The truth is out there: A case report of flucytosine toxicity in intermittent haemodialysis

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Objective: To describe a case of flucytosine toxicity in a haemodialysis (HD) dependent patient despite following published dosing recommendations.

Clinical Features: A 65 year old, 70kg, Caucasian female was admitted to the intensive care unit (ICU) with cryptococcal meningitis. Background history included haemodialysis-dependent chronic renal failure secondary to atypical haemolytic uraemic syndrome (aHUS) which was treated with eculizumab.

Interventions, case progress and outcomes: The patient was commenced on liposomal amphotericin 250mg intravenous (IV) daily and flucytosine 37.5mg/kg (2.5g) IV daily, administered after dialysis on HD days. The dose of flucytosine was adjusted for HD. This dose was supported by an initial search of multiple established renal references (see Table 1).

Table 1: Summary of initial search for flucytosine dosing recommendations in HD

Reference	Dosage recommendation
Cervelli, M. The Renal Drug Reference Guide. 1st ed. Adelaide; 2007. p.168	25-37.5mg/kg q24h (give after dialysis) or 50mg/kg q48h post dialysis titrated to response and serum levels
WSLHD local guidelines: Guidelines for Empiric Treatments of Suspected Invasive Fungal Infections (IFI) and for Targeted Therapy of Proven IFI in Patients with Chronic Kidney Disease, 2012	25-37.5mg/kg q24h or 50mg/kg every 48 hours. Give post dialysis. Monitor levels pre dose.
eTG complete [Internet]. Therapeutic Guidelines. Renal impairment and antimicrobial dosing [updated 2018 Jul; cited 2018 Nov 9]	as for GFR <10mL/min; dose after dialysis. GFR <10mL/min: 25mg/kg q24-48h
Sanford Guide to Antimicrobial Therapy. 2018	25mg/kg q24h, give dialysis day dose after dialysis
Ashley C, Currie A. The Renal Drug Handbook. London: Radcliffe; 2018 [accessed online]	Dialysed. Dose as in GFR<10mL/min, given post dialysis. Monitor trough level pre dialysis and reduce post dialysis dose accordingly. GFR <10mL/min: 50mg/kg then dose according to levels

Therapeutic drug monitoring (TDM) was conducted off-site, once a week causing a delay in reporting of results. Peak levels of < 100mg/L and trough levels between 25-50mg/L are recommended to avoid toxicity and ensure efficacy respectively.

Initial TDM results were not available until day 8 and indicated the patient had flucytosine toxicity. This correlated with clinical signs of cerebellar toxicity the patient was experiencing such as reduced Glasgow Coma Scale (GCS). Flucytosine was subsequently withheld. Flucytosine dosing, TDM results and reporting for this case are summarised in Table 2. Figure 1 summarises the results of successive TDM in relation to target peak and trough levels.

Table 2. Summary of flucytosine dosing, TDM results and timeline of reported levels

Day of therapy	1	2	3	4	5	6	7	8	9	10	11	12	13
Dose of flucytosine	2.5g	1.7g	2.5g	2.5g	2.5g	2.5g	2.5g	W/H	W/H	W/H	W/H	1.7g	1.7g
Peak Level (mg/L)			128	202	234	160							
Trough Level (mg/L)			55.5	111	164	96			41	36	21	20	<20
Day results were reported			8	8	8	8			12	16	16	16	16

A wider review of the literature was conducted to further examine appropriate dosing of flucytosine in HD patients (see Table 3). Results of this review indicated flucytosine should be dosed on HD days only.

On day 12, repeat TDM results showed flucytosine levels were within normal range. The patient's GCS had improved at this stage and flucytosine was recommenced at a dose of 25mg/kg (rounded to 1.7g) given after dialysis **on dialysis days only.** Flucytosine therapy was ceased the next day as advised by the Infectious Diseases team. After cessation of flucytosine, the patient remained on liposomal amphotericin only.

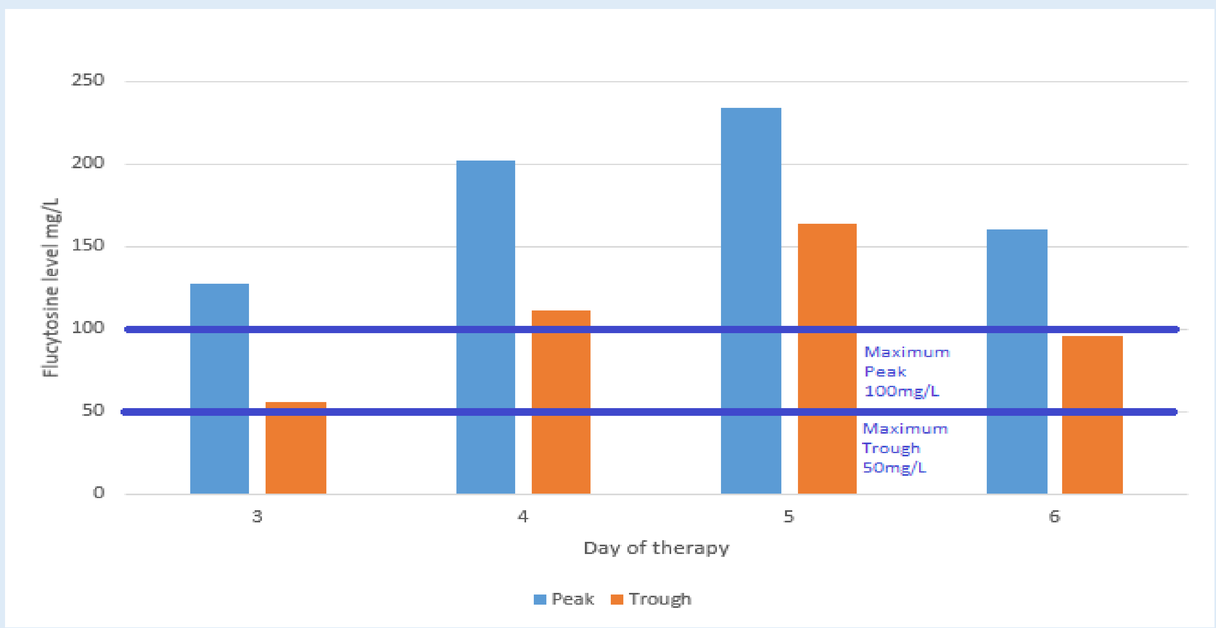
Multiple reference texts and primary literature were reviewed. There was significant ambiguity in dosing recommendations for flucytosine in HD within these texts. Primary literature cited by some texts used small populations, different routes of administration and varied dosage regimens compared to the dosage recommendations stated in the reference texts (see table 3).

Table 3. Summary of findings of further literature review of flucytosine dosing recommendations in HD

Reference	Dosage recommendation
Aronoff G. Drug prescribing in renal failure. 5th ed. Philadelphia: American College of Physicians; 2007. p.70	GFR< 10mL/min: 37.5mg/kg q24-48h Supplement for intermittent haemodialysis (IHD): Dose after dialysis
Grayson M. Kucers' The Use of Antibiotics.7th Ed Volume 2, Boca Raton: Taylor and Francis. 2010. p.2921	25-30mg/kg after dialysis only
Seyffart G. Seyffart's directory of drug dosage in kidney disease. Oberhaching: Dustri-Verl. Feistle; 2011. p.297	50mg/kg on day of dialysis before dialysis session, and daily between dialyses
Block E, Bennett J, Livoti L, Klein W, Macgregor R & Henderson L. Flucytosine and Amphotericin B: Haemodialysis Effects on the Plasma Concentration and Clearance. Annals of Internal Medicine. 1974;80:613-617	A single dose of 25-50mg/kg oral flucytosine with TDM 2 hours post dose and after completion of next dialysis
Cutler R, Blair A & Kelly M. Flucytosine kinetics in subjects with normal and impaired renal function. Clin Pharmacol Ther. 1978;24:333-342	A suggested dose regimen is 20mg/kg dosing immediately after dialysis (when dialysis occurs every 48-72 hours) with concurrent TDM
Fish D. Antifungal Dosing in Dialysis and Continuous Renal Replacement Therapy. Curr Fungal Infect Rep. 2011; 5:75-82	25mg/kg after dialysis. Concentrations should be monitored and adjusted to maintain peak <100microg/mL and trough 10-50microg/mL
Appel G & Neu H. The Nephrotoxicity of Antimicrobial Agents (First of Three Parts). NEJM.1977;296(12):663-670	25-50mg/kg after dialysis
Patel R. Antifungal Agents. Part 1. Amphotericin B Preparations and Flucytosine. Mayo Clinic Proceedings. 1998;73(12):1205-1225	25mg/kg after each haemodialysis

The pharmacokinetic properties of flucytosine were examined in conjunction with reference texts and primary literature to determine the most suitable dosing regimen. Flucytosine has a small molecular weight (129.1 Daltons) and is highly water soluble. It exhibits low protein binding and is extensively excreted by the kidneys. Renal insufficiency prolongs serum half-life and decreases clearance significantly. Flucytosine is readily cleared by dialysis and accumulates on dialysis free days.[1] The pharmacokinetics of flucytosine support dosing after dialysis **on dialysis days only** with concurrent TDM to ensure efficacy and prevent toxicity.

Figure 1: Results of successive TDM in relation to target peak and trough levels



Conclusion:

Ambiguity can exist between reference texts and primary literature. As well as reviewing multiple resources when determining appropriate dosing regimens, pharmacists should use their expert knowledge of pharmacokinetics to critically appraise dosing recommendations in resources. Accurate and timely TDM is also essential to facilitate appropriate management of patients on medications such as flucytosine which have a narrow therapeutic window and significant dose-related adverse effects.

References:

1. Vermes A, Guchelaar H, Guchelaar J & Dankert J. Flucytosine: a review of its pharmacology, clinical indications, pharmacokinetics, toxicity and drug interactions. *Journal of Antimicrobial Chemotherapy*, Volume 46, Issue 2, 1 August 2000, Pages 171–179.