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Letter to the Editor

Ceftriaxone induced neurotoxicity: a word of caution for elderly and patients with renal impairment

Sir,

Ceftriaxone is a third-generation cephalosporin commonly used in inpatient settings and is associated with both hepatic and renal excretion.[1] The cephalosporin group, particularly the fourth generation, including cefepime, has been commonly associated with encephalopathy, but recent literature has also suggested an increasing trend of encephalopathy related to ceftriaxone.[2]

A review of the literature has reported case reports and case series of more than 25 patients who have suffered from acute encephalopathy secondary to ceftriaxone toxicity.[3] Risk factors such as old age, impaired renal function, and hypoalbuminemia are associated with decreased clearance of the drug and increased concentration of unbound fractions, leading to increased drug penetration through the blood-brain barrier responsible for producing neurotoxicity.[4] The symptoms associated with neurotoxicity include seizures, mental status change, myoclonus, choreoathetosis, and encephalopathy.[5]

Ceftriaxone has always been considered a safe drug, with no dosage modification required in cases of renal impairment because of its biliary and urinary excretion.[5] According to current guidelines, even in renally impaired individuals, dosing modification is not required for doses up to IV 2 gm/24 hours.[2] Compared to healthy individuals, ceftriaxone half-life was increased, along with high peak concentration and area under the curve in renal-impaired patients.[4,5]

Ceftriaxone is usually dosed at 1-2 gm every 12-24 hours with normal plasma trough levels of 13-15 µg/ml and a CSF level of 0.18 to 1.04 µg/ml when given a dose of 2 gm ceftriaxone. The studies have reported increased ceftriaxone levels, with plasma levels ranging from 27.9 to 967 µg/ml and CSF levels ranging from 5.9 to 100.7 µg/ml in patients with associated neurotoxicity. High levels of ceftriaxone in the brain are hypothesized to competitively inhibit the γ-aminobutyric acid and lead to neural excitotoxicity effects.[1]

Patients with suspected ceftriaxone neurotoxicity have inconclusive CSF studies and diagnostic imaging. EEG shows diffuse slowing, which is non-specific, and diagnosis requires a high clinical suspicion. The mainstay of treatment in ceftriaxone-induced neurotoxicity is early diagnosis and discontinuation of the offending drug.[1] Ceftriaxone is mainly bound to plasma proteins, leading to the ineffectiveness of its removal through haemodialysis. Neurotoxicity cases have been majorly reported with 2 gm dosage, but previous literature has also reported neurotoxicity with as low as 1 gm dosing.

The clinical symptoms are seen after 2-23 days of ceftriaxone use, and remission occurs after 1-12 days of discontinuation of the offending drug.[3]

Ceftriaxone neurotoxicity has been reported among patients with either impaired renal function or old age (especially over 75) because of its prolonged half-life in both scenarios. Neurotoxicity is mainly caused by unbound ceftriaxone, which has the property to penetrate the blood-brain barrier.

Clinical diseases associated with hypoalbuminemia constitute another risk factor leading to an increase in unbound ceftriaxone levels and blood-brain barrier penetration. These findings suggest ceftriaxone may be used with caution or avoided in patients with older age, impaired renal function, and hypoalbuminemia due to its risk of neurotoxicity.

Therapy can also be monitored with plasma ceftriaxone levels in high-risk individuals to adjust the optimum dose even in the absence of strict guidelines.

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