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Neurotoxicity of Commonly Employed Antimicrobial Agents: A Review

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Abstract

Antimicrobial agents are the most frequently used pharmacological agents by a practising clinician. Many of the commonly used antibiotics are well tolerated. They do have side effects either idiosyncratic or dose dependent. Special caution is needed on monitoring their neurotoxic effects as if not recognized promptly, these may be confused with other neurological states therefore ending up in complications. The practising clinician in most countries, initiates' treatment based upon clinical findings and does not have the luxury of getting confirmatory laboratory results in a timely manner. Factors influence neurotoxicity include old age, decreased renal function, nutritional status, use of other drugs that lower seizure threshold and damage to the blood brain barrier. The role of genetic factors though has been suggested, their effects have not been fully determined. In most instances, the neurological side effects can be reversed by discontinuation of the offending drug. This article highlights the neurological side effects of commonly used antimicrobial agents, thereby enabling clinicians to be aware of these side effects to diagnose and initiate proper treatment apart from stopping the drug in a timely manner.

Keywords: Antimicrobial agents • Neurotoxic effects • Antibiotics • DNA

Introduction

Ever since the discovery of penicillin, antibiotics remain the major drug which is prescribed by doctors. Antibiotics remain the most prescribed drugs in clinical practice. While the discovery of newer antibiotics is extremely useful in the context of emerging infectious diseases, their widespread use has led to resistance to existing and even emerging antibiotics. This antibiotic resistance has led to Uncontrollable infectious diseases whose mortality rates have become increasingly higher each year. Other than this major issue of antibiotic resistance, the side effects due to antibiotics are numerous and some are life threatening. Among these side effects, we wish to focus on the neurotoxicity of commonly used antibiotics which most often is misdiagnosed to be other neurological illnesses leading to delayed and wrong treatments that complicate the issue. We also suggest a step wise approach that can be followed by clinicians to identify neurotoxic features of the antibiotics and administer appropriate care. It is the commonly used antibiotics and their neurotoxic effects.

Aminoglycosides (AG)

Aminoglycosides (AG) are used worldwide against gram negative bacterial infection. Although AG are highly effective and are relatively inexpensive, they are known to have ototoxicity and vestibular toxicity [1]. These symptoms may not be detected until after the acute phase of severe infection is over and thus the diagnosis is delayed. AG accumulates in inner ear and is difficult to metabolize leading to permanent hearing loss. Mechanism of toxicity was due to reduce mitochondrial ATP synthesis, apoptotic hair cell loss in genetically susceptible individuals to AG and mutation in mt DNA, especially A1555G and C1494T mutation in 12S rRNA and also due to over expression of NMDA receptors and the formation of free radicals. Higher the concentration and more frequent dosing of AG the incidence of ototoxicity exceeds. As of this writing, there are nine Aminoglycosides. These are Streptomycin, Neomycin, Tobramycin, Kanamycin, Paromomycin, Gentamicin, Spectinomycin, Netilmicin and Amikacin [1]. Kanamycin, Amikacin, Neomycin and Dihydrostreptomycin are mostly cochleotoxic. Netilmicin, tobramycin, Streptomycin and Gentamicin cause primarily vestibulotoxicity [2]. The side effects usually are manifest within a few days to weeks. The incidence for vestibulotoxicity is 15% whereas Cochlear toxicity occurs in 2%-25% [3]. It is proposed that antioxidants and inhibitors of caspase can effectively prevent apoptosis and Aminoglycosides induced hearing loss.

Beta Lactam Induced Neurotoxicity

Central Nervous system toxicity following administration of beta-Lactam antibiotics is a potential cause of morbidity and mortality. Inhibition of GABA binding to GABA-A receptor lowers the seizure threshold and cause convulsions. Also, direct administration of beta–lactam into the cerebral cisterns produces neurotoxic reactions. Epileptogenic reaction has been observed after giving very high systemic doses. There are considerable differences in the neurotoxic potential of various beta–lactams; penicillin, cefazolin and imipenam/cilastatin appear to be the drugs with higher potential than other compounds. The concentration of drug in the brain and not in the cerebrospinal fluid is the decisive factor for the risk of neurotoxic reactions. Factors increase the neurotoxic reactions are excess dose, reduce renal function, damage to BBB, Pre-existing disease of CNS, old age, and concurrent use of drugs that are nephrotoxic or that may lower seizure threshold. Blockage of transport system which affects the flow of beta-Lactam from CNS also favours more toxicity. Clinical manifestations include confusion, disorientation, twitching, somnolence, myoclonus, and, notably, convulsions ranging from generalized tonic clonic seizures to nonconvulsive status epilepticus. Inhibition of GABA binding to GABA-A receptor is accepted pathogenesis for convulsions induced by beta lactams. Other mechanisms include binding of penicillin to chloride ionophore thus prevents chloride influx. Also binds to allosteric site to prevent chloride conductance [4].

There is also relation between antibiotic structure and neurotoxicity. Betalactam is essential for antibacterial property and side chain determines the spectrum and pharmacokinetics [5]. Epileptogenic properties are due to Beta-lactam ring and thioazolidine ring as well as substitution at 3 and

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7 position of side ring. Neurotoxicity of carbapenems is related to basicity of aminoacid in the side chain. Imipenem is more neurotoxic compared to meropenem due to more basic side chain [6].

Cephalosporin Induced Neurotoxicity

Cephalosporin induced neurotoxicity manifest in a variety of clinical presentation ranging from encephalopathy or mental status changes to myoclonus, Asterixis, seizures, non-convulsive status epilepticus finally coma. Patients who have poor renal function, elderly and with pre-existing neurological disease are more prone for the toxic features. It is due to Inhibition of GABA-A receptor ranges from encephalopathy to myoclonus, asterixis, seizure, non-convulsive status epilepticus and coma. Mechanism is thought to be inhibition of GABA-A receptor. Patients with deranged renal function, prior central nerves system disease and advanced age are more prone to develop neurotoxicity [7,8]. EEG may show diffuse slow wave delta activity, semi periodic triphasic sharp wave activity, or frank periodic discharges [9].

Chloramphenicol

It has been reported to cause optic neuritis and distal sensory neuropathy [10]. Inhibits protein synthesis by binding to 50 S subunit of ribosome. It causes bilateral visual loss with Centro caecal scotomas [11].

Optic Neuritis has been associated with Chloramphenicol therapy both in adults and children. Possible attack on free radical with low Vitamin E and Glutathione may increase side effect. 1/3 of cases were unilateral and 1/3 Optic atrophy was the initial finding. Prognosis is varied 1/3 showed improvement in vision and 1/3 remained unchanged. One third had gradual progression of visual loss. B group vitamin supplement and Vit E might help. Early identification and removing the drug can save further visual loss.

Chloroquine

Amphiphilic properties lead to drug lipid complexes which are indigestible resulting in accumulation of autophagic vacuoles. Cause length dependent neuropathy superimposed with myopathy. Apart from malaria treatment it is widely used in rheumatology, dermatology and for SLE patients. Chloroquines have effects on the peripheral nerves, muscle causing proximal myopathy, NMJ, Retinal and CNS. Hydroxy chloroquine has the potential to produce irreversible maculopathy which usually occurs at higher than the recommended dose. Toxicity associated with age, daily dosage, and weight. HCQ toxicity remains uncommon, it increases with duration of therapy and exceed 1% after 5 to 7 years.

Clarithromycin Induced Neurotoxicity

Mainly due to co-administration of drugs metabolised by cytochrome P 450 CYP3A enzyme. Prior psychiatric disease, renal failure is more prone to develop neurotoxicity. Common CNS adverse effects are delirium, psychosis, hallucinosis, mania, non-convulsive status epilepticus and rarely serotonin syndrome. Drugs commonly implicated in interactions are antidepressants including SSRI, ART, calcium channel blockers. Even with doses less than 1000 mg/day it was reported. Prompt recognition and early discontinuation of drug may result in recovery.

Clioquinol

An antiseptic, prescribed for the treatment of diarrhoea and other bowel symptoms. Its overdosing and long term treatment can lead to subacute myelo optic neuropathy. SMON is a non-inflammatory disease of the spinal cord, optic nerve and peripheral nerve with a pseudo systemic degeneration of posterior and lateral columns [12,13]. It is characterised by green hairy tongue and green urine which is due to chelation of drug with ferric iron [14].

Cycloserine

Used as second line drug in the treatment of TB with other medications. The CNS side effects are usually dose related >500 mg/day. They appear usually in the first two weeks of treatment and have included seizures, tremors, disorientation and Psychosis [10].

Ethambutol

Used in the treatment of Tuberculosis. Reported side effects include Mild sensory neuropathy which resolves after drug withdrawal. Optic neuritis has been reported as well [10]. Interferes with mitochondrial oxidative phosphorylation by chelating the iron and copper in complex 1 and complex 4 respectively. This leads to ATP deficit and cause further damage by superoxide formation [15].

Thus, mitochondrial dysfunction can affect the retinal ganglion cells. Toxicity is usually dose dependent but can be idiosyncratic also. Patients taking dose more than 25 mg/kg/day for more than 2 months are prone to develop optic neuropathy [16]. Usually, they develop centrocaecal scotoma due to involvement of papillomacular bundle, rarely produce bitemporal visual field defect due to optic chiasmal pathology [17].

Fluoroquinolones

Fluoroquinolones are only bactericidal agent that directly inhibits DNA synthesis. They are used to treat both gram negative and gram positive bacterial infections. They can influence both CNS (Central Nervous System) and PNS (Peripheral Nervous System). 0.9%-1.6% experience neurological symptoms of which PNS sensory symptoms are most common (90%), followed by CNS effects (75%), and PNS motor symptoms (55%) [18,19].

CNS symptoms include headache, dizziness, drowsiness, agitation and convulsions. Paraesthesia is the most common symptom. Symptom onset can be as early as 24 hours and can be prolonged for nearly one year in more than 50% of patients [20].

Isoniazid

Used as first line drug in the treatment of TB. Some of the risk factors include Japanese ancestry and Eskimos. It is usually related to high doses and occurs more in malnourished patients and thought be due to pyridoxine depletion. The usual onset is about 4 weeks and this distribution is symmetric and distal. The recovery is slow [10].

Linezolid

Member of oxazolidinone antibiotics. Inhibits protein synthesis by binding with 50 S subunit of ribosome. Toxicity usually occurs with long term use. Usually, reversible. Can also cause peripheral neuropathy which is irreversible [21,22].

Metronidazole

Metronidazole induced encephalopathy

Commonly used antibiotic for anaerobic coverage. Neurotoxicity associated with metronidazole can manifest as seizures, dizziness, vertigo, ataxia, confusion, and tremors. The duration of metronidazole treatment before encephalopathy develops varies between one day to weeks and cumulative doses range from 0.25 g to 1,110 g [23]. Typical MRI findings of metronidazole induced encephalopathy include T2 hyperintense lesions in the cerebellar dentate nuclei, however, the splenium of the corpus callosum, dorsal pons, medulla, inferior colliculus, subcortical white matter, basal ganglia, thalamus and middle cerebellar peduncles can be affected as well [24]. Metronidazole induced encephalopathy is a reversible process that

improves within a few weeks after discontinuation of metronidazole [25,26].

Nitrofurantoin

The reported cases of sensorimotor motor polyneuropathy have been in children. A substantial number of them had poor renal function. The adverse effects resolved with stoppage of the medication [10].

Penicillin

Penicillin, since its discovery in 1928 by Nobel laureate Alexander Fleming has been used as a first line agent to treat predominantly infections by gram positive bacteria. All penicillin are beta lactam antibiotics [10].

Molecular modifications later resulted in extended spectrum family namely, Antistaphylococcal penicillin, Amino penicillin and anti-pseudomonal penicillin. This has helped the clinicians to treat gram negative infections also. All penicillin has been reported to cause a wide variety of CNS side effects. All penicillin have the potential to cause EEG changes and have epileptogenic potential.

Johnson and Walker in 1945 reported neurotoxicity after intraventricular administration of Penicillin [5]. In neonates where Ampicillin is widely used it is difficult to recognize seizures in 50% of patients. While the exact mechanism of neurological side effects is unclear, the accepted theory involves binding of Gamma Butyric acid (GABA) to GABA receptors. Among the Penems, (Meropenem and Imipenem) Meropenem has less potential to cause seizure activity and is attributed to the Imipenem's C-2 side chain.

The usual onset of seizures ranges from 12 hours to 9 days after initiation of beta lactam therapy. Management includes stopping the offending drug and treatment with Barbiturates and benzodiazepines. Clinical data suggest that anticonvulsants such as Phenytoin are less efficacious [27].

Polymyxins

These drugs are not used frequently nowadays. Some of the CNS side effects include polyneuropathy, paraesthesia and neuromuscular blockade. The toxicity of Polymyxin is thought to be dose dependent. In addition, neurotoxic effects of polymyxins are usually mild and resolve after prompt discontinuation of the antibiotics. Furthermore, cases of neuromuscular blockade and apnoea have not been reported in the recent literature. The incidence of neurotoxicity related to the use of polymyxins reported in the old literature was considerably less compared to nephrotoxicity.

Specifically, the most frequently experienced neurological adverse effects were paraesthesia that occurred in approximately 27% and 7.3% of patients receiving intravenous and intramuscular colistimethate sodium, respectively. Furthermore, at least 8 cases were published between 1964 and 1973 correlating the intramuscular administration of polymyxins with the development of episodes of respiratory apnoea. However, recently performed studies in patients without cystic fibrosis are not in accordance with the previously reported data regarding the incidence of polymyxin induced neurotoxicity [27].

Quinolones

There are about 29 Quinolones in the market and three more are in development. The first generation e.g., Nalidixic acid is rarely used today. First and second generation (Ciprofloxacin) fluoroquinolones selectively inhibit the topoisomerase II ligase domain, leaving the two nuclease domains intact [28]. This modification, coupled with the constant action of the topoisomerase II in the bacterial cell, leads to DNA fragmentation via the nuclease activity of the intact enzyme domains. Unlike the first and second generations, the third generation is active against streptococci. e.g., Levofloxacin and grepafloxacin. Fourth generation fluoroquinolones act at DNA gyrase and topoisomerase IV. e.g., Moxifloxacin and Gemifloxacin. This dual action slows development of resistance.

With its increasing usage in modern practice the CNS side effects occur in 1%-2% of patients. Many of the common symptoms are non-specific and include dizziness and drowsiness, insomnia and sleep disorders and agitation. Seizures have been rarely reported. The CNS effects of Quinolones can be due to either directly to the drug or those resulting from drug interactions. The plausible theory indicates that the side chain substitution of R7 position of the fluroquinolone nucleus plays a major role in GABA binding, causing side effects. Among the Quinolones, trovafloxacin has been reported to have the highest CNS side effects. These include dizziness and headache and often resolve with continued therapy. Both Moxifloxacin and gatifloxacin are well tolerated and few adverse CNS effects have been reported. Use of Ciprofloxacin or Moxifloxacin appears to increase the risk of uveitis. The mechanism is not clear. Among the Quinolones, Levofloxacin may pose the least risk for uveitis compared with moxifloxacin and ciprofloxacin [29].

Uveitis has been reported when given systemically, but not topically or intra-ocular. Moxifloxacin has been reported to cause the most cases. They present with bilateral ocular pain and visual impairment. The average time of onset is about 12 days and the inflammation responds to cessation of drug and topical corticosteroids. The U.S Food and Drug administration has required the drug labels to be updated to include serious side effects of peripheral neuropathy. The peripheral neuropathy manifests only when they are ingested or injected. Otic or ophthalmic preparations have not been reported to cause peripheral neuropathy. This disorder can occur at any time during therapy and is not dose related and possibly idiosyncratic [18].

Rifabutins

Rifabutin is a derivative of Rifampin and used in the treatment of MAI infections, mostly in HIV positive patients. The mechanism in which it causes Uveitis is unknown. Drug interactions with Protease inhibitors and clarithromycin can cause uveitis. Intense corticosteroid therapy and stoppage of Rifabutin facilitates recovery.

Sulphonamides

This class has been used for decades. Trimethoprim either alone or when used with Sulfemethoxazole has been reported to cause non-granulomatous uveitis within a few days. Tremor and eosinophilic meningitis have been reported with use of TMP-SMX. The exact mechanism of neurotoxicity is unknown. In part it may be related to the excellent penetration into the CNS [30,31].

Tetracyclines

Pseudotumor Cerebri (PTC) is a reported CNS side effect. It happens more commonly in obese women of child bearing age. Due to the explosion of obesity, the reported incidence of 0.9% may not be accurate. They present with visual disturbances, headache and photosensitivity reactions.

Antibiotics Provoking Seizure

Numerous antibiotics may trigger epileptic seizures or status epilepticus by decreasing inhibitory transmission in the brain, thus lowering the seizure threshold. The most potent epileptogenic effect is exerted by penicillin, cephalosporins, fluoroquinolones and carbapenems. Predisposing factors are a head injury and encephalitis that alter the blood brain barrier. Also, high dose of antibiotics or lack of dose adjustment in renal failure can lower the seizure threshold [32-34].

Antibiotics Causing Myopathy

Penicillin, sulphonamides, quinolones and nalidixic acid reported to produce painful myopathy without neuropathy. Chloroquine is known to produce vacuolar myopathy which is painless. Zidovudine causes mitochondrial myopathy with ragged red fibres [35,36].

Antibiotics and Movement Disorders

Ceftriaxone when prescribed to elderly people or patients with renal failure they can cause choreoathetosis. The neural mechanisms proposed are impaired γ-butyric acid (GABA) modulation and excess of glutamate, an excitotoxic neurotransmitter, have been hypothesized. The imbalance of excitatory and inhibitory motor control pathways within the striatum may cause the occurrence of movement disorders. Orofacial dyskinesia has been reported with fluoroquinolones [37].

Antibiotics and Idiopathic Intracranial Hypertension

Cycline antibiotics have been associated with IIH. Proposed mechanisms are altering the cyclic AMP pathway in arachnoid granulations and thus decreasing the absorption of CSF. Significant association between papilledema and female sex, younger age, and hypertension have been described [38,39].

Antibiotics and Dysguesia

Many antibiotics are associated with taste disorders. Of which Clindamycin which is taken either orally or intravenous can cause bitter taste. This adverse event is closely related to serum level and drug level in saliva and sputum [40].

Antibiotics Causing Aseptic Meningitis

Aseptic meningitis characterised by inflammation of meninges caused by various conditions including infectious viral and nonviral, drugs, malignancy, and systemic illness. Drug Induced Aseptic Meningitis (DIAM) is an important entity and has been reported as an uncommon adverse reaction with numerous agents [41].

The most common drugs are nonsteroidal anti-inflammatory drugs, antibiotics, intravenous immunoglobulin, and muromonab-CD3 monoclonal antibodies of the antibiotics, the most commonly reported offending agents include many antimicrobials, such as trimethoprim-sulfamethoxazole, ciprofloxacin, cephalexin, metronidazole, amoxicillin, penicillin, and isoniazid, are causes of aseptic meningitis.

Quick resolution of symptoms is an important sign that distinguishes DIAM from viral meningitis, in which recovery usually requires 10 to 14 days. CSF glucose levels are usually normal in DIAM, which may help in differentiating it from bacterial meningitis in which glucose levels usually are low. Analysis of CRP levels also may be helpful in distinguishing bacterial from DIAM because CRP levels are usually highly elevated in bacterial meningitis compared with DIAM [42,43].

Amoxicillin-induced aseptic meningitis typically presents with fever, headache, and stiff neck. The time between use of the amoxicillin and onset of the signs and symptoms ranged from 2 to 7 days after drug ingestion. DIAM is a diagnosis of exclusion [44].

Antibiotic Associated Encephalopathy

Delirium is a common complication after hospitalization; although medication is a known cause delirium, antibiotic administration is unrecognized class of medications associated with delirium. There are three distance syndromes. Encephalopathy accompanied by seizure or myoclonus arising within days starting antibiotic (Cephalosporin and penicillin). Encephalopathy associate with psychosis arising within few days of antibiotic administration (quinolones, macrolides, procaine penicillin). Encephalopathy accompanied by Cerebellar signs within weeks with MRI changes (Metronidazole).

Algorithm for Treatment

Assess before initiating treatment

Renal function, Pre-existing CNS diseases, Old age and too young, Weight.

Monitor for neuro toxic effect

Acute: Headache/Delerium/Dizziness/Psychosis/confusion/seizure/Myoclonic jerks/Encephalopathy/Aseptic meningitis. Chronic: Optic neuritis/Visual loss/Hearing/Imbalance while walking/Poly neuropathy/Myopathy.

Investigation

Reassess RFT, Drug level monitoring, EEG, MRI Brain/CT.

Treatment

Reduce dose/remove drug, Add antiepileptic for seizure, HD if necessary, If improved it is drug related if not think alternative diagnosis.

Discussion

Antibiotic induced side effects have variety of presentation. This topic highlights only the neuro toxicity which ranges from simple headache to serious confusion and convulsions. In acute set up in ICU it can produce Aseptic meningitis, Delirium, Psychosis, and Coma. Long term medication can cause Optic atrophy, Optic Neuritis, Peripheral neuropathy and proximal myopathy. Patients with pre-existing neurological diseases, renal insufficiency, and those with other concomitant drug administration and who are too young and old have to be addressed appropriately before choosing the antibiotics. Treatment consists of revisiting the patient medical condition, discontinue of offending drugs, use of antiepileptic drugs in case of seizure or status epilepticus, and Hemodialysis when required particularly for cephalosporin toxicity. If no improved is noted after removing the offending drug are think alternative diagnosis and plan accordingly.

Conclusion

Neuro toxic side effect may be reduced by adjusting the dose in high risk populations with frequent drug level monitoring. Awareness of the potential neuro toxic side effect of antibiotics, clinical manifestations, and a high degree of vigilance in critically ill patients is essential in identifying early the potential serious reversible complications of antibiotic therapy particularly with newer antibiotics.

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Competing Interests

The authors declare that they have no competing interests.

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