Adverse Effects, Treatment, and Precautions

As for Polymyxin B Sulfate, p.318.

Colistin sulfate is poorly absorbed from the gastrointestinal tract and adverse effects do not normally occur with usual oral doses. However, gastrointestinal absorption is limited and unpredictable in infants under 6 months of age and systemic adverse effects such as transient sensory disturbances may occur in this patient group.

Cough and bronchospasm may occur during inhalation; cases of sore throat or sore mouth, possibly due to hypersensitivity or superinfection with *Candida* spp., have also been reported. Neurotoxic reactions such as dizziness, confusion, and visual disturbances can occur during parenteral therapy and patients so affected should not drive or operate machinery. Pain and local irritation are reported to be less troublesome after intramuscular injection of colistimethate sodium than with colistin sulfate or polymyxin B. Overgrowth of nonsusceptible organisms, particularly *Proteus* spp., may occur after prolonged use.

Plasma-concentration monitoring during systemic treatment is recommended in neonates, patients with renal impairment, and those with cystic fibrosis. Peak plasma-colistin concentrations of 10 to 15 mg/litre (about 125 to 200 units/mL) are recommended.

Cystic fibrosis. Intravenous colistin sulfate was reported to be associated with a lower rate of severe nephrotoxicity among 19 patients with cystic fibrosis than has been previously reported in other patient populations.[1] However, fatal acute respiratory distress syndrome (ARDS) has been reported in a cystic fibrosis patient after inhalation of colistimethate sodium 75 mg twice daily.[2] The solution used had been compounded 5 weeks previously, and it was considered that ARDS was caused by the conversion of colistimethate sodium to the active form colistin which may cause airway or alveolar injury. The FDA subsequently warned that inhalation solutions should be used promptly after preparation (see Stability, above).

1. Bosso JA, *et al.* Toxicity of colistin in cystic fibrosis patients. *DICP Ann Pharmacother* 1991; **25:** 1168–70.
2. McCoy KS. Compounded colistimethate as possible cause of fatal acute respiratory distress syndrome. *N Engl J Med* 2007; **357:** 2310–1.

Effects on the cardiovascular system. Significant, but transient, hypotension occurred in a patient after starting aerosolised colistin inhalation.[1] Intravenous colistin, alone or with aerosolised amikacin, had no such effect on blood pressure.

1. Hakeam HA, Almohaizeie AM. Hypotension following treatment with aerosolized colistin in a patient with multidrug-resistant Pseudomonas aeruginosa. *Ann Pharmacother* 2006; **40:** 1677–80.

Porphyria. Colistin has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Interactions

As for Polymyxin B Sulfate, p.318.

Antimicrobial Action

The antimicrobial spectrum and mode of action of colistin is similar to that of polymyxin B (p.318) but colistin sulfate is slightly, and colistimethate significantly, less active.

Pharmacokinetics

Colistin sulfate and colistimethate sodium are poorly absorbed from the gastrointestinal tract of adults and children; however, limited and unpredictable gastrointestinal absorption occurs in infants under 6 months of age. The drugs are not absorbed through mucous membranes, or intact or denuded skin. Peak plasma concentrations usually occur 2 to 3 hours after an intramuscular injection of colistimethate sodium. Plasma protein binding of colistin is reported to be more than 50% but that of colistimethate sodium is low. Colistin is reversibly bound to body tissues, but binding does not occur with colistimethate. Some colistimethate sodium may be hydrolysed to colistin *in vivo*. The serum half-life of colistimethate sodium is 2 to 3 hours but is prolonged in renal impairment; values of 10 to 20 hours have been reported in patients with a creatinine clearance of less than 20 mL/minute. Half-life may initially be prolonged in neonates but has been reported to fall to 2 to 3 hours after 3 or 4 days.

Colistimethate is mainly excreted by glomerular filtration as changed and unchanged drug and up to 80% of a parenteral dose may be recovered in the urine within 24 hours. Excretion is more rapid in children than in adults; it is reduced in patients with renal impairment. Colistin crosses the placenta but diffusion into the CSF is negligible. It is distributed into breast milk.

Cystic fibrosis. References.

1. Reed MD, *et al.* The pharmacokinetics of colistin in patients with cystic fibrosis. *J Clin Pharmacol* 2001; **41:** 645–54.
2. Li J, *et al.* Steady-state pharmacokinetics of intravenous colistin methanesulphonate in patients with cystic fibrosis. *J Antimicrob Chemother* 2003; **52:** 987–92.
3. Ratjen F, *et al.* Pharmacokinetics of inhaled colistin in patients with cystic fibrosis. *J Antimicrob Chemother* 2006; **57:** 306–11.

Uses and Administration

Colistin is a polymyxin antibacterial that has been used in the treatment of severe Gram-negative infections, especially those due to *Pseudomonas aeruginosa*, although other drugs are usually preferred. Colistimethate sodium is used by inhalation in the management of respiratory infections, especially in patients with cystic fibrosis (p.166). Colistin has been given orally as the sulfate for the treatment of gastrointestinal infections. Colistin sulfate is also given orally for bowel preparation before abdominal surgery, and with other drugs in regimens for selective digestive tract decontamination (SDD) in patients at high risk of endogenous infections (see under Intensive Care, p.175).

The usual oral dose of colistin sulfate is 1.5 to 3 million units given 3 times daily. For bowel preparation, the same dose is given for 24 hours with the course being completed 12 hours before surgery.

Colistin is given parenterally, as colistimethate sodium, by intramuscular injection or slow intravenous injection or infusion. In the UK, usual doses are 1 to 2 million units given 3 times daily (maximum dose 6 million units in 24 hours) for patients weighing more than 60 kg; those weighing up to 60 kg may be given 50 000 units/kg daily in 3 divided doses up to a maximum of 75 000 units/kg daily. In the USA, the usual dose is equivalent to colistin base 2.5 to 5 mg/kg daily in 2 to 4 divided doses. Monitoring of plasma concentrations is required in some patients (see Adverse Effects and Precautions, above).

Colistimethate sodium may also be given by inhalation in respiratory infections as an adjunct to systemic antibacterial therapy. The usual dose is 1 to 2 million units given 2 or 3 times daily. A 3-week course of 2 million units twice daily may be given initially, increased to a maximum of 2 million units given 3 times daily for up to 3 months in frequent recurrent infections; 1 to 2 million units twice daily may be given for long-term therapy. Solutions for inhalation should be freshly prepared (see Stability, above).

Doses and dosage intervals should be adjusted in patients with renal impairment (see below).

For details of doses in infants and children, see below.

Colistimethate sodium has also been given by subconjunctival injection and as a bladder instillation. Both colistin sulfate and colistimethate sodium have been applied topically, often with other antibacterials, in the management of ear, eye, and skin infections.

◊ Reviews.

1. Falagas ME, Kasiakou SK. Colistin: the revival of polymyxins for the management of multidrug-resistant gram-negative bacterial infections. *Clin Infect Dis* 2005; **40:** 1333–41. Correction. *ibid.* 2006; **42:** 1819. [dose]
2. Falagas ME, *et al.* The use of intravenous and aerosolized polymyxins for the treatment of infections in critically ill patients: a review of the recent literature. *Clin Med Res* 2006; **4:** 138–46.
3. Li J, *et al.* Colistin: the re-emerging antibiotic for multidrug-resistant Gram-negative bacterial infections. *Lancet Infect Dis* 2006; **6:** 589–601.

Administration in children. The following doses of colistin sulfate may be given **orally** to children according to weight:

- up to 15 kg: 0.25 to 0.5 million units 3 times daily
- 15 to 30 kg: 0.75 to 1.5 million units 3 times daily
- over 30 kg: the usual adult dose (see above)

Parenteral doses of colistimethate sodium may vary between countries.

UK according to weight:

- up to 60 kg: 50 000 units/kg daily in 3 divided doses up to a maximum of 75 000 units/kg daily (the *BNFC* suggests that this dose may be given to those as young as 1 month of age)
- over 60 kg: the usual adult dose (see above)

USA:

- children may be given the usual adult dose, equivalent to colistin base, of 2.5 to 5 mg/kg daily in 2 to 4 divided doses

Monitoring of plasma concentrations is required in some patients (see Adverse Effects, Treatment, and Precautions, above).

For **inhalation** colistimethate sodium may be given in the following doses according to age:

- under 2 years: 0.5 to 1 million units twice daily (the *BNFC* suggests that this dose may be given to those as young as 1 month of age)
- over 2 years: the usual adult dose (see above)

Doses and dosage intervals should be adjusted in patients with renal impairment (see below).

Administration in renal impairment. Dosage of parenteral and inhaled colistimethate sodium must be adjusted in renal impairment; both reduction in dose and decreased frequency of dosing may be required.

In the UK, the following **parenteral** doses of colistimethate sodium, based on creatinine clearance (CC), have been suggested for patients weighing more than 60 kg:

- CC 20 to 50 mL/minute: 1 to 2 million units every 8 hours
- CC 10 to 20 mL/minute: 1 million units every 12 to 18 hours
- CC less than 10 mL/minute: 1 million units every 18 to 24 hours

US licensed product information suggests the following modified doses (equivalent to colistin base) for adults with renal impairment in terms of plasma-creatinine concentrations:

- 1.3 to 1.5 mg/100 mL: 150 to 230 mg given daily in two divided doses
- 1.6 to 2.5 mg/100 mL: 133 to 150 mg given daily as a single dose or in 2 divided doses
- 2.6 to 4.0 mg/100 mL: 100 to 150 mg given every 36 hours

The following doses **by inhalation** have been suggested based on creatinine concentrations:

- 106 to 129 micromoles/litre: 1 to 1.5 million units every 12 hours
- 130 to 214 micromoles/litre: 1 million units every 12 or 24 hours
- 215 to 340 micromoles/litre: 1 to 1.5 million units every 36 hours

Preparations

BP 2008: Colistimethate Injection; Colistin Tablets;
USP 31: Colistimethate for Injection; Colistin and Neomycin Sulfates and Hydrocortisone Acetate Otic Suspension; Colistin Sulfate for Oral Suspension.

Proprietary Preparations (details are given in Part 3)
Arg.: Alfacolin; Alficetin; ***Austral.:*** Coly-Mycin M; ***Belg.:*** Colistineb; ***Canad.:*** Coly-Mycin M; ***Cz.:*** Colimycine†; Colomycin; ***Denm.:*** Colimycin; ***Fr.:*** Colimycine; ***Ger.:*** Diaront mono; ***Gr.:*** Tadim; ***India:*** Walamycin; ***Irl.:*** Colomycin; ***Israel:*** Coliracin; ***Ital.:*** Colimicina; ***Neth.:*** Belcomycine†; Colimycine†; ***Norw.:*** Colimycin; ***NZ:*** Coly-Mycin M†; ***Port.:*** Colixin; ***Spain:*** Colimicina; ***Thai.:*** Colistate; ***UK:*** Colomycin; Promixin; ***USA:*** Coly-Mycin M; ***Venez.:*** Colisil†.

Multi-ingredient: ***Arg.:*** Clarex Compuesto; Eristin; Eubetal Biotic†; ***Fr.:*** Bacicoline; ***Ger.:*** Ecolicin; ***Ital.:*** Colbiocin; Eubetal Antibiotico; ***Mex.:*** Colfur; ***Neth.:*** Bacicoline-B; ***NZ:*** Antibiotic Simplex; ***Philipp.:*** Elicocin; ***Rus.:*** Colbiocin (Колбиоцин); ***USA:*** Coly-Mycin S Otic; Cortisporin-TC.

Co-tetroxazine *(BAN)*

Tetroxoprima y sulfadiazina.
CAS — 73173-12-3.

Profile

Co-tetroxazine, a mixture of tetroxoprim and sulfadiazine in the proportion of 2:5, has properties similar to those of co-trimoxazole (below). It has been given orally, mainly in the treatment of infections of the urinary and respiratory tracts, including pneumocystis pneumonia.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Sterinor†; ***Venez.:*** Esterinor†.

Co-trifamole *(BAN)*

CN-3123; Cotrifamol.
ATC — J01EE04.

Profile

Co-trifamole, a mixture of 5 parts of sulfamoxole and 1 part of trimethoprim, has properties similar to those of co-trimoxazole (below) and has been used similarly.