Chloramphenicol prescribing in adult patients - consensus guidance

Background

This guidance has been produced to support prescribing of chloramphenicol, in non-pregnant, adult patients, in NHS Scotland boards. Systemic chloramphenicol treatment is rarely used in clinical practice, as less toxic antibacterials are preferred. It may be used in certain circumstances where treatment options are limited by resistance, intolerance or allergy, since it is active against a range of bacteria. Detailed advice should be obtained before prescribing to support safe and effective treatment.

Use of systemic chloramphenicol **must be authorised** by a member of the infectious diseases or microbiology teams prior to prescribing. There may be some local exceptions to requirement for approval e.g. for empirical use in meningitis in penicillin allergy as per local NHS board guidance.

Key points to remember when prescribing chloramphenicol

- **Dose adjustment may be needed in patients with obesity, renal impairment or hepatic impairment**
- **Check for potential drug interactions before prescribing**
- **Follow administration instructions carefully to minimise adverse effects**
- **Monitoring of full blood count (FBC), urea & electrolytes (U&Es) and liver function tests (LFTs) is required**
- **Therapeutic drug monitoring is required for treatment over 48 hours duration**
- **Be alert to potential adverse effects and discontinue if hepatic or haematological toxicities**
- **Counsel patients who have received treatment about the risk of aplastic anaemia and ensure note about risk added to primary care clinical record**

Indications for use

Licensed indications: Severe life-threatening infections, including meningitis, particularly those caused by *Haemophilus influenzae*

Off label indications: For other severe infections, if less toxic alternatives are not available or suitable: bone and joint infections, respiratory infections, CNS (central nervous system) infections

Antimicrobial activity: Bacteriostatic (bactericidal at high concentrations)
Usually sensitive:

- Gram positive: Staphylococci, Streptococci, Enterococci

- Gram negative: Haemophilus, Meningococci, Gonococci, Enterobacteriaceae
- Anaerobes: including Bacteroides
- Atypical bacteria

Resistance: *Pseudomonas spp, Mycobacteria*

Clinical notes

- Contra-indications
  - acute porphyria
  - previous history of sensitivity or toxic reaction to chloramphenicol
  - blood dyscrasias and patients taking medicines liable to suppress bone marrow
  - pregnancy and breast feeding
- Avoid repeated courses

Pharmacokinetics

Absorption: Well absorbed (80% bioavailability, some sources quote 90-100%)

Distribution: Small molecule that diffuses well into many body tissues including cerebral spinal fluid (CSF) - even in absence of inflamed meninges, eye, pleural fluid, synovial fluid, ascitic fluid, liver and kidneys.

- CSF concentrations 50%-65% of serum concentrations
- Volume of distribution 0.5–1 L/kg
- Highly lipid soluble, not highly protein bound (≈60%)
- Crosses placenta

Metabolism: Metabolised in liver (90%) to inactive metabolite with very small amounts of active drug are recovered in the bile

Excretion: 90% excreted in urine (only 5-10% as active drug)

- Half-life = 1.5 to 4 hours
- If Creatinine Clearance is less than 40mL/min, urinary concentrations are insufficient to treat susceptible organisms.

Dosage

Usual dose:

- 50mg/kg /day usually in 4 divided doses – usual maximum 4g daily
- 100mg/kg/day can be given for a short period e.g. in the first 24 to 48 hours of meningitis treatment – maximum 2g four times a day (8g daily) then adjust as per levels. European Committee on Antimicrobial Susceptibility Testing (EUCAST) suggests always using intravenous (IV) 2g four times a day (high dose) for meningitis
- Increased risk of bone marrow toxicity if dose is over 4g daily
- Oral dose needs to be rounded to nearest 250mg (as this is only available capsule strength)

- Depending on levels (see below) can reduce total dose and give in 2 or 3 divided doses.

Dosing for patients with obesity:

- Consider use of adjusted body weight (AdjBW) if the patient's total body weight is over 20% over ideal body weight (IBW)
    - Ideal body weight table
    - AdjBW= IBW + 0.4 (actual body weight – IBW)
- As above, maximum 8g daily for the first 24 to 48 hours and then adjust dose based on levels.

Dosing for patients with renal impairment:

- No dose reduction required in patients with renal impairment
- Dialysis patients – dose as per normal renal function
- Do not use for urinary tract infections if creatinine clearance is less than 40mL/min

Dosing for patients with hepatic impairment:

- Avoid or decrease dose in hepatic impairment - conjugated at slower rate to metabolite
- Higher risk of bone marrow suppression - use therapeutic drug monitoring (TDM) to adjust dosing (see below)

Route of administration

This guidance covers oral and parenteral (IV and intramuscular (IM)) routes of administration only.

Oral: Well absorbed (bioavailability at least 80%). Take with or without food.

Intravenous: Pro drug (sodium succinate ester) hydrolysed to active chloramphenicol

- Active drug levels in serum are only 70% of oral levels due to incomplete hydrolysis
- Can be given by IV injection or IV infusion
- When given by IV injection can cause an intensely bitter taste if rapid administration or more concentrated solution
- Refer to NHS Injectable Medicines Guide (Medusa) for information on IV administration

Intramuscular: Non-preferred route

- Whilst this is an option it has important practical implications - administration of a 1g dose would need to be split and given via 3 or 4 sites
- Older reports suggest slow and unpredictable absorption but appears from results of a number of studies to be clinically effective
- 30% unhydrolysed in urine (due to delayed absorption of ester not decreased hydrolysis)

Monitoring

Haematology and biochemistry

- Baseline – FBC, LFTs and U&Es
- Week 1 – FBC, LFTs and U&Es every 2 days (increase frequency if the patient is hospitalised and unwell)
- Week 2 onwards – FBC weekly and take U&Es and LFTs every 2 weeks
- Be aware of potential for delayed blood dyscrasias after course complete

Therapeutic drug monitoring

- Narrow therapeutic index so recommended in any patients where therapy is likely to continue for longer than 48 hours and especially in patients with hepatic disease, those who are elderly, patients with obesity and those who have drug-drug interactions.
- Short half-life so can be done after 24 hours if required.
- Samples sent to the Bristol Antimicrobial Reference Laboratory for measurement of serum levels.
- Pre dose level should ideally be less than 10mg/L but definitely less than 15mg/L. If the level is too high, extend dosage interval e.g. from 6 hourly to 8 hourly.
- Post dose (2 hours) level 10-25mg/L. If level is too high, consider omitting doses and restart at reduced dose.
- Repeat TDM at 5-7 days if in range (or sooner if out with range).

Interactions: Inhibits CYP2C9/2C19/3A4

- Interactions include warfarin, calcineurin inhibitors, anti-epileptics, sulphonylureas, rifampicin
- Can also decrease response to iron and vitamin B12 supplements
- Paracetamol warning in Summary of Product Characteristics (SPC) but refer to information in MedicinesComplete — CONTENT > Stockley's Drug Interactions > Interaction: Chloramphenicol + Paracetamol (Acetaminophen) (oclc.org)

Adverse drug reactions

- Haematologic: discontinue chloramphenicol if haematological toxicities
  - Bone marrow suppression – increased risk with dose higher then 4g daily or if level is higher than 25mg/L
  - Aplastic anaemia (rare but often fatal) – 1:24,000 to 40,000 patients
    - Often not dose related
    - 22% happen around the time of the chloramphenicol course but many happen weeks to months later
    - Counsel patient and request addition to primary care clinical record re risk
  - Liver toxicity – discontinue chloramphenicol if abnormalities of liver function
  - Fever, rash
  - Anaphylactoid reactions
  - Optic atrophy/neuropathy – very rare
  - Ototoxicity
  - Digital parasthesias
  - Minor disulfiram type reactions

- GI symptoms – less common than tetracyclines

References for "Chloramphenicol prescribing in adult patients - consensus guidance"

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