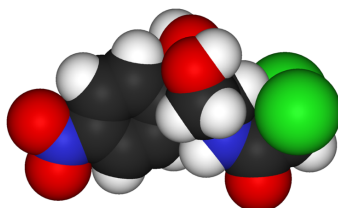
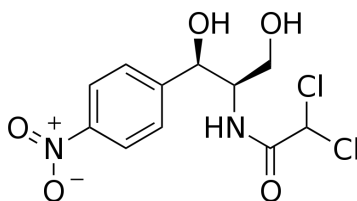


Chloramphenicol

Chloramphenicol



Systematic (IUPAC) name

2,2-dichloro-*N*-[(1*R*,2*R*)-2-hydroxy-1-(hydroxymethyl)-2-(4-nitrophenyl)ethyl]acetamide

Identifiers

CAS number	56-75-7 ^[1]
ATC code	D06 AX02 ^[2] D10 AF03 ^[3] G01 AA05 ^[4] J01 BA01 ^[5] S01 AA01 ^[6] S02 AA01 ^[7] S03 AA08 ^[8] QJ51 BA01 ^[9]
PubChem	CID 298 ^[10]
DrugBank	DB00446 ^[11]
ChemSpider	5744 ^[12]

Chemical data

Formula	$C_{11}H_{12}Cl_2N_2O_5$
Mol. mass	323.132 g/mol
SMILES	eMolecules ^[13] & PubChem ^[14]

Pharmacokinetic data

Bioavailability	75–90%
Metabolism	Hepatic
Half-life	1.5–4.0 hours
Excretion	Renal

Therapeutic considerations

Pregnancy cat.	C (systemic), A (topical)
Legal status	Ocular P, else POM (UK)
Routes	Topical (ocular), oral, IV, IM

✓ (what is this?) (verify)^[15]

Chloramphenicol (INN) is a bacteriocidal antimicrobial. It is considered a prototypical broad-spectrum antibiotic, alongside the tetracyclines.

Chloramphenicol is effective against a wide variety of Gram-positive and Gram-negative bacteria, including most anaerobic organisms. Due to resistance and safety concerns, it is no longer a first-line agent for any indication in developed nations, although it is sometimes used topically for eye infections. Nevertheless, the global problem of advancing bacterial resistance to newer drugs has led to renewed interest in its use.^[16] In low-income countries, chloramphenicol is still widely used because it is inexpensive and readily available.

The most serious adverse effect associated with chloramphenicol treatment is bone marrow toxicity, which may occur in two distinct forms: bone marrow suppression, which is a direct toxic effect of the drug and is usually reversible, and aplastic anemia, which is idiosyncratic (rare, unpredictable, and unrelated to dose) and generally fatal.^[17]

Spectrum of activity

Because it functions by inhibiting bacterial protein synthesis, chloramphenicol has a very broad spectrum of activity: it is active against Gram-positive bacteria (including most strains of MRSA), Gram-negative bacteria and anaerobes.^[18] It is not active against *Pseudomonas aeruginosa*, *Chlamydiae*, or *Enterobacter* species. It has some activity against *Burkholderia pseudomallei*, but is no longer routinely used to treat infections caused by this organism (it has been superseded by ceftazidime and meropenem). In the West, chloramphenicol is mostly restricted to topical uses because of the worries about the risk of aplastic anaemia.

Therapeutic uses

The original indication of chloramphenicol was in the treatment of typhoid, but the now almost universal presence of multi-drug resistant *Salmonella typhi* has meant that it is seldom used for this indication except when the organism is known to be sensitive. Chloramphenicol may be used as a second-line agent in the treatment of tetracycline-resistant cholera.

Because of its excellent BBB penetration (far superior to any of the cephalosporins), chloramphenicol remains the first choice treatment for staphylococcal brain abscesses. It is also useful in the treatment of brain abscesses due to mixed organisms or when the causative organism is not known.

Chloramphenicol is active against the three main bacterial causes of meningitis: *Neisseria meningitidis*, *Streptococcus pneumoniae* and *Haemophilus influenzae*. In the West, chloramphenicol remains the drug of choice in the treatment of meningitis in patients with severe penicillin or cephalosporin allergy and GPs are recommended to carry intravenous chloramphenicol in their bag. In low income countries, the WHO recommend that oily chloramphenicol be used first-line to treat meningitis.

Chloramphenicol has been used in the U.S. in the initial empirical treatment of children with fever and a petechial rash, when the differential diagnosis includes both *Neisseria meningitidis* septicaemia as well as Rocky Mountain spotted fever, pending the results of diagnostic investigations.

Chloramphenicol is also effective against *Enterococcus faecium*, which has led to it being considered for treatment of vancomycin-resistant enterococcus.

Although unpublished, recent research suggests that chloramphenicol could also be applied to frogs to prevent their widespread destruction from fungal infections.^[19]

Chloramphenicol has recently been discovered to be a life saving cure for chytridiomycosis in amphibians.^[20] Chytridiomycosis is a fungal disease, blamed for the extinction of one-third of the 120 frog species lost since 1980.

Adverse effects

Aplastic anemia

The most serious side effect of chloramphenicol treatment is aplastic anaemia.^[17] This effect is rare and is generally fatal: there is no treatment and there is no way of predicting who may or may not get this side effect. The effect usually occurs weeks or months after chloramphenicol treatment has been stopped and there may be a genetic predisposition.^[21] It is not known whether monitoring the blood counts of patients can prevent the development of aplastic anaemia, but it is recommended that patients have a blood count checked twice weekly while on treatment. The highest risk is with oral chloramphenicol^[22] (affecting 1 in 24,000–40,000)^[23] and the lowest risk occurs with eye drops (affecting less than 1 in 224,716 prescriptions).^[24]

Thiamphenicol is a related compound with a similar spectrum of activity that is available in Italy and China for human use, and has never been associated with aplastic anaemia. Thiamphenicol is available in the U.S. and Europe as a veterinary antibiotic, and is not approved for use in humans.

Bone marrow suppression

It is common for chloramphenicol to cause bone marrow suppression during treatment: this is a direct toxic effect of the drug on human mitochondria. This effect manifests first as a fall in hemoglobin levels and occurs quite predictably once a cumulative dose of 20 g has been given. This effect is fully reversible once the drug is stopped and does not predict future development of aplastic anaemia.

Leukemia

There is an increased risk of childhood leukemia as demonstrated in a Chinese case-controlled study,^[25] and the risk increases with length of treatment.

Possible Related Adverse Effects Chloramphenicol is particularly toxic to people sensitive to benzene based preservatives like preservatives 210 and 211. Chloramphenicol poisoning can cause sensitivity reactions to organic acids and salicylates. Chloramphenicol is also known to cause tinnitus and balance problems through inner ear damage. It also causes folic acid depletion resulting in adverse effects to the thyroid, pituitary and prostate through effects on PABA levels. There may also be links to chronic lymphocytic leukemia (CLL) through folic acid "depletion" and resultant high levels of folic acid in the mutant lymphocytes that characterize CLL. Chloramphenicol stops the bodies production of vitamin D and pregnenolone. This results in major hormone depletion, including DHEA and testosterone, that can result in death and also lowers the bodies resistance to viral infection. Chloramphenicol can cause testes pain, possibly through hormone effects. Chinese research shows that chloramphenicol affects motor neurones. It also affects insulin Igf1 levels and glutamate levels. Both of these conditions are considered indicative of a type of motor neurone disease. The adverse genetic effects of chloramphenicol are considered heritable.

Gray baby syndrome

Intravenous chloramphenicol use has been associated with the so called gray baby syndrome.^[26] This phenomenon occurs in newborn infants because they do not yet have fully functional liver enzymes (i.e. UDP-glucuronyl transferase), and so chloramphenicol remains unmetabolized in the body.^[27] This causes several adverse effects, including hypotension and cyanosis. The condition can be prevented by using chloramphenicol at the recommended doses and monitoring blood levels.^{[28] [29] [30]}

Pharmacokinetics

Chloramphenicol is extremely lipid soluble, it remains relatively unbound to protein and is a small molecule: it has a large apparent volume of distribution of 100 litres and penetrates effectively into all tissues of the body, including the brain. The concentration achieved in brain and cerebrospinal fluid (CSF) is around 30 to 50% even when the meninges are not inflamed; this increases to as high as 89% when the meninges are inflamed.

Chloramphenicol increases the absorption of iron.^[31]

Use in special populations

Chloramphenicol is metabolised by the liver to chloramphenicol glucuronate (which is inactive). In liver impairment, the dose of chloramphenicol must therefore be reduced. There is no standard dose reduction for chloramphenicol in liver impairment, and the dose should be adjusted according to measured plasma concentrations. Chloramphenicol is also noted for its cause of "Gray Baby Syndrome" because of infants lack of the enzyme glucuronyl transferase which is the main pathway conjugational excretion, which leads to a buildup of the chemical in infants system-contraindication.

The majority of the chloramphenicol dose is excreted by the kidneys as the inactive metabolite, chloramphenicol glucuronate. Only a tiny fraction of the chloramphenicol is excreted by the kidneys unchanged. It is suggested that plasma levels be monitored in patients with renal impairment, but this is not mandatory. Chloramphenicol succinate ester (the inactive intravenous form of the drug) is readily excreted unchanged by the kidneys, more so than chloramphenicol base, and this is the major reason why levels of chloramphenicol in the blood are much lower when given intravenously than orally.

Chloramphenicol passes into breast milk and should therefore be avoided during breastfeeding if possible.^[32]

Dose monitoring

Plasma levels of chloramphenicol must be monitored in neonates and in patients with abnormal liver function. It is recommended that plasma levels be monitored in all children under the age of 4, the elderly and patients with renal failure. Peak levels (1 hour after the dose is given) should be 15–25 mg/l; trough levels (taken immediately before a dose) should be less than 15 mg/l.

Drug interactions

Administration of chloramphenicol concomitantly with bone marrow depressant drugs is contraindicated, although concerns over aplastic anaemia associated with ocular chloramphenicol have largely been discounted.^[33]

Chloramphenicol is a potent inhibitor of the cytochrome P450 isoforms CYP2C19 and CYP3A4 in the liver.^[34] Inhibition of CYP2C19 causes decreased metabolism and therefore increased levels of, for example, antidepressants, antiepileptics and proton pump inhibitors if they are given concomitantly. Inhibition of CYP3A4 causes increased levels of, for example, calcium channel blockers, immunosuppressants, chemotherapeutic drugs, benzodiazepines,azole antifungals, tricyclic antidepressants, macrolide antibiotics, SSRIs, statins and PDE5 inhibitors.^[35]

Mechanism of action

Chloramphenicol is bacteriostatic (that is, it stops bacterial growth). It is a protein synthesis inhibitor, inhibiting peptidyl transferase activity of the bacterial ribosome, binding to A2451 and A2452 residues in the 23S rRNA of the 50S ribosomal subunit, preventing peptide bond formation.^[36] While chloramphenicol and the macrolide class of antibiotics both interact with ribosomes, chloramphenicol is not a macrolide. Chloramphenicol directly interferes with substrate binding, macrolides sterically block the progression of the growing peptide.^{[37] [38] [39]}

Resistance

There are three mechanisms of resistance to chloramphenicol: reduced membrane permeability, mutation of the 50S ribosomal subunit and elaboration of chloramphenicol acetyltransferase. It is easy to select for reduced membrane permeability to chloramphenicol *in vitro* by serial passage of bacteria, and this is the most common mechanism of low-level chloramphenicol resistance. High-level resistance is conferred by the *cat*-gene; this gene codes for an enzyme called chloramphenicol acetyltransferase which inactivates chloramphenicol by covalently linking one or two acetyl groups, derived from acetyl-S-coenzyme A, to the hydroxyl groups on the chloramphenicol molecule. The acetylation prevents chloramphenicol from binding to the ribosome. Resistance-conferring mutations of the 50S ribosomal subunit are rare.

Chloramphenicol resistance may be carried on a plasmid that also codes for resistance to other drugs. One example is the ACCoT plasmid (A=ampicillin, C=chloramphenicol, Co=co-trimoxazole, T=tetracycline) which mediates multi-drug resistance in typhoid (also called R factors).

Formulations

Chloramphenicol is available as 250 mg capsules or as a liquid (125 mg/5 ml). In some countries, chloramphenicol is sold as chloramphenicol palmitate ester. Chloramphenicol palmitate ester is inactive, and is hydrolysed to active chloramphenicol in the small intestine. There is no difference in bioavailability between chloramphenicol and chloramphenicol palmitate.

The intravenous (IV) preparation of chloramphenicol is the succinate ester, because pure chloramphenicol does not dissolve in water. This creates a problem: chloramphenicol succinate ester is an inactive prodrug and must first be hydrolysed to chloramphenicol; the hydrolysis process is incomplete and 30% of the dose is lost unchanged in the urine, therefore serum concentrations of chloramphenicol are only 70% of those achieved when chloramphenicol is given orally.^[40] For this reason, the chloramphenicol dose needs to be increased to 75 mg/kg/day when administered IV in order to achieve levels equivalent to the oral dose.^[41] The oral route is therefore preferred to the intravenous route.

Manufacture of oral chloramphenicol in the U.S. stopped in 1991, because the vast majority of chloramphenicol-associated cases of aplastic anaemia are associated with the oral preparation. There is now no oral formulation of chloramphenicol available in the U.S.

Oily

Dose: 100 mg/kg (maximum dose 3 g) as a single intramuscular injection. The dose is repeated if there is no clinical response after 48 hours. A single injection costs approximately US\$5.

Oily chloramphenicol (or chloramphenicol oil suspension) is a long-acting preparation of chloramphenicol first introduced by Roussel in 1954; marketed as Tifomycine, it was originally used as a treatment for typhoid. Roussel stopped production of oily chloramphenicol in 1995; the International Dispensary Association has manufactured it since 1998, first in Malta and then in India from December 2004.

Oily chloramphenicol is recommended by the World Health Organization (WHO) as the first line treatment of meningitis in low-income countries and appears on the essential drugs list. It was first used to treat meningitis in 1975^[42] and there have been numerous studies since demonstrating its efficacy.^{[43] [44] [45]} It is the cheapest treatment available for meningitis (US\$5 per treatment course, compared to US\$30 for ampicillin and US\$15 for five days of ceftriaxone). It has the great advantage of requiring only a single injection, whereas ceftriaxone is traditionally given daily for five days. This recommendation may yet change now that a single dose of ceftriaxone (cost US\$3) has been shown to be equivalent to one dose of oily chloramphenicol.^[46]

Oily chloramphenicol is not currently available in the U.S. or Europe.

Eye drops

In the West, chloramphenicol is still widely used in topical preparations (ointments and eye drops) for the treatment of bacterial conjunctivitis. Isolated cases report of aplastic anaemia following chloramphenicol eyedrops exist, but the risk is estimated to be less than 1 in 224,716 prescriptions.^[24] Note. <http://www.patient.co.uk/showdoc/40025037/> suggests that the link between chloramphenicol eye drops and aplastic anemia is "not well founded".

Trade names

Chloramphenicol has a long history and therefore a multitude of alternative names in many different countries:

- **Alficetyn**
- **Amphicol**
- **Biomicin**
- **Chlornitromycin**
- **Chloromycetin** (U.S., intravenous preparation)
- **Chlorsig** (U.S., Australia, eye drops)
- **Dispersadron C** (Greece, eye drops)
- **Edrumycetin 250 mg** (Bangladesh, Capsule)
- **Fenicol**
- **Kemicetine** (UK, intravenous preparation)
- **Kloramfenikol** (Denmark, eye drops)
- **Laevomycetin**
- UK as an eye treatment
 - **Brochlor** (Aventis Pharma Ltd)
 - **Chloromycetin Redidrops** (Goldshield Pharmaceuticals Ltd)
 - **Golden Eye** (Typharm Ltd)
 - **Optrex Infected Eyes**
- **Oftan Chlora** (eye ointment)
- **Optacloran** (Bolivia, eye drops)
- **Phenicol**
- **Posifenicol 1%** (Germany, eye ointment)
- **Medicom**
- **Nevimycin**
- **Renicol** (India, eye drops)
- **Silmycetin** (Thailand, eye drops)
- **Synthomycine** (Israel, eye ointment and skin ointment)
- **Tifomycine** (France, oily chloramphenicol)
- **Vernacetin**
- **Veticol**
- **Orchadexoline** (Egypt , eye drops)
- **Isoptophenicol** (Egypt . eye drops)
- **Cedoctine** (Egypt .intravenous preparation)
- **Chloramex** (South Africa, eye ointment)

History

Chloramphenicol was originally derived from the bacterium *Streptomyces venezuelae*, isolated by David Gottlieb, and introduced into clinical practice in 1949, under the trade name **Chloromycetin**. It was the first antibiotic to be manufactured synthetically on a large scale.

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- [7] http://www.whooc.no/atc_ddd_index/?code=S02AA01
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External links

- MedlinePlus DrugInfo *uspdi-202125* (<http://www.nlm.nih.gov/medlineplus/druginfo/uspdi/202125.html>)
- University of Pennsylvania (http://www.uphs.upenn.edu/bugdrug/antibiotic_manual/chloro.htm)

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