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CLINICAL PHARMACOLOGY OF ERYTHROMYCIN

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ABSTRACT

Erythromycin is a macrolide antibiotic and erythromycin usually is bacteriostatic but may be bactericidal in high concentrations against susceptible organisms. Erythromycin has good activity against streptococci, Streptococcus pneumoniae, methicillin-susceptible and methicillin-resistant Staphylococcus aureus, Enterococcus faecalis, and Enterococcus faecium but macrolide resistance among Streptococcus pneumoniae often coexist with penicillin resistance. Gram-positive bacilli are frequently sensitive to erythromycin, including Clostridium perfringens, Corynebacterium diphtheriae, and Listeria monocytogenes. Erythromycin has modest activity in-vitro against Haemophilus influenzae and Neisseria meningitis and has good activity against Neisseria gonorrhoea Borrelia species, Bordetella pertussis, Mycobacterium pneumoniae, Legionella pneumophilia, and Chlamydia trachomatis. Erythromycin base is incompletely absorbed from the upper small intestine because is inactivated by gastric acid and esters of erythromycin base (e.g. stearate, estolate, and ethylsuccinate) have improved acid stability. Erythromycin has been found to be efficacy and safe, the prevention of bacterial infections with erythromycin, the treatment of bacterial infections with erythromycin, and the trials conducted with erythromycin have been reviewed. The pharmacokinetics of erythromycin have been studied in healthy male volunteers on days 1 and 3 of treatment and the mean elimination half-life of erythromycin in plasma is 1.67 and 2.26 hours on days 1 and 3, respectively, of treatment. The penetration of erythromycin into human tissues, the interaction of erythromycin with drugs, and the toxicity caused by erythromycin have been reviewed. The aim of this study is to review the erythromycin efficacy and safely, prevention of bacterial infections, treatment of bacterial infections, trials, pharmacokinetics, penetration into human tissues, interaction with drugs, and toxicity.

KEYWORDS: Drug-interaction, efficacy-safely, erythromycin, pharmacokinetics, prophylaxis, tissue-penetration, toxicity, treatment, and trials.

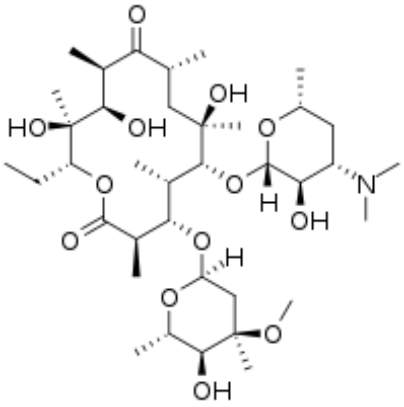
INTRODUCTION

Antimicrobial activity of erythromycin

Erythromycin is a macrolide antibiotic and erythromycin usually is bacteriostatic but may be bactericidal in high concentrations against susceptible organisms. Erythromycin has reasonably good activity against streptococci, Streptococcus pneumoniae, methicillin-susceptible and methicillin-resistant Staphylococcus aureus, Enterococcus faecalis, and Enterococcus faecium but macrolide resistance among Streptococcus pneumoniae often coexist with penicillin resistance. Staphylococci are not reliable sensitive to erythromycin, and macrolide-resistant strains of Staphylococcus aureus are potentially cross-resistant to clindamycin and streptogramin B (quinupristin). Gram-positive bacilli also are frequently sensitive to erythromycin, including Clostridium perfringens, Corynebacterium diphtheriae, and Listeria monocytogenes. Erythromycin is inactive against most aerobic enteric gram-negative bacilli. It has modest activity in-vitro against Haemophilus influenzae and Neisseria meningitis and good activity against most strains of Neisseria gonorrhoeae. Useful antibacterial activity also is observed against Borrelia species, and Bordetella pertussis. Erythromycin is active against Mycobacterium pneumoniae and Legionella pneumophila. Most strains of Chlamydia trachomatis are inhibited by erythromycin.[1]

Absorption, distribution, metabolism and elimination of erythromycin

Erythromycin base is incompletely absorbed from the upper small intestine because is inactivated by gastric acid it is administered as enteric-coated tablets or as capsules containing enteric-coated pellets that dissolve in the duodenum; food may delay absorption. Esters of erythromycin base (e.g. stearate, estolate, and ethylsuccinate) have improved acid stability, and their absorption is less altered by food. Protein binding is about 70% to 80% for erythromycin base and even higher for the estolate. Erythromycin traverses the placenta, drug concentrations in the foetal plasma are about 5% to 20% of those in the maternal circulation. Concentrations in the breast-milk are 50% of those in serum. The elimination half-life of erythromycin in serum is about 1.6 hours. Although the elimination half-life may be prolonged in patients with anuria, dosage reduction is not routinely recommended in patients with renal failure. The drug is not removed significantly by either peritoneal dialysis or haemodialysis.[1]



Erythromycin molecular structure (molecular weight = 733.937 grams/mole).

Literature search

The literature search was performed electronically using PubMed database as search engine and the following key words were used: "erythromycin efficacy, safely", "erythromycin prophylaxis", "erythromycin treatment", "erythromycin trials", "erythromycin pharmacokinetics", erythromycin tissue concentration", "erythromycin drug interactions", and "erythromycin toxicity". In addition the book: Goodman@Gilman's. The Pharmacological basis of Therapeutics[1] has been consulted.

RESULTS

Efficacy and safely of erythromycin

Over a 2-year period, 34 patients with a symptomatic, recurrent, malignant pleural effusion who referred for chest tube drainage and pleurodesis were treated with erythromycin orally at the daily dose of 1 gram. The overall response-rate was 88.2%. Complete response (no accumulation of pleural fluid after 90 days of treatment) was observed in 27 patients (79.4%). Partial response (accumulation of fluid but without symptoms and not requiring drainage) was observed in only 3 patients (8.8%). No response (symptomatic accumulation of fluid that required drainage) was observed in only 4 patients (11.8%). Erythromycin is an effective and safe sclerosing agent for pleurodesis in patients with recurrent malignant pleural effusions.[2] It was compared the adverse-drug-reactions in patients with community-acquired-pneumonia treated with either erythromycin or with clarithromycin. Overall adverse-drug-reactions occurred more frequently in patients treated with erythromycin (P-value < 0.001) and gastrointestinal adverse-drug-reactions occurred more frequently in patients who received erythromycin (P-value < 0.001). Therefore, given that erythromycin is not more effective than clarithromycin, erythromycin should not be selected unless other macrolides cannot be

used.[3] Two-hundred-eight patients with community-acquired-pneumonia were randomized to receive either clarithromycin orally at the dose of 250 mg twice-daily (96 patients 46.1%) or erythromycin stearate orally at the dose of 500 mg 4 times-daily (112 patients 53.8%) each for 14 days. There was no significant difference between the two groups in terms of clinical cure (52% for clarithromycin, 40% for erythromycin stearate) or clinical success (clinical cure and improvement; 89% for clarithromycin, 98% for erythromycin stearate), or radiological response (90% for both groups). The clinical cure-rate after two weeks of treatment was 45.1% in patients who received clarithromycin compared to 25.2% in patients who received erythromycin stearate (P-value = 0.003), whilst improvement in cough was observed in 97% and 80% of patients receiving clarithromycin and erythromycin stearate, respectively (P-value = 0.07). Adverse-effects, mainly gastrointestinal, caused discontinuation of treatment occurred in only 4.2% (4/96) patients who received clarithromycin compared to 18.7% (21/112) patients who received erythromycin stearate (P-value < 0.01). These results indicate that clarithromycin administered at the dose of 250 mg twice-daily is at least as effective as erythromycin stearate administered at the dose of 500 mg 4 times-daily for treatment of patients with community-acquired-pneumonia.[4]

Prevention of bacterial infections with erythromycin

Pertussis, caused by Bordetella pertussis, is well controlled in the UK as a result of an effective vaccination programme. Nevertheless, the disease has not been eliminated, and cases still occur in most vulnerable patients. Erythromycin chemoprophylaxis has been advocated to prevent the dissemination of Bordetella pertussis.[5] Seven infants were found to have bacteriologically proven Bordetella pertussis infection. Erythromycin administration to 7 infants prevented further infection as well as the appearance of clinical disease.[6] Prophylaxis with erythromycin administered orally at the dose of 1.5 to 3 grams daily effectively prevented 7 cases of kidney infection, 1 patient with sarcoidosis, and 5 cases of Legionnaire's disease. It was concluded that erythromycin effectively protects immunocompromised patients.[7] Erythromycin ethylsuccinate, administered orally at the dose of 10 mg/kg twice-daily, was used for prophylaxis of acute otitis media in 45 patients. Acute otitis media occurred in 8 of 45 patients (17.8%) while receiving erythromycin ethylsuccinate and in 22 of 41 (53.6%) following prophylaxis termination (P-value < 0.05). The attack-rate of acute otitis media per 2-month period was 0.86 before prophylaxis and 0.20 during prophylaxis (P-value < 0.05). Antimicrobial prophylaxis with erythromycin ethylsuccinate in patients with recurrent acute otitis media was superior to no prophylaxis.[8]

It was assessed the prophylactic efficacy of oral neomycin sulfate-erythromycin base versus intravenous ceftriaxone-metronidazole preparation in patients undergoing colorectal surgery. No significantly diverging results between the 2 regimens were recorded (1/27 [3.7%] and 2/27 [7.4%] wound infections, respectively) thus both regimens effectively prevented infection in patients undergoing colorectal surgery.[9]

Treatment of bacterial infections with erythromycin

Erythromycin given orally at the daily dose of 1.2 grams for 10 days effectively cured patients with acute amoebic dysentery.[10] Erythromycin was given orally at the dose of 0.2 grams 4 times-daily for 9 days to 20 patients (A) and was given orally at the dose of 0.4 grams 4 times-daily for 8 days to 40 patients (B) and patients had amoebic dysentery. By the end of therapy there were 75% relapses (patients of group A) and 35% relapses (patients of group B) thus the higher dose of erythromycin is preferable.[11] Erythromycin estolate administered orally at the daily dose of 50 mg/kg for 14 days effectively cured patients with pertussis.[12] A total of 106 male patients with uncomplicated non-gonococcal urethritis have been treated with erythromycin orally at the daily dose of 1 gram. Fifty-height patients (54.7%) were cured after the first week of treatment, 26 patients (24.5%) were cured after the second week of treatment, 6 patients (5.7%) had gonococcal infection, and 16 patients (15.1%) had recurrence of non-gonococcal urethritis. Erythromycin effectively cured uncomplicated non-gonococcal urethritis in most patients.[13] Erythromycin estolate administered orally at the daily dose of 1 gram eradicated virulent Corynebacterium diphtheriae from the upper respiratory-tract of patients after 2 days of treatment.[14] One-hundred-fourteen Corynebacterium diphtheriae were isolated from the upper respiratory-tract of patients. Forty-eight hours after institution of therapy with 1 gram of erythromycin estolate 96.3% of the carriers had become culture negative and all carriers became negative by the 4th day of therapy. Erythromycin estolate effectively clears Corynebacterium diphtheriae from the upper respiratory-tract of patients.[15] Twenty-nine patients with syphilis received propionyl erythromycin orally at the daily dose of 10 grams and this treatment showed significant promise as an anti-syphilitic drug but this treatment does not produce a cure comparable to that obtained with penicillin.[16] Forty-five patients with asthma were divided into 2 groups, patients of group A (N = 20) received erythromycin orally at the daily dose of 400 mg for 12 months and patients of group B (N = 25) received erythromycin orally at the daily dose of 400 mg for 6 months. At the end of treatment, the sputum volume significantly decreased in patients of groups A and B. Treatment with erythromycin decreased the total

cell count in patients of group A more effectively than in patients of group B (P-value < 0.01) and decreased the number of neutrophil count in patients of group A more effectively than in patients of group B (P-value < 0.05). Thus erythromycin reduced airway inflammation and the number of both total cells and neutrophils but erythromycin administered for 12 months treats asthma more effectively than erythromycin administered for 6 months.[17] Eighteen women in active preterm labour with pregnancies between 26 and 34 weeks of gestation and intact membranes received erythromycin orally at a dose of 500 mg thrice-daily. Erythromycin treatment resulted in a statistically significant longer delay of delivery (36.4 days) than among the control group (23.1 days, P-value < 0.05), lower neonatal morbidity (22.2 versus 42.2%, P-value < 0.01), and shorter neonatal hospitalization time (9.6 versus 12.1 days, P-value < 0.05). Erythromycin, given to pregnant women, prolongs longer delay of delivery and improves perinatal outcome.[18] Fourteen children, aged 4 to 13 years, with refractory chronic constipation, presenting mega-rectum, and faecal impaction received erythromycin estolate orally at the daily dose of 20 mg/kg for 4 weeks. At the end of treatment, the clinical score decreased from 8.2±2.3 to 2.2±1.0 (P-value < 0.01) and the mean laxative requirement decreased (P-value < 0.05). This treatment was well-tolerated and erythromycin effectively treated severely constipated children.[19]

Trials conducted with erythromycin

A clinical trial compared thoracoscopic erythromycin poudrage versus erythromycin slurry via a chest tube for patients with documented refractory spontaneous pneumothorax. Twenty-four patients who received erythromycin poudrage (80.0%) and 16 patients who received erythromycin slurry (59.3%) had a successful pleurodesis within 5 days of treatment (P-value = 0.087). Patients who received erythromycin poudrage had shorter duration of post-procedural chest tube drainage (6.23±3.04 days) than patients who received erythromycin slurry (10.67±9.81 days; P-value = 0.032). During the follow-up, there was no significant statistical difference in recurrence-rate between the two treatments. Common adverse-effects included fever and chest pain with no significant difference between the two treatments. Erythromycin was an effective and safe sclerosing agent for pleurodesis in management of refractory spontaneous pneumothorax but erythromycin poudrage had shorter duration of post-procedural chest tube drainage than erythromycin slurry.[20] A double-blind, placebo-controlled trial evaluated the effects of 8-week administration of low dose of oral erythromycin (500 mg twice-daily) in steady-state idiopathic bronchiectasis. Patients in the erythromycin group (N = 11, aged 50±15 years) but not patients in the placebo group (N =

10, aged 59±16 years) had significantly improved forced expiratory volume in 1 second, forced vital capacity, and 24-hours sputum volume after 8 weeks of treatment (P-value < 0.05). This trial shows that low-dose erythromycin improved lung function and sputum volume in patients with idiopathic bronchiectasis.[21] A randomized, clinical trial evaluated the efficacy of erythromycin administered orally at the dose of 250 mg twice-daily for 60 days for preventing the infection caused by Streptococcus pyogenes and this treatment prevented the infection.[22] A randomized, double-blind, placebo-controlled, clinical trial was conducted in 140 patients with acute bronchitis. Ninety-one patients (65.0%) received erythromycin orally at the dose of 250 mg 4 times-daily and 49 patients (35.0%) received placebo. Patients treated with erythromycin missed an average of only 0.81±1.1 days of work compared with 2.2±3.2 days for patients who received placebo (P-value < 0.02). Erythromycin effectively reduces the lost time from work.[23] It was assessed the efficacy of erythromycin in treating acute bronchitis, 52 patients were enrolled in a randomized clinical trial comparing one-week course of erythromycin with placebo. Among smokers, no difference in outcome was noted. Among non-smokers, trends favoured more rapid resolution of key symptoms in patients treated with the erythromycin.[24] Randomized, controlled, clinical trials compared the efficacy of erythromycin versus that of azithromycin or clarithromycin in treating community-acquired-pneumonia. Erythromycin use was associated with significantly lower-rates of clinical success (P-value = 0.033), clinical cure (P-value = 0.014), and radiological success (P-value = 0.045) than azithromycin and clarithromycin. Erythromycin is less effective than clarithromycin and azithromycin as empiric treatment of community-acquired-pneumonia.[25] A randomized, controlled, clinical trial compared the adverse-drug-reactions of erythromycin versus those of clarithromycin in patients with community-acquired-pneumonia. A significantly higher discontinuation-rate due to adverse-drug-reactions was found in patients treated with erythromycin compared to patients treated with clarithromycin (P-value < 0.001). Overall, adverse-drug-reactions occurred more significantly in patients treated with erythromycin compared to patients treated with clarithromycin (P-value < 0.001). Gastrointestinal adverse-drug-reactions were higher in patients treated with erythromycin (P-value < 0.001). Therefore, given that erythromycin is not more effective than clarithromycin, erythromycin should not be selected unless other macrolides cannot be used.[26] A clinical trial compared the microbiologic, clinical efficacy, and safely of a 7-day course of clarithromycin versus a 14-day course of erythromycin in children with pertussis. One-hundred-fifty-three children, aged 1 month to 16 years, with pertussis were enrolled. Children received either clarithromycin orally at the dose of 7.5

mg/kg twice-daily for 7 days or erythromycin orally at the dose of 13.3 mg/kg thrice-daily for 14 days. Children who received clarithromycin (N = 76) and children who received erythromycin (N = 77) were well-matched for age and previous pertussis immunization. Microbiologic eradication and clinical cure-rate were 100% for clarithromycin and 96% for erythromycin. Children who received clarithromycin had significantly fewer adverse-effects (45%) than children who received erythromycin (62%, P-value = 0.035) and the compliance with medication regimen (P-value = 0.032) was significantly higher in children who received clarithromycin. A 7-day regimen of clarithromycin and a 14-day course of erythromycin were equally effective for treatment of pertussis but clarithromycin was better tolerated than erythromycin.[27] A randomized, controlled, trial was conducted in adult patients with hepatic encephalopathy and with hepatic cirrhosis. Thirty patients were evaluated and received either erythromycin orally at the daily dose of 250 mg (N = 15) or neomycin orally at the daily dose of 1 gram (N = 15). Patients who received erythromycin achieved a shorter hospitalization stay (P-value = 0.032) and shorter hospitalization duration which was positively correlated with C reactive protein levels measured previous (P-value = 0.015) and after (P-value = 0.01) treatment. Erythromycin was associated with significant reduction in hospital stay and the hospitalization time was positively correlated with C reactive protein levels measured before and after the treatments.[28] An open, randomized, clinical trial was conducted in 132 patients with pyoderma, graded as "severe" on clinical grounds, and randomly received either amoxicillin orally at the daily dose of 50 mg/kg or erythromycin orally at the daily dose of 1 gram. Treatment was successful in 57 of 64 patients (89.1%) treated with amoxicillin and in 58 of 65 patients (89.2%) treated with erythromycin. Amoxicillin was efficacious as erythromycin in the treatment of severe pyoderma.[29] In an open-label, randomized, clinical trial 44 children with diphtheria received benzylpenicillin intramuscularly at the daily dose of 50,000 units/kg for 5 days and 42 children received erythromycin orally at the daily dose of 50 mg/kg for 10 days. The median time to fever clearance was 27 hours for benzylpenicillin recipients and 46 hours for erythromycin recipients (P-value = 0.0004). All isolates of Corynebacterium diphtheriae were susceptible to benzylpenicillin whereas 11 isolates (26.1%) of Corynebacterium diphtheriae were resistant to erythromycin (minimum inhibitory concentration > 64 µg/ml). Benzylpenicillin is recommended as first-line treatment for diphtheria in children.[30] A double-blind, randomised, clinical trial was conducted in 128 severely dehydrated children, aged 1 to 15 years, with cholera. Children were assigned to receive either a single oral dose of 20 mg/kg of azithromycin (N = 65) or erythromycin orally at the dose of 12.5 mg/kg 4 times-daily (N = 63) for 3 days and children stayed in hospital for

5 days. Treatment was clinically successful in 48 children (73.8%) who received azithromycin and in 39 children (61.9%) who received erythromycin (P-value = 0.244) and bacteriologically successful was observed in 45 children (69.2%) who received azithromycin and in 49 children (77.7%) who received erythromycin (P-value = 0.261). Children treated with azithromycin had a shorter duration of diarrhoea (median 24 hours versus 42 hours (P-value = 0.019) and fewer episodes of vomiting 1 versus 4 (P-value = 0.023). Single-dose azithromycin is effective as standard erythromycin therapy for treatment of children with cholera but azithromycin is associated with less diarrhoea and vomiting.[31] A double-blind, controlled, clinical trial compared the efficacy of erythromycin administered orally at the dose of 500 mg twice-daily for 7 days versus that of erythromycin administered orally at the dose of 500 mg 4 times-daily for 4 days in 73 men and women with uncomplicated-genital-urinary chlamydia trachomatis infection. At the start of treatment, 34 of 42 men (80.9%) and 15 of 31 women (48.4%) had symptoms suggesting the presence of chlamydial infections. There was a significantly higher (P-value < 0.0005) bacteriological cure-rate with the 7-day treatment in both men and women compared to the 4-day treatment 2 weeks after the start of the treatment. Treatment with erythromycin administered at the dose of 500 mg twice-daily for 7 days is more effective than the treatment with erythromycin administered at the dose of 500 mg twice-daily for 4 days.[32]

Pharmacokinetics of erythromycin and erythromycin penetration into human tissues

Krasniqi et al.[33] administered erythromycin orally at the dose of 500 mg 4 times-daily for 3 consecutive days to 6 healthy male volunteers, aged 29.17±7.68 years, weighing 72.48±11.49 kg, and with a body-mass-index of 22.57±3.23 kg/m^2. Blood samples were drawn from an antecubital vein for determination of erythromycin concentrations in plasma at baseline, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, and 8 hours after drug administration on days 1 and 3 of treatment. Tissue samples were obtained by an in-vivo micro-dialysis perfusion technique on days 1 and 3 of treatment. Tables 1 and 2 summarize the pharmacokinetic parameters of erythromycin in plasma, muscle, subcutis, and white blood cells (WBCs) on treatment days 1 and 3, respectively.

Table 1: Pharmacokinetic parameters of erythromycin which have been obtained in 6 healthy male volunteers who received erythromycin orally at the dose of 500 mg 4 times-daily on day 1 of treatment. The values are the mean±SD, by Krasniqi et al.[33]

Sample	Peak conc. (ng/ml)	Tmax (h)	AUC_{0-6h} (ng*h/ml)	$AUC_{0-\infty}$ (ng*h/ml)	*Half-life (h)	TBC (L/h)	DV (L)
Plasma	1,371±653	1.75±0.61	3,092±1,150	3,549±1,377	1.67±0.25	58.9±45.5	135±90.5
Muscle	41.9±27.3	3.13±0.88	129±84.2	266±155	3.68±1.43	ND	ND
Subcutis	55.5±23.9	2.50±0.27	147±56.6	218±123	1.98±0.87	ND	ND
WBCs	38,542±32,402	2.00±0.00	116,856±74,953	189,846±138,843	3.49±3.59	ND	ND

WBCs = white blood cells. Tmax = time to reach the peak concentration. AUC = area under the concentration-time curve. *Elimination half-life. TBC = total body clearance. DV = distribution volume. ND = not detectable.

This table shows that the erythromycin is rapidly eliminated in plasma as the mean elimination half-life is 1.67 hours, the peak concentration of erythromycin is higher in muscle, subcutis, and in white blood cells than in plasma. Erythromycin penetrates in muscle less rapidly than in plasma. The area under the concentration-time curve of erythromycin is higher in white blood cells than in plasma and is lower in muscle and in subcutis than in plasma. The elimination half-life of erythromycin is longer in muscle and in white blood cells than in plasma.

Table 2: Pharmacokinetic parameters of erythromycin which have been obtained in 6 healthy male volunteers who received erythromycin orally at the dose of 500 mg 4 times-daily on day 3 of treatment. The values are the mean±SD, by Krasniqi et al.[33]

Sample	Peak conc. (ng/ml)	Tmax (h)	AUC_{0-6h} (ng*h/ml)	$AUC_{0-\infty}$ (ng*h/ml)	*Half-life (h)	TBC (L/h)	DV (L)
Plasma	2,544±1,266	2.17±0.32	8,537±5,419	11,782±9,811	2.26±0.84	18.9±8.47	53.9±17.8
Muscle	154±86.6	2.88±1.58	560±369	1,158±835	4.13±1.11	ND	ND
Subcutis	209±139	2.67±0.72	682±465	1,026±543	2.85±1,28	ND	ND
WBCs	51,120±26,925	2.00±0.00	190,440±101,452	ND	ND	ND	ND

WBCs = white blood cells. Tmax = time to reach the peak concentration. AUC = area under the concentration-time curve. *Elimination half-life. TBC = total body clearance. DV = distribution volume. ND = not detectable.

This table shows that erythromycin is rapidly eliminated in plasma as the man elimination half-life is 2.26 hours, the peak concentration of erythromycin in plasma, muscle, subcutis, and in white blood cells is higher than that observed on day 1 of administration. The time to

reach the peak concentration of erythromycin in plasma, muscle, subcutis, and white blood cells is similar to that observed on day 1 of administration. The erythromycin area under the concentration-time curve in plasma, muscle, subcutis, and white blood cells is higher than that observed on day 1 of administration. The elimination half-life of erythromycin obtained in plasma, muscle, and subcutis is similar to that observed on day 1 of administration. The total body clearance obtained in plasma is lower than that obtained on day 1 of administration and the distribution volume obtained in plasma is lower than that observed on day 1 of administration.

Georgiew et al.[34] administered erythromycin orally at the dose of 1 gram twice-daily to 6 adult patients and measured the concentration of erythromycin in serum and in tonsils. Table 3 summarizes the concentration of erythromycin in serum and tonsils.

Table 3: Erythromycin concentration in serum and in tonsils of 6 patients who received erythromycin orally at the dose of 1 gram twice-daily. Values are the concentration of erythromycin in serum and tonsils of single patients and the mean, by Georgiew et al.[34]

Patient	Time between dose and serum sample	Time between serum and tonsils samples	Erythromycin concentration in serum (µg/ml)	Erythromycin concentration in tonsils (µg/ml)	Concentration of erythromycin in tonsils to serum ratio
1	2 h 30 min	15 min	0.63	< 2.00	About 3.17
2	2 h 15 min	15 min	2.13	4.21	1.98
3	3 h 10 min	20 min	4.56	9.97	2.19
4	3 h 0 min	30 min	4.58	4.90	1.06
5	2 h 30 min	15 min	0.72	2.00	2.78
6	2 h 45 min	15 min	1.68	3.68	2.19
Mean	2 h 55 min	18 min	2.38	4.46	1.87

This table shows that the concentration of erythromycin in tonsils is about twice higher than that in serum.

Bergogne-Bérézin[35] described the penetration of erythromycin in human tissues. Dirithromycin is converted in-vivo into erythromycin and dirithromycin has similar antimicrobial activity as erythromycin. Following the administration of 1 gram of dirithromycin the concentration of erythromycin in lung parenchyma is 3.81 mg/kg 12 hours after the dose which is significantly higher than simultaneous serum concentration. Significant concentration of erythromycin in lung parenchyma remains 12 to 24 hours after the dose. Erythromycin effectively penetrated into bronchial secretions: erythromycin concentrations of 1.0 mg/L after 3 hours and 1.5 mg/L after 12 hours were observed

following a single oral dose of 250 mg of erythromycin. Following a single oral dose of 500 mg of erythromycin, bronchial mucosa concentrations of erythromycin > 1.0 mg/kg were detected 4 to 24 hours after the dose. Following multiple oral doses of erythromycin of 500 mg the concentration of erythromycin in nasal mucosa was 0.59±0.17 and 1.86±0.54 mg/kg 24 and 12 hours, respectively, after administration. After a single oral dose of 500 mg of erythromycin the concentration of erythromycin in tonsils was 0.60±0.55 mg/kg 24 hours after the dose and following the daily oral dose of 1 gram of erythromycin for 2 days the concentration of erythromycin in tonsils was 1.37±0.55 mg/kg 24 hours after the dose. Following a daily oral dose of 1 gram of erythromycin the erythromycin concentration in the prostate tissue ranged from 4.1 to 6.5 mg/kg. In conclusion, erythromycin exhibits good tissue distribution within selected tissues, is rapidly distributed, and persists in significant concentrations up to 24 hours post-dose.

Interaction of erythromycin with drugs

An 86-year-old woman received digoxin intravenously at the daily dose of 0.25 mg and also received erythromycin orally at the daily dose of 1 gram. Her digoxin serum concentration increased from 1.9 to 5.1 nmol/L 6 days after erythromycin was started. Erythromycin inhibits digoxin metabolism by blocking CYP3A4 with consequent increase of digoxin serum concentration.[36] A drug interaction was demonstrated following the association of omeprazole, a proton pump inhibitor, with erythromycin. It was shown that, in presence of omeprazole, the rate of erythromycin N-demethylase activity catalysed by CYP3A4, measured by the formation-rate of formaldehyde, was decreased. Omeprazole inhibits the metabolism of erythromycin by blocking the CYP3A4.[37] A 62-year-old woman received erythromycin orally at the daily dose of 800 mg and oxycodone orally at the daily dose of 60 mg and developed a laxative-resistant constipation. The mechanism of drug interaction between erythromycin and oxycodone is attributable to blocking CYP3A4 by erythromycin with increasing of oxycodone serum concentration.[38]

Toxicity caused by erythromycin co-administered with other drugs

A 4-year-old girl received carbamazepine orally at the daily dose of 15 mg/kg and also received erythromycin orally at the dose of 250 mg 4 times-daily. Carbamazepine is metabolized into the carbamazepine-10,11-epoxide by cytochrome P-450 CYP3A4 and erythromycin interacts with the metabolism of carbamazepine by competitive binding to CYP3A4 thus blocking the metabolism of carbamazepine with consequent increase of

carbamazepine serum concentration. Symptoms of intoxication (ataxic gait, horizontal nystagmus, and slurred speech) appeared within 24 hours after starting the therapy with erythromycin and resolved 48 to 72 hours after discontinuation of both drugs.[39] Four epileptic children received carbamazepine and erythromycin and developed ataxia, dizziness, nausea, and vomiting. Symptoms disappeared after erythromycin was discontinued. In children there was a sharp increase in carbamazepine serum concentration after erythromycin therapy was begun and a rapid fall once erythromycin was discontinued.[40] Erythromycin blocks CYP3A4 causing a decrease of carbamazepine clearance, an elevated serum carbamazepine concentration, and clinical toxicity. Epileptic patients received carbamazepine and erythromycin and the toxicity caused by the co-administration of erythromycin with carbamazepine is drowsiness, lethargy, vomiting, and nystagmus.[41] A 29-year-old woman with familial Mediterranean fever and amyloidosis involving the kidney, liver, and gastrointestinal-tract received colchicine intravenously at the daily dose of 1 mg and also received erythromycin orally at the daily dose of 1 gram. After 2 weeks of erythromycin therapy she was hospitalized for acute life-threatening colchicine toxicity with fever, diarrhoea, abdominal pain, myalgia, lower extremity paraesthesia, later convulsions, and alopecia. The co-administration of colchicine with erythromycin caused severe toxicity.[42]

DISCUSSION

Erythromycin is a macrolide antibiotic and erythromycin usually is bacteriostatic but may be bactericidal in high concentrations against susceptible organisms. Erythromycin has good activity against streptococci, Streptococcus pneumoniae, methicillin-susceptible and methicillin-resistant Staphylococcus aureus, Enterococcus faecalis, and Enterococcus faecium but macrolide resistance among Streptococcus pneumoniae often coexist with penicillin resistance. Gram-positive bacilli are frequently sensitive to erythromycin, including Clostridium perfringens, Corynebacterium diphtheriae, and Listeria monocytogenes. Erythromycin has modest activity in-vitro against Haemophilus influenzae and Neisseria meningitis and has good activity against Neisseria gonorrhoea, Borrelia species, Bordetella pertussis, Mycobacterium pneumoniae, Legionella pneumophilia, and Chlamydia trachomatis. Erythromycin base is incompletely absorbed from the upper small intestine because is inactivated by gastric acid and erythromycin is administered as enteric-coated tablets or as capsules containing enteric-coated pellets that dissolve in the duodenum; food may delay absorption. Esters of erythromycin base (e.g. stearate, estolate, and ethylsuccinate) have improved acid stability and their absorption is less altered by food. Protein binding is

about 70% to 80% for erythromycin base and even higher for the estolate.[1] The efficacy and safely of erythromycin have been reviewed. Patients with symptomatic, recurrent, malignant pleural effusion who referred for chest tube drainage and pleurodesis were treated with erythromycin orally at the daily dose of 1 gram. Complete response (no accumulation of pleural fluid after 90 days of treatment) and partial response (accumulation of fluid but without symptoms and no requiring drainage) are found in 79.4% and in 8.8%, respectively, of patients and no response is found in 11.8% of patients. Erythromycin is an effective sclerosing agent for pleurodesis in patients with recurrent malignant pleural effusion.[2] Adverse-drug-reactions were assessed in patients with community-acquired-pneumoniae who received either erythromycin or clarithromycin. Overall adverse-drug-reactions occurred more frequently in patients treated with erythromycin (P-value < 0.001) and gastrointestinal adverse-drug-reactions occurred more frequently in patients who received erythromycin (P-value < 0.001). As erythromycin is not more active than clarithromycin erythromycin should not be used unless other macrolides cannot be used.[3] Two-hundred-eight patients with community-acquired-pneumonia received clarithromycin orally at the dose of 250 mg twice-daily (96 patients 46.1%) or erythromycin stearate orally at the dose of 500 mg 4 times-daily (112 patients 53.8%). The clinical cure, the clinical success, and the radiological response are similar in patients treated with clarithromycin and in those treated with erythromycin stearate. The clinical cure-rate after two weeks of treatment is significantly higher in patients treated with clarithromycin (P-value < 0.003) whilst improvement in cough is not different (P-value = 0.07) in patients treated with clarithromycin and in those treated with erythromycin stearate. Adverse-effects, mainly gastrointestinal, causing the discontinuous of treatment, occur less frequently in patients treated with clarithromycin (P-value < 0.01). Clarithromycin administered at the dose of 250 mg twice-daily is at least as effective as erythromycin administered at the dose of 500 mg 4 times-daily for treatment of patients with community-acquired-pneumonia.[4] These results indicate that erythromycin is an effective sclerosing agent for pleurodesis in patients with recurrent malignant pleural effusion, erythromycin treats patients with community-acquired-pneumonia as clarithromycin but erythromycin induces more adverse-effects than clarithromycin. The prevention of bacterial infections with erythromycin has been reviewed. The chemoprophylaxis with erythromycin prevents the dissemination of Bordetella pertussis thus prevents pertussis in adult patients[5] and in infants.[6] Prophylaxis with erythromycin administered orally at the dose of 1.5 to 3 grams prevents kidney infection, sarcoidosis, and Legionella disease.[7] Prophylaxis with erythromycin ethylsuccinate administered orally at the dose of 10 mg/kg twice-daily prevents

acute otitis media. Acute otitis media occurs in 17.8% of patients while receiving erythromycin ethylsuccinate and in 53.6% of patients following prophylaxis termination (P-value < 0.05). The attack-rate of acute otitis media per 2 month period is 0.86 and 0.20 before and during prophylaxis (P-value < 0.05), respectively. Antimicrobial prophylaxis with erythromycin ethylsuccinate prevents recurrent acute otitis media.[8] The prophylaxis with oral neomycin-erythromycin base is similar to that with ceftriaxone-metronidazole in preventing infections in patients undergoing colorectal surgery.[9] These results indicate that erythromycin prevents pertussis, kidney infection, sarcoidosis, and Legionella disease, erythromycin ethylsuccinate prevents acute otitis media, and neomycin-erythromycin base prevents infections in patients undergoing colorectal surgery as ceftriaxone-metronidazole. The treatment of bacterial infections with erythromycin has been reviewed. Erythromycin given orally at the daily dose of 1.2 grams for 10 days effectively treats patients with acute amoebic dysentery[10], and erythromycin was given orally at the dose of 0.2 grams 4 times-daily for 9 days (patients of group A) and was given orally at the dose of 0.4 grams 4 times-daily for 8 days (patients of group B) and all patients had amoebic dysentery. At the end of therapy there were 75% and 35% relapses in patients of group A and B, respectively, thus the higher dose of erythromycin is preferable.[11] Erythromycin estolate administered orally at the dose of 50 mg/kg for 14 days effectively cures patients with pertussis.[12] Male patients with uncomplicated non-gonococcal urethritis received erythromycin orally at the daily dose of 1 gram and 54.7% of patients are cured after the first week of treatment, 24.5% of patients are cured after the second week of treatment, 5.7% of patients have gonococcal infection, and 15.1% of patients have recurrence of non-gonococcal urethritis thus erythromycin effectively cures most patients with uncomplicated non-gonococcal urethritis.[13] Erythromycin estolate administered orally at the daily dose of 1 gram eradicates virulent Corynebacterium diphtheriae from the upper respiratory-tract of patients after 2 days of treatment[14], and erythromycin estolate administered orally at the daily dose of 1 gram eradicates Corynebacterium diphtheriae from the upper respiratory-tract in 96.3% of patients.[15] Patients with syphilis received propionyl erythromycin orally at the daily dose of 10 grams and this treatment cures the patients but does not produce a cure-rate comparable to that obtained with penicillin.[16] Patients with asthma received erythromycin orally at the daily dose of 400 mg for 12 months (patients of group A) and other patients received erythromycin orally at the daily dose of 400 mg for 6 months (patients of group B). The sputum volume is decreased in both groups of patients whereas total cell count (P-value < 0.01) and the neutrophil count (P-value < 0.05) decrease more significantly in patients of group A than in

patients of group B. Erythromycin reduces the airway inflammation but erythromycin administered for 12 months treats asthma more effectively than erythromycin administered for 6 months.[17] Women in active preterm labour received erythromycin orally at the dose of 500 mg thrice-daily and this treatment delays the delivery (P-value < 0.05), lowers neonatal morbidity (P-value < 0.01), and shortens the neonatal hospitalization time (P-value < 0.05) compared to women who received the placebo.[18] Children with refractory chronic constipation, presenting mega-rectum, and faecal impaction received erythromycin estolate orally at the daily dose of 20 mg/kg for 4 weeks. At the end of treatment the clinical score (P-value < 0.01) and the mean laxative requirement (P-value < 0.05) decreased. This treatment is well-tolerated and effectively treats children severely constipated.[19] These results indicate that erythromycin treats amoebic dysentery, non-gonococcal urethritis, asthma, delays the delivery in pregnant women, lowers neonatal morbidity, shortens the neonatal hospitalization time, and erythromycin estolate treats pertussis, diphtheria, children severely constipated, and propionyl erythromycin treats syphilis. The trials conducted with erythromycin have been reviewed. A clinical trial compared thoracoscopic erythromycin poudrage versus erythromycin slurry via a chest tube in patients with refractory spontaneous pneumothorax. An 80% of patients treated with erythromycin poudrage and 59.3% of patients treated with erythromycin slurry (P-value = 0.087) have a successful pleurodesis. Patients who received erythromycin poudrage have a shorter duration of post-procedural chest tube drainage (P-value = 0.032). Erythromycin is an effective sclerosing agent for pleurodesis in management of refractory spontaneous pneumothorax but erythromycin poudrage has shorter duration of post-procedural chest tube drainage.[20] A double-blind, placebo-controlled trial evaluated the effect of erythromycin administered orally at the dose of 500 mg twice-daily for 8 weeks versus placebo in steady-state idiopathic bronchiectasis. Patients treated with erythromycin, but not those treated with placebo, have significant (P-value < 0.05) improved forced expiratory in 1 second, forced vital capacity, and 24-hours sputum volume after 8 weeks of therapy. Low-dose of erythromycin improves lung function and sputum volume in patients with steady-state idiopathic bronchiectasis.[21] A randomized, clinical trial confirmed that erythromycin administered orally at the dose of 250 mg twice-daily for 60 days prevents the infection caused by Streptococcus pyogenes.[22] A randomized, double-blind, placebo-controlled, clinical trial was conducted in patients with acute bronchitis. Patients treated with erythromycin orally at the dose of 250 mg 4 times-daily missed less working days than patients who received placebo (P-value < 0.02).[23] A randomized, clinical trial assessed the efficacy of erythromycin in patients with acute bronchitis. One-week course of erythromycin

was compared to placebo and among smokers no difference in outcome is observed whereas among non-smokers erythromycin produces more rapid resolution of key symptoms than placebo.[24] Randomized, controlled, clinical trials compared the efficacy of erythromycin versus that of azithromycin or clarithromycin in treating community-acquired-pneumonia. Erythromycin use is associated with lower-rates of clinical success (P-value = 0.033), clinical cure (P-value = 0.014), and radiological success (P-value 0.045) thus erythromycin is less effective than azithromycin and clarithromycin in treating patients with community-acquired-pneumonia.[25] A randomized, controlled, clinical trial compared the adverse-drug-reactions of erythromycin versus those of clarithromycin in patients with community-acquired-pneumonia. Discontinuation-rate of therapy due to adverse-drug-reactions (P-value < 0.001), overall adverse-drug-reactions (P-value < 0.001), and gastrointestinal adverse-drug-reactions (P-value < 0.001) occurred more frequently in patients treated with erythromycin than in patients treated with clarithromycin. As erythromycin is not more effective than clarithromycin erythromycin should not be used unless other macrolides cannot be used.[26] A clinical trial compared the microbiologic, clinical efficacy, and safely of clarithromycin versus those of erythromycin in children with pertussis. Clarithromycin was administered orally at the dose of 7.5 mg/kg twice-daily for 7 days and erythromycin was administered orally at the dose of 13.3 mg/kg thrice-daily for 14 days. Microbiological eradication and clinical success-rate are similar in children who received clarithromycin and in those treated with erythromycin. Children treated with clarithromycin have fewer adverse-effects (P-value = 0.035) and higher compliance with medication regimen (P-value = 0.032). Treatment of pertussis with clarithromycin is similar to that of erythromycin but clarithromycin is better tolerated.[27] A randomized, controlled clinical trial compared the efficacy of erythromycin versus that of neomycin in treatment of patients with hepatic encephalopathy and hepatitis. Erythromycin was administered orally at the daily dose of 250 mg and neomycin was administered orally at the daily dose of 1 gram. Patients treated with erythromycin have a shorter hospitalization stay (P-value = 0.032) and shorter hospitalization duration which is positively correlated with C reactive protein concentration measured previous (P-value = 0.015) and after (P-value = 0.01) treatment.[28] An open, randomized, clinical trial compared the efficacy of amoxicillin administered orally at the daily dose of 50 mg/kg versus that of erythromycin administered orally at the daily dose of 1 gram in patients with pyoderma grated as severe. Amoxicillin is efficacious as erythromycin in treatment of severe pyoderma.[29] An open-label, randomized, clinical trial assessed the efficacy of benzylpenicillin administered intramuscularly at the daily dose of 50,000 units/kg for 5 days

versus that of erythromycin administered orally at the daily dose of 50 mg/kg for 10 days in children with diphtheria. The median time to fever clearance is shorter (P-value = 0.0004) in children treated with benzylpenicillin. All isolates of Corynebacterium diphtheriae were susceptible to benzylpenicillin whereas 11 isolates were resistant to erythromycin. Benzylpenicillin is recommended as first-line treatment for children with diphtheria.[30] A double-blind, randomized, clinical trial compared the efficacy of a single oral dose of 20 mg/kg of azithromycin versus that of erythromycin administered orally at the dose of 12.5 mg/kg 4 times-daily for 3 days in severely dehydrated children. The successful treatment is similar in children who received azithromycin and in those who received erythromycin but children treated with azithromycin have a shorter (P-value = 0.019) duration of diarrhoea and fewer (P-value = 0.023) episodes of vomiting. Single-dose of azithromycin is effective as standard erythromycin therapy for treatment of children with cholera but azithromycin is associated with shorter duration of diarrhoea and fewer episodes of vomiting.[31] A double-blind, controlled, clinical trial compared the efficacy of erythromycin administered orally at the dose of 500 mg twice-daily for 7 days versus that of erythromycin administered orally at the dose of 500 mg 4 times-daily for 4 days in patients with uncomplicated-genital-urinary chlamydia trachomatis infection. The treatment with erythromycin administered at the dose of 500 mg twice-daily for 7 days is more effective (P-value < 0.0005) than the treatment with erythromycin administered at the dose of 500 mg 4 times-daily for 4 days.[32] Several trials have been conducted with erythromycin. A trial showed that (1) erythromycin poudrage treats pleurodesis as erythromycin slurry but erythromycin poudrage has shorter duration of post-procedural chest tube drainage, (2) erythromycin improves lung function and sputum volume in patients with steady-state idiopathic bronchiectasis, (3) treats infection caused by Streptococcus pyogenes, and (4) acute bronchitis. A trial showed that erythromycin (1) is less effective than azithromycin and clarithromycin in treatment of patients with community-acquired-pneumonia, (2) clarithromycin induces less adverse-drug-reactions than erythromycin, (3) the treatment of pertussis with clarithromycin is similar to that with erythromycin but clarithromycin is better tolerated. A trial compared the efficacy of erythromycin versus that of neomycin in treatment of patients with hepatic encephalopathy and hepatitis. Erythromycin is associated with a reduction of hospital stay and the hospitalization time is positively correlated with C reactive protein concentration measured before and after treatment. A trial showed that (1) amoxicillin is efficacious as erythromycin in treatment of severe pyoderma, (2) benzylpenicillin is more effective than erythromycin in treatment of diphtheria, (3) a single-dose of azithromycin is effective as standard

erythromycin therapy for treatment of children with cholera but azithromycin is associated with shorter duration of diarrhoea and fewer episodes of vomiting, and (4) the treatment with erythromycin administered at the dose of 500 mg twice-daily for 7 days is more effective than the treatment with erythromycin administered at the dose of 500 mg 4 times-daily for 4 days. Krasniqi et al.[33] studied the pharmacokinetics of erythromycin in 6 healthy male volunteers, erythromycin was administered orally at the dose of 500 mg 4 times-daily for 3 consecutive days, and the pharmacokinetic parameters of erythromycin were determined on days 1 and 3 of treatment. Erythromycin is rapidly absorbed as the time to reach the peak concentration in plasma is 1.75±0.61 and 2.17±0.32 hours on days 1 and 3, respectively, of treatment and erythromycin is rapidly eliminated as the elimination half-life in plasma is 1.67±0.25 and 2.26±0.84 hours on days 1 and 3, respectively, of treatment. These authors also determined the penetration of erythromycin in muscle, subcutis, and in white blood cells on days 1 and 3 of treatment. The peak concentration of erythromycin is higher in plasma than in muscle and in subcutis whereas it is higher in white blood cells than in plasma and the area under the concentration-time curve is higher in plasma than in muscle and in subcutis whereas it is higher in white blood cells than in plasma. Erythromycin penetrates rapidly in muscle, subcutis, and in white blood cells as the time to reach the peak concentration is usually less than 3 hours and erythromycin is rapidly eliminated in muscle, subcutis and in white blood cells as the elimination half-life is usually less than 4 hours. Georgiew et al.[34] studied the penetration of erythromycin in serum and in tonsils and the concentration of erythromycin is about twice higher in tonsils than in serum. Bergogne-Bérézin[35] described the penetration of dirithromycin and erythromycin in human tissues. Dirithromycin is converted in-vivo into erythromycin and dirithromycin has similar antimicrobial activity as erythromycin. Following the administration of 1 gram of dirithromycin erythromycin concentration in lung parenchyma is 3.81 mg/kg 12 hours after the dose. Following a single oral dose of 250 mg of erythromycin the concentration of erythromycin in bronchial secretion is 1.0 and 1.5 mg/L 3 and 12 hours, respectively, after the dose. Following a single oral dose of 500 mg of erythromycin the erythromycin concentration in bronchial mucosa is > 1.0 mg/kg 4 to 24 hours after the dose and following oral doses of 500 mg of erythromycin the concentration of erythromycin in nasal mucosa is 0.59±0.17 and 1.86±0.54 mg/kg 24 and 12 hours, respectively, after the dose. After a single oral dose of 500 mg of erythromycin the concentration of erythromycin in tonsils is 0.60±0.55 mg/kg 24 hours after the dose and following the daily dose of 1 gram of erythromycin for 2 days the erythromycin concentration in tonsils is 1.37±0.55 mg/kg 24 hours after the oral dose. The concentration of erythromycin

in the prostate tissue ranges from 4.1 to 6.5 mg/kg following the daily dose of 1 gram of erythromycin. These results are consistent with the view that erythromycin penetrates into human tissues is significant concentration and persists in tissues in significant concentrations up to 24 hours after the dose. The interaction of erythromycin with drugs has been reviewed. An old woman received digoxin intravenously at the daily dose of 0.25 mg and also received erythromycin orally at the daily dose of 1 gram and digoxin serum concentration increased from 1.9 to 5.1 nmol/L 6 days after erythromycin was started. Erythromycin inhibits the metabolism of digoxin by blocking the cytochrome P-450 CYP3A4 thus increases the digoxin serum concentration.[36] Omeprazole, a proton pump inhibitor, decreases the rate of erythromycin N-demethylase by blocking CYP3A4.[37] An old woman received erythromycin orally at the daily dose of 800 mg and oxycodone orally at the daily dose of 60 mg. Erythromycin blocks CYP3A4, increases the oxycodone serum concentration, and causes a laxative-resistant constipation.[38] These results indicate that erythromycin interacts with drugs. The toxicity caused by the co-administered of erythromycin with drugs has been reviewed. Carbamazepine is metabolized into carbamazepine-10, 11-epoxide by CYP3A4 and erythromycin blocks CYP3A4 thus increases the serum concentration of carbamazepine. A young girl received carbamazepine orally at the daily dose of 15 mg/kg and also received erythromycin orally at the dose of 250 mg 4 times-daily and developed ataxic gait, horizontal nystagmus, and slurred speech 24 hours after starting erythromycin and the toxicity resolved 48 to 72 hours after discontinuous of both drugs.[39] Four epileptic children received carbamazepine and erythromycin and developed ataxia, dizziness, nausea, and vomiting and symptoms disappeared after erythromycin was discontinued.[40] Epileptic patients received carbamazepine and erythromycin and developed drowsiness, lethargy, vomiting, and nystagmus.[41] A woman with familial Mediterranean fever and amyloids received colchicine intravenously at the daily dose of 1 mg and also received erythromycin orally at the daily dose of 1 gram. After 2 weeks of erythromycin therapy she developed life-threatening colchicine toxicity with fever diarrhoea, abdominal pain, myalgia, lower extremity paraesthesia, later convulsions, and alopecia.[42] These results indicate that erythromycin co-administered with drugs can induce toxicity.

In conclusion, erythromycin is a macrolide antibiotic and erythromycin usually is bacteriostatic but may be bactericidal in high concentrations against susceptible organisms and erythromycin is active against gram-positive and gram-negative bacteria. Erythromycin base is incompletely absorbed from the upper small intestine because is inactivated by gastric

acid and esters of erythromycin base such as stearate, estolate, and ethylsuccinate have improved absorption. The efficacy and safely of erythromycin, the prevention of bacterial infections with erythromycin, the treatment of bacterial infections with erythromycin, and the trials conducted with erythromycin have been reviewed. The pharmacokinetics of erythromycin have been studied in healthy volunteers and erythromycin is rapidly absorbed following oral administration as the time to reach the peak concentration in plasma is about 2 hours and erythromycin is rapidly eliminated as the elimination half-life in plasma is about 2 hours. The penetration of erythromycin in human tissues has been reviewed and erythromycin penetrates in human tissues in significant concentrations and persists in tissues in significant concentrations up to 24 hours after the dose. Erythromycin interacts with drugs and the co-administration of erythromycin with drugs may induce toxicity. The aim of this study is to review the clinical pharmacology of erythromycin.

Conflict of interests

The authors declare no conflicts of financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employments, gifts, and honoraria. This article is a review and drugs have not been administered to men or animals.

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