Single or 2-Dose Micafungin Regimen for Treatment of Invasive Candidiasis: Therapia Sterilisans Magna!

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The time the earth takes to rotate its axis (the day) has dictated how often pharmaceutical compounds are dosed. The scientific link between the 2 events is materia medica arcana. As an example, in the treatment of invasive candidiasis, antifungal therapy with intravenous micafungin is dosed daily. A literature review revealed population pharmacokinetic analyses, in vivo pharmacokinetics/pharmacodynamics studies, and maximum-tolerated-dose studies of micafungin that examined optimal micafungin dosing strategies. The half-life of micafungin in patient blood was 14 hours in several studies, but was even longer in different organs, so that the concentration will persist above minimum inhibitory concentrations of Candida species for several days. Studies in mice and rabbits with persistent neutropenia and disseminated candidiasis, otherwise fatal, demonstrated that a single large dose of micafungin could clear disseminated candidiasis, even though the micafungin half-life in such animals is shorter than in humans. Human pharmacokinetics/pharmacodynamics studies confirmed this link between micafungin efficacy and the ratio of the area under the concentration-time curve, and the optimal exposures initially identified in neutropenic animals. Maximum tolerated dose studies have demonstrated safety of 900 mg administered daily for several weeks, whereas case reports demonstrate efficacy and safety of single 1400-mg doses. Thus, a single dose of micafungin, or 2 such doses within a few days of each other, is not only logical, but might even lead to faster clearance of Candida.

Keywords. pharmacokinetics/pharmacodynamics; intermittent therapy; maximum tolerated dose; micafungin; invasive candidiasis.

Therapeutic results with the mouse have been exceptionally favorable. It has been possible with the help of this substance to cure mice which were on their second day of infection and would have died in a few hours. This is a result which a priori would not have been considered possible. We have found a series of these compounds which are able to quickly and in high proportion effect a cure which I have called ‘Therapia sterilisans magna.’

That is to say, a complete sterilization of a highly infected organism with one dose.

—Paul Ehrlic, 1908 [1]

Invasive candidiasis is one of the most common community-acquired conditions to afflict immunocompromised patients throughout the world. In hospitalized patients, invasive candidiasis, especially from Candida albicans and Candida glabrata, is a common nosocomial infection [2, 3]. In severely sick patients, such as those in the intensive care unit, fungal infections (mainly candidiasis) are the third most common group of infections after gram-negative and gram-positive bacteria [4]. Left untreated, invasive candidiasis has mortality rates of 35%–60%; even when treated it is associated with longer length of stay in hospitals and high hospitalization costs. Treatment of invasive candidiasis is recommend- ed with 1 of 3 classes of agents: polyenes, triazoles, or...
Echinocandins [5]. Factors associated with poor outcome include severity of illness, organ dysfunction, abdominal source, inadequate source control, and inadequate antifungal therapy [3, 6, 7]. Specifically, echinocandins may be superior to other classes of antifungal agents for the treatment of candidemia and other forms of deeply invasive candidiasis [8, 9].

The echinocandin micafungin is indicated for the treatment of candidemia and other forms of deeply invasive candidiasis, and has clinical cure rates of approximately 72%, similar to that of other echinocandins. Although this is a good success rate, it nevertheless means that there is room for improvement if therapy is further optimized, perhaps to the upper 90% range. All currently licensed echinocandins, including micafungin, are not absorbed by the gastrointestinal tract, and as a result must be administered intravenously [10]. Thus, for the treatment of candidiasis, echinocandins are administered as daily intravenous therapy for at least 2 weeks of therapy [5]. To achieve this, patients need long-dwelling intravenous catheters, and either stay hospitalized, or receive the intravenous therapy via an outpatient infusion program.

**Echinocandin Inhibition of (1→3)-β-D-glucan Synthase is Concentration-Dependent**

Echinocandins kill *Candida* species because they inhibit (1→3)-β-D-glucan synthesis; as glucan constitutes 60% of the fungal cell wall, this leads to cell lysis. The inhibition of (1→3)-β-D-glucan synthase by echinocandins is concentration-dependent [11–13]. This means more and faster fungal cell lysis as drug concentration increases. In addition, as the cell wall is not encountered in human cells, and echinocandins have a specific target in the fungal cell wall component (1→3)-β-D-glucan, echinocandins tend to have a wide safety profile. This is particularly true with micafungin, which does not need a special vehicle for solubility and is dissolved in normal saline, obviating concerns of toxicity from vehicles used to solve solubility problems of some other intravenous antifungal agents. This makes micafungin attractive for high-dose intermittent therapy.

**Pharmacokinetic Considerations for Intermittent and Single Doses of Micafungin**

Micafungin is a 2-compartment-model drug, which means that the time-course and elimination rates of the drug behave as if there were 2 compartments in the body (systemic circulation and peripheral compartment). Given this, micafungin’s baseline population pharmacokinetic parameter estimates as a 2-compartment model were found to be remarkably similar between adult patients in 4 independent studies [14–17]. A large proportion of the between-patient variability is driven by patient weight, based on fractal geometry power laws, so that the relationship between total micafungin clearance and weight$^{3/4}$ leads to predictable pharmacokinetics, ranging from 2.5-kg infants to obese 250-kg adults [15, 18–20]. The population pharmacokinetic parameter estimates are shown in Table 1. The “average” terminal (β-) half-life of micafungin in the central compartment or systemic circulation is about 14.1 ± 1.1 hour; the half-life is even longer in peripheral tissues and organs (compartment 2) [15, 16]. Thus if one gave doses 7- to 14-fold higher than currently administered, which achieve a peak concentration of up to 70 mg/L, then the micafungin concentrations would remain higher than the minimum inhibitory concentrations (MICs) of >99% of *Candida* species for more than a week [21].

**Pharmacokinetics/Pharmacodynamics “To Cure Mice Which Were on Their Second Day of Infection and Would Have Died in a Few Hours”**

Gumbo et al performed a 24-hour dose-response pharmacokinetics/pharmacodynamics (PK/PD) study in severely neutropenic mice with disseminated *C. glabrata* [22]. The study, which examined 3 different organs, the spleen, lung, and kidney, found that the dose mediating 50% of maximal kill (ED$_{50}$) was similar for all 3 organs (Figure 1A). Next, we examined the effect of a single micafungin dose administered at the start of the week on daily kidney fungal burden for an entire week. The concentration-time profile of micafungin in the mice is shown in Figure 1B, which demonstrates a half-life of 6.1 hours in mouse serum, <50% than in humans. Despite that shorter half-life, as doses increased, a single dose was reached at which there was no fungal regrowth, despite the severe neutropenia (Figure 1C). The dose-effect curve at the end of 7 days after a single dose is shown in Figure 1D. Thus, a single dose of micafungin that is large enough will result in sustained antifungal effect, even during severe neutropenia. As the drug is virtually gone

**Table 1. Population Pharmacokinetic Parameter Estimates of Micafungin**

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>Estimate</th>
<th>Relative Standard Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central compartment volume, L</td>
<td>11.7</td>
<td>55.7%</td>
</tr>
<tr>
<td>Clearance from peripheral compartment, L/h</td>
<td>26.5</td>
<td>70.9%</td>
</tr>
<tr>
<td>Volume of peripheral compartment, L</td>
<td>18.3</td>
<td>42.4%</td>
</tr>
<tr>
<td>Systemic clearance, L/h</td>
<td>1.04 x (weight/66)$^{3/4}$</td>
<td>6.99%$^a$</td>
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$^a$ Relative standard error for slope.
from site of infection by that time, this is true in vivo post antifungal effect.

Daily doses mediating 34%, 50%, and 80% of maximal kill (ED$_{34}$, ED$_{50}$, and ED$_{80}$, respectively) were delivered as either daily doses, or the cumulative 7-day dose was combined (ie, 7 × daily dose) and delivered as a single dose at the start of therapy, or split into 2 equal doses and delivered on days 0 and 3.5, to neutropenic mice with disseminated candidiasis. Thus, all mice within a dose group received the same cumulative dose for the week, and therefore the same 0- to 168-hour area under the concentration-time curve (AUC) to MIC, but with proportionally higher peak concentrations for the intermittent doses. Figure 2A shows the ED$_{34}$ results, which demonstrate fungal regrowth with the once-weekly dose, whereas the twice-weekly and daily therapy regimens gave identical kill rates. In contrast, the ED$_{50}$ dose (Figure 2B) demonstrates that the once-weekly schedule led to identical fungal burden to the daily therapy by day 7. In fact, the single dose killed faster than the daily therapy. Figure 2C shows that a single ED$_{99}$ dose at start of therapy killed without any regrowth in the kidneys. This study illustrates that if an optimal single dose is administered, there is no fungal regrowth. Importantly, this illustrates a fundamental principle with micafungin, which is that one can add each of the daily doses for half a week, or even for the entire week, to administer intermittently at the start of therapy and would still get the same efficacy as the divided doses given daily. This property is what makes micafungin an AUC/MIC-driven drug. This means that combining the entire daily doses for the 2 weeks and delivering as a single dose will lead to the same final microbial kill as daily dose, but at a faster rate.

Figure 1. Pharmacokinetics/pharmacodynamics on micafungin in neutropenic mice with disseminated candidiasis. A, The 24-hour dose-response curve showing the dose mediating 50% of maximal kill (ED$_{50}$) for one Candida glabrata strain. In 3 other C. glabrata strains, the ED$_{50}$ ranged from 0.49 to 0.58 mg/kg. Error bars are standard deviation. B, Micafungin serum and tissues concentrations after a single dose of micafungin, demonstrating higher kidney concentrations than serum in the mice. Walsh et al have also demonstrated higher concentrations in some lung tissues than serum in humans [16]. C, Time-kill curves for different single doses of micafungin. There is fungal regrowth with lower doses; however a dose is eventually reached that “crosses the rubicon,” after which there is no Candida regrowth in these severely neutropenic mice. This is achieved between the doses of 25 mg/kg and 50 mg/kg. D, Day 7 kidney fungal burden after a single dose at the beginning of the week, demonstrating a dose-effect relationship. Abbreviations: AUC$_{0-24}$, 0–24 hour area under the concentration-time curve; CFU, colony-forming units.
Andes et al wanted to identify the particular AUC/MIC threshold value associated with maximal micafungin fungal kill of 14 different Candida species strains with a wide MIC distribution of 0.008–0.25 mg/L [23]. Mice were infected with Candida and then treated with a daily micafungin dose for 4 days. The AUC/MIC associated with optimal efficacy was independent of Candida species. Moreover, micafungin exposure associated with stasis (holding the fungal burden constant) was a total AUC/MIC ratio of approximately 3000 or a non-protein-bound (free-drug) ratio of 7.5. The micafungin exposure associated with fungicidal effect was a total AUC/MIC of approximately 6000 (free-drug ratio = 14). Given these target exposures, a once-weekly dose for stasis would be a total AUC/MIC of 21,000, whereas that of a single dose once every 2 weeks would be 42,000.

Petraitiene et al examined fungal burden dynamics in rabbits using the dose-scheduling approach [24]. They also specifically examined the impact of micafungin dosing schedule on liver and kidney toxicity, as well as efficacy in the central nervous system and vascular tissues. The rabbits were made neutropenic using antineoplastic chemotherapy, were started on antibacterial therapy as in patients with febrile neutropenia, infected with C. albicans, and developed disseminated disease. On “the second day of infection,” the rabbits received micafungin therapy as either 1 mg/kg every day, 2 mg/kg every other day, or 3 mg/kg every 72 hours; rabbits were sacrificed on day 6. The mean fungal burden was examined in 7 different organs. In every organ the most intermittent dose sterilized the tissues, as compared to daily therapy, which sterilized in 4 of 7 organs; nevertheless, there was no statistically difference in fungal burden by dosing schedule. There were no differences in liver function tests, or renal function or electrolyte concentration. Thus, the higher-dose intermittent approach was efficacious without increased toxicity.

**BEYOND MICE AND SICK BUNNIES: PK/PD EVIDENCE FROM CLINICAL TRIALS**

Andes and colleagues recently examined the factors associated with optimal cure of candidemia and deeply invasive candidiasis in 493 patients enrolled in phase 3 trials who were treated with micafungin for invasive candidiasis [17]. They employed an agnostic method, classification and regression tree analysis, which identifies predictors of microbial and clinical cure and ranks them by order of importance [25, 26]. They identified the following factors as predictive of cure: severity of illness, a micafungin total AUC/MIC > 3000 for all Candida species, or AUC/MIC > 5000 for non-Candida parapsilosis species, an MIC < 0.5 mg/L, and a history of steroid use. If patients had micafungin AUC/MIC > 3000, they had a clinical and mycological cure rate of 98%. In humans, micafungin protein binding is...
about 99.75%, so that an AUC/MIC > 3000 translates to a free drug ratio of 7.5, whereas the AUC/MIC > 5000 translates to a free drug ratio of 12.5 [17, 27]. These values are virtually identical to those identified in neutropenic mice, discussed earlier [22, 23]. Thus, micafungin doses and dosing schedules (AUC/MIC values) identified in mice and bunnies directly translate to humans with invasive candidiasis.

Patients with esophageal candidiasis were randomized to micafungin either 150 mg daily or 300 mg every other day in multicenter randomized controlled trials [28]. Mycological response at end of therapy was 145 of 184 (79%) with daily doses vs 115 of 132 (87%) on every-other-day dosing (P = .056); relapse rates were 22 of 181 (12%) vs 7 of 126 (6%), respectively (P = .051) [28]. Thus, the more intermittent dose improved cure rates to close to 90% and halved relapse rates. The AUCs were identical between the dosing regimens; however, the 300 mg dose every other day had a 2-times-higher peak than the 150-mg dose, but a lower trough concentration, suggesting that the larger peak concentration could have driven efficacy. The more intermittent the cumulative dose, the higher the peak concentration, which means that based on this clinical study, it may be more desirable to give intermittent dosing instead of daily therapy. This is similar to PK/PD findings in rabbits and mice, reinforcing that PK/PD-derived dosing schedules in these animals translate well to the clinic.

. . . BUT CAN PATIENTS TOLERATE HIGH-DOSE MICAFUNGIN?

A main concern has been that administering micafungin at high doses could lead to increased rates of cardiovascular and hepatic toxicity. These worries arose because of concerns with the dose of 300 mg every other day, which at one point was viewed as associated with more adverse events than the 150-mg daily dose. However, in our study of adult volunteers, in whom approximately 60% had chronic comorbid conditions such as the metabolic syndrome, who were carefully monitored in a medical unit with before-and-after biochemistry tests and 4 hourly examinations, there was no higher toxicity after a single 300-mg infusion (maximum dose 7.0 mg/kg) compared to 100 mg (maximum dose 2.2 kg) [15]. Indeed, several other studies in which micafungin 3–4 mg/kg was administered to children intermittently revealed no toxicity [29, 30].

Two formal maximum tolerated dose (MTD) studies have been performed, and give an indication of the total micafungin doses that patients can tolerate. In the first study, Hiemenz et al enrolled 74 patients undergoing bone marrow transplant who were treated with daily micafungin doses of 12.5–200 mg for up to 4 weeks [31]. The MTD was not reached. The rate of adverse events did not increase with doses up to 200 mg each day. Sirohi et al also performed a formal MTD study of 36 adult patients undergoing bone marrow transplant who received 3, 4, 6, or 8 mg/kg daily for 7 to 28 days [32]. Actual doses administered ranged from 170 mg to 900 mg each day, administered over 1 hour. Patients were carefully monitored prior to therapy, during therapy, and at the end of therapy for serious adverse events. Adverse events assessed as at least possibly related to micafungin were phlebitis, gastrointestinal symptoms, and injection site reactions. These were not dose dependent; no patients had grade 3 or 4 adverse reaction. Rash and pruritus were observed in 2 patients, both of whom received 8 mg/kg/day, but were considered mild. The relationships between dose categories, dose, duration of therapy, changes in creatinine, and changes in aspartate aminotransferase, are shown in Figure 3, which demonstrates no increased hepatotoxicity or renal failure, even in patients who received mean total cumulative doses of 12,000 mg [32]. The MTD was not reached up to 900 mg each day, a cumulative dose multi-fold that of 2 doses of 1000 mg once each week or 2000 mg as a single dose. Clearly, higher doses than currently licensed can be tolerated by patients.

USE OF MICAFUNGIN ONCE EVERY 2 WEEKS DUE TO DIFFICULT PATIENT CIRCUMSTANCES

High-dose intravenous micafungin has been used on a number of occasions, mainly due to lack of alternatives in particular challenging patient situations. In one such case, a 27-year-old schoolteacher with a history of recurrent esophageal candidiasis and candidemia was admitted with fever, rigors, and hypotension, consistent with prior multiple episodes of sepsis-like syndrome each year that had led to multiple hospitalizations. Blood cultures grew C. albicans. While it was recognized that she had an immunodeficiency, it was nevertheless still unclear if this was a variant of common variable immunodeficiency, or another immunodeficiency. Thus, she was not on immunoglobulin replacement therapy. To try and prevent the candidiasis, various strategies had been tried in the past, including prophylactic oral fluconazole of up to 400 mg a day, which always failed due to poor fluconazole absorption, as was the case with the current admission. During the admission, the patient was treated with 100 mg of micafungin each day, and was discharged home to complete 2 weeks of intravenous micafungin. At the end of therapy, she was seen in the outpatient clinic accompanied by her mother. She informed the physician that she wanted to try high-dose intermittent micafungin therapy (based on her Google search of mouse studies), but did not want to come to a physician’s office several times a week or receive home care. The patient was counseled that what she proposed was not the licensed dose for micafungin, but she was insistent. A test regimen of micafungin 700 mg was administered in the clinic in week 1, followed by 1400 every other week, with follow-up of liver function tests 3 days after each dose. She did well for 12
weeks (a total of seven 1400-mg infusions once every 2 weeks), with no recurrence of esophageal candidiasis or candidemia. A week after the last infusion, she was readmitted with elevated liver function tests indicative of hepatotoxicity, and was switched to liposomal amphotericin B. However, toxicology results revealed that she had taken advantage of her intravenous line to infuse a high-dose mixture of recreational drugs that included acetaminophen, cocaine, and narcotics she had bought illegally on the street. Her liver function tests resolved during the hospitalization. On discharge, she resumed intermittent 1400 mg intravenous micafungin without elevation of liver function enzymes, until she was started on intravenous immunoglobulin G after discharge.

WHY SHOULD THE TIME THE EARTH TAKES TO ROTATE ITS AXIS DICTATE WHEN TO DOSE MICAFUNGIN?

The pharmacokinetics of micafungin, the PK/PD properties in animal models, and the PK/PD properties in clinical studies, suggest that high intermittent doses of micafungin could be useful. An optimal enough dose, administered at least as 2 doses, or even as a single dose, will not lead to fungal regrowth; indeed, there could be faster fungal kill and sterilization with such doses.

The concern of increased toxicity on such high doses will continue, and should indeed be taken seriously. Available clinical data of tolerance of large doses of approximately 1000 mg administered daily, and even 1400 mg administered every 2 weeks in case reports, suggest that such doses are likely well tolerated. Nevertheless, a formal study that examines single doses between 1000 mg and 2000 mg is still warranted. However, it is safe to say that there seems to be no obvious link between the Copernican revolutions, including the earth’s rotation around its axis, and the efficacy of antibiotics such as micafungin.

Given that micafungin clearance increases with patient weight, there is a decrease in drug concentrations at patient weights >66 kg. To compensate for this decrease in micafungin concentrations, we derived the formula “dose (mg) = patient weight + 42” to be used by clinicians at the bedside [19]. In such patients, the daily dose would be derived first, and then just multiplied by 14 days for a single dose, or 7 days for 2 doses. It should be noted that this increased dose will not lead to concentration-related toxicity as the dose increase is to counter low micafungin peak and AUC concentrations. However, it may be safer to escalate the doses, starting with 700 mg, and then stepping up the dose if patient tolerates.

When, and under what circumstances, should high-intermittent doses be investigated? First, the approach would
not be used as an excuse to delay therapy and wait for positive Candida cultures. Delay in therapy, especially in neutropenic patients, is well known to increase therapy failure and obviate the benefits of micafungin therapy [34–36]. Moreover, new technologies such as matrix-assisted laser desorption/ionization time-of-flight and polymerase chain reaction–based methods that can diagnose candidemia as well as drug resistance within hours mean that definitive evidence of on infection can now be obtained within hours [37–40]. Such diagnostics will obviate delay of therapy and allow rapid escalation of intermittent micafungin doses. The combined effect of rapid diagnosis and a rapidly fungicidal dosing regimen could be synergistic in improving patient outcomes.

A single dose, or even 2 doses of micafungin, delivered for the treatment of invasive candidiasis could be a win-win-win, for patients, their physicians and nurses, and the hospital. For the patient, advantages include decreased need for long-dwelling venous catheters and their attendant complications; that they do not need to stay in hospital for treatment or, if they go home, do not need visits to and from infusion centers; and that they may have faster recovery from invasive candidiasis to close that gap between the 72% and 98% response rates [33]. For doctors and hospital staff, the advantages include decreased time related to preparing drug each day and decreased nursing time related to hanging and administering the intravenous infusions. The approach of a single dose or 2 doses of micafungin would also make the lack of oral echinocandin formulation less relevant.

Notes

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