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Acute hepatotoxicity due to clonazepam in a girl using oxcarbazepine

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Benzodiazepines generally used as sedating, antianxiety, or anticonvulsant agents. In particular, diazepam (DZ), lorazepam (LZ), and clonazepam (CZ) are widely used for the management of acute epileptic seizures or status epilepticus[1]. Benzodiazepines (BDZ) are highly protein bound in plasma, and undergo extensive hepatic biotransformation. Due to a predominant hepatic metabolism, liver disease can significantly affect the metabolism of various benzodiazepines[2]. Antiepileptic drugs (AED) as therapeutic agents have been associated with severe hepatotoxicity. In a large series of drug-induced liver injury (DILI) reported to the Danish authorities in the 1970s and 1980s, a total of 8.3% out of all reports were AED[4]. We report a girl who developed hepatotoxicity due to clonazepam, which resolved promptly after cessation of therapy.

A 7-year-old girl using oxcarbazepine followed with the diagnosis of cerebral palsy and epilepsy in our outpatient children for 5 years. She had a history of perinatal asphyxia. On physical examination, she had severe psychomotor retardation and could not walk and speak. Previously she used phenobarbital (4.2 mg/kg/d) for 4 years. She was using oxcarbazepine (22 mg/kg/d) for 2 years. Clonazepam (0.05 mg/kg/d) was added to the therapy because of increment of her convulsion. Before initiation of clonazepam, hemogram, serum electrolytes, renal and liver function tests (aspartate aminotransferase (AST); 26 U/L, alanine aminotransferase (ALT); 20 U/L) were normal. On the 7 th day of clonazepam therapy she was readmitted to our outpatient clinic because her convulsion were continued. On that time hemogram, serum electrolytes, renal function tests were normal but AST and ALT were 195 U/L and 227 U/L, respectively. TORCH serology and the serologic profile of Hepatitis A, B and C were unremarkable. Abnormal liver function tests were thought due to clonazepam and it was immediately discontinued. 5 th day of cessation of clonazepam, serum AST and ALT levels were 33 and 31, respectively.

DILI is a potential complication of many drugs. This is not surprising given the fact that the liver plays a central role in drug metabolism. Clobazam, clonazepam, diazepam, lorazepam and midazolam are commonly used BDZ in the treatment of epilepsy[3]. All BZDs share similar neuropharmacologic properties including anxiety reduction, sedation, sleep induction, anticonvulsant effects and muscle

relaxation[5]. Diazepam and lorazepam are primarily used for management of seizure emergencies, whereas clobazam, clonazepam and clorazepate are commonly used in chronic epilepsy management[5]. The main limitations in the use of clonazepam have been side effects and the development of tolerance to its antiepileptic efficacy[6]. Many authors consider the side effects to be dose-dependent and found them to be diminished when the dose was reduced[6]. Barker *et al*[7], concluded that long term BZD users show recovery of function in visuospatial skills, attention/concentration, general intelligence, psychomotor speed and nonverbal memory assessments after withdrawal. A few case reports showing mild to moderate elevations in liver tests have been reported in association with oxcarbazepine[8].

In conclusion, our case showed that hepatotoxicity might be seen during clonazepam therapy in children using oxcarbazepine.

Conflict of interest statement

We declare that we have no conflict of interest.

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