FLUCLOXACILLIN

01. Assay Details

CH Labs Test Reference Guide

02. Therapeutic Range

Interpretation of flucloxacillin concentrations is complex and varies with organism, site and severity of infection, and underlying patient parameters such as immune system integrity. For hospitalised patients with moderate to severe infection caused by methicillin-susceptible Staphylococcus aureus (MSSA), it is reasonable to maintain unbound free (f) plasma flucloxacillin concentrations 1-4× the minimum inhibitory concentration (MIC) of the infecting organism for 50-100% of the dosing interval (50-100% ƒT>1-4×MIC). When the MIC is not known, a trough free flucloxacillin concentration of at least 0.5 mg/L (equivalent to the MIC for 90% of MSSA isolates) may be reasonable for moderate-severe infections. Consult Infectious Diseases or Clinical Pharmacology for assistance with interpretation.

Note: To enable comparison with MIC, the free (ƒ) flucloxacillin concentration (biologically active) needs to be measured. This is done routinely at CHL. If total flucloxacillin (i.e. the combination of free and bound concentrations) is required, this needs to be specified on the lab form.

How well established:

*ƒ*T>MIC correlates with efficacy of bacterial kill of β-lactam antimicrobials in vitro, and in human and animal models ("time-dependent killing"). Optimal efficacy is associated with *ƒ*T>MIC ≥50% of the dosing interval. In vitro, maximal bacterial killing rates occur with free concentrations around 4× the MIC, leading some centres to advocate this more aggressive target. Insufficient β-lactam exposure based on these parameters is associated with poorer clinical outcomes. Less aggressive targets may be appropriate for mild-moderate infections; in these situations, therapeutic drug monitoring (TDM) is less likely to provide clinical benefit.

TDM may be particularly valuable in situations where standard dosing regimens are associated with a high risk of not achieving these targets, due to increased clearance or increased volume of distribution (see below in Pharmacokinetics and Other PK data).

TDM may be used to optimise drug exposure in some serious bacterial infections requiring prolonged antibiotic treatment, particularly in deep seated infection e.g. brain abscess, endocarditis.

Although flucloxacillin has a wide therapeutic index, measurement of concentrations may be useful in settings where there is a concern regarding supra-therapeutic concentrations (such as in renal failure) and for the differential diagnosis of potential side effects such as nausea, electrolyte disturbances, and seizures.

03. Pharmacokinetics

Oral availability: 50-70%
PB: 0.95 (variable)
fe: 0.7
Metabolism: limited hepatic

Vd: 8-21 L in a 70kg person
$t_{1/2}$: 1 hr (0.75-1.5 hr)
Cl: 5.3 L/hr in a 70kg person

Vd = volume of distribution, Cl = clearance, t½ = terminal half-life of

elimination, fe = fraction excreted unchanged in the urine, PB = protein binding

Other PK data:
Volume of distribution is increased in critical illness, sepsis and burns because of capillary leak and fluid loading. It is also increased with larger body size. Increased Vd results in a lower peak plasma flucloxacillin concentration, and may prolong time to steady state.
Food decreases oral bioavailability. However, it increases time to peak concentrations, akin to use of a slow release formulation. Administration with food is likely to have a neutral or beneficial effect on efficacy and tolerability.
Clearance is higher in increased (augmented) renal clearance such as in critical illness, and decreased in renal impairment (fe 0.7).

Protein binding is affected by other drugs (e.g. probenecid), albumin concentration, renal dysfunction, free fatty acids, pH, and hyperbilirubinaemia. These factors typically reduce the protein binding, leading to free concentrations contributing a higher proportion to the total concentration.

04. Indications
Indicated for the treatment of infections due to susceptible Gram-positive organisms, including infections caused by methicillin-susceptible Staphylococcus aureus and β-haemolytic streptococci such as skin and soft tissue infections, respiratory tract infections, osteomyelitis, endocarditis, and septicaemia.

05. Loading Dose
Not required in standard dosing schedules. Consider a loading dose (e.g. 3000 mg) if increased volume of distribution is suspected.

06. Maintenance Dose
IV 1000-2000 mg every four to six hours
PO 500-1000 mg three to four times daily
Higher maintenance dosing may be required if augmented renal clearance is suspected.

07. Notes on Administration
See Notes on Injectable Drugs
http://cdhbintranet/medicalandsurgical/pharmacyservices/NOIDS/FLUCLOXACILLIN.pdf

08. When to Monitor
Trough concentrations should be obtained just prior to a dose, at steady state, i.e. 4-5 half-lives after a dose change or treatment commencement. In normal renal function t1/2 is short relative to dosing interval (1 hour), thus trough concentrations can be taken immediately before the second (or subsequent) doses.

More precise PK information relevant to target attainment is possible for oral or IV dosing by taking one or more timed mid-dose samples and pharmacokinetic modelling. Discuss with Clinical Pharmacology.

09. Dose Individualisation

Dose adjustment: Concentrations increase proportionally to dose due to linear pharmacokinetics.

Prolonged or continuous infusions may be useful in situations where it is difficult to achieve adequate drug exposure with standard doses - consult with Infectious Diseases and/or Clinical Pharmacology.
Renal impairment: dose adjustment may be considered in significant renal impairment (fe=0.7)

10. Adverse Effects

1-10%	GI:	diarrhoea
<1%	GI: Blood: Misc:	nausea, vomiting, dyspepsia, severe drug-induced liver injury anaemia, thrombocytopenia, eosinophilia, leukopenia, agranulocytosis cholestasis, rashes, nephritis, haematuria, abnormal LFTs, *C. difficile*

11. Drug Interactions

Probenecid reduces clearance of flucloxacillin by reducing renal tubular active secretion. This interaction is used therapeutically to increase flucloxacillin concentrations achievable with oral dosing.

12. Factors that may give a False Assay Result

Nil known

13. Overdose

See TOXINZ

14. Dialysability

Haemodialysis does not significantly affect the elimination rate of flucloxacillin because of high protein binding.

15. Comments

Nil.

16. Key References

Selected references

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3. Roberts JA, Paul SK, Akova M et al. DALI: defining antibiotic levels in intensive care unit patients: are current β-lactam antibiotic doses sufficient for critically ill patients? Clin Infect Dis 2014; 58: 1072–83.
4. Landersdorfer CB, Kirkpatrick CM, Kinzig-Schippers M et al. Population pharmacokinetics at two dose levels and pharmacodynamic profiling of flucloxacillin. Antimicrob Agents Chemother. 2007 Sep;51(9):3290-7.
5. Turnidge J (2010). Isoxazolyl Penicillins: Oxacillin, Cloxacillin, Dicloxacillin and Flucloxacillin. In Grayson ML et al (Ed.), Kucers' The Use of Antibiotics 6th Ed (vol 1, pp. 100-114).

17. Author/Date

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