

ERYTHROMYCIN LACTOBIONATE INTRAVENOUS

Description

Erythromycin is a macrolide antibiotic produced by the growth of certain strains of *Streptomyces erythreus*. Erythromycin Lactobionate is produced by the combination of erythromycin and lactobionic acid.

Pharmacology

The mode of action of erythromycin has been well characterised as erythromycin binds to the ribosomes of bacteria to inhibit protein synthesis without affecting nucleic acid synthesis. Erythromycin selectively binds only to the ribosomes of bacteria but not to the cytoplasmic ribosomes of the host cells. This highly specific interaction of erythromycin with bacterial ribosomes is a possible explanation for the low toxicity and exceptional clinical safety record of erythromycin.

Erythromycin diffuses readily into most body fluids, except the cerebrospinal fluid. However in cases of meningeal inflammation, higher concentrations are apparent.

The apparent volume of distribution of erythromycin is around 45% of body weight in normal subjects. This large distribution volume is consistent with the extensive tissue penetration of erythromycin.

In the presence of normal hepatic function, erythromycin is concentrated in the liver and excreted in the bile; the effect of hepatic dysfunction on excretion of erythromycin by the liver is not known.

Between 12% to 15% of intravenously administered erythromycin is excreted in active form in the urine.

The drug is also excreted in the faeces.

The plasma elimination half-life in patients with normal renal function is about 2 hours. In severe renal impairment the half-life may be prolonged to between 4 and 7 hours.

Microbiology: Erythromycin is bacteriostatic and bactericidal depending on its concentration and the type of organism. It inhibits protein synthesis in susceptible organisms by binding to 50S ribosomal subunits, consequently inhibiting translocation of aminoacyl transfer-RNA and inhibiting polypeptide synthesis without causing any alteration in the nucleic acid cycle.

Indications

Intravenous administration of erythromycin is indicated in the treatment of serious infections caused by erythromycin sensitive organisms when the oral route is unsuitable, or when it is necessary to produce high drug serum levels to control severe infections. Oral administration should replace parenteral administration as soon as practicable.

Specimens for bacteriologic culture should be obtained prior to therapy in order to isolate and identify the causative organisms and to determine their susceptibility to erythromycin. Therapy may be instituted before results of susceptibility studies are known; however, antibiotic treatment should be re-evaluated when the results become available or if the clinical response is not adequate.

In vitro erythromycin has shown activity against the following organisms:

Staphylococcus aureus (resistant organisms may emerge during treatment)

Group A β -haemolytic streptococcus

α -haemolytic streptococcus (*viridans* group)

Corynebacterium diphtheriae

Corynebacterium minutissimum

Listeria monocytogenes

Treponema pallidum

Legionella pneumophila

Bordetella pertussis

Neisseria gonorrhoea

Mycoplasma pneumoniae

Ureaplasma urealyticum
Chlamydia trachomatis
Entamoeba histolytica

Many strains of *Haemophilus influenzae* may not be sensitive to erythromycin alone.

Proteus, *Pseudomonas*, *Escherichia coli*, *Enterobacter* and *Klebsiella* species are relatively resistant to erythromycin.

Contraindications

Erythromycin is contraindicated in patients with known hypersensitivity to the drug.

Erythromycin should not be administered to patients who are receiving terfenadine, astemizole, cisapride or pimozone (see Interactions with Other Drugs).

Warnings

Allergic reactions, ranging from urticaria and mild skin eruptions to anaphylaxis, have occurred. If an allergic reaction occurs, administration of the drug should be discontinued. Adrenaline and other appropriate measures should be used in cases of severe hypersensitivity reactions.

The use of Erythromycin Lactobionate for Intravenous Infusion can lead to the development of severe colitis as a result of colonization with *Clostridium difficile*, a toxin producing organism. The colitis, which may or may not be accompanied by the formation of a pseudomembrane in the colon, can be fatal. If significant diarrhoea occurs (this may, however, begin up to several weeks after cessation of antibiotic therapy), Erythromycin Lactobionate for Intravenous Infusion should be discontinued. This may be sufficient treatment in the early stages although cholestyramine orally may help by binding the toxin in the colonic lumen. In severe cases oral vancomycin in a dose of 250mg every 6 hours for 5-10 days has proved effective. Vancomycin is not effective if given parenterally. Treatment with bacitracin has also been reported to be successful. Drugs which delay peristalsis e.g. opiates and diphenoxylate with atropine (Lomotil) may prolong and/or worsen the condition and should not be used. Fluids, electrolytes and protein replacement therapy should be provided when indicated.

Prolongation of the QT interval and development of ventricular arrhythmias (some of which have been fatal), including atypical ventricular tachycardia (torsades de pointes), have been reported with the intravenous administration of erythromycin. Limited data suggests that these adverse effects may be associated with abnormally elevated serum erythromycin levels following rapid administration. Erythromycin must therefore not be administered rapidly by direct intravenous injection (IV push).

Precautions

1. Superinfection: As with other antibiotics, the use of erythromycin, particularly in prolonged or repeated therapy, may give rise to overgrowth of non-susceptible organisms. If this occurs, the drug should be discontinued and appropriate measures initiated.
2. Liver disease or hepatic dysfunction: Erythromycin is excreted principally via the liver and caution should be exercised administering the antibiotic to patients with impaired hepatic function.
3. Venous irritation: Occasional venous irritation has been encountered, but if the injection is given slowly, in dilute solution, preferably by continuous intravenous infusion over 20-60 minutes, pain and vessel trauma are minimized.

Use in Pregnancy: Category A.

Erythromycin crosses the placental barrier and produces levels that are 6-20% of the maternal value, depending on the time of gestation.

Use in Lactation:

Erythromycin is excreted in breast milk with concentrations of 0.5-6.2 micrograms/mL. It is not known whether it is harmful to the newborn. Therefore, administration is not recommended for nursing mothers unless the expected benefits outweigh any potential risk.

Interactions with Other Drugs:

Astemizole: Concomitant administration of erythromycin and astemizole is contraindicated. Concomitant administration of these drugs has been associated with increased blood levels of astemizole and an increased risk of serious cardiac arrhythmias.

Carbamazepine: Erythromycin can cause an increase in carbamazepine blood levels, resulting in toxicity. Patients receiving carbamazepine and erythromycin should be monitored and erythromycin therapy stopped or carbamazepine dosage reduced if carbamazepine toxicity occurs.

Cisapride: Concomitant administration of erythromycin and cisapride is contraindicated. The concurrent administration of cisapride and drugs that inhibit its cytochrome P450 metabolism, including erythromycin, has been associated with increased blood levels of cisapride and an increased risk of life threatening cardiac arrhythmias. These may include torsades de pointes, prolongation of the QT interval, ventricular tachycardia and fibrillation.

Cyclosporin: An increase in the blood levels of cyclosporin may occur. It is recommended that erythromycin should be avoided whenever possible when patients are receiving cyclosporin. When the use of erythromycin with cyclosporin is unavoidable careful monitoring of plasma cyclosporin concentrations and appropriate modification of cyclosporin dose are essential.

Digoxin: The bioavailability of digoxin is increased in about 10% of patients. Patient monitoring for digoxin toxicity rather than dose alteration is recommended here.

Ergotamine/ Dihydroergotamine: Concurrent use of erythromycin and ergotamine or dihydroergotamine has been associated in some patients with acute ergot toxicity. This is manifested as ischaemic reactions, characterised by severe peripheral vasospasm and dysaesthesia.

Lincomycin/ Clindamycin: Antagonism of bactericidal activity has been observed between erythromycin and clindamycin or lincomycin *in vitro*. Because of possible clinical significance, these drugs should not be administered concurrently.

Lovastatin: Cases of rhabdomyolysis have been reported in seriously ill patients receiving concomitant lovastatin and erythromycin. Therefore, patients receiving erythromycin and lovastatin should be carefully monitored.

Oral anticoagulants: Caution should be observed when erythromycin and oral coagulants are used concurrently since prolonged prothrombin time may occur. If such an interaction occurs, alternative antibiotic therapy should be initiated or the response monitored and the dosage of warfarin adjusted accordingly.

Penicillin: Erythromycin, in low bacteriostatic concentrations, may inhibit the actions of bactericidal drugs, e.g. penicillin, but in high concentrations it may act synergistically with penicillin.

Phenytoin/ Hexobarbitone: There have been reports of rises in plasma levels of phenytoin, hexobarbitone and other drugs metabolised by the cytochrome P450 system during concomitant administration of erythromycin.

Pimozide: Concomitant administration of erythromycin and pimozide is contraindicated. Ventricular arrhythmias and prolongation of the QT interval have been associated with the concurrent use of macrolide antibiotics and pimozide. Specifically, two sudden deaths have been reported when clarithromycin was added to ongoing pimozide therapy.

Terfenadine: The concurrent use of terfenadine and erythromycin is contraindicated because of the potential for an interaction which is manifested as QT interval prolongation.

Theophylline: Blood levels of theophylline can be significantly elevated, especially when erythromycin is taken concomitantly for 10 days or more. In the case of theophylline toxicity and/or elevated serum theophylline levels, the dose of theophylline should be reduced while the patient is receiving concomitant erythromycin therapy.

Triazolam/ Midazolam: Erythromycin has been reported to decrease the clearance of triazolam and midazolam and thus may increase the pharmacological effect of triazolam and midazolam. Triazolam plasma concentrations may approximately double when erythromycin is co-administered, due to a reduction in clearance and increase in elimination half-life but drug accumulation has not been observed with repeated dosing. Therefore consideration of dose reduction may be appropriate in patients treated concurrently with triazolam and erythromycin. Potentially, this interaction may occur with other benzodiazepines which are metabolised by similar pathways in the liver.

Interactions with clinical, laboratory and other tests:

Erythromycin may falsely elevate levels of urinary catecholamines, 17-hydroxycorticosteroids, 17-ketosteroids, serum alanine and aspartate aminotransferase levels. Unidentified metabolites of erythromycin may interfere with colorimetric determinations resulting in falsely elevated AST levels. There may be a decrease in serum folate assay results due to inhibition of *Lactobacillus casei* growth, but results appear to be unaffected if Landon's chromatographic procedure is used. Erythromycin in the blood may also interfere with the diagnosis of *Mycoplasma pneumoniae* by masking a rise in the titre of the tetrazolium reduction inhibition neutralizing antibody to this organism.

Adverse Effects

More Common Reactions:

Irritative effects: Thrombophlebitis and venous irritation have occurred following intravenous administration. This trauma can be reduced if the injection is given slowly, in dilute solution preferably by continuous intravenous infusion (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Gastrointestinal: Gastrointestinal adverse reactions to erythromycin lactobionate, after intravenous administration, include nausea, vomiting, abdominal pain, cramping and diarrhoea. These correlate with the rate of infusion and plasma erythromycin concentration.

Less Common Reactions:

Ototoxicity: Intravenous administration of large doses of erythromycin has resulted in transient perceptible deafness. The risk is greatest in elderly patients, those with impaired renal or hepatic function or those receiving very high doses of erythromycin. Recovery occurred within a few days after withdrawal of the drug.

Hypersensitivity Reactions: These occur in less than 0.5% of treated patients, as maculopapular rashes, pruritus, urticaria or angioneurotic oedema. Anaphylaxis has been reported (see WARNINGS).

Cardiovascular: Prolongation of the QT interval and development of ventricular arrhythmias (some of which have been fatal), including atypical ventricular tachycardia (torsades de pointes), have been reported with the intravenous administration of erythromycin. Limited data suggest that these adverse effects may be associated with abnormally elevated serum erythromycin levels following rapid administration. There have been isolated reports of other cardiovascular symptoms such as chest pain, dizziness and palpitations; however a causal relationship has not been established.

Dosage and Administration

Dosage:

General: Dosage of erythromycin lactobionate is expressed in terms of erythromycin. The usual dose for adults and children for severe infections is 15 to 20 mg/kg/day. High doses of up to 4g daily in divided doses have been used for very severe infections.

Patients with Impaired Hepatic Function: Caution should be exercised in administration of the drug in these patients (see PRECAUTIONS).

Patients with Impaired Renal Function: Clearance of erythromycin is not influenced markedly by renal impairment. Thus, dosage modification in these patients is not deemed necessary. However, ototoxicity has been reported in patients with severe renal impairment, and therefore, testing of hearing acuity before and after treatment, with appropriate dosage reduction, is recommended.

Geriatric Patients: Use normal adult dosage with care, taking into consideration any liver or biliary function impairment.

Legionnaires' Disease: Dosage of 1 to 4g daily in divided doses have been given alone or in combination with rifampicin. The optimal dose and duration of therapy, however, have not been established.

Administration:

Due to the local irritative effects of erythromycin as well as reports of QT interval prolongation and ventricular arrhythmias (some of which have been fatal) being associated with elevated serum levels of erythromycin, the drug must not be administered rapidly by direct intravenous injection (IV push) (see WARNINGS and ADVERSE REACTIONS).

Intravenous infusion by continuous drip is the preferred method of administration. However, intermittent I.V. infusion at intervals not greater than every six hours is also used. In either case, the reconstituted solution must be further diluted before administration (see RECONSTITUTION AND DILUTION). As rapid infusion is more likely to be associated with arrhythmias or hypotension it is recommended that erythromycin be administered over a minimum period of 60 minutes. A longer period of infusion should be used in patients with risk factors or previous evidence of arrhythmias.

One quarter of the total daily dose of erythromycin lactobionate should be administered by intermittent intravenous infusion over a minimum of 60 minutes and repeated no more frequently than every six hours.

Reconstitution and Dilution

Reconstitute the powder with Sterile Water for Injections to make a 50mg/mL stock solution by shaking to fully dissolve the powder, as shown in Table 1.

Table 1 Reconstitution

Vial Size	Volume to be added to Vial	Erythromycin* Concentration	Expected Time to Dissolution
300mg	6mL	50mg/mL	2 minutes
1g	20mL	50mg/mL	4 minutes

*N.B. The product contains a 10% manufacturing excess to compensate for the volume expansion observed when the powder is reconstituted.

Use of diluents other than Sterile Water for Injections may cause precipitation during reconstitution. Do not use diluents containing preservatives or inorganic salts.

Further dilution is required.

For continuous intravenous infusion: (1mg erythromycin/1mL infusion fluid).

For continuous intermittent intravenous infusion: (1 to 5mg erythromycin /1mL infusion fluid).

The reconstituted stock solution (containing 50mg/mL of erythromycin) can be further diluted with Sodium Chloride Intravenous Infusion 0.9%. Glucose Intravenous Infusion 5% may also be used provided that prior to the addition of the reconstituted stock solution, the glucose solution is first buffered with Sterile Sodium Bicarbonate Solution 4% (1mL of Sodium Bicarbonate Solution per 100mL of Glucose Intravenous Infusion 5%). Buffering is necessary because in acidic solutions the potency of Erythromycin Lactobionate rapidly declines.

Stability and Storage of Parenteral Solutions: When reconstituted as directed, the resulting erythromycin stock solution 50mg/mL should be used as soon as possible. However, the solution is stable for 24 hours when stored at room temperature (below 25°C), or for 14 days when stored refrigerated at 2°C to 8°C. To avoid the risk of microbiological contamination the reconstituted injection should be used soon after preparation. Infusion solutions diluted to 1mg/mL as directed above, should be used within 8 hours when stored at room temperature (below 25°C).

Incompatibilities: Erythromycin is most stable in the pH range of 6.5 to 7.5 and decomposes rapidly at pH less than 5.5. Inactivation due to low pH occurs when erythromycin is combined with tetracyclines or vitamin B complex with vitamin C. Inactivation due to high pH occurs when erythromycin is combined with aminophylline. Erythromycin is also incompatible with sodium salts of macromolecules. Precipitation has been reported with heparin sodium, cephalothin sodium and chloramphenicol sodium succinate. No drug or chemical agent should be added to reconstituted Sterile Erythromycin Lactobionate, DBL, without first determining the effect on the physical and chemical stability of the solution.

Overdosage

No specific treatment for accidental overdosage has been proposed, other than general supportive measures. Studies in animals show that erythromycin has very low toxicity.

Storage

Store vials (prior to reconstitution) below 25°C.

Presentation

Erythromycin Lactobionate for Intravenous Infusion.

Code	Strength (Erythromycin Activity)	Pack
2360C	300mg(300,000 I.U.)	5 x 10mL vials
2370A	1g (1,000,000 I.U.)	1 x 30mL vial
2370D	1g (1,000,000 I.U.)	10 x 30mL vials

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