TDM monograph Flucytosine

Synonyms: Ancotil, 5-FC

Summary

Indication:	Patients with invasive cryptococcosis, candidiasis, chromoblastomycosis, and urinary tract infections caused by Candida species.* Off-label indications: Candida retinitis/endophtalmitis. Indication TDM: TDM is recommended (evidence level 2, for detailed information see monograph). Indication DPD testing: DPD testing is recommended to as soon as possible in cases of toxicity, not routinely before 5-FC treatment. 5-FC is contraindicated in complete DPD deficiency; partial deficiency requires close clinical monitoring. ** 5-FC is typically administered as part of combination therapy because resistance develops rapidly during monotherapy. In rare cases, and under strict conditions, it may be used alone for the treatment of urinary tract infections caused by Candida species.*
Sample material:	Serum or plasma
Time of sampling:	Sampling for peak and trough concentration should be performed between 24 and 72 hours after treatment initiation. Frequency: once a week. More frequent sampling is recommended differences in renal function or existing bone marrow depression. Peak concentration (C_{max}): p.o. 2 hours after ingestion. i.v.: 30 minutes after administration. Trough concentration (C_{min}): just before next dose.
Storage conditions:	2-8°C and -20°C during at least 28 days.
Interpretation:	Pharmacokinetic/pharmacodynamic relationship: Time above the minimum inhibitory concentration (T>MIC) is considered the best predictor of antifungal efficacy – based op preclinical studies. Therapeutic concentrations: Intermittent therapy i.v./p.o.: Trough concentration > 25 mg/l (25-50 mg/L) Peak concentration < 100 mg/l (50-100 mg/L) Toxic concentration: > 100mg/L Alternative mode of administration: Continuous infusion: 50 mg/L (30-70 mg/L)
Evidence level:	2

Contents

Summary 1
Introduction 2
Dosing guidelines 2
Indications/Criteria for TDM 3
Reference values 4
Sampling & storage conditions 5
Background information [extended] 5
PK parameters 7
Population models 7
Literatuur 7
Colophon 9
Revision 9

Introduction

Flucytosine (5-FC) is an antifungal agent used in the treatment of invasive yeast infections caused by *Cryptococcus neoformans* and *Candida species*. 5-FC is less effective against moulds (*Aspergillus*). Within the fungal cell 5-FC is converted into 5-fluorouracil (5-FU) (1,2). After further enzymatic conversions, it interferes with RNA and protein synthesis, resulting in a fungistatic effect. After an extended exposure, a fungicidal effect often occurs as well (3). 5-FC is generally given in combination with amphotericin B due to the rapid onset of resistance during monotherapy. Combination therapy with amphotericin B increases the clinical effect of 5-FC but possibly also its (renal)toxicity (2). In urinary tract infections caused by Candida species, 5-FC is sometimes given as a short-term monotherapy due to the very high concentrations of 5-FC achieved in the urine (3).

In the Netherlands, the parenteral form of 5-FC is readily available, the oral form can only be procured via specialized distributors. The KNMP Kennisbank and the Kinderformularium also refer to oral administration of 5-FC. Therefore, data regarding oral administration is also included in this monograph.

Dosing guidelines

Invasive cryptococcosis, candidiasis, chromoblastomycosis and urinary tract infections caused by Candida species

Adults: Combination therapy (PO or IV): 25 mg/kg four times daily is preferred in accordance with the SmPC (3,4). Alternatively, a continuous infusion may be used, with a loading dose of 30mg/kg in 30 minutes followed by 70mg/kg every 24 hours (5).
Monotherapy (PO or IV): 37.5 mg/kg four times daily*

** 5-FC is typically administered as part of combination therapy because resistance develops rapidly during monotherapy. In rare cases, and under strict conditions, it may be used alone for the treatment of urinary tract infections caused by Candida species.*

Dosing guidelines in children and adolescents

Children: Age 1 month-18 years, combination therapy (PO or IV): 25-37,5 mg/kg four times daily (6)
Neonates: Full-term neonate, combination therapy (PO or IV):50-100 mg/kg/day in 1-2 doses (6,7).

Dosing guidelines in patients with altered pharmacokinetics

Effect of renal function:
Excretion mainly occurs via glomerular filtration (80-95%) in unchanged form, without tubular reabsorption or secretion (2,8,9). As a result, very high concentrations of 5-FC are found in urine (10). A small fraction of flucytosine is metabolized to 5-FU by gut bacteria; 5-FU is cleared renally. The clearance of 5-FC is linearly correlated with creatinine clearance; various formulas to calculate the half-life using creatinine clearance have been described (8,10,11). The half-life in normal renal function is 3-6 hours but can increase up to 85 hours in renal impairment (8–11).

As 5-FC is often co-administered with amphotericin B, which is associated with renal toxicity, renal function should be closely monitored to allow for early detection of potential reductions in renal clearance.

5-FC is effectively cleared by hemodialysis, hemofiltration, and peritoneal dialysis, with clearance by hemodialysis being more effective than by peritoneal dialysis (10,12).

Clearance of 5-FC by hemodialysis and peritoneal dialysis is similar to that of creatinine through the same process. Clearance of 5-FC increases proportionally with the filtration rate by the dialysis machine during hemodialysis, continuous veno-venous hemofiltration (CVVH), and peritoneal dialysis (8,10,12–14). In CVVH, the clearance rate also depends on the concentration in serum and the type of membrane used (larger pores provide higher clearance) (12).

Adults and children (>3 months) with renal dysfunction (3,4,6):
50-80 ml/min: No dose adjustment needed.
30-50 ml/min: Combination therapy (PO or IV): 25 mg/kg twice daily
10-30 ml/min: Combination therapy (PO or IV): 25 mg/kg daily
<10 ml/min: Combination therapy (PO or IV): Loading dose of 25mg/kg, subsequent dosing interval based on TDM following the first dose.
CVVH: Combination therapy (PO or IV): Loading dose of 25mg/kg, subsequent dosing interval based on TDM following the first dose.

Haemodialysis: 20-25mg/kg after every hemodialysis session (8,13–15)

Indications/Criteria for TDM

TDM is useful in both adults and children due to the high variability in the pharmacokinetics of 5-FC (16,17), the possible concentration-related toxicity, and efficacy (18,19). However, it has been shown that TDM in ICU patients cannot always prevent the onset of toxicity (hepatotoxicity and bone marrow depression) (20). TDM is particularly useful to prevent the risk of toxicity in case of impaired renal function due to accumulation of 5-FC (21).

In intermittent therapy, prolonged 5-FC concentrations exceeding 100 mg/L have been associated with hepatotoxicity and bone marrow suppression (18,22), whereas trough concentrations below 25 mg/L are considered subtherapeutic and, based on in vitro studies, may increase the risk of resistance (19). Hence, the recommended TDM targets are 50–<100 mg/L for peak concentrations and 25<-50 mg/l for trough concentrations. Based on expert opinion, a target mid concentration of 30-70 mg/L has been suggested.

This range may also be applied to continuous infusion of 5-FC, for which a target concentration of 50 mg/L has been suggested, although based on limited evidence (5,23). Given its short half-life (3–6 hours in patients with normal renal function), TDM should be performed between 24 and 72 hours after treatment initiation. Weekly sampling is recommended thereafter to avoid persistence or recurrence of potentially toxic concentrations.

In summary, TDM is recommended for all patients receiving 5-FC. The strength of evidence for TDM of 5-FC is level 2. Use TDM to check whether the trough concentration is sufficiently high and whether the peak and trough concentration are not toxic.

Reference values

Target group	Peak concentration (mg/l)	Trough concentration (mg/l)	Target concentration (mg/l)	Reference
Adults and children intermittent therapy	50 - 100	25 - 50	-	(2,18,19,21,22)
Adults continuous infusion	-	-	50	(5,23)

Efficacy

Human data demonstrating a correlation between 5-FC serum concentrations and clinical efficacy are lacking. Evidence from in vitro studies and mouse models suggests that maintaining 5-FC concentrations above the minimum inhibitory concentration (MIC) for a sufficient time of the dosing interval (T>MIC) is the best predictor of antifungal efficacy (24,25). For Candida species, a suggested exposure target is to maintain serum concentrations above the MIC for about 45% of the dosing interval (24,26). For Cryptococcus species, the MIC is generally believed to be higher (27). However, the European Committee on Antimicrobial Susceptibility Testing (EUCAST) does not currently provide clinical breakpoints for 5-FC for either Candida or Cryptococcus species(28).
Importantly, with current standard dosing regimens, the target values for T>MIC are generally achieved, and, to date, no clinical studies have shown associations with 5-FC serum concentrations and efficacy.

Relationship with occurrence of side effects & toxicity

5-FC, particularly when administered orally, can lead to relatively mild gastrointestinal side effects such as nausea, vomiting, diarrhea, and diffuse abdominal pain (occurrence 6%). Liver toxicity and bone marrow depression are serious and (probably) concentration-dependent side effects of 5-FC that are dose-limiting (2). As a small proportion of 5-FC is metabolized to 5-FU, asessment of DPD activity is recommended in cases of confirmed or suspected flucytosine-related toxicity.

Bone marrow depression:
Bone marrow depression is the most serious side effect of 5-FC. Leukopenia, thrombocytopenia, and pancytopenia occur with the use of 5-FC (2). Bone marrow toxicity is usually reversible within 2-4 weeks after dose reduction or discontinuation of 5-FC (18). This side effect appears to be concentration-related, with peak levels above 100 mg/L for 2 weeks or more increasing the risk of developing this side effect. Single elevated levels do not seem to be associated with the onset of toxicity (18).

Hepatotoxicity:
The occurrence of hepatotoxicity is described in the literature, with reports of elevated transaminases and alkaline phosphatase in serum. The elevation of these values is almost always reversible upon discontinuation of 5-FC or through dose reduction. In exceptional cases, hepatotoxicity may decrease with constant dosage (2).
The mechanism of hepatotoxicity is unknown but appears to be concentration-related and may be preventable by keeping the peak level below 100 mg/L (18). Renal impairment can lead to high 5-FC levels, making it a risk factor for the development of hepatotoxicity (20). Patients treated with continuous infusion appear to develop hepatotoxicity less frequently than those receiving intermittent infusion. However, this was observed in a small study, and the difference in liver values were only significantly different for gamma-GT levels (20).

Prolonged 5-FC concentrations >100 mg/L are linked to increased toxicity (18). However, an occasional elevated concentration above 100 mg/L is not predictive of toxicity. A retrospective observational study of 53 ICU patients found that those with 5-FC concentrations >100 mg/L had a significantly higher incidence of thrombocytopenia and elevated liver enzymes ($P < 0.05$) (20). Furthermore, in patients treated with 5-FC plus amphotericin B for cryptococcal meningitis, toxicity occurred in 23 of 37 (62%) patients with serum concentrations >100 mg/L for ≥2 weeks, compared with 15 of 48 (31%) with concentrations <100 mg/L ($P = 0.005$) (18). Six of seven patients with hepatotoxicity had concentrations >100 mg/L for at least 2 weeks; a single transient 5-FC concentration >100 mg/L did not predict toxicity (18).

Sampling & storage conditions

5-FC levels should be determined within 24-72 hours after the start of therapy to allow for early dose adjustment. Both peak and trough levels should be measured after starting therapy. Additionally, TDM is necessary in cases of signs of toxicity and changes in renal function (9).

For intravenous administration, the peak concentration should be measured 30 minutes after starting the treatment. For oral administration, it should be measured 2 hours after the first dose, and for continuous intravenous administration, at least 24 hours after the start.

It is recommended to monitor trough concentrations weekly. However, if renal impairment or bone marrow suppression is present, more frequent monitoring is necessary.

Additional information concerning the interpretation of results

Background information [extended]

Pharmacodynamics

5-FC is a fluorinated pyrimidine analogue that requires activation inside fungal cells. After uptake through cytosine permease, it is converted by cytosine deaminase into 5-FU, which is further metabolized to active nucleotides. These metabolites interfere with both RNA and DNA synthesis within the fungal cell, resulting in a fungistatic effect. After an extended exposure, a fungicidal effect often occurs as well (3). Because mammalian cells lack cytosine deaminase, 5-FC is not converted to 5-FU in human cells, which explains why human cells are not affected by the drug (29).

Resistance can emerge rapidly, especially in monotherapy, due to mutations in genes encoding for enzymes responsible for uptake of 5-FC and conversion into 5-FU and its toxic metabolites (29).

Pharmacokinetics

5-FC is absorbed almost completely (70-90%) after oral administration. It is scarcely bound to proteins (<4%) and penetrates well into cerebrospinal fluid (approximately 75% of serum concentration), ocular fluid, peritoneal fluid, and inflamed joints. This is due to the high water solubility of 5-FC, low molecular weight, and low protein binding (5,30,31). Approximately 90% of an orally administered dose is excreted unchanged in the urine.

5-FC is metabolized to a very small extent (<4%) to 5-FU or dihydrofluorouracil by cytosine permease. Cytosine permease is not present in human cells but is likely secreted by intestinal bacteria. A correlation has been found between the flora status in the intestine and the degree of conversion of 5-FC to 5-FU metabolites. Plasma concentrations of 5-FU in some patients receiving oral 5-FC have been shown to be comparable to those observed in patients treated directly with 5-FU for an oncological indication(32).
As 5-FU is known to cause bone marrow suppression and gastrointestinal toxicity, this conversion of 5-FC to 5-FU may contribute to the development of toxicity during 5-FC therapy (4,30,31). Importantly, this phenomenon appears to be primarily relevant for oral administration, as the conversion occurs in the gut.

Pharmacogenetics

As described in the previous section, a small proportion of 5-FC is metabolized to 5-FU outside fungal cells, which may contribute to systemic toxicity. 5-FU is subsequently metabolized into inactive metabolites through dihydropyrimidine dehydrogenase (DPD). Several studies have demonstrated that reduced DPD activity leads to accumulation of 5-FU and an increased risk of toxicity (33).

Consequently, 5-FC is contraindicated in patients with known complete DPD deficiency. In patients with partial DPD deficiency, close clinical monitoring is recommended, and treatment discontinuation should be considered if severe adverse effects occur (34). In the Caucasian population, approximately 3–5% have a partial DPD enzyme deficiency, whereas complete DPD deficiency occurs in approximately 0.1–0.2% (35).

According to EMA recommendations, because treatment for severe fungal infections should not be delayed, routine pre-treatment DPD testing is not required before initiating flucytosine (34). However, assessment of DPD activity is recommended as soon as possible in cases of confirmed or suspected flucytosine-related toxicity.

Pharmacodynamic interactions

Nephrotoxic substances can increase exposure to 5-FC. Amphotericin B is often coadministered with 5-FC and is known for renal toxicity. Although liposomal formulations of amphotericin B have a lower risk of nephrotoxicity compared with amphotericin B deoxycholate, renal impairment may still occur within days to weeks after initiation of therapy. As 5-FC is predominantly excreted renally, the development of – generally reversible – renal impairment after initiation of amphotericin B may result in increased 5-FC concentrations and a prolonged half-life, thereby increasing the risk of toxicity (2).
Cytarabine can antagonize the action of 5-FC by competing with the same transport system in yeast cells (36).

PK parameters

	F (%)	Cl (L/h^{-1})	Vd (L/kg)	$t_{1/2}$ (h^{-1})	f_u (%)	T_{max} (h)	Refe-rence
Normal renal function (p.o./i.v.)	70-90	0,1236	0,7	3-6	96-98	1-2* 6**	(33,37)
Premature infants	i.v.	2.052 (/1.73m^2)	1,1(0.4–2)	6,5-7		2,5±1,3	
End stage renal disease	75-90	0,001–0,009315	0,9	12,3-430	96-98	4-5	(8,10,11,13)

* P.o. fasting
** P.o. with food

Population models

	Vd (L/kg)	K_{elr} (h^{-1}/ml/min)	K_{elm} (h^{-1})	K_{12} (h^{-1})	K_{21} (h^{-1})	Reference
General	0,231 ± 0,34	0,0057 ± 0,012	-	3,71 ± 2,85	1,65 ± 0,51	(8)
IC population	0,541 ± 0,084	0,00858 ± 0,000143	-	0,0313 ± 0,0138	0,0353 ± 0,0145	(23)

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Colophon

This guideline has been constituted by authors: Y. Polak (PharmD), Y. Bijleveld (PharmD, PhD) under the auspices of TDM, Toxicology and Pharmacogenetics committee (TTF) of the Dutch Association of Hospital Pharmacists (NVZA) and the International Association of Therapeutic Drug Monitoring and Clinical Toxicology (IATDMCT)
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Revision

This guideline has been revised by Tom Jacobs, PharmD, PhD; Asma al Mokkhadam, PharmD; Inger van Heijl, PharmD, PhD; and Prof. Roger Brüggemann, PharmD, PhD.
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This guidelines was updated based on most recent literature and translated to English.