

Beta- Lactam Antibiotics Induced Neurotoxicity

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Abstract: Beta-lactam antibiotics are a group of products that have a chemical structure characterized by a β -lactam ring and are one of the most commonly used wide spectrum antibacterial agents. The mechanism of action of beta-lactam antibiotics is usually by inhibiting the enzyme responsible for the bacterial cell wall synthesis. While these antimicrobial agents are generally well tolerated, these drugs are not without their associated side effects (SEs), both dose-dependent and idiosyncratic in nature. All most all classes of Beta lactam antibiotics can cause a variety of adverse effects on the nervous system, including seizures, encephalopathy, optic neuropathy, peripheral neuropathy, and exacerbation of myasthenia gravis. Neurotoxicity is although rare but very important side effect because they may lead to a significant morbidity and even mortality. Factors known to increase the risk of neurotoxicity are excessive doses, decreased renal function, damage to the blood-brain barrier, preexisting diseases of the central nervous system, old age and concurrent use of drugs that are nephrotoxic or that may lower the seizure threshold. Another factor that may be of importance is blockage of the transport system that is responsible for transport of beta-lactams out of the central nervous system. The neurotoxic effects of Beta- lactams antibiotics are however reversible if identified in early stage. Clinical pharmacist can play a vital role in the identification, prevention, monitoring and treatment of such adverse events.

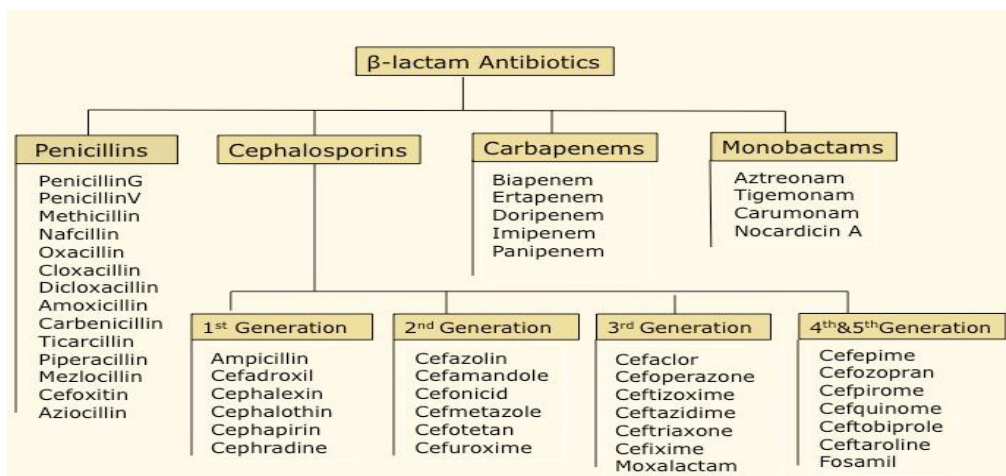
Keywords; Beta-lactam, Antibiotics, Idiosyncratic, Neurotoxic, Clinical pharmacist.

I. INTRODUCTION

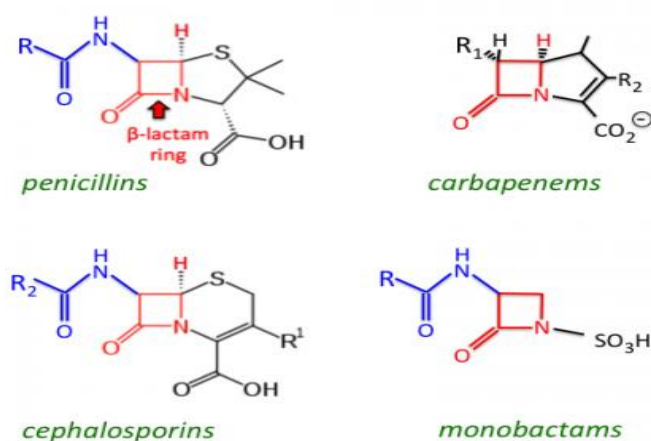
Antibiotics are powerful drugs that help our bodies ward off diseases caused by bacteria. When used appropriately, they quickly and effectively eliminate infections, from our body and make us to feel better in a matter of days. An antibiotic is a naturally occurring, semi synthetic or synthetic type of agent that destroys or inhibits the growth of micro-organisms⁽¹⁾. When used appropriately, antibiotics and other anti-infectives can save lives and eliminate life- threatening organisms; while these antimicrobial agents are generally well tolerated, these drugs are not without their associated side effects (SEs), both dose-dependent and idiosyncratic in nature⁽²⁾. Antibiotics can cause an array of adverse drug reactions (ADRs), from the common, gastrointestinal upset, to the uncommon, neurotoxicity. Antibiotics can cause a variety of adverse effects on the nervous system, including seizures, encephalopathy, optic neuropathy, peripheral neuropathy, and exacerbation of myasthenia gravis. Many of these neurotoxic events are reversible if identified early therefore; health-care providers and physicians need to be aware of their clinical presentations^(3, 4). The exact incidence of neurotoxic ADRs with anti- infectives is unknown, although it is estimated to be < 1%. Although such SEs are rare, awareness of them is important to prevent misdiagnosis or delayed treatment. Beta-lactams and quinolones are the antibiotics most commonly associated with neurotoxic side effects. It should, however, be noted that many other antibiotics such as aminoglycosides, tetracyclines, clindamycin, erythromycin, polymyxins, ethambutol, isoniazid, and chloramphenicol may also cause serious neurotoxicity⁽⁵⁾. This article aims to review the most common and important neurotoxic adverse events associated with Beta- lactam antibiotics and mechanism of neurotoxicity.

Beta- lactam Antibiotics

Beta-lactam antibiotics are one of the most commonly prescribed drug classes with numerous clinical indications. From a biochemical point of view, these drugs have a common feature, which is the 3-carbon and 1-nitrogen ring (beta-lactam ring) that is highly reactive⁽⁶⁾. This class divided into four subtypes:



- **Penicillins-** These antibiotics (most of which end in the suffix *-cillin*) contain a nucleus of 6-animopenicillanic acid (lactam plus thiazolidine) ring and other ringside chains. The group includes natural penicillins, beta-lactamase-resistant agents, aminopenicillins, carboxypenicillins, and ureidopenicillins.
- **Cephalosporins-** They contain a 7-aminocephalosporanic acid nucleus and side-chain containing 3,6-dihydro-2 H-1,3- thiazane rings. Cephalosporins are traditionally divided into five classes or generations, although acceptance for this terminology is not universal.
- **Carbapenems-** Their defining structure is a carbapenem coupled to a beta-lactam ring that confers protection against most beta-lactamases, although resistance to these compounds is a significant issue and occurs mainly among gram-negative pathogens (e.g., *Klebsiellapneumoniae*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*) which produce different classes of beta-lactamases termed as carbapenemase.
- **Monobactams-** The beta-lactam ring stands alone and not fused to another ring⁽⁶⁾.

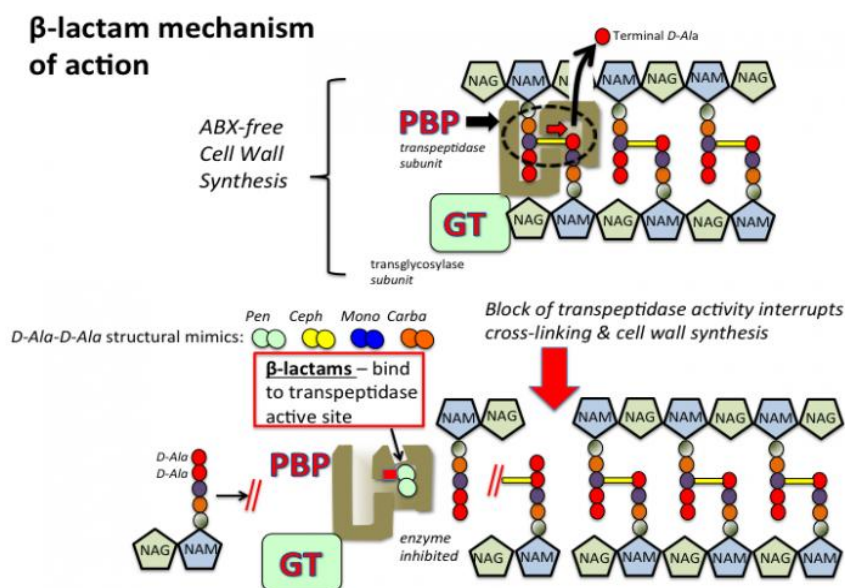


Core structure of beta-lactam antibiotics.

Mechanism of Action

The mechanism of action of beta-lactam antibiotics is usually by inhibiting the enzyme responsible for the bacterial cell wall synthesis⁽⁷⁾. The stability of cell wall is essential for the shape and protection of the cell in hostile and hypertonic environment the cell wall is comprised of two alternating units which are the N-acetylmuramic acid (NAM) and N-acetyl glucosamine (NAG), these two units are linked together by enzyme transglycosidase. Pentapeptide is attached to each NAM unit which includes D-alanine-D-alanine. The cross-link between the two Dalanine of two NAM is catalyzed by PBP. The cross-linked between the adjacent glycans gives the rigidity of the cell wall^(8, 9). The ring of beta-lactams antibiotics is similar to the pentapeptide's D-alanine-D-alanine of N-acetylmuramic acid, because of this similarity the penicillin binding proteins uses beta-lactam as building blocks for the synthesis of cell wall instead of NAM Pentapeptide⁽¹⁰⁾. This result in the acylation of the enzyme PBP subsequently rendering the enzyme incapable of catalyzing further transpeptidation reactions⁽¹¹⁾. When this reaction comes to a halt, Peptidoglycans autolysis commence which

result to the compromises of the integrity of the cell wall and increase its permeability .thus the beta-lactam mediated activity (inhibition) causes the lyses of the cell and the death of the bacteria ⁽¹²⁾.



Neurotoxicity of Beta- lactam Antibiotic

Patients were deemed to have symptomatic neurotoxicity if one or more of the following clinical features were present:

- i. Deteriorating consciousness as per the Glasgow coma scale (GCS). Patient GCS scores were retrieved from medical files and were determined based on standard criteria and scored between 3 and 15⁽¹³⁾. Where medical files indicate that the patient was intubated, a verbal response score was estimated retrospectively using linear regression model ⁽¹⁴⁾. Cognitive impairment was assessed using patients' neurological SOFA (nSOFA) subscore. To assess neurotoxicity, baseline neurological function based on nSOFA scores (nSOFA_{Baseline}) was compared with the patient's cognitive status at the time of TDM (nSOFA_{TDM}; ± 24 h). Neurological worsening status (NWS) was defined as $\Delta nSOFA$ (nSOFA_{TDM} - nSOFA_{Baseline}) ≥ 1 for an nSOFA_{Baseline} of 0–2. Patient $\Delta nSOFA$ were tabulated with the corresponding antibiotic serum concentration at the time of TDM to determine correlation.
- ii. Abnormal electroencephalograph (EEG). In instances where patients underwent an EEG within ± 24 h of TDM, reports were evaluated to verify a diagnosis of diffuse drug-induced encephalopathy. In the absence of an alternative diagnosis, patients with EEG reports indicating the presence of slowing and generalized semiperiodic discharges with triphasic morphology ranging from 0.5–2 Hz were deemed to have experienced antibiotic-induced neurotoxicity⁽¹⁵⁾. This EEG pattern has been described as characteristic of β -lactam-induced encephalopathy, notably with cephalosporins⁽¹⁶⁻¹⁷⁾.
- iii. Neurotoxicity symptoms recorded in the clinical notes. A method of evaluating antibiotic-induced neurotoxicity reported by Zhang *et al*⁽¹⁸⁾ was implemented. Patient medical charts were reviewed at baseline and at ± 24 h of TDM for descriptive indicators of drug-induced neurotoxicity. Symptoms indicative of severe neurotoxicity included status epilepticus, non-convulsive status epilepticus (NCSE), and seizure or commencement of anticonvulsant therapy. Other neurotoxic symptoms presenting acutely were considered mild to moderate. These included tremor, bizarre behaviour, delirium, slurred or incoherent speech, drowsiness/sleepiness, retrograde amnesia, myoclonus, hallucination, confusion, ataxia/loss of coordination and disorientation.

In the absence of an underlying brain disease or a contributing medical condition, associated neurological symptoms were attributed to neurotoxicity precipitated by CNS exposure to elevated concentrations of the prescribed β -lactam antibiotic. TDM results at which the neurotoxic complications became apparent were analysed to determine a concentration-dependent presentation. The temporal association of the symptom onset, drug administration and symptom relief after drug discontinuation were used to evaluate the adverse drug reaction⁽¹⁹⁾.

Neurotoxicity of Penicillins

The penicillins, including benzylpenicillin, penicillin G, piperacillin, ticarcillin, ampicillin, amoxicillin, and oxacillin, are among the well-known neurotoxic antibiotics. They may cause a wide variety of neurotoxic complications, such as psychological problems, confusion, disorientation, myoclonus, seizure, encephalopathy, and nonconvulsive status epilepticus. They may cause a wide variety of neurotoxic complications, such as psychological problems, confusion, disorientation, myoclonus, seizure, encephalopathy, and nonconvulsive status epilepticus^(20, 21). The epileptogenic properties of penicillin were first reported by Johnson and Walker in 1945. The risk of neurotoxicity after intrathecal and intravenous administration of penicillin has been documented in humans. The risk factors that may be associated with penicillin-induced neurotoxicity are previous central nervous system (CNS) diseases renal insufficiency low-birth weight in newborns, and an increased permeability of the blood–brain barrier (BBB)^(22- 24). The major cause of penicillin-induced neurotoxicity is suggested to be an inhibitory effect on gamma-aminobutyric acid (GABA) transmission⁽²⁵⁻²⁶⁾. This effect is thought to be due to the structural resemblance of their beta-lactam ring with GABA, because an enzymatic cleavage of this ring resulted in the loss of epileptogenic activity. In addition, the thiazolidine ring and side- chain length may also contribute to the epileptogenic potential of penicillin. A study on rats has suggested that penicillins are capable of reducing the number of benzodiazepine receptors and thus reducing inhibition and altering neuronal excitability^(27- 29).

Neurotoxicity of Cephalosporins

Neurologic side effects of cephalosporin are infrequent; however, there have been reports of associated encephalopathy, cognitive disorders, hallucinations, myoclonus, and seizures⁽³⁰⁻³¹⁾. The main mechanism of cephalosporin neurotoxicity involves a decrease of γ -aminobutyric acid (GABA) released from nerve terminals and subsequent increase of excitatory neurotransmission. GABA is the major inhibitory neurotransmitter of the CNS and acts via GABA receptors: GABA-A, GABA-B, and GABA-C. Inhibition of GABA-A receptor functions by β -lactams in general leads to hyper- excitability of neurons and depolarization of the postsynaptic membrane, thereby lowering the seizure threshold⁽³²⁾. Of the β -lactams, penicillins bind to GABA receptors non- competitively, whereas cephalosporins bind competitively, implicating the latter's greater potential for neurotoxicity⁽³³⁾. The fact that benzodiazepines, such as clonazepam, and barbiturates are effective in treating cephalosporin-associated epileptiform activity also supports the theory of a GABA-mediated mechanism. Other postulated mechanisms for cephalosporin neurotoxicity include induction of endotoxins and release of cytokines including tumor necrosis factor- α (TNF- α)⁽³⁴⁻³⁵⁾. The most frequent neurotoxicity reports are seen with first-generation cephalosporins such as cefazolin, second-generation cephalosporin such as cefuroxime, third-generation cephalosporins such as ceftazidime (CTD), and fourth-generation cephalosporins such as CPM.

Neurotoxicity of Carbapenems

Carbapenems including imipenem, meropenem, panipenem, ertapenem, doripenem, and ceftaroline are components of another group of beta-lactam antibiotics with known neurotoxic side effects such as headache, seizures, and encephalopathy. Renal insufficiency, infections of the CNS (such as meningitis), a history of seizure, old age, and a low body weight are presumed to be the risk factors responsible for the carbapenem-induced neurotoxicity⁽³⁶⁻³⁹⁾. The main mechanism is believed to be an inhibition of GABA-A receptors, and possibly binding to glutamate. *N*-methyl-D-aspartate (NMDA) and alpha-amino-3-hydroxy-5-methylisoxazolepropionate receptor complex interactions have also been suggested as possible mechanisms responsible for causing epilepsy^(40, 41). Due to their structural differences, the risk of neurotoxicity differs between various subclasses of carbapenems. For example, it has been shown that due to differences in the C-2 side chain, meropenem is less neurotoxic than imipenem^(41, 42).

Neurotoxicity of Monobactams

Aztreonam (the only commercially available monobactam) is a synthetic drug based upon a simpler monobactam isolated from *Chromobacterium violaceum*. Its spectrum of activity closely resembles that of aminoglycosides⁽⁴³⁾. Currently, there is not enough evidence or data present to support the neurotoxicity of monobactams.

Cause of neurotoxicity

Risk factors for medication-induced cognitive side effects can include underlying neurologic disorders, advanced age, polypharmacy, kidney impairment, and medical comorbidities⁽⁴⁴⁾. Underlying neurologic disorders such as epilepsy or cerebrovascular disease may increase the risk of neurotoxicity as a result of increased blood-brain barrier (BBB) permeability⁽⁴⁵⁾. Elderly patients are at an increased risk of drug-induced cognitive side effects because of alterations in neurotransmission and signal transduction, changes in pharmacokinetics and pharmacodynamics, and increased medication burden⁽⁴⁶⁾. Multiple medications

predispose individuals to more drug interactions. Since many medication side effects are dose related, side-effect profiles of multiple medications can be synergistic⁽⁴⁷⁾. Kidney impairment can prevent medication excretion, leading to toxic levels. Additionally, uremia can increase medication BBB penetration, and decreases in albumin can increase the free fraction of drugs⁽⁴⁸⁾. Comorbidities that lead to a change of oxygen and nutrient delivery to the central nervous system (CNS), such as myocardial infarction, heart failure, or respiratory failure, may predispose to delirium⁽⁴⁹⁾.

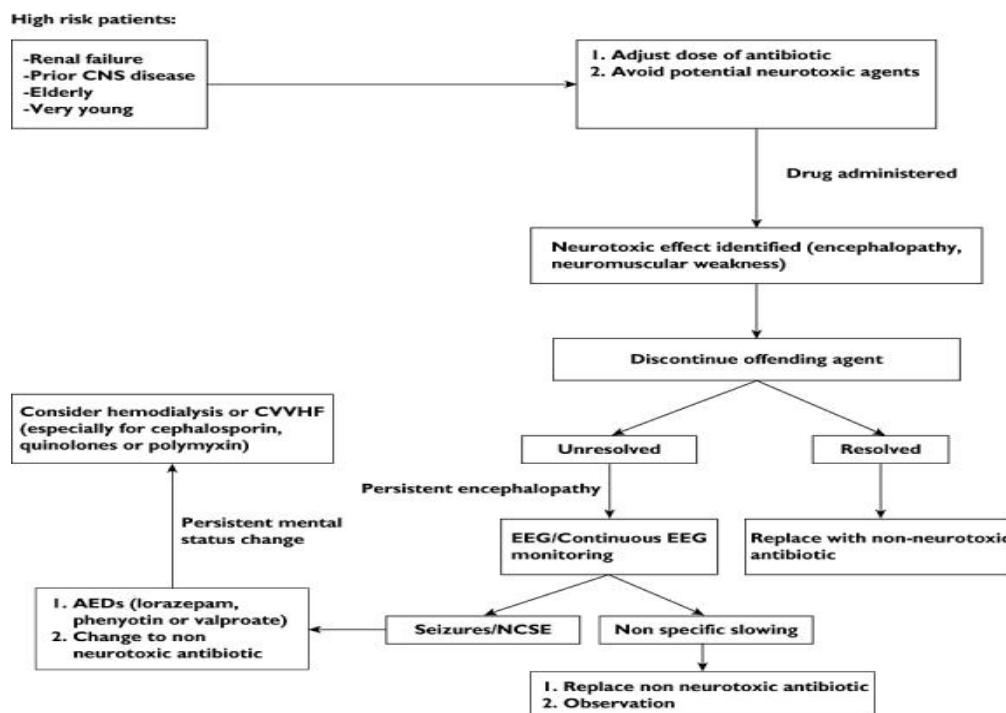
Two main factors accounting for drug-induced cognitive side effects have been proposed: pharmacodynamic and pharmacokinetic effects. Pharmacodynamic mechanisms can be described by medication interactions with neurotransmitters or the sensitivity of an individual to a medication, and are generally correlated with age^(44, 48). Pharmacokinetic mechanisms can be defined by absorption, distribution, metabolism, and excretion of drugs. Blood flow, volume of distribution, phases I and II metabolism, and glomerular filtration rate are just several mechanisms contributing to medication efficacy, inefficacy, or toxicity. In addition to basic pharmacodynamic and pharmacokinetic principles of medications, side effects are oftentimes caused by drug interactions that potentiate medication toxicity^(46, 47). Drug interactions may also be pharmacokinetic or pharmacodynamic in nature. Many common drug interactions are known to affect phase-I drug metabolism, involving the cytochrome P450 (CYP) enzyme system. Although drug interactions can occur through various mechanisms, the ultimate effects involve either enhancement or antagonism of a medication's effects.

II. MANAGEMENT

Identification of risk factors associated with neurotoxicity is imperative and perhaps the most important initial step.

The potential strategies to overcome β -lactam antibiotic-triggered toxicity are as follows:

- Replacing the toxic β -lactam with a non-allergic/toxic one,
- In cases of seizures or NCSE, anticonvulsants may be needed, albeit temporarily.
- Using phage therapy instead of chemicals,
- Using β -lactamase inhibitors,
- Using other chemicals in combination with β -lactams,
- Performing a haemodialysis or haemofiltration (for very severe cases)⁽⁵⁰⁾,
- Rational drug prescribing and treatment monitoring.
- Identification of those populations at increased risk of these neurotoxicities will allow for better care of the patient⁽⁵¹⁾.



Management algorithm for antibiotic neurotoxicity: high risk patients

III. CONCLUSION

Antibiotics are frequently prescribed life saving drugs, but as any other drug it also has some side effects. One such side effect of antibiotics is 'Neurotoxicity'. Neurotoxicity is although rare but very important side effect because they may lead to a significant morbidity and even mortality. Beta (β)-lactam antibiotics are wide-spectrum antibiotics used for various bacterial infections, Beta lactam antibiotics can also cause different neurotoxic side effect. They are more common in the elderly patients with renal dysfunction, and in patients with preexisting problems in the central nervous system (CNS). Knowledge of neurotoxic effects, careful selection of antibiotics and dosages is essential in older patients, as well as in patients with renal insufficiency, and/or in patient with pre-existing neurological disorder, in order to prevent avoidable iatrogenic neurologic complications. In order to prevent such adverse events in clinical setting, the role of clinical pharmacist is very important. They can help in the identification and reporting of such adverse drug reactions (ADR's) as well as helpful in the selection of precise drug regimen that can lead to the increase in life expectancy and quality of life of the patients.

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