Hypersensitivity Reactions due to Antiepileptic Drugs: A Chemical Structure Based Association?

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Background: Antiepileptic drugs (AEDs) can cause various hypersensitivity reactions, ranging from mild urticarial eruptions to potentially lifethreatening events such as Stevens-Johnson syndrome. The mechanism by which AEDs induce hypersensitivity is unknown. One of the main hypotheses is that AEDs containing an aromatic ring in their chemical structure can form an arene-oxide intermediate that may be responsible for these adverse effects. This theory is mainly based on case reports and in vitro experiments. So far, no cohort studies have been published supporting this theory.

Objective: The aim of this study was to assess whether the presence of an aromatic ring in chemical structures of AEDs are associated with symptoms of hypersensitivity in reports submitted to the Netherlands Pharmacovigilance Centre.

Methods: In The Netherlands health professionals and patients can report suspected adverse drug reactions (ADRs) to the Netherlands Pharmacovigilance Centre Lareb. All reported ADRs related with AEDs as suspected drug were included in this case/non-case study. Cases were defined as those ADRs containing symptoms of hypersensitivity. All other ADRs were controls. Symptoms of hypersensitivity were classified according to the Gell and Coombs classification (type I-IV). AEDs were classified as aromatic if their chemical structure contained at least one aromatic ring (carbamazepine, felbamate, lamotrigine, oxcarbazepine, phenytoin, phenobarbital, primidone and zonisamide). All other AEDs were classified as non-aromatic. We assessed the strength of the association between aromatic AEDs versus non-aromatic AEDs and ADRs for hypersensitivity reactions and expressed these associations as reporting odds ratios (RORs).

Results: Between 1985 and 2007, 303 hypersensitivity ADRs associated with the use of AEDs were reported. Aromatic AEDs were suspected in relation to 64.4% (195/303) of these reports. A significant ROR of 2.56 (95% CI: 1.98-3.32) was found for aromatic AEDs and all hypersensitivity reactions. IgE mediated response reactions (type I) corresponded with 62 ADRs (20.5%), IgG and Fc-receptor mediated response reactions (type II) with 94 ADRs (31.0%), immunocomplex deposition reactions (type III) with 36 ADRs (11.9%) and T-cell mediated hypersensitivity reactions (type IV) with 111 (36.6%). Aromatic AEDs were significantly associated with type I hypersensitivity reactions (ROR: 2.45; 95% CI: 1.32-3.82) and type IV reactions (ROR: 8.64; 95% CI: 4.97-15.01). Type II and III reactions did not show disproportionality.

Conclusion: This study shows that a commonality in chemical structures of AEDs may explain specific types of hypersensitivity reactions. Symptoms of hypersensitivity were reported two times as frequent with aromatic AEDs as with non-aromatic AEDs. The association was strongest for T cell mediated (type IV) reactions.

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