Stanford Medication Usage Guide
Flucytosine

Usage

- Flucytosine is FDA approved for use as an adjunctive treatment of systemic fungal infections (eg, septicemia, endocarditis, UTI, meningitis, or pulmonary) caused by susceptible strains of *Candida* or *Cryptococcus*.
  - In many studies, flucytosine has demonstrated a synergistic effect with other antifungal agents; avoid use as monotherapy due to rapid development of resistance
  - **MOA:** penetrates fungal cells and is converted to fluorouracil which competes with uracil interfering with fungal RNA and protein synthesis

Dosing

CrCl	Dosing
>40	Typical Dose: 50 to 150 mg/kg/day in divided doses every 6 hours Cryptococcosis: 100 mg/kg/day in divided doses every 6 hours
20 – 40	25 mg/kg/dose every 12 hours
10 – 20	25 mg/kg/dose every 24 hours
<10	25 mg/kg/dose every 48 hours
IHD	25 to 50 mg/kg/dose every 48 to 72 hours; administer dose after hemodialysis

- **Preparations:** 250 mg or 500 mg capsules. May be compounded for oral suspension (see Lexi-Comp)

Cost

- Daily cost may exceed $2,000 given that each 500mg capsule ~$160-180 (AWP 2019). Obtain early outpatient coverage if outpatient therapy is planned.

Pharmacokinetics/Pharmacodynamics

Flucytosine pharmacokinetics	
Bioavailability	78% - 89%
Distribution	Vd 0.6 L/kg
Metabolism	Minimally hepatic; deaminated both in yeasts and possibly via gut bacteria to 5-fluorouracil
Half-life elimination	Adults: 2 to 5 hours; End-stage renal disease (ESRD): 75 to 200 hours
Time to peak, serum	~1 to 2 hours
PK-PD	Linear pharmacokinetics; demonstrates time-dependent killing and has very weak concentration-dependent effects
Excretion	Urine (>90% as unchanged drug)

Monitoring Parameters

Timing of peak	Target peak	Monitoring parameters
Obtain 2 hours post-dose within 72h after initiation or after 3 to 5 doses have been administered*	25 - 100 mg/L	SCr**, CBC, LFTs***

* This lab is a send out and takes several days to result so important to time level appropriately the first time
** changes in renal function can have a dramatic effect on flucytosine serum concentrations given > 90% excretion in the urine → challenging when used with a nephrotoxic agent like amphotericin B
*** Levels > 100 mg/L increase risk of bone marrow suppression and hepatic dysfunction

- Considerations for managing out of range levels
  - Supratherapeutic: hold dose(s) as needed. If due to renal impairment, decrease dosing frequency
  - Subtherapeutic: data is limited but one strategy is to increase the dose by 50%. Use clinical discretion.

References:

1. Schwarz P, Janbon G, Dromer F, Lortholary O, Dannaoui E. Combination of amphotericin B with flucytosine is active in vitro against flucytosine-resistant isolates of Cryptococcus neoformans. Antimicrob Agents Chemother. 2007;51(1):383-5.
2. https://www.accessdata.fda.gov/drugsatfda_docs/label/2006/017001s027lbl.pdf
3. HHS Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf. Accessed April 11, 2019.
4. Lexicomp
5. https://aac.asm.org/content/53/1/24
6. https://link.springer.com/article/10.1007/s40588-015-0019-x
7. Ashbee HR et al. Therapeutic drug monitoring (TDM) of antifungal agents: guidelines from the British Society for Medical Mycology. J Antimicrob Chemother. 2014;69(5):1162–76. Comprehensive clinical guidelines from the British Society for Medical Mycology on the use of TDM for itraconazole, voriconazole, posaconazole, and flucytosine. The authors summarize relevant literature and provide recommendations for TDM.

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C. Review and Renewal Requirement

This document will be reviewed every three years and as required by change of law or practice

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