TDM monograph flucloxacillin

Indication:	Based on the current available information, TDM is not advised for all patients treated with flucloxacillin. TDM might be of use in specific cases, such as in patients with difficult-to-treat infections, altered pharmacokinetics (for example augmented renal clearance), or in case of toxicity possibly caused by flucloxacillin
Sample material:	Plasma (preferred) or serum [1-3]
Time of sampling:	Intermittent infusion: sample just before next infusion (Ctrough) Continuous infusion: sample at any time point during infusion Sampling should occur ≥ 24 h post-initiation of therapy
Storage conditions:	Preferably store immediately at 2-8 °C after sample collection. Stability was tested for total as well as unbound flucloxacillin in different matrices: EDTA whole blood [4]: • 3 days at room temperature (patient samples) • 3 days at 2-8˚C (patient samples) EDTA plasma [4, 5]: • 24 hours at room temperature (patient samples and spiked EDTA plasma) • 3 days at 2-8˚C (patient samples and spiked EDTA plasma) • 13 months at -40˚C (spiked EDTA plasma) • 6 months at -80˚C (spiked EDTA plasma, no investigation performed >6 months)
Interpretation:	Efficacy, critically ill patients: • 100% $fT_{>MIC}$, corresponding to an unbound concentration of >0.5 mg/L • In some cases 100% $fT_{>4xMIC}$ can be considered, corresponding to an unbound concentration of >2.0 mg/L Toxicity [6]: • Total flucloxacillin trough concentration >125 mg/L
Evidence level:	2

Inleiding

Flucloxacillin is a beta-lactam antibiotic that belongs to the penicillins. Flucloxacillin exerts an antibacterial effect by its action on the synthesis of the bacterial wall, where it inhibits the crosslinking of peptidoglycans. This causes the bacterial wall to weaken, leading to bacterial death due to lysis. It is considered a narrow-spectrum antibiotic and is frequently used in the treatment of different infections caused by Gram-positive bacteria, such as penicillinase-producing staphylococci, including *methicillin-sensitive staphylococci* (MSSA) but not *methicillin-resistant staphylococci* (MRSA). [7]
Flucloxacilin is metabolized to a limited extent and the unchanged drug and metabolites are excreted in the urine by glomerular filtration and tubular secretion. It has a half-life of about 1 hour. Data obtained from healthy volunteers suggest protein binding of 95%. [8] Data from hospitalized patients show a large range of protein binding; 65-97% for non-critically ill patients [3] and 28-97% for critically ill patients [9, 10].

Flucloxacillin exhibits large interindividual variability in pharmacokinetics, especially in clearance. These differences in flucloxacillin clearance between individuals are not fully explained by the individual estimated glomerular filtration rates (eGFR) [9, 10].

The effectiveness of beta-lactam antibiotics in clinical studies is suggested to be time dependent: it depends mainly on the duration of the presence of the unbound drug at a concentration superior to the target pathogen's MIC, *f*T>MIC. [11] Flucloxacillin is considered to have a wide therapeutic index, with a large range of registered dosing regimens depending on the indication [7].

Criteria for TDM

Flucloxacillin fulfills some, but not all of the criteria for TDM to be useful [12]. It exhibits large interindividual variability in pharmacokinetics, there is a relationship between flucloxacillin exposure and clinical effect and the pharmacological response is not readily assessable. At this time, there is no international consensus on the target concentrations and a well-studied upper limit of concentration associated with toxicity is missing (see also *Referentiewaarden*). In the Netherlands there are several hospital pharmacies that can measure total flucloxacillin concentrations by a validated bio-analytical assay in routine clinical practice. The possibilities for routine measurement of unbound flucloxacillin concentrations are limited.

Indications for flucloxacillin TDM

Based on the current available information, TDM is not advised for all patients treated with flucloxacillin. TDM might be of use in specific cases. Examples of cases where TDM can be of use are (critically ill) patients with difficult-to-treat infections and possibly a compromised immune system, and/or where a pathogen with a high MIC is targeted. Patients with altered pharmacokinetics (for example augmented renal clearance), or in case of toxicity possibly caused by flucloxacillin.

Doseringsrichtlijnen

For dosing recommendations, see the National Antibiotic Guidelines from the SWAB:
https://adult.swabid.nl/nl/node/1434

Referentiewaarden

Efficacy

The PK/PD index associated with optimal beta-lactam activity is the time that the unbound drug concentration (*f*T) remains above the minimum inhibitory concentration (MIC) of the targeted

pathogen. Earlier pre-clinical data suggested a PK/PD index of 40-70% *f*T>MIC. Recent clinical studies report an association between a beta-lactam exposure of 100% *f*T>MIC with improved clinical outcome in critically ill patients [13-15]. The vast majority of the patients included in these studies received beta-lactam antibiotics via intermittent infusion.
Some suggest to use higher targets in specific cases, for example in the critically ill, based on the finding that killing of bacteria by beta-lactam antibiotics is maximal at around four times the minimum inhibitory concentration *in vitro* [16]. This target of 100% *f*T>4xMIC was also evaluated in the above-mentioned clinical studies, but no significant association with clinical outcome was found.
A recently published position paper written by an international group of experts in the field of antimicrobial TDM, recommends using a target of 100% *f*T>MIC for adult critically ill patients to achieve maximum bactericidal effect[17]. No clinical data for non-critically ill and pediatric patients is available at this time.

MIC

At this time, there are no possibilities for MIC measurement of flucloxacillin in clinical practice. As a result, MIC distributions for flucloxacillin are lacking in the overview of the EUCAST (https://mic.eucast.org/Eucast2/). The MIC distribution of flucloxacillin is suggested to be similar to cloxacillin [18] and therefore the epidemiological cut-off value (ECOFF) of cloxacillin of 0.5 mg/L [19] for MSSA is commonly used in clinical practice.

Where the MIC is not available for an individual pathogen, the highest MIC should be selected from all probable organisms in order to cover all susceptible organisms.

Also for patients with polymicrobial infections, the pathogen with the highest MIC is used to calculate the pharmacodynamic target

Toxicity

Very limited data on the relationship between exposure and toxicity is available. Only one, retrospective, clinical trial investigated this matter and reported that a total flucloxacillin trough concentration of 125 mg/L was associated with an increased likelihood of neurotoxicity, but not nephrotoxicity or hepatotoxicity [6]. The neurotoxicity is probably mediated by interference with gamma-aminobutyric acid (GABA-A). This threshold has not yet been prospectively confirmed. There is no reported threshold for unbound flucloxacillin toxicity.

Summary

Efficacy, for critically ill patients:

- 100% $fT_{>MIC}$, corresponding to an unbound concentration of >0.5 mg/L
- In some cases 100% $fT_{>4xMIC}$ can be considered, corresponding to an unbound concentration of >2.0 mg/L

No clinical data for non-critically ill and pediatric patients is available at this time.

Toxicity [6]:

- Total flucloxacillin trough concentration > 125 mg/L

Spiegelafname

- Intermittent infusion: sample just before next infusion (Ctrough)
- Continuous infusion: sample at any time point during infusion

Sampling should occur ≥ 24 h post-initiation of therapy

Interpretatie resultaten

Total versus unbound concentrations

Flucloxacillin is highly protein bound, predominantly to serum albumin. It exhibits non-linear, saturable protein binding, where the unbound fraction increases with increasing flucloxacillin concentrations. Furthermore, there is extensive inter-individual variability in the unbound fraction, especially in the critically ill. [9, 10]. Part of this variability can be explained by the serum albumin concentration. [3, 9, 10] Consequently, assuming an unbound fraction of 5% is not accurate and will in many patients (non-critically ill and critically ill) result in an underestimation of the unbound concentration. [20, 21]

In a recent meta-analysis, a mechanistic protein binding model was developed with the aim to predict the unbound flucloxacillin concentration from the total concentration and the serum albumin concentration [22]. The binding model predicted the unbound flucloxacillin concentrations more accurately than assuming an unbound fraction of 5%. Still, the performance of the mechanistic model was deemed clinically unacceptable with a bias of >25% and an imprecision of >60%. Therefore, it is highly recommended to measure the unbound flucloxacillin concentration.

Site of infection

In case the pathogen is not located in the bloodstream, plasma concentrations are used as a surrogate value for concentrations at the site of infection. At this time, there is no suitable method in routine clinical practice for determining the flucloxacillin concentration at the site of infection. Measurement of the unbound concentration gives the best approximation of the concentration at the site of infection, since only the unbound drug can penetrate in the infected tissue. Tissue concentrations might be lower than plasma concentrations. [23] Therefore, in specific cases it might be recommended to target higher plasma concentration to ensure adequate tissue concentrations.

Bio-analytical assay

The binding affinity for flucloxacillin to albumin is higher at room temperature than at physiological temperature (37 °C). Therefore, ultrafiltration performed at room temperature might lead to an underestimation of the unbound fraction [22, 24, 25] and ultrafiltration performed at 37 °C is likely to give a better representation of the protein binding *in vivo*.

Toxiciteit

See *Referentiewaarden*.

Achtergrondinformatie

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Interacties

For drug-drug interactions with flucloxacillin, see KNMP Kennisbank: https://kennisbank.knmp.nl/

PK parameters

Data from SmPC [7]:

Cl: 7-12 L/h

Vd: 17 L

$T_{1/2}$ (adequate renal function): 1 h

Protein binding: 95%

See *Populatiemodellen* for more information in different patient populations.

Populatiemodellen

- Healthy volunteers: Landersdorfer et al.[26]
- Non-critically ill (hospitalized) patients: Wilkes et al.[3]
- Critically ill (hospitalized) patients: Ulldemolins et al.[27], Jager et al.[9], Wallenburg et al.[10]

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Colofon

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Bijlage

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Revisie

20210701 changes:

Added that unbound concentrations should be analysed instead of total concentrations. Changed the reference concentrations from total to unbound reference concentrations. Some parts of the text were rewritten according to the most recent literature (published after February 2018).