Flucytosine for treatment of Cryptococcus neoformans meningitis in an obese patient and the challenges of Therapeutic Drug Monitoring (TDM).

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Case presentation

Mr DR is a 56-year-old Caucasian male (Weight: 111kg, Height: 182cm, BMI: 33.5) who presented to the Prince of Wales Hospital in April 2018 for investigations of lower limb weakness with leptomeningeal enhancement on MRI.
A lumbar puncture was completed during his admission, and returned positive for Cryptococcal antigen and subsequently grew Cryptococcus neoformans var grubii at 24 days incubation. Meningeal biopsy had no growth and no fungal elements were seen. HIV serology was negative.
A diagnosis of Cryptococcal meningitis was made, and the Infectious Diseases) team proceeded to treat Mr DR with a combination of oral flucytosine (5-FC) and intravenous liposomal amphotericin.
Flucytosine was used in combination with amphotericin B to limit the development of resistance that is observed with monotherapy[2]. Combination therapy results in earlier cerebrospinal fluid sterilisation and improved mortality when compared to amphotericin alone[1].

Table 1: Pharmacokinetic parameters of oral flucytosine[1,2]:

Absorption	**Oral: 76-89% bioavailability**
Distribution	**Penetrates cerebrospinal fluid** **Vd 0.6-0.9L/kg at steady state** **Highly water soluble** **Minimal serum protein binding (2-4%)**
Metabolism	**Minimal**
Half life	**2.5-6 hours (normal renal function)**
Elimination	**Predominantly renal – excreted unchanged in urine**
Dosing	**25mg/kg six hourly based on ideal body weight**

Clinical Pharmacist Involvement

Dosing recommendations

- ***Pharmacist intervention for inappropriately charted dose of flucytosine***
- ***Initial dose charted by medical staff was dosed on actual body weight***
- ***Pharmacist recommended dose adjusted for ideal body weight[2] (5-FC has a small volume of distribution and is not well distributed into adipose tissue[2]; Mr DR had a BMI of 33.5)***

Pre-hydration and renal function monitoring

- ***Pharmacist recommended pre-hydration with sodium chloride 0.9% prior to each dose of IV amphotericin and adequate daily hydration to minimise the risk of renal impairment***
- ***Risk for nephrotoxicity remains with liposomal amphotericin formulation. Pharmacist recommended ongoing monitoring of creatinine clearance***

Toxicity Monitoring

- ***Due to delay in receiving flucytosine level result, documentation by Pharmacist for team to specifically monitor daily for bone marrow toxicity and hepatotoxicity as a surrogate marker of drug accumulation***
- ***If neutrophil count < 0.5 x 10^9/L, platelets < 75 x 10^9/L, deranged liver function tests, treatment with flucytosine would be reviewed***

Therapeutic Drug Monitoring

- ***TDM is recommended in all patients receiving concomitant amphotericin and flucytosine***
- ***Pharmacist ensured that flucytosine levels were measured 72 hours post initiation and liaised with the nursing and medical staff to ensure levels were taken 2 hours post flucytosine dose to reflect peak levels as requested by the external pathology laboratory***
- ***Peak level returned at 62mg/L on day 13 of flucytosine treatment reflecting that the current dose was not toxic and fell within the therapeutic range for treatment.***

Table 2: Flucytosine level types[1,2,3]

Type of Level	Peak	Trough
Timing	**1-2 hours post dose**	**30 minutes prior to dose**
Reference Range	**50 – 100mg/L** **Toxicity associated with peak levels > 100mg/L**	**Aim > 25mg/L for clinical efficacy**

Patient Outcome

Patient successfully completed 2 weeks of induction therapy with remarkable improvement and no adverse effects. He transitioned to oral fluconazole for 8 weeks as consolidation therapy.

References

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