Chapter 10
Bioavailability of Antibiotics and Their Toxicity

Izhar Ullah, Essa Ali, and Fakhar-ud-Din

Abstract Antimicrobial agents are the gift of science against pathogenic microorganisms causing infectious diseases. Antibacterial drugs are specifically used against bacteria and are of two types, i.e., bacteriostatic that can inhibit bacterial growth and bactericidal that can cause death of bacteria. Antibacterial mainly target either cell wall synthesis (like beta-lactams, vancomycin), bacterial protein synthesis (like tetracycline, clindamycin, streptogramins, chloramphenicol, aminoglycosides, and linezolid), or nucleic acid metabolism of bacteria (like sulfonamides, trimethoprim, quinolones). Infectious diseases are the major reason of premature deaths. Mortality rate due to these ailments raised up to 50,000/day deaths in last decades. Over the past few years, optimization of the use of antibiotics has gained much concern owing to the alarming increase in bacterial resistance and lack of new antibiotic classes under development. For the optimum effect and low toxicity we prefer those antimicrobials having high oral bioavailability. Bioavailability is the portion of dose after administration by route that is bioavailable in systemic circulation without any change in characteristics for its therapeutic effect. It is one of the basic pharmacokinetic properties of drugs. Bioavailability is an important factor because it defines the dose of drug to be administered for its desired therapeutic effect. The more bioavailable a drug is, the less of its amount will be required to attain therapeutic effect and so lower will be the body exposure for high dose.

Keywords Bioavailability · Antibiotics · Toxicity

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10.1 Introduction

Antimicrobial drugs are the gift of science against infectious diseases. Antibacterial drugs are mainly classified as bacteriostatic that can inhibit bacterial growth and bactericidal that can cause death of bacteria. Antibacterial mainly target either cell wall synthesis (like Beta-lactams, vancomycin), bacterial protein synthesis (like tetracycline, clindamycin, streptogramins, chloramphenicol, aminoglycosides, and linezolid), or nucleic acid metabolism of bacteria (like sulfonamides, trimethoprim, quinolones) (Dasgupta 2012). Normal flora consists of microorganisms, mainly bacteria, which reside inside and outside the body without causing any infection. New microorganisms can also colonize to overcome individual's defense system. Whenever there is a decline in the body immune system either by diseases or by drugs (anticancer or immunosuppressant), the same microorganisms become pathogenic. If individual is immunocompromised, then these microbes may cause diseases very frequently (Hemaiswarya et al. 2008). Infectious diseases are the main reason of premature deaths. Mortality rate due to these diseases raised up to 50,000 deaths per day in last decades. These diseases are also a great danger for the cancer and immunocompromised patients (Resistant 2007). Bacteria are majorly classified as gram-positive and gram-negative bacteria. Gram-positive bacteria differ from gram-negative by their external structure, i.e., bacterial cell wall. Gram-positive bacteria have thicker layer of peptidoglycan above inner cytoplasmic membrane (Beveridge 1999). Gram-negative bacteria contain lipopolysaccharide which is absent in gram-positive bacteria.

Changes in society, technological innovations, and the pathogenic microorganisms are the factors contributing to the emergence of new diseases, re-emergence of the diseases once managed, and the development of resistance to antimicrobial drugs (Cohen 2000). Inappropriate use of antimicrobial drugs, inadequate diagnosis, comprehensive use of antibiotics in medical centers, and use of antimicrobials in animal feeds and agriculture are few of the main causes of resistance development in pathogenic microorganisms (Swartz 1997).

Over the past few years, optimization of the use of antibiotics has gained much concern owing to the alarming increase in bacterial resistance and lack of new antibiotic classes under development (Bosso 2005; Van Bambeke et al. 2006). In this regard, advancement in the field of anti-infective pharmacology has led to the emergence of a new discipline "(PK/PD) pharmacokinetics/pharmacodynamics of antibiotics", which is referred to as the "discipline that focuses to understand the relationships between drug concentrations and its desirable (antibacterial effect) and undesirable effects (e.g., side effects) (Pai et al. 2014).

Bioavailability is the portion of dose after administration by route that is bioavailable in systemic circulation without any change in characteristics for its therapeutic effect. It is one of the basic pharmacokinetic properties of drugs. Bioavailability is an important factor because it defines the dose of drug to be administered for its desired therapeutic effect. The more bioavailable a drug is, the less of its amount will be required to attain therapeutic effect. However, it is also worth mentioning that most of the newly discovered therapeutic agents have poor solubility and it thus

renders them less bioavailable (Siddiqui et al. 2017). One of the basic tools in pharmacokinetics is bioavailability, as it should be measured when calculating dosages for routes other than intravenous route of administration (Allam et al. 2011). For bioavailability we are mainly concerned when drug is administered orally as this route faces various barriers to reach the systemic circulation. Strongly lipophilic and hydrophilic drugs are not suitable for oral administration because of inability to permeate through GI mucosa and low solubility in aqueous medium of GI. Log *P* value (Partition coefficient) will affect the transport characteristics of active pharmaceutical ingredient; API (drug) with log *P* value (partition coefficient) above 03–01 will show poor transport characteristics because best passive absorption through lipid membrane is at log *P* value of 3–1 (Agarwal et al. 2014).

From recent past years drug bioavailability has become a subject of interest not only in drug development but also in early stages of drug discovery. It is due to the fact that most of the candidate drugs failed during clinical trials were because of problems in absorption, distribution, metabolism, excretion (ADME), and toxicological parameters, rather than lack of efficacy. Recent advances are being made in pharmaceutical industry to improve success rates by considering the pharmacokinetic parameters ADME and toxicological aspects in drug discovery in early stage. Therefore, the numbers of publications on drug bioavailability have been increasing steadily from recent past.

Oral drug delivery has many advantages such as patient compliance, low cost, and avoidance of problems related to parenteral administration, such as infection risk and pain (Ensign et al. 2012). However, bioavailability is the main factor that needs to be considered when designing formulations for oral administration because poor bioavailability of drug may lead to development of resistance in case of antibiotics which further leads to therapeutic failure. Various factors such as limited permeability, poor solubility, and high rate of drug degradation in GIT are mainly responsible for inadequate bioavailability of the drugs. To overcome these problems nanotechnology is a promising tool. Antibiotics can be endowed with new and improved properties when combined with nanotechnological approaches like high surface:volume area and better bioavailability (Sharma et al. 2012).

Nanotechnology offers wide range of approaches to overcome the problems associated with antibiotics like their poor solubility and low bioavailability. Among these, solid lipid nanoparticles (SLNs) are the most suitable tool as they are made up of generally regarded as safe excipients like biodegradable and biocompatible lipids. These nanoparticles efficiently improve the bioavailability of poorly soluble drugs without any cytotoxicity against the mammalian cells. They enhance the bioavailability either by improving the solubility of drugs or by prolonging their release and residence time. They also offer protection to the drugs from excessive degradation in the GIT, thus increasing the concentration of drug in plasma (Lin et al. 2017). Mesoporous silica nanoparticles (MSNs) are another recently developed approach investigated for bioavailability enhancement of poorly soluble drugs. These nanoparticles like the SLNs impart stability to the drug molecules against the harsh conditions of GIT like low pH (Hata et al. 1999). Moreover, their high surface:volume ratio and large pore volume facilitate the delivery of higher concentrations of drug molecules to the target tissues and organs (Florek et al. 2017).

According to the European Medicines Evaluation Agency (EMEA), bioavailability is "The rate and extent to which an active moiety is absorbed from a pharmaceutical form and becomes available in the systemic circulation." There are two types of bioavailability:

1. Absolute bioavailability is referred to as the fraction/amount of dose from the extra vascular route, e.g., oral dose in unchanged form that reaches the systemic circulation in reference to dose given by an intravenous route.

   It can be measured by calculating the respective AUC after oral administration and intravenous administration as depicted in Eq. (10.1). /Dose_{po} and/ Dose_{test} in equation 10.1 and 10.2, respectively should be in line with their respective equations and not in second line which make equations incorrect.

   Therefore to avoid the effect of nonlinearity, the plasma concentrations following both intravenous and oral dosing should be similar.

$$\text{Absolute bioavailability} = \text{AUC}_{po} / \text{AUC}_{iv} \times \text{Dose}_{iv} / \text{Dose}_{po} \tag{10.1}$$

2. Relative bioavailability is referred to the fraction of a dose of drug reaching the systemic circulation relative to a reference product. Calculated as given by Eq. (10.2).

$$\text{Relative bioavailability} = \text{AUC}_{test} / \text{AUC}_{ref} \times \text{Dose}_{ref} / \text{Dose}_{test} \tag{10.2}$$

   Oral bioavailability is measured by the fraction of given dose absorbed in the GIT (f_a) and fraction that is not metabolized in liver (f_h) and the intestinal tract (f_g) as in Eq. (10.3) (El-Kattan and Lee 2017).

$$F = f_a \cdot f_g \cdot f_h \tag{10.3}$$

   Area under the curve (AUC) is probably the most single determinant of bioavailability (Spyker et al. 1977).

There are two major factors effecting bioavailability of a drug, i.e., product oriented like drug solubility, the rate of in vivo dissolution, and permeability, and secondly by patient factors such as physiological status, the integrity of the gastrointestinal tract, site of drug absorption, presystemic drug metabolism (intrinsic variables), membrane transporters, and extrinsic variables such as the effect of food or concomitant medication (Martinez and Amidon 2002). The fraction of drug absorbed is mostly considered the bioavailable fraction (Bioavailability) that joins the systemic circulation (Musser and Anderson 2001). In case of antibiotics while dealing with infectious diseases we are much concerned with the concentration. The effectiveness of an antibiotic can be predicted by a number of pharmacokinetic and pharmacodynamic principles. One of the starting point for predicting a drug's efficacy and maintenance of serum concentration is detecting the serum concentration of drug and its MIC for target pathogen. Achieving the MIC for a pathogen has become general guideline for conventional antimicrobial therapy (MacGregor and Graziani 1997; Pillai et al. 2010). Suboptimal target site concentrations have major clinical

implications, as they may contribute to therapeutic failures (Brunner et al. 2000; Joukhadar et al. 2001) particularly for bacteria for which in vitro MICs are higher. Furthermore, it can be conceived that bacterial resistance is triggered by subinhibitory concentrations in tissue. Therefore, according to the recommendations of standard reference texts on current medical treatment, impaired target site distribution is considered particularly when there is inconsistency between susceptibility testing and clinical response. Important clinical data can be extracted by data on tissue penetration of drugs as many studies have demonstrated that target site concentration profile is an important indicative of clinical outcome and in this respect it is more predictive than the plasma drug concentration (Pai et al. 2014).

10.2 Penicillin

Penicillins are β-lactam antibiotics and are cell wall synthesis inhibitors. Due to cell wall synthesis inhibiting action these antibacterial are bactericidal and kill the bacteria at particular concentration reached to the site of infection. Penicillins are classified into following five major groups; description is given in Table 10.1 (Nathwani and Wood 1993).

10.2.1 Bioavailability and Toxicity

For bioavailability of any drug we are mainly concerned with other than intravenous route of administration as this route provides 100% bioavailability. Penicillins differ markedly in their oral absorption. Some acid labile compounds like penicillin G, antipseudomonal penicillins, and methicillin are poorly absorbed through GIT while acid-stable compounds can have high oral absorption pattern differences.

Table 10.1 Classification of penicillins

Classes of penicillins	Members
Natural penicillins	Penicillins G
	Penicillin V
Penicillinase resistant penicillins	Methicillin,
	Nafcillin
	Isoxazolyl penicillin
Aminopenicillins	Ampicillin
	Amoxicillin
Carboxypenicillins	Carbencillin
	Ticarcillin
Acylureidopenicillins	Azlocillin
	Mezlocillin
	Pipracillin

Amoxicillin is absorbed highly (74–80%) after oral administration and food does not affect its absorption while ampicillin absorption is decreased by food and has lesser oral absorption (33–54%) compared to amoxicillin (Bennett et al. 2014). In 1977 a study demonstrated that there is no significant difference of absorption extent and AUC when amoxicillin was administered orally and through intramuscular rout. This study showed more than 80% of amoxicillin absorption through both routes of administration (Spyker et al. 1977). While dealing with penicillin G and penicillin V the oral absorption is higher for penicillin V (60%) and food interact with the absorption of penicillin-G while penicillin V absorption is not affected. Total drug concentration after oral administration of 500 mg dose for penicillin G and penicillin V is about 2 and 3.5 μg/mL, respectively, taken fasting. Oxacillin, dicloxacillin, flucloxacillin, and cloxacillin have 33%, 37%, 44%, and 49% absorption after oral dose while these drugs interact with food and their absorption is decreased while nafcillin has very low oral absorption and also interact with food. Ticarcillin and piperacillin is not absorbed through GIT (Barza and Weinstein 1976; Humbert et al. 1979; Josefsson and Bergan 1982; Klein and Finland 1963; Libke et al. 1975; Lode et al. 1984; Meyers et al. 1980; Nauta and Mattie 1975).

Jose Alexander invented a novel method for enhancing the bioavailability of poorly absorbed orally administered drugs including the penicillin antibiotics like amoxicillin, oxacillin, nafcillin, cloxacillin, dicloxacillin, ticaricillin, penicillin G, penicillin V, methicillin, and nafcillin. The method utilizes the acylcarnitines absorption enhancing agents. These compounds used as bioavailability enhancers are pharmaceutically acceptable salts which are more potent than other absorption promoting agents and pose less risk of tissue damage at the concentrations used for absorption enhancement (Alexander and Fix 1985).

10.2.2 Adverse Effects and Toxicity

Penicillins show hypersensitivity reactions as the most important adverse effects which range from rash to anaphylaxis in severity. When penicillins are administered, they can act as haptens and combine to the human proteins. Penicillins allergy is mainly provoked by the two derivatives, i.e., penicilloyl and penicillanic acid (Yates 2008). Very common reaction to penicillins is serum sickness which is characterized by urticaria, fever, angioneurotic edema, and joint pain. Stevens-Johnson syndrome and exfoliative dermatitis are rarely occurring allergic reactions to penicillins. Penicillins cause neutropenia uncommonly but this reaction recovers if causative agent is discontinued (Kerr et al. 1972). Penicillins cause interstitial nephritis (Appel and Neu 1977), which more commonly occurred with methicillin. Hypokalemia is another adverse effect of penicillins when administered in high doses, particularly of ticarcillin. High doses of penicillin G can provoke seizures as CNS toxicity (Barrons et al. 1992). Gastrointestinal disturbances may occur using oral dose of all penicillins but frequency with ampicillin is high (Maraqa et al. 2002).

10.3 Cephalosporins

Cephalosporins are also β-lactam antibiotics and their discovery was reported in 1945 (Bo 2000). Their mechanism of antibacterial action is same to the other β-lactam drugs. They target the peptidoglycan cross linkage and thus inhibit the synthesis of cell wall and are considered as bactericidal (Vogelman and Craig 1986; Wise and Park 1965). Cephalosporin is classified into four classes (Marshall and Blair 1999) as given below in Table 10.2.

10.3.1 Absorption and Bioavailability

Cephalosporins have very variable bioavailability. Cefazolin is parentally administered drug and is available in both IV and IM formulations. Cefazolin was studied in animal model and was observed to have very good absorption after IM injection and showed 78.4 ± 18.8% bioavailability (Sams and Ruoff 1985) and its intraperitoneal (IP) administration also showed almost same bioavailability (77.9 ± 3.1%) (Low et al. 2000) (Fig. 10.1).

Cephalothin and cephapirin are also parentally administered drugs of first generation and their mean systemic bioavailability given IM are 65.0 ± 20.5% and

Table 10.2 Classification of cephalosporin is given in this table

Classes of cephalosporin's	Members
First generation	Cefazolin
	Cephalothin
	Cephapirin
	Cephradine
	Cefadroxil
	Cephalexin
Second generation	Cefamandole
	Cefonicid
	Cefaclor
	Cefprozil
	Cefuroxime
Third generation	Cefoperazone
	Cefotaxime
	Ceftazidime
	Ceftizoxime
	Ceftriaxone
	Cefdinir
	Cefditoren
	Cefixime
Fourth generation	Cefepime

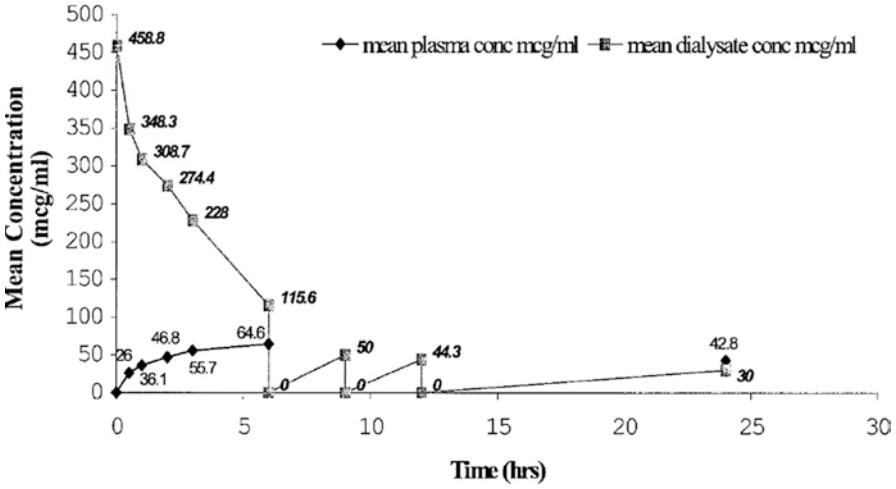

Fig. 10.1 Concentration–time profile of plasma and dialysate after intraperitoneal administration of cefazolin. Adopted from" Pharmacokinetics and bioavailability of cefazolin in horses" (Sams et al. 1985) with permission

67.89%, respectively (El-Komy 1995; Ruoff and Sams 1985). Cephradine of first-generation cephalosporin is found in both oral and parental dosage forms and its relative bioavailability is approximately 94% and its absorption was almost complete relative to IV dosing. Cefadroxil was found in a study to have bioavailability ranged from 90% to 100% estimated from plasma levels or from the amounts of drug excreted in the urine (García-Carbonell et al. 1993) (Fig. 10.2).

Cephalexin after oral administration showed rapid and complete absorption with peak levels reached within 1 h in suspension form; cephalexin appeared in serum within 9 min while in the form of capsule it takes 28 min. The oral absorption (Bioavailability) parameter varies if cephalexin is taken with food (Griffith and Black 1970; Nightingale et al. 1975). Cefprozil is a second-generation cephalosporin and is available in oral dosage form. Cefprozil exhibits linear pharmacokinetics and is essentially completely absorbed after oral administration and plasma as well as urine data show about 90% bioavailability (Shyu et al. 1992). Cefuroxime by itself is not absorbed orally and is given in the form of cefuroxime-axetil which showed absolute bioavailability of 35–45% in various studies while food increased its absorption (Williams and Harding 1984). Cefdinir belongs to third-generation cephalosporin and is available in oral dosage form having bioavailability of 16–21% in capsule dosage form and 21% in suspension form. Food exerts no clinically significant effect on cefdinir bioavailability (Williams and Harding 1984). Cefexime is another member of third-generation cephalosporins. The absolute bioavailability of this drug was determined through assays to be 52.3% and 47% after administration of 200 mg of oral solution and capsule, respectively (Faulkner et al. 1988). The fourth-generation drug cefepime is available only in parenteral dosage form.

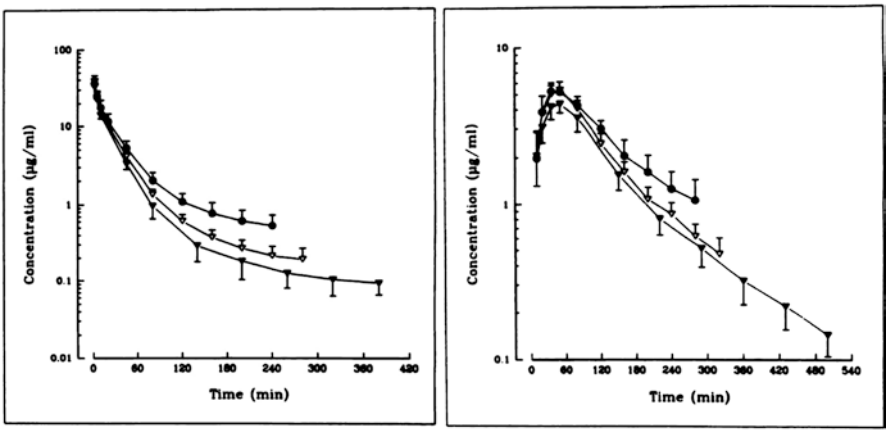

FIG. 2A *Mean plasma levels and standard deviations of cefadroxil after intravenous administration of 2.5 (●), 10 (▽), and 15 mg (▼).*

FIG. 2B *Mean plasma levels and standard deviations of cefadroxil after oral administration of 2.5 (●), 10 (▽), and 15 mg (▼).*

Fig. 10.2 Mean plasma levels and standard deviations of cefadroxil after intravenous administration (**a**) and oral administration (**b**). Adopted from "Pharmacokinetics and bioavailability of cephalothin in horse mares" (Ruoff et al. 1985) with permission

Krutika K et al. prepared cefdinir nanosuspension to increase its oral bioavailability. The particle size of resultant nanosuspension was 224.2 ± 2.7 nm while the zeta potential was found to be −15.7 ± 1.9 mV. Upon in vivo evaluation, a threefold increase in oral bioavailability was revealed as compared to the marketed formulation (Adcef) (Sawant et al. 2016).

10.3.2 Adverse Effects and Toxicity

The adverse effects profile of all the four generations can vary to some extent but remain same within single class. Like other β-lactam antibiotics hypersensitivity reactions are also the adverse effects caused by cephalosporins (Kelkar and Li 2001), but the frequency of hypersensitivity reactions occurrence is lower than penicillins. Cutaneous rashes accompanied with eosinophilia and sometimes fever occur in 7% or less individuals taking these drugs (Norrby 1987). Other severe reactions like anaphylaxis, serum sickness, or angioedema occur less commonly. These reactions are mediated by immunoglobulin E (IgE) and can occur in less than 1 patient out of 100,000 (Romano et al. 2002). In children and with the use of cefaclor the frequency of serum sickness may increase (Hebert et al. 1991). Cephalosporins can cause other adverse reactions like GIT disturbances (diarrhea, nausea, vomiting, biliary sludge, and transient transaminase elevation) and interstitial nephritis. Some hematologic reactions are eosinophilia, neutropenia, thrombocytopenia, impaired platelet aggregation, and hemolytic anemia. They can affect CNS very rarely by inducing seizures and encephalopathy in less than 1% patients taking these drugs.

Other rare adverse reactions are drug fever, disulfiram-like reaction, and phlebitis (Barza et al. 1986; Fainstein et al. 1983; Foster et al. 1980; Ingalls and Freimer 1992; Shearer et al. 1988).

10.4 Carbapenems

Ertapenem, meropenem, imipenem, and doripenem are the drugs occurring in this group. Carbapenems are β-lactam antibiotics and are bactericidal by inhibiting cell wall synthesis. All the abovementioned members of this group are poorly absorbed through GIT; therefore they are formulated in parenteral dosage form. Bioavailability of ertapenem after IM administration is approximately 90% (Keating and Perry 2005). Meropenem administered through IV, IM, or subcutaneous route has average bioavailability of 93–99% while imipenem has 89% bioavailability after IM administration (Albarellos et al. 2016; Craig 1997; Signs et al. 1992). Oral bioavailability of meropenem is low because it is BCS class 4 drug with low permeability and low solubility. Nanosuspension of meropenem was prepared to enhance is dissolution and solubility which will lead to an increased bioavailability. The in vitro evaluation suggested that the solubility and dissolution of meropenem was significantly enhanced as compared to pure drug (Chirumamilla et al. 2017).

10.4.1 Adverse Effects and Toxicity

Generally carbapenems are well-tolerated drugs. Some major adverse effects are like coagulation abnormalities, Clostridium difficile associated colitis, hepatotoxicity, or nephrotoxicity. Some commonly occurring adverse reactions are diarrhea, nausea, vomiting, phlebitis, and headache. All these drugs are believed to cause seizures due to their structural similarity with γ-aminobutyric acid (GABA) and seizures frequency is increased with imipenem compared to other members (Miller et al. 2011; Mori et al. 2007).

10.5 Monobactams

Monobactams are monocyclic β-lactam antibiotics having a 2-oxoazetidine-1-sulfonic acid moiety. The only member of this group is aztreonam (Sykes and Bonner 1985). This drug is administered through i.v. or i.m. route and has very poor bioavailability through oral route (Hopefl 1985; Swabb et al. 1983). Aztreonam is well tolerated but can cause local reactions like phlebitis in nearly 2% patients. Nausea, vomiting, diarrhea, and rashes can occur in less than 1% patients (Squibb and Sons n.d.).

10.6 Aminoglycosides

Aminoglycosides are very important part of the antibacterial family. Streptomycin produced by Streptomyces species and was the first member of this aminoglycoside family. Names of this family members that are derived from Streptomyces spp. end with "mycin" while those derived from Micromonospora spp. end with "micin." They are the protein synthesis inhibitors by binding to the 30s subunit of prokaryotic ribosomes causing misleading the protein synthesis which leads to accumulate nonfunctional proteins in bacteria (François et al. 2005; Lynch and Puglisi 2001; Rando 2001). Different classes of aminoglycosides are given as below in Table 10.3.

10.6.1 Absorption and Bioavailability

As discussed earlier, aminoglycosides are available mostly in parenteral dosage form. Streptomycin was studied for its pharmacokinetic profile and showed 88% bioavailability after i.m. administration (Zhu et al. 2001). Complete bioavailability occurs while administered through i.m. and subcutaneous (SC) routes in gouts (Uppal et al. 1997). Dibekacin, tobramycin, kanamycin, gentamicin, and isepamicin were studied for their pharmacokinetic profile and they all showed complete absorption and 100% bioavailability after intramuscular injection (Driessen et al. 1978; Radwanski et al. 1997; Segal et al. 1988; Verbist et al. 1982). Netilmicin and sisomicin also have bioavailability greater than 90% after intramuscular administration (Chung et al. 1981; Humbert et al. 1978). Framycetin and Neomycin are not absorbed through GIT and are mostly used topically (Breen et al. 1972). Paromomycin shows very poor oral absorption (Bissuel et al. 1994; Hens et al. 2014). However, like other

Table 10.3 Classification of aminoglycosides

Classes of aminoglycosides	Members
Streptomycin	Streptomycin
Kanamycin	Amikacin
	Arbekacin
	Tobramycin
	Dibekacin
	Kanamycin
Gentamicin	Gentamicin
	Sisomicin
	Isepamicin
	Netilmicin
Neomycin	Framycetin
	Paromomycin
	Neomycin
Spectinomycin	Spectinomycin

aminoglycosides, its absorption is nearly 100% from IM injection (Kip et al. 2018). Bioavailability of spectinomycin after i.m., sc and oral administration was 136.1% and 128.8%, respectively. The oral bioavailability was 11.8% and 26.4% after 50 and 100 mg/kg body weight, respectively. Previous studies showed that tobramycin exhibit poor oral absorption due to the increased efflux via the P-gp efflux pump. Encapsulating tobramycin in solid lipid nanoparticles (SLNs) inhibits the efflux of the drug, thus increasing its absorption and bioavailability (Bargoni et al. 2001).

10.6.2 Adverse Effects and Toxicity

A common and frequent potential of causing nephrotoxicity exist among all the aminoglycosides but neomycin is the most and streptomycin is the least toxic drug (Denamur et al. 2008; Sandoval et al. 2006). Various drugs like vancomycin and teicoplanin can increase nephrotoxic risk of aminoglycosides (Fabre et al. 1976). Clinical trial data show that many days of treatment is needed for aminoglycosides to cause nephrotoxicity (Buchholtz et al. 2009). Aminoglycosides can cause vestibular and cochlear damage showed by in-vivo studies (Xie et al. 2011). Hearing loss and dizziness can be caused by streptomycin (Hinshaw and Feldman 1945). Aminoglycosides can cause neuromuscular blockade in very rare cases but is a lethal toxic effect of this group of drugs. This toxic effect was determined through various experiments for streptomycin, neomycin, kanamycin, gentamicin, tobramycin, netilmicin, and amikacin (Nordström et al. 1990; Pittinger and Adamson 1972). Isepamicin can induce oto-toxicity, nephrotoxicity, and vestibulotoxicity. However, animal and clinical studies show that isepamicin is one of the less toxic aminoglycosides (Tod et al. 2000).

10.7 Tetracyclines

Chlortetracycline, the first tetracycline, was discovered by Benjamin M. Duggar in Duggar 1948 and since the time of discovery this class remained an important part of antibiotics (Duggar 1948). They have wide range of activity and are broad-spectrum bacteriostatic drugs. They cause antibacterial effect by inhibiting protein synthesis of bacteria by binding to the 30S bacterial ribosomal subunit reversibly (Craven et al. 1969). Classification of tetracycline are given in Table 10.4.

10.7.1 Absorption and Bioavailability

Tetracyclines are primarily absorbed in the GIT parts, stomach, and proximal small bowel. Oxytetracycline is the most least absorbtion (60%) after oral administration (Singh et al. 2005). Tetracycline has bioavailability in the range of 77–88% (Wood

Table 10.4 Classification of tetracycline (Fuoco 2012)

Classes of tetracyclines	Members
First generation	Tetracycline, chlortetracycline, oxytetracycline, demeclocycline
Second generation	Doxycycline, lymecycline, meclocycline, methacycline, minocycline, rolitetracycline
Third generation	Tigecycline

et al. 1975). Demeclocycline is 66% absorbed when administered orally while chlortetracycline has 30% absorption through GIT (Agwuh and MacGowan 2006). Doxycycline and minocycline are almost completely absorbed with a bioavailability of more than 80% and with an average of 95% (Chopra 2011; Saivin and Houin 1988). Tigecycline has limited oral absorption and is administered through IV route (Agwuh and MacGowan 2006). Multivalent cations like calcium, iron, aluminum, and magnesium decrease absorption of tetracyclines by 50–90% due to chelate formation.

10.7.2 Adverse Effects and Toxicity

Generally as class tetracyclines are well tolerated but a French review showed that minocycline has more serious and frequent adverse effects compared to other members of the class (Smith and Leyden 2005). This class of antibiotics affects GIT and cause diarrhea, nausea, vomiting, epigastric pain, and heart burn. These effects are more common with doxycycline (Hey et al. 1982; Winckler 1981). The hypersensitivity reactions (facial edema, anaphylaxis, urticaria) are rarely occurred due to tetracyclines but more frequent with minocycline. Tetracycline users can face photosensitive rashes when exposed to sun (Smith and Leyden 2005). This reaction is caused by drug accumulation in the skin and can associate with papules, oncholysis, vesiculations, and edema (Bethell 1977). Tetracyclines adverse reaction of hyperpigmentation is also well reported and commonly caused by minocycline (Smith and Leyden 2005). As a result of chelation with calcium, the tetracyclines deposit in bones and teeth and as a result teeth can become stained (Demers et al. 1968; Moffitt et al. 1974). Doxycycline has a lower bones and teeth deposition potential compared to other tetracyclines (Chiu et al. 1998). In early life when children receive tetracyclines the deposition in deciduous teeth occurs. This deposition can also occur in developing fetus if the mother takes tetracyclines during late pregnancy (Madison 1963). Tetracyclines deposition can also decrease the growth of bones in infants (Cohlan 1963). These drugs can also cause fatal hepatotoxicity and is more frequent with tetracycline intravenous administration in high dose (Schultz et al. 1963). Doxycycline appeared to be safe regarding liver toxicity (Vial et al. 1997). Other toxic effect is nephrotoxicity. Tetracyclines can exaggerate renal impairment by inhibiting protein synthesis and cause hyperphosphatemia, azote-

mia, and acidosis (Shils 1963). Minocycline also affects central nervous system by causing reversible vertigo, dizziness, lack of concentration, and tinnitus. Women are more exposed to the vestibular adverse effects compared to men (Fanning et al. 1977). Tetracycline, minocycline, and doxycycline are also noticed to cause idiopathic intracranial hypertension (Lochhead and Elston 2003).

10.8 Chloramphenicol

Chloramphenicol was isolated from soil organism *Streptomyces venezuelae* and since 1949 it is in clinical use as a broad-spectrum antibiotic (Ehrlich et al. 1947). It remained and inexpensive drug that is broad spectrum and can target many gram-positive, gram-negative, anaerobic, and atypical organisms but due to aplastic anemia risk this drug is no more drug of choice for any infection (Rich et al. 1950). Chloramphenicol is a protein synthesis inhibitor and binds to the 50S subunit of the bacterial ribosome (Green et al. 1975). Bioavailability of chloramphenicol is approximately 80% when administered in capsule form and is rapidly absorbed in intestinal tract (Ambrose 1984; Pestka 1971; Smith and Weber 1983).

10.8.1 Adverse Effects and Toxicity

The most significant toxic effect of this drug is its toxicity towards bone marrow. Chloramphenical suppresses the bone marrow reversibly which is due to its direct pharmacological effect. As a result, any combination of reticulocytopenia, leukemia, anemia, or thrombocytopenia may occur (Manyan et al. 1972; Yunis 1973). Chloramphenicol can also cause hemolytic anemia with glucose-6-phosphate dehydrogenase deficiency (Mccaffrey et al. 1971). The other hemolytic toxicity is the uncommon but mostly fatal aplastic anemia. Due to this toxic effect chloramphenicol use is now very limited (Balbi 2004). A circulatory collapse called gray baby syndrome occur in newborn and premature infants which is associated to high concentration of chloramphenicol (Sutherland 1959). Gray baby syndrome is characterized by abdominal distension, vomiting, cyanosis, flaccidity, gray color, circulatory collapse, and ultimately death (Suarez and Ow 1992; Werner et al. 1985). Prolong therapy with chloramphenicol can cause optic atrophy and blindness. These symptoms are mostly reversible but blindness can be permanent (Fung et al. 2011; Woolf 1965). It can cause Jarish-Herxheimer reactions and can induce bleeding if used orally for prolonged duration (Cahill 1962). Chloramphenicol can disturb immunity development during active immunization (Ambrose and Coons 1963).

10.9 Macrolides

Macrolides antibiotics class has various members like erythromycin, clarithromycin, and azithromycin, and erythromycin is the first member of this class of antibiotics and was derived in 1952 from a strain of *Saccharopolyspora erythraea.* They cause their antibacterial effect by binding to 50S ribosomal subunit and so inhibiting RNA-dependent protein synthesis (Edelstein 2004; Leclercq and Courvalin 2002).

10.9.1 Absorption and Bioavailability

The absolute bioavailability of erythromycin was determined through in vivo experiment which was 32 ± 7% for enteric coated 250 mg capsule and for the 250 mg duodenal solution was 43 ± 14% (Somogyi et al. 1995). Clarithromycin has good absorption potential after oral administration and has almost 50% bioavailability (Piscitelli et al. 1992). Azithromycine has 37% bioavailability after oral administration in 500 mg single dose (Schentag and Ballow 1991). Azithromycin has low bioavailability owing to its poor solubility. Chen Dong Hou et al. prepared azithromycin nanosuspension to increase its solubility that will further enhance the bioavailability of the drug. Results of in vitro release and solubility studies showed an obvious enhancement in the solubility and dissolution rate as compared to the raw drug. Similarly nanoparticles of azithromycin were prepared solvent/antisolvent precipitation method to achieve an increase in the solubility and oral bioavailability of drug due to reduction in particle size that offers larger surface area. The particle size ranged from 200 to 400 nm. These nanoparticles of azithromycin offered a 2.93-fold increase in the dissolution as compared to the raw drug (Hou et al. 2012; Pouretedal 2014).

SLNs loaded with clarithromycin were prepared to increase its oral bioavailability. Results of pharmacokinetic studies in rats revealed a 2.3-fold increase in $C_{max,}$ twofold increase in $T_{max,}$ 1.4-fold increase in mean residence time, and fivefold enhancement in the relative oral bioavailability of clarithromycin on oral administration of clarithromycin loaded SLNs (Sharma et al. 2016).

10.9.2 Adverse Effects and Toxicity

Except for *C. difficile* colitis and ventricular arrhythmias the other unwanted events caused by erythromycin are not life threatening. Erythromycin causes irritative reactions including abdominal cramps, diarrhea, nausea, vomiting, and gas more commonly (Ellsworth et al. 1990). High concentration given through IV route can cause thrombophlebitis which can be decreased by its dilution. Allergic reactions include fever, skin rash, and eosinophilia. Cholestatic hepatitis can occur with the use of erythromycin rarely (Inman and Rawson 1983). Reversible hepatotoxicity

including jaundice has occurred with the use of erythromycin stearate salt and also with the ethylsuccinate ester of erythromycin (Carson et al. 1993). When used in high concentration through IV route, erythromycin lactobionate or oral dose of erythromycin can cause transient hearing loss (Eckman et al. 1975; Karmody and Weinstein 1977). Other adverse effects include polymorphic ventricular tachycardia, superinfection, and infantile hypertrophic pyloric stenosis (Cooper et al. 2002; Katapadi et al. 1997; Ray et al. 2004; SanFilippo 1976).

At usual doses clarithromycin and azithromycin have very low adverse effects potential. The most commonly occurring adverse events are GIT disturbances like nausea, vomiting, diarrhea, and abdominal pain (Bahal and Nahata 1992; Piscitelli et al. 1992). In few patients acute phychosis or "mania" has been reported taking clarithromycin (Katapadi et al. 1997). Clarithromycin can cause teratogenic effects and is discouraged to take in pregnancy (Turner and Aziz 2002). Hepatic toxicity, dizziness, tinnitus, and reversible hearing loss are the some events reported with the use of azithromycin (Kolkman et al. 2002; Longo et al. 1997; Wallace Jr et al. 1993). Torsades de pointes (Polymorphic tachycardia) cases also increased when risk factors like increasing age, concomitant drug use (like cisapride), and female gender occur (Shaffer et al. 2002).

10.10 Glycopeptides

10.10.1 Vancomycin

Vancomycin was isolated from *Amycolatopsis orientalis* and is the first glycopeptides antibiotic developed in the mid-1950s. The glycopeptides inhibit the late stages of cell wall synthesis in multiplying bacteria (Fraser et al. 2005; Lipsky et al. 1999). Vancomycin is not absorbed orally and is mostly administered intravenously (Shively and Thompson 1995). Clinical uses of vancomycin showed sever ototoxicity in six patients using 1–2 g daily dose. After measuring the vancomycin level it showed 80 and 100 μg/mL concentration which induced ototoxicity but this adverse effect was later on studied and was concluded to be very rare adverse effect of vancomycin (Geeaci et al. 1958). Since the start of vancomycin clinical use, nephrotoxicity has been associated which was thought to be related to impurities related to the early preparations of vancomycin (Elyasi et al. 2012). Some factors are like high dose (≥4 g/day), weight of patient (≥101.4 kg), critically ill patients, and decreased creatinine clearance (<86.6 mL/min) and the most common side effects with vancomycin are infusion-related reactions. Rapidly developing pruritus or erythematous rash affects face, neck, upper trunk, and head and can be associated with hypotension and angioedema. These reactions are commonly known as red neck of red man syndrome reported during vancomycin infusion (Myers et al. 2012). Neutropenia can also be observed due to long-term vancomycin administration in frequency up

to 13%. Thrombocytopenia is very rarely reported with the use of vancomycin. Cases of more severe reaction than maculopapular or erythematous rash such as toxic epidermal necrolysis, Steven-Johnson syndrome, and linear IgA bullous dermatosis have also been reported (Blumenthal et al. 2012; Von Drygalski et al. 2007).

10.11 Sulfonamides

Sulfonamides are clinically important antimicrobials derived from sulfanilamide, which is structurally similar to para-aminobenzoic acid (PABA), required factor for the synthesis of folic acid. Sulfonamides are bacteriostatic and inhibit bacterial growth by hindering with the folic acid synthesis of microorganisms (Eyster 1943). Sulfonamides are classified in Table 10.5 given below.

10.11.1 Absorption and Bioavailability

Most of the short-acting and medium-acting sulfonamides are absorbed almost completely and rapidly from the stomach and small intestine. Sulfisoxazole is completely absorbed after intramuscular and oral administration and bioavailability ranges more than 97% (Kaplan et al. 1972; Suber et al. 1981). Mostly these sulfonamides are administered in combination with trimethoprim-like drugs. Sulfadiazine showed bioavailability in animal models in range of 80% (Abu-Basha et al. 2009; Baert et al. 2003). The absolute bioavailability of sulfaguanidine was studied in animal model which was 56% in neonates and is many times lower in adults (Mizuno et al. 1986).

Table 10.5 Classification of sulfonamides (Actor et al. 2000; Smith and Powell 2000)

Classes of sulfonamides	Members
Short acting or medium acting sulfonamides	Sulfisoxazole
	Sulfadiazine
	Sulfamethoxazole
Long acting sulfonamides	Sulfadoxine
Sulfonamides limited to GI tract	Sulfaguanidine
	Sulfasuxidine
	Sulfathalidine
Topical sulfonamides	Sulfacetamide
	Mafenide

10.11.2 Adverse Effects and Toxicity

Sulfonamides can cause diarrhea, nausea, vomiting, fever, rash, depression, jaundice, headache, hepatic necrosis, and drug-induced lupus (Price and Venables 1995). Excessively high dose of sulfadiazine is associated with tubular deposits of sulfonamide crystals and crystalluria. More toxic effects of sulfonamides may include aplastic anemia, acute hemolytic anemia, agranulocytosis, leukemia, and thrombocytopenia. Sulfonamides compete for bilirubin-binding sites on plasma albumin if administered during the last month of pregnancy and may cause increased unconjugated bilirubin in fetal blood, which increase the risk of kernicterus. Sulfonamides administered through any route can significantly increase hypersensitivity reactions. Erythema multiforme, erythema nodosum, vasculitis, fixed drug eruption, and anaphylaxis are the most important reactions (Wolkenstein et al. 1995).

10.12 Quinolones

Nalidixic acid is the first member of this class of antimicrobials which was identified in 1962 by Lesher and associates as by-product of chloroquine synthesis. Different quinolones like sparfloxacin, travofloxacin, temafloxacin, and gatifloxacin were identified and due to their severe toxicities they were removed from clinical use. In the 1970s, oxolinic acid as well as cinoxacin were also developed before identification of more potent and wide spectrum fluorine and piperazinyl-substituted derivatives. With good oral absorption, wide spectrum of activity, and good safety profile these newer fluoroquinolones resulted in extensive clinical use. Peprazinyl include norfloxacin, enoxacin, and ciprofloxacin, methyl-piperazinyl include perfloxacin, ofloxacin, lomefloxacin, fleroxacin, temafloxacin, levofloxacin, grepafloxacin, and gatifloxacin. Sparfloxacin is a dimethylpiperazinyl (Domagala 1994). The quinolones cause rapid bacterial cell death by inhibiting bacterial DNA synthesis (Aldred et al. 2014). Norfloxacin upon oral administration exhibits low bioavailability (40%) and poor permeability (Gips and Soback 1996). Zhao dong et al. prepared norfloxacin SLNs with the objective to improve its bioavailability. Pharmacokinetic studies in rats showed sustained release of norfloxacin while the relative bioavailability was enhanced by 12-fold without any cytotoxicity (Dong et al. 2011).

10.12.1 Absorption and Bioavailability

Most of the drugs in this class are well absorbed through GIT approaching from 50% to 100%. Peak concentration in serum is mostly attained in 1–3 h after administration. Their absorption is not affected by food or achlorhydria but food can delay

the time to achieve peak serum concentration (Sörgel and Kinzig 1993; Staib et al. 1989). Norfloxacin, ciprofloxacin, and gemifloxacin have 50%, 70%, and 71% bioavailability, respectively, while pefloxacin, ofloxacin, and levofloxcin have bioavailability more than 95%. Moxifloxacin has bioavailability in range of 86–100% (Bennett et al. 2014).

10.12.2 Adverse Effects and Toxicity

Sulfonamides can cause gastrointestinal adverse effects more frequently like nausea, vomiting, anorexia, and abdominal discomfort and less frequently can cause diarrhea (Kuhlmann et al. 2012; Owens Jr and Ambrose 2005). The next common adverse effects are of central nervous system like dizziness, headache, insomnia, and mood alteration. Sulfonamides can cause delirium, hallucinations, psychosis, and seizures (Tomé and Filipe 2011). Sulfonamides caused allergic and skin reactions in 0.4–2.8% of patients during clinical trials (Ball et al. 2004). Drug fever angioedema, serum sickness like syndromes, urticaria, vasculitis reactions are uncommon. Quinolones can inhibit potassium channels and so can delay repolarization in cardiac tissue and so can prolong QT interval on the ECG (Finch et al. 2002). Eosinophilia and leucopenia mostly occur in below than 1% of users (Davidson et al. 2002). Hypoglycemic events are also reported in sulfonamides users (Abramowicz 2003).

10.13 Antimycobacterial Agents

Antimycobacterial agents are commonly classified as first-line drugs with acceptable toxicity and better efficacy, and second-line drugs with greater toxicity and less efficacy. First-line agents include isoniazid (INH), ethambutol, rifampin, and pyrazinamide (PZA), while streptomycin, linezolid, quinolones, amikacin, capreomycin, para-aminosalicylic acid, kanamycin, and ethionamide are second-line drugs (Bennett et al. 2014; Blumberg et al. 2003; Iseman et al. 1993).

10.13.1 Absorption and Bioavailability

Isoniazid is completely and rapidly absorbed after oral and intramuscular administration (Weber and Hein 1979). Rifampicin oral bioavailability of single dose is about 93% which can be decreased to 68% after 3 weeks of chronic administration (Loos et al. 1985). Isoniazid due to its short plasma half-life (1–4 h) requires higher doses repeated to maintain the plasma drug levels. Bhandari et al. incorporated isoniazid in SLNs and its oral pharmacokinetics were evaluated in rat model.

The results showed that the relative bioavailability in plasma was enhanced by sixfold while a fourfold increase was found in brain as compared to the free drug (Bhandari and Kaur 2013).

10.13.2 Adverse Effects and Toxicity

The major and severe toxic effect of INH and rifampin is hepatitis while the most feared toxicity is fulminant hepatic failure (Mitchell et al. 1976). INH can cause neurotoxic effect, hypersensitivity reactions, metabolic acidosis, seizures, hyperglycemia, and coma. Rifampin can cause hypersensitivity with flushing, pruritus, fever, cutaneous vasculitis, thrombocytopenia eosinophilia, and hemolysis. Gastrointestinal disturbance is very frequent with the use of rifampin (Bennett et al. 2014). The most frequently occurring adverse effects of PZA are nausea and vomiting, and in nearly 15% users it may cause hepatotoxicity (Zierski and Bek 1980). Various adverse effects of PZA are rhabdomyolysis with myoglobinuric renal malfunctioning, interstitial nephritis, and photosensitivity (Namba et al. 1991; Sanwikarja et al. 1989; Zierski and Bek 1980). Neuropathy is the major toxic effect of ethambutol causing peripheral neuropathy (Chatterjee et al. 1986). Hyperuricemia, hypersensitivity, and gastrointestinal intolerance can occur infrequently with ethambutol.

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