ejpmr, 2018,5(11), 222-228

SJIF Impact Factor 4.897

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

ANTIMICROBIAL TOXICITIES: COMMON SIDE EFFECTS & ALLERGIC REACTIONS

Rajandeep Kaur* and Gurpreet Singh

Adesh Institute of Pharmacy and Biomedical Sciences, Adesh University, Bathinda-151001, Punjab.

***Corresponding Author: Rajandeep Kaur**

Adesh Institute of Pharmacy and Biomedical Sciences, Adesh University, Bathinda-151001, Punjab.

Article Received on 12/09/2018 **Article Revised on 02/10/2018** **Article Accepted on 22/10/2018**

ABSTRACT

The overall incidence of ADRs to antimicrobials increases day by day. Generalized adverse events are common to most antibiotics (e.g., gastrointestinal distress with any oral antibacterial drug), but certain antibiotics are associated with specific effects. Some adverse events are mild, e.g., yellowing of the teeth for tetracyclines. More serious side effects include photosensitivity and anaphylactic reactions observed with many agents, ototoxicity following aminoglycoside therapy, chondrotoxicity and retinopathy with fluoroquinolones. Penicillins are known to cause a wide spectrum of neurotoxic manifestations including encephalopathy, behavioural changes, myoclonus, seizures as well as NCSE. Populations at risk of neurotoxicity associated with various groups of antibiotics include those with extremes of age, critical illness, renal dysfunction and prior neurological disease. Knowledge of neurotoxic effects is essential for clinicians in order to avoid this preventable complication. Knowledge of selection of an appropriate antibiotic, pharmacokinetics and dosage adjustments in those at risk may aid in the prevention of toxicity associated with these drugs.

KEYWORDS: ADRs, Antibiotic toxicity, Neurotoxicity.

INTRODUCTION

The principle of antimicrobial therapy is that of selective toxicity in that one hopes to employ an agent which will be toxic to the organism causing the infection without damaging the cells of the host. To translate this into biochemical terms, it means that one is launching an attack against some metabolic process within the bacteria which either is not present in the host cells or is segregated within some organelle inside the cell (e.g. mitochondria) in such a way that the antimicrobial agent does not gain access to it. The fact that various bacteria have different metabolic processes, biochemically speaking, determines the variation in response from one species to another and is the factor which defines what we call the spectrum of any antibiotic. Resistance strains can develop in a species to bacterium which is usually sensitive to a given antibiotic, indicating that a degree of variability in this metabolism is possible without necessarily interfering with the ability of the organism to grow and to continue to be pathogenic.[1]

The desired activity of an antibiotic is to kill or prevent the growth of offending pathogenic bacteria, and yet these drugs may impact the host in an injurious manner. Generalized adverse events are common to most antibiotics (e.g., gastrointestinal distress with any oral antibacterial drug), but certain antibiotics are associated with specific effects. Some adverse events are mild, e.g., yellowing of the teeth for tetracyclines[2,3], increased intestinal peristalsis related to erythromycin therapy, and reversible orange discoloration of skin and body fluids as observed with rifampin treatment Altered drug metabolism is a common side effect that, in the absence of co-drug therapy, could also be considered mild. More serious side effects include photosensitivity and anaphylactic reactions observed with many agents, ototoxicity following aminoglycoside therapy, chondrotoxicity and retinopathy with fluoroquinolones, neuropathies associated with metronidazole and linezolid and lactic acidosis and serotonin syndrome attributed to linezolid. Other consequences can be severe or even devastating such as: the dermonecrotic Stevens-Johnson syndrome associated with sulfonamide antimicrobial agents nephrotoxicity related to aminoglycosides[4,5]; aplastic anemia due to chloramphenicol; hepatitis caused by many drugs including isoniazid[6,7]; neuromuscular blockade related to aminoglycoside[8,9] or lincosamide therapy; myopathies due to ionophores[10]; and neoplasia related to metronidazole.[11] All of these side effects are likely to have unique etiologies given the diverse array of events, the unrelated pharmacodynamic properties of certain antimicrobial classes, and the unique chemical nature of these agents. However, as new evidence is unveiled, mitochondrial alterations form the basis for a divergent array of adverse effects observed in association with chemically distinct drugs. Mitochondrial components (e.g., ribosomes, gyrases, and topoisomerases) share little homology with prokaryotic

cohorts and thus are less likely to be inhibited by antibiotics than are prokaryotic ribosomes, gyrases, 4046 aac.asm.org and topoisomerases.[12,13] However, it appears that some inhibitors of prokaryotic ribosomes, gyrases, and topoisomerases can elicit unexpected effects on mitochondria that lead to side effects of these antibiotics. Inhibition of protein synthesis, the major impetus for the antibacterial effects of rRNA inhibitors[14], appears to be relevant to many of the mitochondrion-based toxicity.

MIC & MBC Minimal inhibitory concentration and the minimal bactericidal concentration Despite acknowledged exceptions with certain drug–bacteria combinations, antibacterial drugs are usually divided into two groups: those that are primarily bacteriostatic (i.e., inhibit growth of the organism) and those that are primarily bactericidal (i.e., kill the organism). Bacteriostatic drugs require the aid of host defenses to clear tissues of the infecting microorganism; if host defenses are systematically inadequate (eg, agranulocytosis) or host defenses are impaired locally at the site of infection (e.g., the cardiac vegetation in left sided endocarditic and cerebrospinal fluid in meningitis), the residual pathogen resumes growth after stopping the bacteriostatic drug and the infection relapses. Bacterial infection in these circumstances requires use of bactericidal drugs. Bacteriostatic drugs are sufficient for most other infections.[15]

Antimicrobial activity of drugs is usually assessed by determination of the minimal inhibitory concentration (MIC) and the minimal bactericidal concentration (MBC) of the drug in vitro after overnight aerobic incubation in a protein-free liquid medium at pH 7.2. These in vitro conditions are likely very different from those expected at the site of infection, where the milieu is frequently acidic and anaerobic, and tissue protein may bind a variable amount of the drug. The MIC and MBC, which are determined at a fixed point in time after exposure to drug concentrations that remain constant throughout an overnight incubation period, do not provide information on the time course of the antimicrobial effect of fluctuating levels that are present in a patient treated with the drug. In addition, the MIC and MBC are measured against a standard bacterial inoculum (about 105 colony-forming units [CFU] per milliliter) that does not necessarily correspond to bacterial densities at site of infection (108–10 CFU per gram of tissue or pus).[15]

Epidemiology

The overall incidence of ADRs to antimicrobials in study was 6.12%. A study done in 1991 by Audi et al observed that the incidence of ADRs to antimicrobials was 4%.6 Because of differences in study design, data collection, and definition of ADRs, the diversity of drugs used, and the heterogeneity of the investigated populations, the reported incidence of ADRs varies greatly in the literature. The present study showed an incidence of 6.12% for antimicrobial-related ADRs in hospitalized patients treated with antimicrobials.[16]

In the analysis of antimicrobial-related ADRs, it was found that most episodes were type A (87.05%). Surprisingly, in a study done by Hsin Yun Sun et al in 2008 the incidence of type B ADRs was 93.1%.12 This observation differs from the traditional concept that type A reactions are more common than type B reactions. In this study majority of the ADRs episodes 106(54.9%) were judged as probable, 44(22.8%) as possible, and 43(22.3%) as definite. This assessment of causality was based on Naranjo algorithm. There is no formula for an absolute and safe outcome since this analysis always involves personal evaluation and allows for different interpretations.[17]

1. General toxicities cum adverse reactions of antimicrobial agents

1.1 Dizziness

The troubling sensation of spinning, unsteadiness, or light-headedness, and vertigo, a false sensation of movement of the body or the environment, can be caused by malfunction of the vestibular labyrinth (inner ear) secondary to certain antibiotics (e.g., aminoglycosides). Other symptoms and signs of vestibular damage include nausea, vomiting, nystagmus, and ataxia. These disturbances can be especially problematic for an elderly individual in whom balance and stability may already be challenging secondary to vision problems, neuropathy, or arthritis.[18,19]

1.2 Renal toxicity and vestibular and auditory toxicity

Risk factors for renal, vestibular, and auditory toxicity include older age; frequent or very high dosages; very high drug blood levels; long duration of therapy (e.g., >3 days); preexisting renal disorder; and concomitant administration of amphotericin B, cyclosporine, or vancomycin. The coadministration of contrast agents increases the risk for renal toxicity, while coadministration of loop diuretics (e.g. bumetanide, ethacrynic acid, furosemide, torsemide) and preexisting hearing problems increase the risk for auditory toxicity.[19]

1.3 Antibiotic-associated pseudomembranous colitis

Clostridium difficile–associated diarrhea has a disease spectrum ranging from mild diarrhea with little or no inflammation to severe colitis often associated with pseudomembranes, which are adherent to necrotic colonic epithelium (pseudomembranous colitis). C difficile occurs most frequently in geriatric patients in hospitals and nursing homes, potentially due to environmental contamination transferred on the hands of facility staff. Pseudomembranous colitis may also be caused by an overgrowth of underlying C difficile; overgrowth is referred to as a superinfection by drug-resistant microorganisms and is considered a complication of antibiotic therapy. Of note, there is a

strong association between fluoroquinolone use and C difficile–associated diarrhea and pseudomembranous colitis, especially due to the hypervirulent C difficile ribotype with outbreaks currently reported in the U.S., Canada, and Europe. Antibiotic-associated diarrhea with no evidence of C difficile infection occurs in a smaller number of patients.[20] While virtually all antibiotics have been implicated, the most Antibiotic Therapy: Adverse Effects and Dosing Considerations common are clindamycin, cephalosporins, ampicillin or amoxicillin, and, most recently, fluoroquinolones; the less common are other penicillins and erythromycin.

1.4 Antimicrobial agents induced hyperkalemia and blood dyscrasias

TMP can decrease renal tubular potassium excretion, leading to hyperkalemia. Hyperkalemia can be problematic in patients who have renal impairment or cardiac disease and who may be receiving drugs that increase potassium, such as ACE inhibitors and potassium-sparing diuretics.[21] Folic acid deficiency is one of the most common vitamin deficiencies in the U.S.; poor eating habits make this deficiency more common in the elderly. Folic acid deficiency may lead to megaloblastic anemia.[22]

1.5 Seizures

Fluoroquinolones are associated with central nervous system (CNS) stimulatory effects; the most prominent CNS effects are headache, dizziness, and lightheadedness. While seizures are rare, these agents should be used with caution or avoided in patients with CNS disorders, such as epilepsy. Ciprofloxacin interferes with theophylline metabolism and may evoke seizures.[23]

1.6 Doxycycline-related esophageal ulcerations and strictures

While the esophagus is not easily damaged, the esophageal lining may incur erosion from gradual insult over months to years secondary to gastroesophageal reflux and many drugs, including antibiotics (e.g., doxycycline, clindamycin).[18] Since seniors are more likely to have comorbidities involving multiple medication therapy, esophageal damage from medications (e.g., aspirin, bisphosphonates, nonsteroidal anti-inflammatory drugs [NSAIDs]) is more common among these individuals, and the concomitant administration of a potentially offending antibiotic should be considered and avoided if possible. A doxycycline capsule or tablet should be administered orally with at least of water, and the patient should sit up for at least 30 minutes after taking it to reduce the risk of esophageal irritation and ulceration.[24]

1.7 Acute liver injury secondary to prolonged therapy with amoxicillin plus clavulanic acid

Amoxicillin plus clavulanic acid is considered one of the drugs of choice in the outpatient treatment of community-acquired pneumonia in the elderly. When prolonged therapy is warranted, periodic monitoring of renal, hepatic, and hematologic function is recommended.[24]

1.8 Superinfections

Resulting from a difficult-to-treat overgrowth of opportunistic organisms (e.g., fungi or resistant bacteria), usually occur with broad-spectrum antimicrobials, prolonged use, or combinations of agents that alter the normal microbial flora of the upper respiratory, intestinal, and genitourinary tracts.[23] An example is C difficile–associated diarrhea and pseudomembranous colitis secondary to fluoroquinolone use.

1.9 Hypersensitivity

Adverse reactions to an antibiotic (e.g., penicillin) or its metabolic products can frequently occur, causing serious problems ranging from urticaria (hives) to anaphylactic shock. In the case of a delayed dermatologic reaction to penicillin (i.e., rash), the patient can generally receive a cephalosporin. Patients with a history of anaphylaxis to penicillin, however, should not be given any beta-lactam again (including for skin testing), except in a very rare situation when no alternative can be found. In this case, special precautions and desensitization regimens must be used. Alternatives to the cephalosporins include aztreonam, fluoroquinolones, sulfonamide antibiotics, or vancomycin, depending on the type of coverage required.[25]

1.10 Direct toxicity

Results from high serum levels of certain antibiotics that directly affect cellular processes in the host. An example of the result of direct toxicity is ototoxicity secondary to aminoglycosides.[23]

2. Aminoglycosides and ototoxicity

Aminoglycosides are irreversible inhibitors of the 30S, and less commonly the 50s, bacterial ribosomal subunit, thereby serving as inhibitors of protein synthesis. Most aminoglycosides are bactericidal, which is likely related to toxic peptides synthesized by the 30S subunit after the aminoglycoside-ribosome interaction. The nature of this interaction is potentially related to the electrochemical polarity of these drugs. Aminoglycosides are so polar that oral bioavailability is very poor, resulting in limited drug passage through lipid membranes in the gut. This Polarity may contribute to a covalent interaction with the 30S subunit. There has long been an association between aminoglycosides (streptomycin, kanamycin, neomycin, gentamicin, tobramycin, and amikacin) and ototoxic side effects in 20% of human patients receiving any of these drugs.[26,27] The main site of action for the aminoglycoside ototoxicity is either the cochlea or the vestibulum, resulting in hear in glossodoris equilibrium, respectively. There is an increase in toxicity when more than one ototoxic drug is used in combination with another. Premature infants and children may be more susceptible to ototoxicity as the inner ear develops.

3. Chloramphenicol and aplastic anemia

Chloramphenicol limits bacterial growth by binding to the 50S ribosomal subunit and inhibitin G-protein synthesis in prokaryotes. Unfortunately, ribosomal similarities between bacteria and mitochondria may provide the basis for mitochondrial sensitivity to chloramphenicol-mediated inhibition of protein synthesis.[28] Mitochondrial DNA codes for 13 polypeptides involved in metabolic activities, and none of these genes are expressed from the nucleus. Expression of the transfer it in receptor seems to be the most relevant to the chloramphenicol-mitochondrion interaction. Specifically, chloramphenicol diminishes mitochondria-on-basedtransferr it in receptor expression, resulting inferring depletion in mitochondria. The Resulting imbalance between organic and inorganic iron coincides with an excess of non ferritin iron in the mitochondria of patients receiving chloramphenicol.[29]

Aplastic anemia has been associated with chloramphenicol therapy for many years, and this finding is the basis for the banon chloramphenicol use in food-producing animals.

The lipoidal nature of chloramphenicol results in a large volume of distribution that includes many "privileged" sites such as the brain and the bone marrow. Chloramphenicol can readily cross most cell membranes, and yet the side effects are presented in the marrow. Maturing hematopoietic cells are completely dependent upon transfer it in for iron intake, and these cells are exquisitely sensitive to hypo ferritinization. Consequently, ferritin free mitochondria are metabolically dysfunctional, and affected erythrocytes manifest this phenomenon via hypochromic-microcytic anemia during the dose-dependent anemia associated with chloramphenicol.[30]

4. Cephalosporins and neurotoxicity

Cephalosporins Neurotoxicity has been reported with first generation cephalosporins such as cefazolin, second generation such as cefuroxime, third generation such as ceftazidime and fourth generation such as cefepime and can range from encephalopathy to non-convulsive status epileptics. Clinical presentations of cephalosporin-associated neurotoxicity include tardive seizures, encephalopathy, myoclonus, truncal-asterixis, seizures, non-convulsive status epilepticus (NCSE) and coma.[31]

Other postulated mechanisms for cephalosporin neurotoxicity also include induction of endotoxins and, possibly, glutaminergic mechanisms. Laboratory studies also show that cephalosporins with high affinity for GABA-A receptors and those with high penetrance through the blood-brain barrier are more neurotoxic.[32]

5. Penicillins and neurotoxicity

Penicillins are known to cause a wide spectrum of neurotoxic manifestations including encephalopathy, behavioural changes, myoclonus, seizures as well as NCSE. A history of CNS disease has been described as a risk factor for encephalopathy associated with beta-lactam use.[31] Piperacillin has been implicated in cases of tardive seizures. In one report, two patients treated with piperacillin for pneumonia during a course of electroconvulsive therapy (ECT) for schizophrenia, developed recurrent seizures over 2 day period approximately 8 days after the third ECT session. Each of these lasted 15 to 40s and occurred intermittently 5 to 15 times daily. Interictal EEG was without any focal abnormality.[33]

Though reportedly less neurotoxic in comparison with benzylpenicillin, piperacillin has been implicated in an encephalopathy characterized by dysarthria, tremor, behavioural changes, progressive confusion, and nally several generalized tonic-clonic seizures in patients with end-stage renal disease.[34,35]

Ampicillin-induced neurotoxicity has also been described in the literature in very low birth weight neonates. This particular population is thought to be at risk for neurotoxic effects secondary to elevated drug serum concentrations which translate to elevated CSF concentrations (due to immature transport mechanisms and renal immaturity), as well as increased permeability of the blood-brain barrier (possibly due to meningeal inflammation, immaturity of the cerebrovascular system or underlying CNS disease). Detecting seizures in infants' remains problematic as more than 50% of neonates are estimated to have seizures without any obvious clinical manifestations, and when they are often suitable.[36]

Flucloxacillin was shown to induce irritable patterns on EEG such as bursts of spikes and polyspikes. Penicillins are believed to exert an inhibitory effect on GABA transmission due to their beta-lactam ring structure, which shares similar structural features to those of GABA neurotransmitters. This is further supported by studies in which the beta-lactam ring is enzymatically cleaved and the epileptogenic potential is subsequently lost. Thiazolidine ring and side chain length may have an impact on the epileptogenic potential. In addition, it has been demonstrated in rat studies that penicillin can quantitatively reduce benzodiazepine receptors and thus reduced inhibition and altered neuronal excitability.[37,38]

6. Other beta lactams: carbapenems

Carbapenems are reported to be associated with seizures with an estimated incidence of 3%. Risk factors associated with this neurotoxicity again are advanced age, history of disease, insufficiency, as well as low body weight. There are several reports neurotoxic effects consisting of encephalopathy both in patients with end-stage renal disease or mild renal dysfunction several days following intravenous administration of imipenem. Serum concentrations of imipenem were elevated in some cases suggesting that toxicity is from reduced clearance in the setting of renal insufficiency. In

addition, carbapenems also associated with seizures, mostly generalized tonic-clonic seizures, though simple and complex partial seizures have also been reported. The neurotoxic potential of carbapenems also had serious potential implications in the treatment of bacterial meningitis. The newer beta-lactam antibiotics include doripenem, ceftobiprole and ceftaroline. Post-marketing studies suggest that doripenem maybe associated with the potential for epileptogenicity seen with other carbapenems. The seizure provocation of carbapenems is likely related to inhibition of GABA-A receptors, and possibly binding to glutamate.[39]

7. Tetracyclines

Tetracyclines have been associated with cranial nerve toxicity and neuromuscular blockage. In addition, some cases of benign intracranial hypertension have been attributed to a tetracycline-induced neurotoxic event.[40]

8. Trimethoprim/Sulfamethoxazole

Trimethoprim/sulfamethoxazole (TMP-SMX) has been reported to be associated with encephalopathy and psychosis. A case of transient psychosis secondary to trimethoprim-sulfamethoxazole administration was reported, where the patient developed an acute delirium with agitation, visual and auditory hallucinations. Once the offending medication was discontinued, psychosis/ delirium slowly resolved. In elderly or immunocompromised patients, cases of encephalopathy and aseptic meningitis have been described. Patterson et al. also described a case of transient tremors occurring in an immunocompetent patient taking TMP-SMX. While the neurotoxic effects are thought to be at least in part related to the excellent CNS penetration of TMP SMX, the exact mechanism of neurotoxicity is unknown.[41]

9. Macrolides/azalides

Macrolides are extensively used in the treatment of upper respiratory infections and have been linked to ototoxicity via damage to the cochlea. This may result in equilibrium dysfunction in addition to hearing impairment. Early detection (which may be quite challenging for critically ill patients) is essential in order to minimize future risk of permanent damage to the vestibulocochlear system.[42]

10. Quinolones and neurotoxicity

Neurotoxic manifestations associated with quinolones include seizures, confusion/encephalopathy, myoclonus High affinity binding to CNS Blocking acetylcholine receptors; Prolonged depolarization via calcium depletion CSF inflammatory response Cerebellar/brain stem lesions Axonal damage Co-administration of narcotics, anaesthetics, muscle relaxants; Myasthenia gravis Renal failure Cystic fibrosis Impaired renal function and toxic psychosis. One case report described generalized myoclonus with delirium with ciprofloxacin. In contrast to ciprofloxacin, ofloxacin has an increased CNS permeability of 50% of the serum concentration, though interestingly less cases of neurotoxicity have been reported for ofloxacin than for ciprofloxacin.[43] New Quinolone derivatives or gyrase inhibitors include levofloxacin, sparfloxacin, grepafloxacin, trovafloxacin, gatifloxacin and moxifloxacin and are the most commonly implicated drugs causing neurotoxic side effects among quinolones.[44] Levofloxacin is the active levo-stereoisomer of ofloxacin, and a third-generation fluorinated quinolone, which is reported to cause pronounced acute delirium associated with psychotic features as well as seizures.[45] Similar acute psychotic reactions were also reported with ofloxacin. In post-marketing reports CNS toxic effects of gyrase inhibitors have an incidence of 0.89%, with primarily symptom listed as headache, insomnia, dizziness and restlessness and, less commonly, delusions and hallucinations.[46] Quinolone treatment also resulted in extrapyramidal manifestations such as gait disturbance, dysarthria and choreiform movements. Gemifloxacin, another quinolone, is associated with neurotoxicity, which manifests as an encephalopathy.[47]

11. Oxazolidinones

These broad-spectrum antibiotics are traditionally reserved for treatment of vancomycin-resistant enterococcal (VRE) infections. There has been at least one case report of probable linezolid-related encephalopathy as well as a case report of Bell's palsy coinciding with linezolid treatment for osteomyelitis which occurred a second time with rechallenge of the implicated antibiotic for recurrent infection. In addition, a persistent, painful peripheral neuropathy has also been associated with use of this antibiotic, particularly with extended use and with concomitant use of selective serotonin reuptake inhibitors (SSRIs). Optic neuropathy has been associated with use of linezolid.[48]

Management strategies

Identification of risk factors associated with neurotoxicity is imperative and perhaps the most important initial step. As previously mentioned, these include extremes of age, impaired renal function, history of central nervous system disease, and/or damage to the blood-brain barrier. Other important factors to consider are body size (volume of distribution), as well as co-administration with other medications with neurotoxic and/or nephrotoxic effects, as well as any epileptogenic potential.[38] Apart from altered mental status induced by the antibiotic itself, the nephrotoxicity sometimes induced by antibiotics may itself be responsible for the encephalopathy. Early diagnosis is therefore essential in minimizing neurotoxic adverse effects. Thus avoidance of neurotoxic agents in patients with the above-mentioned risk factors is critical in preventing neurotoxicity.

Proper diagnosis may be obscured by the overall clinical picture as changes in mental status may easily be attributed to the infectious process that is mandating the use of antibiotic treatment, or to an underlying metabolic disorder such as renal failure.[49]

REFERENCES

1. Leekha, Surbhi, Christine L. Terrell, and Randall S. Edson. "General principles of antimicrobial therapy." *Mayo Clinic Proceedings* Elsevier., 2011; 86(2): 156-167.
2. Sánchez A, Rogers RI, Sheridan P. Tetracycline and other tetracycline- derivative staining of the teeth and oral cavity. Int. J. Dermatol., 2004; 43: 709–715.
3. Schwachman H, Schuster A. The tetracyclines: applied pharmacology. Pediatr. Clin. North Am., 1956; 3: 295–303.
4. Pannu N, Nadim M. An overview of drug-induced acute kidney injury. Crit. Care Med., 2008; 36(4): S216 –S223.
5. Rougier F, Claude D, Maurin M, Maire P. Aminoglycoside nephrotoxicity. Curr. Drug Targets Infect. Disord., 2004; 4: 153–162.
6. Robles M, Andrade R. Hepatotoxicity by antibiotics: update in 2008. Rev. Esp. Quimioter, 2008; 21: 224 –233.
7. Sun F, Chen Y, Xiang Y, Zhan S. Drug-metabolising enzyme polymorphisms and predisposition to anti-tuberculosis drug-induced liver injury: a meta-analysis. Int. J. Tuberc. Lung Dis., 2008; 12: 994 –1002.
8. Parsons T, Obaid A, Salzberg B. Aminoglycoside antibiotics block voltage-dependent calcium channels in intact vertebrate nerve terminals. J. Gen. Physiol., 1992; 99: 491–504.
9. Pasquale T, Tan J. Nonantimicrobial effects of antibacterial agents. Clin. Infect. Dis., 2005; 40: 127–135.
10. Rozza D, Vervuert I, Kamphues J, da Cruz C, Driemeier D. Monensin toxicosis in water buffaloes (*Bubalus bubalis*). J. Vet. Diagn. Invest., 2006; 18: 494–496.
11. Friedman G, et al. Epidemiologic evaluation of pharmaceuticals with limited evidence of carcinogenicity. Int. J. Cancer, 2009; 125: 2173–2178.
12. Jones C, Miller C, Tenenbaum A, Spremulli L, Saada A. Antibiotic effects on mitochondrial translation and in patients with mitochondrial translational defects. Mitochondrion, 2009; 9: 429–437.
13. Wilhelm JM, Pettit SE, Jessop JJ. Aminoglycoside antibiotics and eukaryotic protein synthesis: structure-function relationships in the stimulation of misreading with a wheat embryo system. Biochemistry, 1978; 17: 1143–1149.
14. Carter A, et al. Functional insights from the structure of the 30S ribosomal subunit and its interactions with antibiotics. Nature, 2000; 407: 340– 348.
15. Levison, Matthew E. "Pharmacodynamics of antimicrobial drugs." *Infectious Disease Clinics.*, 2004; 18(3): 451-465.
16. Shamna, M., et al. "A prospective study on Adverse Drug Reactions of antibiotics in a tertiary care hospital." *Saudi pharmaceutical journal*, 2014; 22.4: 303-308.
17. Sun, Hsin-Yun, et al. "A prospective study of antimicrobial-related adverse drug reactions in hospitalized patients." *Journal of microbiology, immunology, and infection= Wei mian yu gan ran za zhi*, 2008; 41.2: 151-159.
18. Beers MH, Jones TV, Berkwits M, et al. *The Merck Manual of Health & Aging*. Whitehouse Station, NJ: Merck Research Laboratories, 2004: 232,738.
19. Beers MH, Porter RS, Jones TV, et al. *The Merck Manual of Diagnosis and Therapy*. 19th ed. Whitehouse Station, NJ: Merck Research Laboratories, 2011: 1180-1225.
20. Wald A. The large bowel. In: Fillit HM, Rockwood K, Woodhouse K, eds. *Brocklehurst's Textbook of Geriatric Medicine and Gerontology*. 7th ed. Philadelphia, PA: Saunders Elsevier, 2010: 661-677.
21. McDonald LC, Killgore GE, Thompson A, et al. An epidemic toxin gene variant strain of *Clostridium difficile*. *N Engl J Med.*, 2005; 353: 2433-2441.
22. Cook K, Ineck BA, Lyons WL. Anemias. In: DiPiro JT, Talbert RL, Yee GC, et al, eds. *Pharmacotherapy: A Pathophysiologic Approach*. 8th ed. New York, NY: McGraw-Hill Inc., 2011; 1717-1740.
23. Harvey RA, Champe PC, eds. *Pharmacology*. 4th ed. Philadelphia, PA:Lippincott Williams & Wilkins, 2009; 347-406.
24. Semla TP, Beizer JL, Higbee MD. *Geriatric Dosage Handbook*. 17th ed. Hudson, OH: Lexi-Comp, Inc., 2012; 1069-1072.
25. Burgess DS. Antimicrobial regimen selection. In: DiPiro JT, Talbert RL, Yee GC, et al, eds. *Pharmacotherapy: A Pathophysiologic Approach*. 8th ed. New York, NY: McGraw-Hill Inc., 2011; 1813-1823.
26. Forge A, Schacht J. Aminoglycoside antibiotics. Audiol. Neurootol, 2000; 5: 3–22.
27. Selimoglu E. Aminoglycoside-induced ototoxicity. Curr. Pharm. Des., 2007; 13: 119 –126.
28. Grivell L, Walg H. Subunit homology between *Escherichia coli*, mitochondrial and chloroplast ribosomes. Biochem. Biophys. Res. Commun., 1972; 49: 1452–1458.
29. Leiter L, et al. Chloramphenicol-induced mitochondrial dysfunctionis associated with decreased transferrin receptor expression and ferritin synthesis in K562 cells and is unrelated to IRE-IRP interactions. J. Cell. Physiol., 1999; 180: 334 –344.
30. Yunis A. Drug-induced bone marrow aplasia. Rev. Bras. Pesqui. Med. Biol., 1978; 11: 287–295.
31. Grill MF, Maganti R. Cephalosporin-induced neurotoxicity: clinical manifestsations, potential pathogenic mechanisms, and the role of electroencephalographic monitoring. Ann Pharmacother, 2008; 42: 1843–50.
32. Sugimoto M, Uchida I, Mashimo T, Yamazaki S, Hatano K, Ikeda F, Mochizukie Y, Terai T, Matsuoka N. Evidence for the involvement of

GABA(A) receptor blockage in convulsions induced by cephalosporins. Neuropharmacology, 2003; 45: 304–14.
33. Calandra G, Lydick E, Carrigan J, Weiss L, Guess H. Factors predisposing to seizures in seriously ill infected patients receiving antibiotics: experience with imipenem/cilastatin. Am J Med, 1988; 84: 911–918.
34. Lin CS, Cheng CJ, Chou CH, Lin SH. Piperacillin/tazobactam-induced seizure rapidly reversed by high flux hemodialysis in a patient on peritoneal dialysis. Am J Med Sci., 2007; 333: 181–184.
35. Huang WT, Hsu YJ, Chu PL, Lin SH. Neurotoxicity associated with standard doses of piperacillin in an elderly patient with renal failure. Infection, 2009; 37: 374–376.
36. Shaffer CL, Davey AM, Ransom JL, Brown YL, Gal P. Ampicillin-induced neurotoxicity in very-low-birth-weight neonates. Ann Pharmacother, 1998; 32: 482–484.
37. Contreras S, Kramer MV, Pesce ME. Electroencephalographic effects of flucloxacillin in rats. Pharmacol Toxicol, 1993; 72: 205–207.
38. Schliamser SE, Cars O, Norrby SR. Neurotoxicity of beta-lactam antibiotics: predisposing factors and pathogenesis. J Antimicrob Chemother, 1991; 27: 405–425.
39. Lankerani L, Baron E. Photosensitivity to exogenous agents. J. Cutan. Med. Surg., 2004; 8: 424–431.
40. McKee E, Ferguson M, Bentley A, Marks T. Inhibition of mammalian mitochondrial protein synthesis by oxazolidinones. Antimicrob. Agents Chemother, 2006; 50: 2042–2049.
41. Nagiec EE, et al. Oxazolidinones inhibit cellular proliferation via inhibition of mitochondrial protein synthesis. Antimicrob. Agents Chemother, 2005; 49: 3896 –3902.
42. Narita M, Tsuji B, Yu V. Linezolid-associated peripheral and optic neuropathy, lactic acidosis, and serotonin syndrome. Pharmacotherapy, 2007; 27: 1189 –1197.
43. Schwartz MT, Calvert JF. Potential neurologic toxicity related to ciprofloxacin. Drug Intell Clin Pharm, 1990; 24: 138–140.
44. Fennig S, Mauas L. Ofloxacin-induced delirium (letter). J Clin Psychiatry, 1992; 53(4): 137–138.
45. Kushner JM, Peckman HJ, Snyder CR. Seizures associated with fluoroquinolones. Ann Pharmacother, 2001; 35: 1194–1198.
46. Jungst G, Mohr R. Side effects of ofloxacin in clinical trials and in postmarketing surveillance. Drugs, 1987; 34: S144–S149.
47. MacLeod W. Case report: severe neurologic reaction to ciprofloxacin. Can Fam Physician, 2001; 47: 553–555.
48. Thai XC, Bruno-Murtha LA. Bell's palsy associated with linezolid therapy: case report and review of neuropathic adverse events. Pharmacotherapy, 2006; 26: 1183–1189.
49. Lam S, Gomolin IH. Cefepime neurotoxicity: case report, pharmacokinetic considerations, and literature review. Pharmacotherapy, 2006; 26: 1169–1174.