Flucytosine

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Flucytosine (5-fluorocytosine; 5-flucytosine; 5-FC) is one of the oldest antifungal agents in use [1]. It was initially synthesized in 1957, but was not discovered to possess significant antifungal properties until 1964, when activity against *Cryptococcus neoformans* and *Candida* species was shown [2]. Human clinical trials were initiated in the late 1960s for both cryptococcal meningitis and disseminated candidiasis [3, 4]. The rapid emergence of flucytosine resistance was observed, particularly among *C. neoformans* isolates, limiting its utility as single-agent therapy [5–7]. Presently, flucytosine is utilized as single-agent therapy in only a limited number of settings, including urinary candidiasis and chromoblastomycosis [8]. The seminal studies of combination therapy of flucytosine with amphotericin B for patients with cryptococcal meningitis were the first to firmly establish a role for combination antifungal therapy for a well-defined invasive fungal infection [9, 10].

Mechanism of Action

Flucytosine is taken up by fungal cells by a unique fungal-specific cytosine permease. Two important and independent pathways for fungal cell injury occur: one leading to protein synthesis inhibition and the other resulting in DNA synthesis inhibition. Flucytosine is converted by intracellular deamination to 5-fluorouracil and ultimately processed into 5-fluorouridine triphosphate, which is incorporated into fungal RNA. This results in miscoding during translation from RNA into amino acid sequencing, causing structural abnormalities during protein synthesis [11, 12]. The second mechanism of action is characterized by the conversion of 5-fluorouracil to 5-fluorodeoxyuridine monophosphate, which inhibits thymidylate synthetase and subsequently DNA biosynthesis [13]. Resistance to flucytosine may arise from mutations that affect the production of three key enzymes (uridine monophosphate pyrophosphorylase, cytosine permease, and cytosine deaminase) or through increased production of pyrimidines [14].

Pharmacology

Both intravenous and oral formulations of flucytosine have been developed and are in clinical use. However, in the USA, only the oral formulation of flucytosine is available and comes as 250- and 500-mg capsules. Following oral administration, 78–89% of the drug is absorbed, with peak concentrations achieved in approximately 2 h [15]. Food, antacids, and renal insufficiency can impair absorption. Over 90% of the drug is eliminated by urinary excretion unchanged [16]. As such, impaired renal function leads to drug accumulation and dramatically alters the serum half-life from approximately 4 h in those with normal renal function (range 2.4–4.8 h) to over 85 h in those with severe renal impairment [17]. Consequently, the daily dose must be adjusted for patients with renal dysfunction [18]. Hemodialysis, hemofiltration, and peritoneal dialysis reduce plasma flucytosine levels [19]. Flucytosine demonstrates only limited protein binding (approximately 3–4%). The penetration of flucytosine into cerebrospinal, peritoneal, and synovial fluids is approximately 75% of simultaneous plasma concentrations [11].

Following oral administration of 2 g of flucytosine in subjects with normal renal function, peak serum levels reach 30–40 mcg/mL. Repeated dosing every 6 h results in peak concentrations of 70–80 mcg/mL. Serum concentrations of greater than 100 mcg/mL are associated with increased toxicity and can rapidly be achieved in the setting of renal failure, particularly that caused by concomitant amphotericin B administration [18, 20]. For these reasons, it is important to monitor renal function closely among all patients receiving flucytosine and adjust dosing for changes in renal function. A nomogram for flucytosine dosing is shown in Table 1.

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Table 1 Dose adjustment of flucytosine with renal insufficiency

Renal function (mL/min)	Oral dosing
>40	25 mg/kg every 6 h
20–39	25 mg/kg every 12 h
10–19	25 mg/kg every 24 h
<10	25 mg/kg after dialysis and monitor peak levels

Modified from Stamm et al. [18]

Estimate of renal function can be made by the Cockroft-Gualt Equation:

$$eCc_{\tau} = \frac{(140 - \text{age}) \times \text{mass (in kg)} \times [0.85 \text{ if female}]}{72 \times \text{serum creatinine (in mg/dL)}}$$

This formula expects weight to be measured in kilograms and creatinine to be measured in milligrams per deciliter (mg/dL), as is standard in the USA. The resulting value is multiplied by a constant of 0.85 if the patient is female

For creatinine in μmol/L:

$$eCc_{\tau} = \frac{(140 - \text{age}) \times \text{mass (in kg)} \times \text{constant}}{\text{serum creatinine (in μmol/L)}}$$

Where constant is 1.23 for men and 1.04 for women

Dosage and Administration

The current standard daily dose of flucytosine is 100 mg/kg daily given in four divided doses in persons with normal renal function. Doses ranging between 50 and 150 mg/kg daily have been utilized successfully among patients with established fungal infection, but the 150 mg/kg daily dose is often associated with serious side effects [10, 18, 20].

Early studies among patients with cryptococcal meningitis used flucytosine doses of 150 mg/kg daily, but in these studies, serum levels were monitored carefully and adjustments in dosing were made based on these determinations. Recent studies have employed lower-dose regimens of flucytosine (100 mg/kg daily) for shorter periods (2–4 weeks) and have relied less on monitoring serum levels [21–26].

Serum flucytosine levels are not universally available, and delays in obtaining test results often reduce or limit the clinical impact of the information. When available, flucytosine levels can be a helpful adjunct to monitoring therapy and preventing hematologic toxicities. Frequent monitoring of white blood cell and platelet counts can be used as a means of monitoring toxicity if flucytosine levels are not available; the dosage should be decreased at the first sign of a decrease in white blood cell or platelet counts. Alternatively, flucytosine serum levels can be reasonably predicted based upon population pharmacokinetic studies [27]. When monitored, serum levels should be maintained between 50 and 70 mcg/mL although lower levels may be effective [14].

Clinical Indications

Flucytosine is indicated for patients with cryptococcosis, various forms of candidiasis, and chromoblastomycosis. Development of drug resistance is more common in patients treated with flucytosine alone. The most common use of flucytosine is in the management of serious infections caused by *C. neoformans* [28, 29]. In this setting, flucytosine is usually combined with amphotericin B [9, 10, 22, 26, 30, 31] or fluconazole [21, 25, 32], and occasionally with itraconazole [33–36]. Combinations of an azole or amphotericin B with flucytosine have generally been shown to result in more rapid culture conversion of the cerebrospinal fluid from positive to negative and to improved clinical outcomes when compared to single-agent therapy.

Flucytosine can be employed as a single agent or in combination with amphotericin B against organisms responsible for chromoblastomycosis, e.g., *Fonsecaea* and *Cladosporium* species, with moderate success [37–39]. Evaluation of in vitro activity of flucytosine against over 8,500 clinical isolates of *Candida* species showed that primary resistance to flucytosine was very uncommon among all species with the exception of *C. krusei* (only 5% susceptible) [40]. Even though most *Candida* species are susceptible to flucytosine, most invasive *Candida* infections are not treated with flucytosine alone. However, combination therapy with flucytosine and amphotericin B has been used successfully for several forms of invasive candidiasis [41–44]. Given the availability of effective alternative agents, such as the azoles and the echinocandins, flucytosine as part of combination therapy with amphotericin B is an increasingly uncommon approach to serious *Candida* infections. However, recent guidelines recommend flucytosine in combination with amphotericin B for selected patients with central nervous system candidiasis, *Candida* endocarditis, and *Candida* endophthalmitis [45]. In addition, flucytosine is sometimes used as a single agent to treat urinary candidiasis [45].

Aspergillus species may respond to the combination of amphotericin B and flucytosine, but the benefit of adding flucytosine is not well established [46–49]. *Histoplasma capsulatum*, *Coccidioides* species, *Blastomyces dermatitidis*, *Sporothrix schenckii*, and *Scedosporium apiospermum* are not susceptible to flucytosine and therefore this drug has no role in these fungal infections. Although *Penicillium marneffei* is inhibited in vitro by flucytosine [50], the therapeutic utility of flucytosine for penicilliosis is not established.

Adverse Effects

The most common adverse effects associated with flucytosine use are gastrointestinal complaints of nausea, vomiting, and diarrhea. These events are rarely serious, and can often

be ameliorated by taking the oral medication over 15–30 min. Hepatic toxicities, including elevated transaminase and alkaline phosphatase levels, have been reported in 0–25% of subjects taking flucytosine. Rarely, hyperbilirubinemia occurs with flucytosine administration, but bilirubin levels usually decline once the drug is stopped [51]. Clinically significant hepatitis is rare, but deaths have been attributed to flucytosine-induced hepatic disease. The gastrointestinal and hepatic side effects have not been demonstrated to be dose dependent [52]. Although the mechanism of gastrointestinal toxicity is not well established, it is postulated to result from 5-fluorouracil accumulation from intestinal microflora metabolism of flucytosine [53, 54].

Serious adverse effects usually arise from bone marrow injury [18, 20]. Thrombocytopenia, granulocytopenia, and anemia may arise at any time during the course of therapy, particularly if flucytosine drug levels accumulate because of decreased renal clearance associated with concomitant amphotericin B administration. Bone marrow toxicity has been observed in 60% of subjects with flucytosine serum levels greater than 100 mcg/mL, whereas only 12% developed bone marrow toxicity when serum levels were less than 100 mcg/mL [20]. Although flucytosine-induced blood dyscrasias are usually reversible on discontinuation of drug, fatal bone marrow suppression has been reported. Prior radiation therapy appears to exacerbate the potential for bone marrow toxicity.

Therapeutic monitoring of serum flucytosine levels followed by adjustment of flucytosine dose may reduce the frequency of severe bone marrow toxicity. A complete blood and platelet count provides a good indication of flucytosine toxicity when serum levels are unavailable. Flucytosine may be safely employed in settings with limited ability to monitor drug levels through very careful observation of renal function and white blood cell and platelet counts; dosage adjustments must be made if renal function changes or white blood cell or platelet counts fall.

Cytosine arabinoside has been reported to inactivate flucytosine [55]. No other significant drug–drug interactions are known.

Precautions

Flucytosine should be used with care during pregnancy. Teratogenic effects have been observed in rats and rabbits (spinal fusion, cleft lip and palate, and micrognathia); thus, this agent is assigned pregnancy category C by the US Food and Drug Administration. On occasion, flucytosine has been given during pregnancy with success [56, 57]. Flucytosine has not been approved for use in children, but there has been considerable experience in this age group, particularly for treatment of central nervous system and urinary infections due to *Candida* species [58, 59]. Nursing mothers should avoid flucytosine as it may be excreted in breast milk.

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