Flucytosine
Newborn use only

2023

Alert	Flucytosine is a SAS product. Use in consultation with a paediatric infectious disease physician. Flucytosine should always be used in combination with other antifungal agents because of the rapid development of resistance to flucytosine monotherapy.
Indication	Cryptococcal meningitis in combination with Amphotericin B or Fluconazole. Systemic candidiasis - In combination with Amphotericin B.
Action	Antimetabolite drug. It inhibits protein and DNA synthesis following conversion from flucytosine to 5-fluorouracil inside fungal cells.
Drug type	Antifungal
Trade name	Flucytosine
Presentation	Oral: 10 mg/mL oral suspension, prepared in-house.
Dose	100 mg/kg/day in 6 to 12 hourly divided doses.(1) **Refer to special comments section for further information.**
Dose adjustment	Therapeutic hypothermia: Limited data. ECMO: Limited data. Renal impairment : Increases risk of haematological toxicity; reduce dose as follows GFR 30–50 mL/minute/1.73m2: 25 - 37.5 mg/kg dose q8h GFR 10–29 mL/minute/1.73m2: 25 - 37.5 mg/kg dose q12h GFR <10 mL/minute/1.73m2: 25 - 37.5 mg/kg dose q24h Hepatic impairment: Use cautiously.
Maximum dose	150 mg/kg/day.(22)
Total cumulative dose	
Route	Oral
Preparation	No preparation required.
Administration	Administer orally or via intra-gastric tube with feeds.
Monitoring	Monitor full blood count, liver function and renal function at baseline, then each day initially, and then twice each week. Flucytosine concentrations should be measured after 3-5 doses and in the first 72 hours of therapy or change in dose.(3) Desired plasma drug levels:(4-6) Peak (2 hours after a dose): 50–80 mg/L (toxicity > 100 mg/L) Trough concentration: 20–50 mg/L
Contraindications	Known complete dihydropyrimidine dehydrogenase enzyme deficiency, hypersensitivity to flucytosine or any component of the formulation.
Precautions	Bone marrow depression, myelosuppressive medications, radiation treatment, acquired immunodeficiency syndrome (AIDS): increased risk of blood dyscrasias
Drug interactions	Concurrent use with amphotericin B may enhance the adverse effects of flucytosine. Concurrent use with chloramphenicol (ophthalmic) may enhance its myelosuppressive effect. Food decreases the rate of absorption however, the extent of absorption is not affected.
Adverse reactions	Bone marrow suppression with anaemia, leucopenia and thrombocytopenia and hepatotoxicity usually occur with high plasma concentration >100 mg/L. Hypokalaemia, acidosis, diarrhoea, nausea, vomiting, and rash.
Compatibility	Not applicable.
Incompatibility	Not applicable.
Stability	Oral suspension stable for 7 days.
Storage	Oral suspension: Store below 25°C (stable for 60-90 days in amber plastic prescription bottles)
Excipients	
Special comments	Length of therapy depends on the infection, infection site and any comorbidities. Discuss with paediatric infectious diseases consultant. Long-term treatment with consolidation and maintenance antifungal therapy is required after initial induction treatment to prevent recurrence. Use with other antifungal agents for chromoblastomycosis.
Evidence	**Efficacy**

There are no clinical trials to evaluate efficacy of flucytosine in neonates. The data in neonates are limited to case reports and extrapolated from children and adults.

Cryptococcal meningitis

One comparative study used either Amphotericin B alone or in combination with flucytosine in 66 adults with cryptococcal meningitis. More rapid sterilisation of cerebrospinal fluid, higher cure rate (68 vs 47%), lower mortality (24 vs 47%), reduced relapse rates and reduced nephrotoxicity were observed in the group of patients who received flucytosine in combination with Amphotericin B.[13] Similarly, a review of nationwide database involving 517 adults with cryptococcal meningitis reported reduced mortality (6 vs 11%) in patients who received combination of liposomal Amphotericin B with flucytosine compared to liposomal Amphotericin B alone.[14] Li et. al. compared efficacy of flucytosine in combination with either Amphotericin B or Fluconazole in 90 immunocompetent adults with cryptococcal meningitis. No differences were seen in cryptococcus clearance or treatment time but flucytosine and fluconazole treatment had lower total adverse events (90 vs 20%).[15]

Systemic candidiasis

Invasive candidiasis is reported in 1.5% to 9% very low birth weight neonates.[7,8] It is associated with high mortality (20-40%) and neurodevelopmental disability (50-60%) in survivors.[9]

Neonatal studies

Smith et. al described a series of 8 extremely preterm and 2 term neonates with systemic candidiasis. The age of diagnosis of candida infection varied from 16 to 58 days. Flucytosine alone was used for initial treatment in all neonates. Amphotericin was added in two neonates after 48 hours for ongoing clinical deterioration. The starting doses of flucytosine were 100 to 200 mg/kg/day and blood concentrations measured on 3rd day were at the upper end of therapeutic range.[10] Four neonates in the cohort died but no deaths were attributable to either candidiasis or the treatment. No recurrence was noted in any of the treated infants. McDougall reported successful treatment of multisystem candida infection and meningitis in two extremely low birth weight infants with flucytosine in combination with Amphotericin B.[11]

Adult studies

The efficacy of either combination of Amphotericin B with flucytosine or fluconazole alone for treatment systemic candida infection of was studied in a randomised trial by Abele-Horn. Thirty-six patients received Fluconazole and 36 received Amphotericin B with flucytosine for 14 days. Regarding treatment of candida pneumonia and sepsis, there was no statistically significant difference in clinical outcome. However, Amphotericin B and flucytosine combination was more effective than Fluconazole (55% vs 25%) for treatment of abdominal infection and peritonitis. Furthermore, Amphotericin B and flucytosine combination was found to be superior to Fluconazole in regard to pathogen eradication (86% vs 50%). On the other hand, Fluconazole was associated with less toxicity compared to Amphotericin B and flucytosine combination.[12]

Safety

Several minor and serious adverse effects are associated with flucytosine therapy. The mechanism of toxicity is not fully understood but high drug levels (> 100 mg/L) and conversion to active metabolites such as 5-flurouracil have been postulated.

Common reported gastrointestinal side effects include nausea, vomiting, diarrhoea and diffuse abdominal pain. Ulcerating inflammatory enterocolitis and bowel perforation with peritonitis are also described in case reports.[16,17]

Hepatotoxicity and bone marrow suppression are the most commonly reported serious adverse events. Studies quote incidence of hepatotoxicity between 0-40 %.[18] In most cases it involves reversible increase in serum concentrations of hepatic enzymes, bilirubin and hepatomegaly. However, severe hepatic necrosis can also occur with flucytosine therapy.[19] Flucytosine induced bone marrow suppression can result in life threatening leucopenia, thrombocytopenia and pancytopenia.[20]

Pharmacokinetics

Approximately 80-90% is absorbed following oral administration. Due to low protein binding it is widely distributed in body with volume of distribution between 0.6 to 0.9 L/kg.[21] Flucytosine concentrations in the cerebrospinal fluid are approximately 60-80% of serum concentrations, whereas urine concentrations are generally several-fold higher than serum concentrations. Up to 96 percent of the total dose of flucytosine is eliminated as unchanged drug in the urine, primarily by glomerular filtration. The elimination half-life in neonates (7 hours) is nearly twice as long as in adults.[22] Flucytosine has a narrow therapeutic index so routine monitoring of drug blood levels has been recommended.[23] It is suggested that serum

	flucytosine concentrations should be measured after approximately three to five doses and blood sample obtained two hours after a dose has been administered to determine peak drug level.[3] Soltani et al, published retrospective data on peak and trough concentration of flucytosine in 198 children including 83 neonates in the UK over a 12 year period. The preceding standard clinical practice was to use a total dose of 150–200 mg/kg daily in four divided doses. In their report, pre-dose concentrations were low (< 30 mg/L) in 18% and high (> 80mg/L) in 10% neonates. The post dose drug concentrations were high (> 80 mg/L) in 39% neonates.[4] In nearly 11% neonates, the peak drug levels were > 120 mg/L suggesting very high risk of flucytosine toxicity. Based on the data, authors recommend reduction of flucytosine dose to 100 mg/kg/day in neonates. Similarly, Pasqualotto measured trough and peak concentration (30 min after IV and 2 hours after PO dose) of flucytosine in 233 patients including 33 neonates. In only 21% participants, the flucytosine levels were in the therapeutic range. The levels were low in 40%, high in 39% and toxic (> 100 mg/L) in 10%.[5]
Practice points	
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