ANTICONVULSANT DRUGS

LAMOTRIGINE FOR ABSENCE SEIZURES

The effectiveness and safety of lamotrigine (Lamictal) monotherapy in newly diagnosed typical absence seizures in 45 children and adolescents, aged 3-15 years, were evaluated in a placebo-controlled, double-blind trial at centers in Norfolk, VA; Akron, OH; Boston, MA; and Research Triangle Park, NC. EEG with hyperventilation and ambulatory 24-hr EEG recordings were used to confirm diagnoses and assess freedom from seizures. In the initial open-label dose escalation phase, 71% of patients (intent-to-treat) or 82% (per protocol analysis) became seizure free on doses of 2-15 mg/kg/day (median, 5.0). In the controlled trial, 62% of patients remained seizure free when treated with LTG and 21% when receiving placebo ($p<0.02$). Mean plasma LTG concentrations showed a linear relation to the dose. Adverse effects included rash, nystagmus, and depression, but none was severe. Pre-treatment inattention and hyperactivity in 3 patients were improved following LTG.(Frank LM, Enlow T, Holmes GL et al. Lamictal (lamotrigine) monotherapy for typical absence seizures in children. Epilepsia July 1999;40:973-979). (Reprints: Dr LM Frank, Neurodevelopmental Center of the Children's Hospital of the King's Daughters, Monarch Research Associates, 850 Southampton Avenue, Norfolk, VA 23510).

COMMENT. Lamotrigine monotherapy is effective and relatively free from serious side effects in children with typical absence seizures. Skin rash can be troublesome, but risk of serious rash may be lessened by adhering to recommended dosage guide-lines.

LAMOTRIGINE-ASSOCIATED SKIN RASH

The risk factors and methods of minimizing the occurrence of serious rash during treatment with lamotrigine (LTG) were evaluated by an international panel of experts and by review of published and unpublished reports. Stevens-Johnson syndrome and hypersensitivity syndrome with rash, necessitating hospitalization, occurred in 1 of 300 adults and 1 of 100 children in clinical trials. An allergic skin reaction occurred in 10% of patients, mainly in the first 8 weeks of therapy. The risk of skin rash was greatest with overrapid titration of initial doses of LTG and with concurrent valproate therapy. The panel outlines recommendations for minimizing the risk of serious rash with LTG: dosage guidelines for monotherapy, for therapy concurrent with VPA or other enzyme-inducing AED, and dosages in children. As add-on therapy in children (aged 2-12 years) taking valproate, initial total daily doses of 0.2 mg/kg for weeks 1 and 2, and 0.5 mg/kg once daily for weeks 3 and 4 are recommended. With other enzyme-inducing AED, 2 mg/kg/day in 2 divided doses for weeks 1 and 2, and 5 mg/kg/daily for weeks 3 and 4 are suggested. Maintenance and maximal suggested doses are achieved by slow increments every 1-2 weeks. The reader should consult the report for details of LTG dosage and management of rash. (Guberman AH, Besag FMC, Brodie JM et al. Lamotrigine-associated rash: risk/benefit considerations in adults and children. Epilepsia July 1999;40:985-991). (Reprints: Dr AH Guberman, Division of Neurology, Ottawa General Hospital, 501 Smyth Rd, Ottawa, Ontario K1H8L6, Canada).

COMMENT. Skin rash can be a serious side effect of anticonvulsant medications, especially in children, and some forms may be life-threatening. Attention to guidelines for the gradual introduction of lamotrigine, and avoidance

of concurrent valproate therapy when possible, may lessen the risk of serious rash.

VIGABATRIN FOR INFANTILE SPASMS

The efficacy of vigabatrin (VGB) as the first, and adrenocorticotropin hormone (ACTH) or valproate (VPA) as the second, treatment of choice for newly diagnosed infantile spasms was evaluated in 42 infants treated at the University of Helsinki, Finland. Response was measured by total control of spasms for a minimal duration of 1 month and confirmation by video-EEG. Spasms were cryptogenic in 10 and symptomatic in 32. Vigabatrin (50-100 mg/kg/day) controlled spasms in 11 (26%); 5 were cryptogenic and 6 symptomatic. ACTH offered in combination with VGB in 22 and VPA in 4, not controlled by VGB alone, were effective in 11 (50%) and 1 (25%), respectively. Overall, 26 (62%) infants responded to treatment; 100% response with cryptogenic cases and 50% with symptomatic etiology. Side effects were more severe with ACTH than VGB or VPA. Relapse after a spasm-free period of >4 months occurred in only 1 infant treated with VGB, but in none who received ACTH combined with VGB. ACTH should be considered after an initial trial of VGB in increasing doses from 50 to 150 mg/kg for 10-14 days. (Granstrom M-L, Gaily E, Liukkonen E. Treatment of infantile spasms: results of a population-based study with vigabatrin as the first drug for spasms. Epilepsia July 1999;40:950-957). (Reprints: Dr M-L Granstrom, Epilepsy Unit, Hospital for Children and Adolescents, University of Helsinki, Lastenlinnantie 2, 00250 Helsinki, Finland).

COMMENT. Vigabatrin is suggested as the first treatment for all infants with infantile spasms. In non-responders, ACTH should be considered. Response should be confirmed by video-EEG of 3-4 hours during waking and sleep, and visual responses should be carefully monitored when practical. Etiology of spasms is the most important determinant of treatment outcome; cryptogenic cases benefit more frequently than those with acquired causes. Most infants with symptomatic etiology are mentally retarded at follow-up. See Ped Neur Briefs (June 1999;13:47) for report of a previous study of ACTH cf vigabatrin in infantile spasms. In one study, VGB was recommended as first-line therapy for infantile spasms. In another, also from Finland, asymptomatic visual field constriction is reported in 2 children treated with VGB.

Vigabatrin-induced aminoaciduria. Fourteen children treated for epilepsy in Sheba Medical Center, Tel-Aviv University, Israel, had increased urinary excretion of amino acids, particularly B-alanine, g-aminobutyric acid, and B-aminoisobutyric acid, while receiving VGB. (Lahat E et al. Pediatr Neurol July 1999;21:460-463). A metabolic screen, including amino acid and organic acid analyses, is recommended prior to starting VGB therapy for seizures.

Aminoaciduria and epilepsy. Hyperaminoaciduria has been reported previously in children with absence and other idiopathic epilepsies (Millichap JG, Ulrich JA. Mayo Clin Proc 1962;37:307; Millichap JG, Jones JD. Epilepsia 1964;5:2349). The abnormal excretion was not associated with renal disease and could not be explained as a side effect of antiepileptic medication. In fact, the hyperaminaciduria was decreased during therapy with AEDs (trimethadione, phenobarbital, mephobarbital) or the ketogenic diet, suggesting a correlation between the aminoaciduria and epilepsy.

Ketosis and epilepsy. P31 magnetic resonance spectroscopic imaging studies were performed in 7 patients with intractable epilepsy, before and after the ketogenic diet. Significant increases in high-energy phosphates and metabolism occurred with the diet. (Pan JW et al. Epilepsia June 1999;40:703-707).