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ANTIEPILEPTIC DRUGS

RISK OF SERIOUS SKIN RASH WITH ANTIEPILEPTIC DRUGS

The risk of serious cutaneous reactions during the introduction of antiepileptic drug treatments was evaluated by a cohort study of prescription and hospitalization files for the Province of Saskatchewan, Canada, conducted at Worldwide Epidemiology, Glaxo Wellcome, Research Triangle Park, NC; and the Department of Dermatology, Beth Israel Hospital, Harvard Medical School, Boston, MA. All first-time users of phenytoin (PHY), carbamazepine (CBZ), and valproic acid (VPA) were identified for 1978-1987 and 1990. Of 8,888 new PHY users, 8 were hospitalized for serious cutaneous reactions: 1 Stevens-Johnson syndrome (SJS), 3 hypersensitivity syndromes (HSS), 2 angioedema, 2 erythema multiforme (risk of 9 per 10,000 users). Of 9,738 new CBZ users, 6 were hospitalized: 4 with HSS, 2 exfoliative dermatitis (risk of 6.2 per 10,000). Of 1,504 new VPA users, 1 had erythema multiforme, but this was attributed to concomitant PHY treatment. None was fatal. (Tennis P, Stern RS. Risk of serious cutaneous disorders after initiation of use of phenytoin, carbamazepine, or sodium valproate: a record linkage study. Neurology Aug 1997;49:542-546). (Reprints: Dr Patricia Tennis, Worldwide Epidemiology, Glaxo Wellcome, PO Box 13398, Research Triangle Park, NC 27709).

COMMENT. Hypersensitivity syndromes accounted for the majority of serious cutaneous reactions to the initiation of antiepileptic treatment with phenytoin and carbamazepine. None had toxic epidermal necrolysis (TEN) and none was fatal.

Skin rash, especially Stevens-Johnson syndrome, is one of the most disturbing side-effects of AEDs. The introduction of any anticonvulsant, especially carbamazepine, should be accompanied by a warning of possible skin rash, particularly during the first two weeks of treatment. The risk of skin rash with the initiation of CBZ, PHY, or phenobarbital in children has been estimated at 5 to 10 per cent. Although serious, sometimes fatal, cutaneous reactions such as SJS and TEN are rare, the milder hypersensitivity syndromes are relatively common and may require hospitalization, if the diagnosis is

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delayed and the drug treatment is continued.

The newer anticonvulsant, lamotrigine (Lamictal®), chemically unrelated to conventional AEDs, and introduced as adjunctive therapy of partial seizures, may also cause skin rash, especially within the first six weeks of therapy, in patients receiving concomitant VPA, and in those receiving doses higher or escalated faster than generally recommended. (Glaxo Wellcome product information).

AED-induced skin rash in children treated with CBZ and lamotrigine is reviewed in Progress in Pediatric Neurology III, 1997, pp 143-146; and VOL II, 1994, pp 107-109; PNB Publishers, Chicago.

DIET, CARNITINE, AND VALPROATE-INDUCED AMMONEMIA

The effect of a protein-rich meal (45 g protein) before and after L-carnitine (50 mg/kg/day) for 7 days in 11 epileptic children treated with valproate (VPA) was studied in relation to the magnitude and duration of the VPA-induced hyperammonemia at the University of Wisconsin School of Pharmacy and Department of Neurology, Madison, WI. After a protein meal, the 2-hour plasma ammonia level was increased by 86% over baseline before carnitine administration compared to 38% after carnitine. Ammonia levels approached baseline at 4 hours after a protein meal and were not related to changes in VPA concentrations. (Gidal BE, Inglese CM, Meyer JF, Pitterle ME, Antonopolous J, Rust RS. Diet- and valproate-induced transient hyperammonemia: effect of L-carnitine. Pediatr Neurol May 1997;16:301-305). (Respond: Dr Gidal, University of Wisconsin School of Pharmacy and Department of Neurology, 425 N Charter St, Madison, WI 53706).

COMMENT. VPA increases plasma ammonia in almost 50% of children treated. The degree of hyperammonemia is related to diet. It is exacerbated by a protein rich meal, and the postprandial transient elevation of plasma ammonia is significantly reduced by L-carnitine administration and is unrelated to changes in VPA concentration. Both fasting and 2-hour postprandial plasma ammonia levels should be measured to determine the magnitude of a VPA-induced hyperammonemia.

Valproate-induced liver failure is reported in one of two siblings with Alpers disease treated at the University of Minnesota, Minneapolis. (Schwabe MJ, Dobyns WB, Burke B, Armstrong DL. Pediatr Neurol May 1997;16:337-343). Both were developmentally delayed and suffered from seizures from 5 years of age. The proband receiving VPA for only 5 days had minimal liver abnormalities at autopsy at age 8 years. The younger brother treated with VPA for 4 weeks developed acute liver necrosis and died 5 weeks after admission. VPA is not recommended in children with suspected Alpers disease, characterized by developmental delay, ataxia, and epilepsia partialis continua.

GABAPENTIN-INDUCED CHOREOATHETOSIS

Two institutionalized, severely retarded adults, aged 42 and 41, with intractable epilepsy, developed choreoathetosis within 14 days when gabapentin in dosages of 1200 to 1800 mg/d were added as adjunctive therapy to valproic acid or phenytoin, in a report from University of Texas Southwestern Medical Center, Dallas, and Denton State School, Texas Mental Health and MR System. In case 1, also receiving valproic acid, intermittent choreoathetosis occurred for many weeks after gabapentin was discontinued,