THE NORTHERN HOSPITAL

COLISTIN

Introduction

Colistin (also known as **polymyxin E**) is an old class **bactericidal polymyxin** antibiotic.

It is produced by certain strains of *Paenibacillus polymyxa* var. *colistinus*, a gram positive bacteria found in soil, plant roots, and marine sediments.

Colistin is a **decades old drug** that fell out of favor because of concerns over its nephrotoxicity, but now has again found use as one of one of the last-resort antibiotics for multidrug-resistant **gram negative** bacteria such as the **CRE.**

Colistin's parenteral drug form is **Colistimethate Sodium** (or colistin methanesulfonate) which is hydrolysed to colistin in the body.

The use of colistimethate sodium has been limited to Gram-negative infections resistant to all other drug classes, due to reports of severe adverse effects (renal toxicity and neurotoxicity). However, recent evidence suggests that the risk of toxicity may have been overestimated.

History

Colistin is a very old antibiotic that was first in **1949.**

Colistin was initially used therapeutically in Japan and in Europe during the 1950s and in the United States in the form of colistimethate sodium in 1959.

It's parenteral use fell out of favor in the 1908s because of concerns over nephrotoxicity, but now it has again found use as one of one of the last-resort antibiotics for multidrug-resistant gram negative bacteria such as the CRE.

Because colistin was introduced into clinical practice over 50 years ago, it was never subject to the regulations that modern drugs are subject to, and therefore there is no standardized dosing of colistin and no detailed trials on pharmacology or pharmacokinetics:

The optimal dosing of colistin for most infections is therefore uncertain.

Chemistry

Polymyxins are antibiotics with a general structure consisting of a **cationic** cyclic decapeptide linked to a long hydrophobic fatty acid tail.

Classification

The polymyxins, are a group of polypeptide antibiotics that consist of 5 chemically different compounds: polymyxin A,B,C,D and E

The polymyxin antibiotics that are **used clinically** today include:

- Polymyxin B
- Polymyxin E (or **Colistin)**

Preparation

Colistin's **parenteral** and **inhalational** drug form is **Colistimethate Sodium** (also known as **colistin methanesulfonate**) which is **hydrolysed** to **colistin** in the body.

Colistimethate Sodium preparations include: [2]

Strengths expressed as colistin base:

Ampoules: 150 mg (4.5×10^6 IU) powder for reconstitution.

Nebules for inhalation: 33.33 mg (1×10^6 IU) powder.

Colistin sulfate is an orally administered form (tablets or syrup) for bowel decontamination and topically as a powder for the treatment of bacterial skin infections.

Mechanism of Action

Polymyxins are bactericidal antibiotics.

They disrupt the structure of the bacterial cell membrane by interacting with its phospholipids.

They are produced by non-ribosomal peptide synthetase systems in Gram-positive bacteria such as *Paenibacillus polymyxa* and are selectively toxic for Gram-negative bacteria due to their specificity for the lipopolysaccharide molecule that exists within many Gram-negative outer membranes.

After binding to lipopolysaccharide (LPS) in the outer membrane of Gram-negative bacteria, polymyxins disrupt both the outer and inner membranes. The hydrophobic tail is important in causing membrane damage.

Binds to phospholipids in the bacterial cell wall changes its permeability and kills the cell.

Pharmacokinetics

Absorption:

- Colistin can be given **IV (**or **IM**, but IV is preferred) or via **inhalation.**

  Some polymyxins have been used extensively worldwide in **topical** otic and ophthalmic solutions

  Relatively low systemic absorption occurs via the inhaled route.

  In the body colistimethate sodium → colistin
  ↑
  Hydrolysis

Polymyxins are not absorbed from the gastrointestinal tract and so are not given orally.

Distribution:

- Old experimental studies have shown that colistin is tightly bound to membrane lipids of cells of many body tissues, including liver, lung, kidney, brain, heart, and muscles.

  Release of tissue-bound drug is very slow and is not completed even at 5 days after the last administered dose.

Metabolism and excretion:

- Colistin is eliminated predominantly by renal excretion.

  No biliary excretion has been reported in humans.

Pharmacodynamics

Polymyxin antibiotics have excellent bactericidal activity against many **Gram-negative bacteria** including many CRE and strains of *Pseudomonas aeruginosa* and *Acinetobacter baumannii* that are resistant to other drug classes

Note that, as for all antibiotics, the prevalence of bacterial resistance may vary geographically and over time for selected species and local information on resistance is also important, particularly when treating severe infections.

Indications

These include:

1. Acute or chronic infection due to multidrug resistant Gram-negative bacteria, e.g. **CRE** when other agents are unsuitable.

2. Respiratory infection (including colonisation) with *P. aeruginosa* in cystic fibrosis (inhaled)

Contraindications/ Precautions

1. Known allergy to the polymyxins.

2. Renal impairment:

   Reduce doses in renal impairment

   This is because of:

   - Greater risk of toxicity
   - Risk of worsening renal impairment.

3. Concurrent treatment with other nephrotoxic drugs may increase the risk of nephrotoxicity.

4. Myasthenia gravis:

   - May worsen.

Pregnancy

Colistin is classed as a category B2 drug with respect to pregnancy. [2]

Category B2 drugs are those drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.

Breast feeding

Limited data; therefore use with caution.

There is only low concentration in breast milk and it is poorly absorbed from the baby's GIT (but may cause loose bowel actions in the baby).

Adverse Effects

These include:

1. Nephrotoxicity:

    - This was a major factor in colistin's loss of favour decades ago, however current expert opinion is that this was risk may have been overestimated. [1]

      Much information about its adverse effects derives from old literature, when higher doses were used, and it was used in renal impairment without suitable dose reduction.

      Risk may be related more to **total dose.**

      Reported effects include increased serum creatinine, haematuria, proteinuria, oliguria, rarely tubular necrosis.

2. Neurotoxic effects:

    - Paraesthesia
    - Muscle weakness/ neuromuscular blockade:
        - ♥ **With very toxic levels, there can be interference of nerve transmission at the neuromuscular junctions which may result in muscle weakness and even apnoea.**
        - ♥ Worsening of myasthenia gravis.
    - Ataxia
    - Confusion
    - Visual effects

3. Colistin may prolong action of non-depolarising neuromuscular blockers

4. Allergic reactions (rare).

5. Inhalation:

    - Coughing, bronchospasm (FEV_1 may also decrease).

6. Mild GIT upset.

Dosing

The dosing of colistimethate sodium is complex.

According to the eTG dosing recommended in the *product information* is not appropriate. [1]

Colistimethate sodium should only be used with expert supervision.

In general terms:

Dosage is given in terms of **colistin base**.

- **80 mg of colistimethate sodium = colistin base 33.33 mg (1x10 ^{6} units).** [2]

IV/IM: [2]

- Adult, child: 2.5- 5 mg/kg daily (0.075 - 0.15 x 10 ^{6} units/kg daily) in 2 - 4 doses. [2]

For IV injection, give slowly over 5 minutes.

Maximum daily dose should not exceed 5 mg/kg/day with normal renal function.

Inhalation: [2]

Adult, child >2 years:

Use bronchodilator first, and then colistin after inhalations.

Treatment:

- 66.66 mg (2 x 10 ^{6} units) inhaled twice daily for 3 weeks. For recurrent infections, the dose may be increased to 66.66 mg (2 x 10 ^{6} units) 3 times daily for up to 3 months.

Chronic colonisation:

- 33.33 - 66.66 mg (1- 2 x 10 ^{6} units) inhaled twice daily.

References

1. eTG - March 2015.

2. Colistin in Australian Medicines Handbook, Website Accessed June 2015.

3. Colistin in MIMs 1 September 2014.

4. Matthew E. Falagas, Sofia K. Kasiakou**:** Colistin: The Revival of Polymyxins for the Management of Multidrug-Resistant Gram-Negative Bacterial Infections. CID 2005; 40: 1333- 41

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