AmpC producing	89	0.25–4	1	2
Proteus mirabilis	160	0.5–16	4	8
Serratia marcescens	160	0.25–8	1	2
Salmonella enterica ser Enteritidis	229	0.12–2	0.5	1
Shigella sonnei	274	0.06–1	0.25	0.5
Pseudomonas aeruginosa	160	0.25–32	8	16
Acinetobacter baumannii	158	0.03–4	0.5	2
Anaerobes				
Bacteroides fragilis	425	0.015–32	1	4
Prevotella spp.	81	0.015–1	0.12	0.5
Clostridium difficile	63	≤0.06–0.5	0.25	0.5
Clostridium perfringens	70	0.03–4	0.06	0.5
Peptostreptococcus spp.	99	0.015–0.25	0.06	0.25

Table 3. Results from clinical trials with tigecycline.

Study	Indication	Patients (#)	Dose	Clinical Cure Rate TOC	Microbiological cure rate at TOC	Clinical cure rate EOT	Microbiological cure at EOT
Postier et al.[10]	cSSTI	160	25 mg 50 mg	67% 74%	56% 69%	78% 85%	62% 74%
Murray et al.[11]	cIAI	111	100 mg LD, 50 mg q12h	66.7%	66.7%	75.8%	75.8%
300 and 305[14]	cSSTI	422	100 mg LD, 50 mg q12h	86.5%	79.7%	NA	NA
301 and 306[14]	cIAI	512	100 mg LD, 50 mg q12h	86.1%	80.2%	NA	NA

cSSTI = complicated skin and soft tissue infections; cIAI = intra-abdominal infections; TOC = test of cure; EOT = end of treatment; LD = loading dose; NA = not available.

Sixty-six patients met the inclusion criteria and had a diagnosis of perforated gangrenous appendicitis, complicated cholecystitis, perforated diverticulitis, or peritonitis and a follow-up visit. All patients received a 100 mg IV tigecycline loading dose, followed by 50 mg IV every 12 hours for 5 to 14 days. Clinical cure rates at the test-of-cure and end-of-treatment visits were 67% and 76%, respectively (**Table 3)**.

Prescribing information for tigecycline highlights two phase III clinical trials for the treatment of cSSSI and two phase III clinical trials for the treatment of cIAI. Results from these trials are also summarized in **Table 3**.

Toxicity and Safety

A complete list of adverse events with tigecycline have recently been published.[14] Specific warnings in the prescribing information for tigecycline are to avoid use in pregnancy, during tooth development, and any persons with known hypersensitivity to tigecycline. Tigecycline, like all antibiotics, has the potential to cause pseudomembranous colitis.[14] The most common adverse events in clinical trials were nausea, vomiting, and diarrhea. (**Table 4**) In a study utilizing tigecycline for complicated skin infections, both the 25 mg and 50 mg doses were well tolerated.[10] Most adverse events did not result in dicontinuation of study drug. Six of 160 study patients (4%) discontinued therapy due to nausea and vomiting (2), diarrhea (1), paresthesia (1) and allergic reaction (1). Laboratory abnormalities included elevated serum transaminases in 5 patients, elevated serum alkaline phosphatase in 2 patients, elevated blood urea nitrogen in one patient and anemia in one patient. No patient discontinued therapy due to abnormal lab results.

Dosing and Administration

In pharmacokinetic studies, tigecycline doses have range from 12.5 mg to 300 mg daily.[6,12,13] Tigecycline is only available as a parenteral infusion. In clinical trials, tigecycline was administered as a 100 mg IV loading dose, followed by 50 mg IV every 12 hours for 5 to 14 days. According to a pharmacokinetic study by Muralidharan,[6] the maximum tolerated fasting dose of tigecycline was 100 mg and the maximum non-fasting dose was 200 mg. GI adverse events increased with increasing tigecycline doses and doses above 300 mg were poorly tolerated. Varying the infusion time from 30 minutes to 4 hours had no effect on adverse events. The approved dose of tigecycline for patients 18 years and older is an initial dose of 100 mg, followed by 50 mg every 12 hours. IV infusions of tigecycline should be administered over 30-60 minutes.[14]

Cost

Tigecycline is available in packages that contain ten 50 mg vials. The cost for 10 vials is $452.30. Thus, a course of tigecyline is expected to cost anywhere from $226.15 to $633.22 (5-14 days) depending on duration. (Personal communication with Wyeth, September 8, 2005)

Summary

Tigecycline is a broad-spectrum glycylcycline antibiotic approved for the treatment of complicated intra-abdominal infections (cIAI) and complicated skin and skin structure infections (cSSSI). It demonstrates activity against gram-positive, gram-negative, anaerobic, and atypical bacteria. Tigecy-

Table 4. Adverse events of tigecycline during clinical and pharmacokinetic trials.

	Postier et al.[11]		Muralidharan et al.[6]
Adverse event	25 mg Tigecycline n = 79	50 mg Tigecycline n = 81	12.5 – 300mg Tigecycline
Nausea	22%	35%	48.5%
Vomiting	13%	19%	29.4%
Diarrhea	11%	9%	NR
Pulmonary physical finding	11%	4%	NR
Headache	8%	5%	NR
Pain	6%	6%	NR
Fever	5%	6%	NR
Insomnia	5%	6%	NR
Dizziness	5%	3%	NR
Hypertension	5%	3%	NR
Anemia	5%	1%	NR

cline's activity includes resistant organisms, such as MRSA, PRSP, and VRE, while possessing a low potential for inducing resistance. Pharmacokinetic data suggests significant distribution of tigecycline into tissues, which increases the drug concentration at the site of infection and allows for a shorter duration of therapy. Tigecycline possesses a long half-life. This characteristic allows for convenient dosing and maintains tigecycline's serum concentration above the MIC for longer time intervals. Nausea and vomiting are the most common adverse events of tigecycline, but can be reduced at dosages of 100 mg or less on a full stomach. Current and future clinical trials, with larger numbers of patients, should help define tigecycline's role in therapy.

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