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ß-Lactam Induced Neurotoxicity

Introduction and Pathophysiology

ß-lactams represent the cornerstone of antibacterial therapy for a wide range of infections. While these agents are generally thought of as relatively safe antimicrobials, they are still associated with a broad range of adverse effects and must be monitored in clinical practice. Although ß-lactam induced neurotoxicity represents a rare adverse effect, it is becoming increasingly recognized in clinical practice, particularly within the critically ill patient population. Recognition of ß-lactam induced neurotoxicity is imperative to allow for appropriate intervention.

While the underlying mechanism of ß-lactam induced neurotoxicity has not been fully elucidated, multiple mechanisms have been hypothesized. The structural similarity between the ß-lactam ring and gamma-aminobutyric acid (GABA) allows ß-lactams to bind directly to the $GABA_A$ receptor, which keeps the receptor in an open conformation and prevents ion conduction.[1] More specifically, ß-lactams demonstrate concentration-dependent inhibition of the subunits of the $GABA_A$ receptor complex, which causes an overall decrease in GABA neuroinhibitory effects and an increase in glutaminergic excitatory neurotransmission. Notably, enzymatic cleavage of the ß-lactam ring results in loss of epileptogenic activity.[2] Cephalosporins exhibit competitive inhibition of the $GABA_A$ receptor complex subunits while penicillins exhibit non-competitive inhibition.[1]

Incidence

Cumulative incidence of ß-lactam induced neurotoxicity has been difficult to define, with conflicting rates reported in the literature alongside varying definitions of neurotoxicity. A large retrospective study of 2090 critically ill patients from Haddad et al. in 2022 found an incidence rate of 2-3%, with higher rates of 3-4% for the subset of patients receiving cefepime.[3] The authors noted that a more stringent definition of neurotoxicity was utilized in this study compared to previous studies.

Higher incidence rates have been reported such as in a retrospective study of 100 ICU patients treated with cefepime which reported a neurotoxicity incidence rate of 7-15%.[4] Incidence rate variations are likely based on the specific patient population, neurotoxicity definition used and the specific ß-lactam being studied.

Clinical Manifestations and Diagnosis

The manifestations of ß-lactam induced neurotoxicity consist of a wide range of clinical signs and symptoms, including altered mental status, reduced consciousness, agitation, encephalopathy, myoclonus, seizures, and non-convulsive or convulsive status epilepticus. While manifestations vary considerably between patients, neurologic events also differ according to the specific offending agent. For example, piperacillin-tazobactam and ertapenem are more likely to cause hallucinations and seizures, whereas cefepime and ceftazidime are more likely to cause abnormal movements.[5] Electroencephalogram (EEG) changes may show abnormalities including tri-phasic waves, multi-focal sharp waves, generalized slowing, non-convulsive status epilepticus, or myoclonic status epilepticus.[6] This broad range of symptoms can make diagnosis challenging, particularly in critically ill patients who may have alternative etiologies for these signs and symptoms.

Standardized diagnostic criteria have yet to be established, thus ß-lactam induced neurotoxicity tends to be a diagnosis of exclusion. When ß-lactam induced neurotoxicity is on the differential diagnosis, it is critical to consider the temporal relationship between drug initiation, neurotoxicity development, and resolution of toxicity following intervention. This temporal relationship is best described with cefepime, in which the median onset of neurotoxic effects is 4 days after drug initiation, although they can develop as early as 1 day after drug initiation.[7,8] Without any intervention,

symptoms progressively worsen. Once the ß-lactam is discontinued, improvement or resolution of symptoms generally occurs within 2 days.[7] The Naranjo Adverse Drug Reaction (ADR) Probability Scale can be useful in these cases to assess the causality of the neurotoxicity and to help classify it as a definite, probable, possible, or doubtful ADR.[9]

Risk Factors

Numerous risk factors for ß-lactam induced neurotoxicity have been described, especially with the use of cefepime. Renal dysfunction, whether acute or chronic, has been implicated as a major risk factor for toxicity due to the potential for significant increases in serum drug concentrations.[3,11,12] A systematic review from Payne et al. revealed supratherapeutic cefepime troughs, which they defined as concentrations >20 mg/L, in a majority of patients who developed toxicity.[6] However, toxicity has been reported even in cases where cefepime has been appropriately dose adjusted for renal insufficiency. In a 2017 systematic review, 26% of patients who experienced cefepime induced neurotoxicity had received appropriate doses of cefepime based upon renal function. Numerous case reports have also described this phenomenon.[13–15] It is possible that these cases of toxicity in the setting of normal renal function or appropriate renal-dose adjustments are due to overestimation of creatinine clearance with serum creatine based estimations in critically ill patients.

Blood-brain barrier dysfunction also may lead to increased permeability and thus increased cefepime central nervous system penetration, which increases the neurotoxic potential.[5] Additionally, elderly patients are at increased risk of neurotoxicity due to alterations in pharmacokinetic properties associated with advanced age.[16] A recent study also found increased risk of ß-lactam induced neurotoxicity with increasing body mass index (BMI), which may be attributed to alterations in the lipophilicity and volume of distribution of ß-lactams.[3] Awareness of these risk factors is critical to the early detection of ß-lactam induced neurotoxicity.

Defining the Threshold for Toxicity

The relationship between ß-lactam concentrations and the development of neurotoxicity is still being explored. Cefepime has been associated with neurotoxicity in 50% of patients at trough concentrations >22 mg/L when administered via intermittent infusion and steady-state concentrations >35 mg/L when administered via continuous infusion.[11,17] This same risk is associated with meropenem trough concentrations >64 mg/L and piperacillin-tazobactam concentrations >157 mg/L.[18,19] These proposed toxicity thresholds from relatively small, retrospective studies, highlight an opportunity for additional study in this area.

Management

If ß-lactam induced neurotoxicity is on the differential diagnosis, clinicians must first rule out other potential causes of altered mental status, encephalopathy, myoclonus, seizures, etc. Once other etiologies are ruled out, if ß-lactam induced neurotoxicity is strongly suspected then discontinuation of the drug is necessary to prevent symptom progression. In the case of cefepime-induced neurotoxicity, while it may present as altered mental status or reduced consciousness, it may progress to myoclonus or seizures if appropriate interventions are not taken in a timely manner. If an institution has therapeutic drug monitoring capabilities, sending a ß-lactam trough concentration may be helpful if concentrations are supratherapeutic. An improvement or resolution in clinical symptoms within 2 days after discontinuation of the suspected offending agent can help confirm the diagnosis of ß-lactam induced neurotoxicity.[1] In patients presenting with seizure activity, treatment with one or more antiepileptic drugs may be necessary. Additionally, hemodialysis is an option to facilitate drug removal in severe cases. In the systematic review by Payne et al., following one of the aforementioned interventions, 50% of patients with cefepime induced neurotoxicity experienced complete resolution of their symptoms and 39% of patients experienced partial resolution.[7] Patients who experience ß-lactam induced neurotoxicity should be switched to a non-ß-lactam antibiotic or a less epileptogenic ß-lactam to complete appropriate treatment for their infection

based upon microbiologic culture results and susceptibilities.

Conclusion

While ß-lactam antibiotics are generally considered to be one of the safest classes of antimicrobials, it is important to keep in mind their potential for causing neurotoxicity. While this is a diagnosis of exclusion and represents a rare adverse event, it is being increasingly recognized within critically ill patients with specific risk factors, such as renal dysfunction, older age and higher BMIs. Given the vast clinical presentation and potential for alternative etiologies, particularly in patients with additional comorbidities, a high suspicion for ß-lactam induced neurotoxicity is prudent for early recognition and intervention.

Key Points

- **ß-lactam induced neurotoxicity can present as a wide range of clinical signs and symptoms**
- **Diagnosis is based upon clinical presentation, EEG changes, and improvement or resolution of symptoms following ß-lactam discontinuation**
- **Risk factors include renal dysfunction, excessive ß-lactam levels, blood brain barrier dysfunction, advanced age, and elevated BMI**
- **Trough toxicity thresholds have been proposed but need further validation in clinical studies**
- **Appropriate management includes discontinuation of the offending ß-lactam and use of an alternative antibiotic**

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