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Clinical Pharmacology of Amoxicillin

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ABSTRACT

Background: Amoxicillin is a β-lactam antibiotic which is bactericidal for sensitive gram-positive and gram-negative bacteria and amoxicillin extends the spectrum of activity of penicillin G.

Method: The literature search was performed using PubMed database as search engine.

Results: Amoxicillin is active against meningococci, Listeria monocytogenes, Streptococcus pyogenes, and many strains of Haemophilus influenzae. Some bacteria possess β-lactamases which destroy the β-lactam ring; thus, amoxicillin is co-formulated with clavulanic acid, a β-lactamase inhibitor, and amoxicillin/clavulanate extends the spectrum of β-lactamase-producing Haemophilus influenzae, Escherichia coli, Klebsiella, Proteus, Moraxella, and Bacillus fragilis. Amoxicillin is used to treat sinusitis, otitis media, acute exacerbations of chronic bronchitis, and epiglottitis. The efficacy, safety, prophylaxis, treatment, and trials with amoxicillin/clavulanate have been studied, and the penetration of amoxicillin into the cerebrospinal fluid, treatment of meningitis, transfer across the human placenta, and migration into the breast milk with amoxicillin have also been studied. In addition, the pharmacokinetics of amoxicillin and clavulanic acid have been studied.

Conclusion: the aim of this study is to review amoxicillin efficacy and safety, prophylaxis, treatment, trials, penetration into the cerebrospinal fluid, treatment of bacterial meningitis, transfer across the human placenta, migration into the breast milk, and amoxicillin and clavulanic acid pharmacokinetics.

Introduction

Aminopenicillins

Ampicillin and amoxicillin expand the spectrum of activity of penicillin G in a different direction from the penicillinase-resistant penicillins and they allow for useful activity against some gram-positive and gram-negative organisms. Ampicillin and amoxicillin are destroyed by β-lactamases (from both gram-positive and gram-negative bacteria); thus, further expansion of their activity is enabled through co-formulation with β-lactamase inhibitors: clavulanate or sulbactam [1].

Antimicrobial Activity of Amoxicillin

Amoxicillin is generally bactericidal for sensitive gram-positive and gram-negative bacteria. The meningococci and Listeria monocytogenes are sensitive. Many pneumococcal isolates have varying levels of resistance to amoxicillin, and penicillin-resistant strains should be considered amoxicillin-resistant. Haemophilus influenzae and the viridians group of streptococci exhibit varying degrees of resistance. From 30% to 50% of Escherichia coli, a significant number of Proteus mirabilis and practically all species

of Klebsiella are resistant. Most strains of Shigella, Pseudomonas, Serratia, Acinetobacter, Bacillus fragilis, and indole positive Proteus also are resistant to amoxicillin. Resistant strains of Salmonella are recovered with increasing frequency. Concurred administration of a β-lactamase inhibitor, clavulanate acid, to amoxicillin markedly expands the spectrum of activity, particularly against Haemophilus influenzae, Escherichia coli, Klebsiella, Proteus, and Bacillus fragilis [1].

Therapeutic Indication of Amoxicillin

Amoxicillin is active against Streptococcus pyogenes and many strains of Haemophilus influenzae. Amoxicillin constitutes effective therapy for sinusitis, otitis media, acute exacerbations of chronic bronchitis, and epiglottitis caused by sensitive stains of these organisms. Amoxicillin is the most active of all the oral β-lactam antibiotics against both penicillin-susceptible and penicillin-nonsusceptible Streptococcus pneumoniae. Based on the increasing prevalence of pneumococcal resistance to penicillin, an increased dose of amoxicillin (from 40 to 45 up to 80 to 90 mg/kg daily) for empiric treatment of acute otitis media in children is recommended. The addition of a β-lactamase inhibitor to amoxicillin (clavulanic aid) extends the spectrum to β-lactamase-producing Haemophilus influenzae and Moraxella. Amoxicillin is an alternative treatment to penicillin for bacterial pharyngitis [1].

Treatment of Urinary-Tract Infections with Amoxicillin

Most uncomplicated urinary-tract infections are caused by Enterobacteriaceae and Escherichia coli. Amoxicillin is an effective agent for urinary-tract infections, but the high prevalence of resistance amongst Escherichia coli and Klebsiella makes the empiric use of amoxicillin for urinary-tract infections challenging. Enterococcal urinary-tract infections are treated with amoxicillin alone [1].

Absorption, Distribution, Metabolism, and Elimination of Amoxicillin

Amoxicillin is penicillinase-susceptible, semisynthetic penicillin it is a chemically related, and pharmacologically relative of ampicillin. Amoxicillin is stable in acid, designed for oral use, and is absorbed rapidly and completely from the gastrointestinal tract. The antimicrobial spectrum of amoxicillin is less effective than ampicillin. Peak plasma concentrations of amoxicillin are 2 to 2.5 times greater than those of ampicillin after oral administration of the same dose. Food does not interfere with amoxicillin absorption. Although the elimination half-life of amoxicillin is similar to that of ampicillin, effective concentrations of amoxicillin are detectable in the plasma for twice as long as with ampicillin because of the more complete absorption of amoxicillin. For all these reasons, amoxicillin is generally preferred over ampicillin for oral administration. About 20% of amoxicillin is protein bound in plasma. Most of a dose of amoxicillin is excreted in an active form in the urine, dose adjustment is required in renal dysfunction, and probenecid delays the excretion of amoxicillin [1] (Figures 1 & 2).

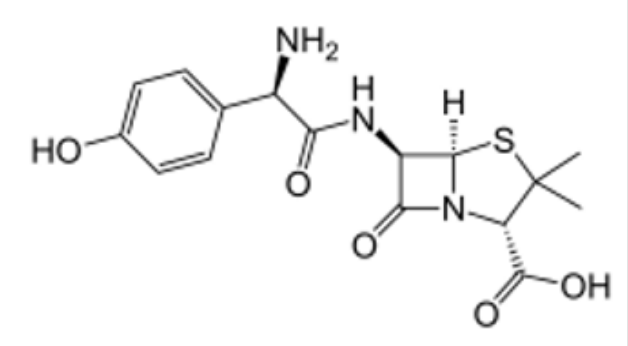

Figure 1: Amoxicillin molecular structure (molecular weight = 365.4 grams/mole).

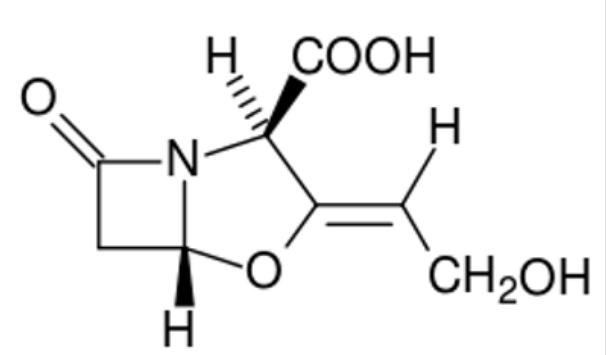

Figure 2: Clavulanic acid molecular structure (molecular weight = 199.16 grams/mole).

Literature Search

The literature search was performed electronically using PubMed database as search engine and the following key words were used: "amoxicillin efficacy safety", "amoxicillin pharmacokinetics", "amoxicillin prophylaxis" "amoxicillin treatment", "amoxicillin trials", amoxicillin CSF", "amoxicillin meningitis", "amoxicillin placental transfer", and "amoxicillin breast milk". In addition, the book "The pharmacological basis of therapeutics" [1] has been consulted.

Results

Efficacy and Safety of Amoxicillin/Clavulanate

Amoxicillin is efficacious and safe in treatment of inflammatory acne [2]. Amoxicillin/clavulanate, given at a dose of 1,000/62.5 mg

twice-daily for 10 days, is clinically effective and safe in treatment of community-acquired pneumonia in adult patients [3]. Amoxicillin/clavulanate, given at a dose of 2,000/125 mg, is generally well tolerated and provides a suitable option for empiric therapy of bacterial rhinosinusitis in adults [4]. The short 5-day course of amoxicillin/clavulanate, given at a dose of 2,000/125 mg, is safe and clinically effective as a longer 7-day course of amoxicillin/clavulanate, given at a dose of 875/125 mg, in patients with acute exacerbations of chronic bronchitis [5]. Azithromycin, given at a dose of 1 gram once-daily for 3 days, is at as effective as amoxicillin/clavulanate, given at a dose of 875/125 mg twice-daily for 7 days, in treatment of adult patients with community-acquired pneumonia [6]. Gemifloxacin, administered at a mean dose of 320 mg once-daily for 7 days, is clinically, bacteriologically, and radiologically effective as 10 days of amoxicillin/clavulanate given at a dose of 1,000/125 mg thrice-daily for treatment of pneumococcal community-acquired pneumonia [7]. Ampicillin/sulbactam or amoxicillin/clavulanate was administered to 102 patients for 10 days and ampicillin/sulbactam is safe and effective as amoxicillin/clavulanate in the empiric treatment of upper respiratory infections in adults [8]. Cefuroxime axetil, given at a dose of 250 mg twice-daily, is effective as amoxicillin/clavulanate given at a dose of 500/62.5 mg thrice-daily in treatment of acute bacterial maxillary sinusitis in adults [9]. Cefuroxime axetil, given at a dose of 250 mg twice-daily, is effective as amoxicillin/clavulanate given at 500/125 mg thrice-daily in treatment of adults with acute sinusitis [10]. Cefprozil, given at a dose of 500 mg twice-daily, has comparable clinical efficacy as amoxicillin/clavulanate administered at a dose of 500/125 mg thrice-daily in the treatment of adults with severe sinusitis [11].

Pharmacokinetics of Amoxicillin and Clavulanic acid in Healthy Volunteers

Mostafavi, et al. [12] studied the pharmacokinetics of amoxicillin and clavulanic acid in 14 healthy volunteers, aged 21 to 38 years weighing 57 to 85 kg, and the treatment consisted in a single dose of 125/62.5 mg of amoxicillin/clavulanic acid (Treatment 1) or 250/62.5 mg of amoxicillin/clavulanic acid (Treatment 2) and both formulations were administered orally. The Table 1 shows that the pharmacokinetic parameters are similar according to the two treatments, amoxicillin is rapidly absorbed as Tmax is 1.2 hours, amoxicillin is rapidly eliminated as the elimination half-life is about 1 hour, and there is a limited interindividual variability in the pharmacokinetic parameters as the healthy volunteers have similar demographic characteristics. The Table 2 shows that the pharmacokinetic parameters are similar according to the two treatments, clavulanic acid is rapidly absorbed as Tmax is 1 hour, clavulanic acid is rapidly eliminated as the elimination half-life is about 1 hour, and there is a limited interindividual variability in the pharmacokinetic parameters as the health volunteers have similar demographic characteristics.

Table 1: Pharmacokinetic parameters of amoxicillin which have been obtained in 14 healthy volunteers following a single oral dose of amoxicillin/clavulanic acid of 125/62.5 mg (treatment 1) or amoxicillin/clavulanic acid 250/62.5 mg (Treatment 2). Values are the mean±SD, by Mostafavi, et al. [12].

Treatment	Peak conc. (µg/ml)	Tmax (h)	Elimination half-life (h)	Total body clearance (L/h)	AUC (µg*h/ml)
Treatment 1	7.59±1.45	1.20±0.4	1.17±0.16	26.34±3.68	19.32±2.66
Treatment 2	7.32±1.68	1.26±0.45	1.28±0.14	25.65±4.16	18.57±3.11

Note: Tmax = time to reach the peak concentration. AUC = area under the plasma concentration-time curve of amoxicillin.

Table 2: Pharmacokinetic parameters of clavulanic acid which have been obtained in 14 healthy volunteers who received a single oral dose of amoxicillin/clavulanic acid of 125/62.5 mg (Treatment 1) or amoxicillin/clavulanic acid of 250/62.5 mg (Treatment 2). Values are the mean±SD, by Mostafavi, et al. [12].

Treatment	Peak conc. (µg/ml)	Tmax (h)	Elimination Half-life (h)	Total body clearance (L/h)	AUC (µg*h/ml)
Treatment 1	2.60±0.68	1.00±0.18	1.03±0.12	22.2±5.9	6.11±1.38
Treatment 2	2.43±0.50	1.00±0.23	1.02±0.15	22.9±3.7	5.91±1.20

Note: Tmax = time to reach the peak concentration. AUC = area under the plasma concentration-time curve of clavulanic acid.

Prophylaxis with Amoxicillin for Bacterial Infections

Oral amoxicillin is the antibiotic of choice to reduce bacteraemia [13]. Prophylaxis with amoxicillin prevents gastrointestinal infections [14]. Prophylaxis with amoxicillin has a significant impact on the incidence, nature, and duration of bacteraemia dental restorative, cleaning procedures, and dental extraction after nasal intubation [15]. In the prophylaxis of oral or dental procedures, the initial amoxicillin dose is reduced to 2 grams and a further antibiotic dose is not necessary [16]. Prophylaxis with amoxicillin, given as a single dose of 3 grams, prevents bacterial infections in genitourinary-tract and gastrointestinal-tract [17]. Prophylaxis with amoxicillin, given intravenously at a dose of 40 mg/kg, prevents the infection caused by Streptococcus pyogenes [18].

Treatment of Bacterial Infections with Amoxicillin or with Amoxicillin/Clavulanate

The treatment with amoxicillin for chest-indrawing pneumonia for 3 days is non-inferior to treatment for 5 days in children [19]. Using once-daily or twice-daily dose of amoxicillin, with or without clavulanic acid, treats acute otitis media [20]. Amoxicillin/clavulanate given in high dosage is the preferred treatment of acute otitis media in children [21]. High-dose amoxicillin/clavulanate is the recommended treatment of acute otitis media in children [22]. Amoxicillin or amoxicillin/clavulanate is the preferred treatment of respiratory bacterial infections in children [23]. Amoxicillin/clavulanate is the first-line agent for treatment of sinusitis in children [24]. Amoxicillin, given once-daily or twice-daily, is equally effective in treatment of pharyngitis caused by the group A β-haemolytic streptococci [25]. Amoxicillin/clavulanate treats respiratory infections, sinusitis, and otitis media but this treatment may induce adverse-effects [26]. Amoxicillin administered pre- or post-operatively treats pain in patients undergoing third molar extraction [27]. Oral amoxicillin is effective as intravenous ampicillin in curing typhoid fever caused by chloramphenicol-resistant Salmonella typhi [28].

Trials with Amoxicillin or with Amoxicillin/Clavulanic Acid

Lower-dose of oral amoxicillin is non-inferior to higher-dose, and 3-day treatment duration is non-inferior to 7 days, in treatment of community-acquired pneumonia in children [29]. In adult patients, with community-acquired complicated pneumonia, amoxicillin/clavulanate treatment could be safely discontinued by day 14 if clinical stability is obtained [30]. In children, younger than 5 years with non-severe pneumonia, the treatment with amoxicillin is more effective than placebo [31]. High-dose of amoxicillin is more effective than high-dose of penicillin in adults with uncomplicated community-acquired pneumonia [32]. In HIV-uninfected children, aged 2 to 59 months, amoxicillin is more effective than placebo in treating non-severe fast-breathing pneumonia [33]. Amoxicillin/clavulanate treats non-severe exacerbations of bronchiectasis in children and remains the first-line oral antibiotic in this setting [34]. Azithromycin is non-inferior to amoxicillin/clavulanate for resolving exacerbations in children with non-severe bronchiectasis [35]. High-dose of oral amoxicillin is similar to high-dose of parenteral ampicillin in treatment of severe pneumonia in children [36]. Amoxicillin treats uncomplicated gonococcal urethritis in males and cervical gonorrhoea in females and this treatment is more effective than that with ampicillin [37].

Penetration of Amoxicillin into the Cerebrospinal Fluid (CSF)

Strausbaugh, et al. [38] described the penetration of amoxicillin in 10 patients with tuberculous meningitis. Table 3 reports amoxicillin concentration in serum and in CSF following oral amoxicillin administered at a dose of 1 gram, Table 4 provides the amoxicillin concentration in serum and in CSF at different times after intravenous administration of 2 grams of amoxicillin. This table shows that amoxicillin readily crosses the blood-CSF barrier in patients with meningeal inflammation. Amoxicillin CSF concentration ranges from 0.2 to 0.9 μg/ml and this concentration is similar to the minimum inhibitory concentration of most meningeal pathogens which is usually 0.5 μg/ml. In addition, there is a remarkable interindividual variability in the serum and CSF concentration of amoxicillin. This variable reflects not only individual differences in amoxicillin absorption but also differences in dosage which ranges from 15 to 45 mg/kg. This table shows that amoxicillin readily crosses the blood-CSF barrier in patients with meningeal inflammation. Amoxicillin CSF concentration ranges from 1.5 to 40.0 μg/ml, 1 hour after amoxicillin administration, and this concentration exceeds the minimum inhibitory concentration of most meningeal pathogens which is usually 0.5 μg/ml. In addition, there is a remarkable interindividual variability in the serum and CSF concentrations of amoxicillin. This variability reflects not only individual differences in amoxicillin absorption but also differences in dosage which ranges from 33 to 143 mg/kg. Amoxicillin CSF concentrations, obtained after amoxicillin administration intravenously at a dose of 2 grams, are several times higher than those obtained following an amoxicillin oral dose of 1 gram.

Table 3: Serum and cerebrospinal fluid (CSF) concentrations of amoxicillin which are obtained in 10 patients with tuberculous meningitis after oral administration of 1 gram of amoxicillin. Values are the minimum, maximum, mean, and standard deviation, by Strausbaugh, et al. [38].

Value	Dose (mg/kg)	§Serum concentration (μg/ml)	*CSF concentration (μg/ml)	%Penetration CSF/serum concentration x 100%
Minimum	15	4.2	0.2	0.9
Maximum	45	23.3	0.9	21.1
mean	24.8	10.6	0.61	7.4
±SD	3.7	1.9	0.17	4.4

Table 4: Serum and cerebrospinal fluid (CSF) concentrations of amoxicillin which are obtained in 10 patients with tuberculous meningitis after intravenous administration of 2 grams of amoxicillin. Values are the minimum, maximum, mean, and standard deviation, by Strausbaugh, et al. [38].

		Serum concentration (µg/ml)		CSF concentration (µg/ml)		%Penetration CSF/serum concentration x 100%	
Value	Dose (mg/kg)	*1.5 h	4 h	1.5	4h	1.5 h	4 h
Minimum	33	25	2.1	2.9	2.6	8	47
Maximum	143	66	10.2	40	27	87	475
Mean	60.2	37.6	4.5	14.7	10.2	48.6	214
±SD	11.5	4.9	0.79	4.3	2.3	10.2	39.5

Bakken, et al. [39] administered amoxicillin and potassium clavulanic acid at a dose of 2 grams and 1 gram, respectively, to 21 patients with inflamed meninges aged 14 to 76 years. Both amoxicillin and potassium clavulanic acid were detectable in the CSF 1 hour after dosing and both drugs reached a peak concentration by approximately 2 hours after dosing. The highest mean CSF concentrations were 2.25 µg/ml for amoxicillin and 0.25 µg/ml for potassium clavulanic acid. The CSF to plasma ratio of amoxicillin and potassium clavulanic acid is 5.8 and 8.4%, respectively. The concentrations of amoxicillin and potassium clavulanic acid are effective in treatment of meningitis caused by β-lactamase-producing pathogens. Clumeck, et al. [40] investigated the penetration of amoxicillin and ampicillin into the CSF. Twenty volunteers, with absence of meningeal inflammation, received amoxicillin or ampicillin intravenously at a dose of 33 mg/kg. Amoxicillin and ampicillin were detected in the CSF and ampicillin tended to produce higher CSF concentration than amoxicillin although the difference was small whereas the serum concentration of amoxicillin equalled that of ampicillin.

Treatment of Bacterial Meningitis with Amoxicillin

In literature there is only one study on the treatment of bacterial meningitis with amoxicillin and it has been reported by Nolan, et al. [41]. Eleven children with bacterial meningitis were treated with amoxicillin sodium intravenously at a dose of 200 mg/kg. The infecting organisms were Haemophilus influenzae in 9 children and Streptococcus pneumoniae in 2 children. The mean peak concentration of amoxicillin in the cerebrospinal fluid was 3.14 µg/ml (about 7% of the concomitant mean peak serum concentration) early during therapy. Meningeal penetration of amoxicillin declined to a mean peak of 0.63 µg/ml on the final day of therapy. Children had optimal response to treatment and bacteria were eradicated from CSF. Thus, intravenous amoxicillin sodium provides a therapy for meningitis caused by Haemophilus influenzae or by Streptococcus pneumonia.

Transfer of Amoxicillin Across the Human Placenta

In literature there is only one study on the transfer of amoxicillin across the human placenta and it has been reported by Tran, et al. [42]. The transfer of amoxicillin across the human placenta was studied in 44 pregnant women on delivery who received amoxicillin at a dose of 1 gram or 2 grams intravenously. The peak concentration of amoxicillin in the venous umbilical cord serum is 18% of the maternal peak concentration of amoxicillin. These results are consisting with the view that amoxicillin poorly crosses the human placenta.

Migration of Amoxicillin into the Breast milk

In literature there is only one study on the migration of amoxicillin into the breast-milk and it has been reported by Kafetzis, et al. [43]. After a single oral amoxicillin dose of 1 gram to 6 lactating women, the peak concentration of amoxicillin occurred 4 to 5 hours after the dose. Average milk concentration of amoxicillin was 0.69 µg/ml (range, 0.46 to 0.88) at 4 hours and 0.81 µg/ml (range, 0.39 to 1.3) at 5 hours after the dose. Milk to serum ratio of amoxicillin increased as serum concentrations of amoxicillin were declining. After administration of a single oral dose of 125 or 250 mg amoxicillin, the peak serum concentration of amoxicillin is about 7 µg/ml [12] thus amoxicillin poorly migrates into the breast-milk.

Discussion

Amoxicillin is a β-lactam antibiotic, is active against sensitive gram-positive and gram-negative bacteria, amoxicillin is bactericidal, and expands the spectrum of activity of penicillin G. Amoxicillin is active against meningococci, Listeria monocytogenes, Streptococcus pyogenes, and many strains of Haemophilus influenzae. Some bacteria possess β-lactamases which destroy the β-lactam ring; thus amoxicillin is co-formulated with clavulanic acid, an inhibitor of β-lactamases, and amoxicillin/clavulanate expands the spectrum of β-lactamase-producing Haemophilus influenzae, Escherichia coli, Klebsiella, Proteus, Moraxella, and Bacillus fragilis. Amoxicillin is used to treat sinusitis, otitis media, acute exacerbations of chronic bronchitis, epiglottitis, and the urinary-tract infections caused by sensitive organisms. Amoxicillin may be administered intravenously or orally, as amoxicillin is resistant in acid, it is formulated for oral dosing and after oral administration amoxicillin is rapidly and completely absorbed by

the gastrointestinal-tract and food does not interfere with amoxicillin absorption [1]. The efficacy and safety of amoxicillin have been extensively studied [2-11]. Amoxicillin effectively and safely treats inflammatory acne [2]. Amoxicillin/clavulanate, given at a dose of 1,000/62.5 mg twice-daily for 10 days, effectively and safely treats community-acquired pneumonia in adults [3], amoxicillin/clavulanate, given at a dose of 2,000/125 mg, is well tolerated and treats bacterial rhinosinusitis [4], and amoxicillin/clavulanate, administered at a dose of 875/125 mg for 7 days, effectively treats acute exacerbations of chronic bronchitis [5]. Azithromycin, given at a dose of 1 gram once-daily for 3 days, effectively and safely treats community-acquired pneumonia as amoxicillin/clavulanate given at a dose of 875/125 mg twice-daily for 7 days [6], and amoxicillin/clavulanate, administered at a dose of 1,000/125 mg thrice-daily, effectively treats pneumococcal community-acquired pneumonia as gemifloxacin given at a mean dose of 320 mg once-daily for 7 days [7]. Ampicillin/sulbactam is safe and efficacy as amoxicillin/clavulanate in treatment of upper respiratory infections [8], and cefuroxime axetil, given at a dose of 250 mg twice-daily, is effective and safe as ampicillin/clavulanate administered at a dose of 500/62.5 mg thrice-daily, in treatment of acute bacterial maxillary sinusitis [9] and cefuroxime axetil, given at a dose of 250 mg twice-daily, is affective as amoxicillin/clavulanate, administered at a dose of 500/125 mg thrice-daily, in treatment of acute sinusitis in adults [10]. Cefprozil, given at a dose of 500 mg twice-daily, is effective as amoxicillin/clavulanate administered at a dose of 500/125 mg thrice-daily in treatment of severe sinusitis in adults [11]. The pharmacokinetics of amoxicillin and clavulanic acid have been studied in adult volunteers following a single oral dose of amoxicillin/clavulanic acid of 125/62.5 mg or 250/62.5 mg [12]. The elimination half-life of amoxicillin and clavulanic acid is 1.2 and 1 hours, respectively, and amoxicillin and clavulanic acid are rapidly absorbed as the time to reach the peak concentration is about 1 hour. The prophylaxis with amoxicillin has been studied [13-18]. Prophylaxis with oral amoxicillin reduces bacteraemia [13], prophylaxis with amoxicillin prevents oral and gastrointestinal infections [14], prophylaxis with amoxicillin reduces the incidence, nature, and duration of bacteraemia in dental restorative, cleaning procedures, and dental extraction [15]. An initial dose of 2 grams of amoxicillin is recommended for prophylaxis of oral or dental procedures [16]. Prophylaxis, with a single dose of 3 grams amoxicillin, prevents bacterial infections of genitourinary-tract and gastrointestinal-tract [17], and the prophylaxis with intravenously amoxicillin, given at a dose of 40 mg/kg, prevents the infection caused by Streptococcus pyogenes [18]. The treatment of bacterial infections with amoxicillin has been extensively studied [19-28]. In children, treatment of chest-indrawing pneumonia with 3 days amoxicillin is non-inferior to the treatment with 5 days amoxicillin [19], treatment of acute otitis media with amoxicillin, given once-daily or twice-daily with or without clavulanic acid, is comparable to three doses of amoxicillin [20], high-dose of amoxicillin/clavulanate is the preferred treatment of children with otitis media [21,22], amoxicillin or amoxicillin/clavulanate is the preferred treatment of respiratory bacterial infections in children [23], amoxicillin/clavulanate is the first-line agent for the treatment of sinusitis in children [24]. Amoxicillin, given once-daily or twice-daily, effectively treats the pharyngitis caused by group A β-haemolytic Streptococcus [25]. Amoxicillin/clavulanate treats respiratory infections, sinusitis, and otitis media but this treatment may induce adverse-effects [26]. Amoxicillin treats pain in patients undergoing dental extraction [27]. Oral amoxicillin is effective as intravenous ampicillin in curing typhoid fever caused by chloramphenicol-resistant Salmonella typhi [28]. The trials with amoxicillin or with amoxicillin/clavulanate have been extensively studied [29-37]. In children, with community-acquired pneumonia, lower-dose of oral amoxicillin is non-inferior to higher-dose and 3-day treatment duration is non-inferior to 7-day treatment [29]. In adults, with community-acquired complicated para-pneumonic effusions, the treatment with ampicillin/clavulanate may be discontinued by day 14 of treatment [30]. In young children with non-severe pneumonia, the treatment with amoxicillin is superior to placebo [31]. High-dose of amoxicillin is more effective than high-dose penicillin in treatment of community-acquired pneumonia in adults [32]. In young children, amoxicillin is more effective than placebo in treating non-severe fast-breathing pneumonia [33]. Oral amoxicillin/clavulanate is the first-line treatment of non-severe exacerbations of bronchiectasis in children [34]. Azithromycin is non inferior to amoxicillin/clavulanate in treating exacerbations in children with non-severe bronchiectasis [35]. High-dose of oral amoxicillin is similar to high-dose of parenteral ampicillin in treating severe pneumonia in children [36]. Amoxicillin treats uncomplicated gonococcal urethritis in males and cervical gonorrhoea in females and treatment with amoxicillin is superior to that with ampicillin [37]. The penetration of amoxicillin into the cerebrospinal fluid has been reported in three studies [38-40]. The penetration of amoxicillin into the cerebrospinal fluid has been studied following oral amoxicillin administered at a dose of 1 gram or following amoxicillin given at a dose of 2 grams intravenously [38]. Following intravenous administration of 2 grams of amoxicillin, the amoxicillin concentration in the cerebrospinal fluid averages to 14.7 and 10.2 μg/ml 1.5 and 4 hours after dosing, respectively, and these concentrations are several times higher the minimum inhibitory concentration of most meningeal pathogens which usually is 0.5 μg/ml. Amoxicillin/potassium clavulanate was administered at a dose of 2 grams/1 gram and the highest concentration of amoxicillin and potassium clavulanic acid in the cerebrospinal fluid is 2.25 and 0.25 μg/ml, respectively [39]. Amoxicillin or ampicillin was

intravenously administered at a dose of 33 mg/kg, both amoxicillin and ampicillin were detected in the cerebrospinal fluid, ampicillin concentration in the cerebrospinal fluid tended to be higher than that of amoxicillin, but the difference is small [40]. The treatment of bacterial meningitis was performed with 200 mg/kg amoxicillin given to 11 children [41]. Nine children had the meningitis caused by Haemophilus influenzae and 2 children had the meningitis caused by Streptococcus pneumoniae and the mean peak concertation of amoxicillin is 3.14 μg/ml early during treatment and amoxicillin cured the meningitis in all children. The transfer of amoxicillin across the human placenta was studied in 44 pregnant women at delivery who received 1 gram or 2 grams of amoxicillin and the peak concentration of amoxicillin in the plasma of the umbilical cord vein is 18% of the maternal plasma concentration [42]. The migration of amoxicillin into the breast milk has been studied in 6 lactating women who received a single oral dose of 1 gram amoxicillin, and the average milk concentration of amoxicillin is 0.69 μg/ml suggesting than amoxicillin poorly migrates into the breast-milk [43].

Conclusion

In conclusion, amoxicillin is a β-lactam antibiotic, is bactericidal for sensitive gram-positive and gram-negative bacteria, and expands the spectrum of activity of penicillin G. Amoxicillin is active against meningococci, Listeria monocytogenes, Streptococcus pyogenes and many strains of Haemophilus influenzae. Some organisms possess the β-lactamases which destroy the β-lactam ring thus amoxicillin is co-formulated with clavulanic acid an inhibitor of β-lactamases. Amoxicillin/clavulanate extends the spectrum of activity to β-lactamase-producing Haemophilus influenzae, Escherichia coli, Klebsiella, Moraxella, and Bacillus fragilis. Amoxicillin is used to treat sinusitis, otitis media, acute exacerbations of chronic bronchitis, and epiglottitis caused by sensitive organisms. Amoxicillin may be administered intravenously or orally, and after oral administration of amoxicillin/clavulanate, amoxicillin and clavulanic acid are rapidly absorbed as the time to reach the peak concentration is about 1 hour and amoxicillin and clavulanic acid are rapidly eliminated as the elimination half-life of amoxicillin and clavulanic acid is about 1 hour. The efficacy and safety, prophylaxis, treatment, and trials with amoxicillin/clavulanate have been extensively studied. Amoxicillin penetrates into the cerebrospinal fluid in significant amounts and following an intravenous dose of 2 grams of amoxicillin, amoxicillin concentration in the cerebrospinal fluid is higher than the minimum inhibitory concentration of the common meningeal pathogens. Amoxicillin administered intravenously at a dose of 200 mg/kg treats the meningitis caused by Haemophilus influenzae or by Streptococcus pneumoniae. Amoxicillin is poorly transferred across the human placenta and poorly migrates into the breast milk. The aim of this study is to review the clinical pharmacology of amoxicillin.

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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