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SEIZURE DISORDERS

LOW-DOSE ACTH FOR WEST SYNDROME

The initial effects, adverse effects, and long-term outcome in 138 patients with West syndrome (WS) treated with low-dose synthetic ACTH were analyzed in a multi-institutional retrospective study reported from the Department of Pediatrics, Shiga Medical Center, Moriyama, Japan. Age at onset of spasms ranged from 1.5 to 60 months (mean 7.8 mos), and the interval to time of treatment was from 5 to 810 days (mean 94 days). WS was cryptogenic in 23 patients and symptomatic in 115. All patients except one had previously received vitamin B6, valproic acid, clonazepam, nitrazepam, other anticonvulsants, gamma-globulin or thyrotropin releasing hormone, without benefit. The initial therapy was continued in the same dosage and ACTH (Cortrosyn-Z, Organon) was added in a daily dosage that ranged from 0.005 to 0.032 mg/kg body wt (0,2 to 1.28 IU/kg/day). Daily injections were continued for 1 to 5 weeks, the total dosage ranging from 0.1 to 0.87 mg/kg (4 to 34.8 IU/kg). Seizure control was initially complete in 106 (76%), partial (50% decrease) in 23 (17%), and poor (<50%) in 9 (7%). All EEG seizure discharges had disappeared in 53 (38%), hypsarrhythmia was suppressed but focal spikes persisted in 76 (55%), and hypsarrhythmia was uncontrolled in 9 (7%). Factors correlating with a good initial seizure response included cryptogenic etiology, age at onset over 3 months, and a short time interval between seizure onset and ACTH therapy. Long-term evaluation in 98 patients followed for more than 2 years found 51 (52%) patients seizure-free, 6% with normal mental function, 16% mildly retarded, 27% moderately retarded, and 51% with severe mental retardation. A good seizure outcome correlated especially with cryptogenic etiology, and complete control of seizures and EEG at follow-up correlated with a good mental outcome. Initial seizure control and long-term outcome were not dependent on the dosage of ACTH, but severity of adverse effects correlated with the total dosage of ACTH. The severity of brain volume loss caused by ACTH was significantly correlated with daily and total dosage; a dose of 0.019 mg/kg/day or 0.404 mg/kg total dose was associated with moderate to severe brain loss whereas 0.013 mg/kg/day or 0.318 mg/kg total dose was not ($p<0.01$). Severe brain volume loss on CT/MRI occurred in 4%, moderate loss in 23% and slight loss

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in 64%. Adverse effects including brain loss were severe in 7%, moderate in 23%, and slight in 47%. Low-dose synthetic ACTH therapy was as effective in WS as higher doses used in previous studies. (Ito M, Aiba H, Hashimoto K et al. Low-dose ACTH therapy for West syndrome. Initial effects and long-term outcome. Neurology January (1 of 2) 2002;58:110-114). (Reprints: Dr Masatoshi Ito, Department of Pediatrics, Shiga Medical Center for Children, 5-7-30 Moriyama, Moriyama 524-0022, Japan).

COMMENT. Low-dose synthetic ACTH therapy for West syndrome is effective and is associated with less toxicity than higher dose regimens. Control of seizures and EEG hypsarrhythmia and favorable long-term outcome are correlated with a cryptogenic etiology and avoidance of delay in initiation of ACTH treatment. The frequency of serious adverse effects may be decreased by using the lowest effective dose of ACTH for the shortest duration. Ito and his colleagues have previously reported on the effectiveness of low-dose ACTH regimens for infantile spasms (Pediatr Neurol, 1990; see Progress in Pediatric Neurology I, PNB Publishers, 1991:pp 33-34). For a 10 kg-10 mos old infant, the dose of ACTH used in Japan was approximately 10 units daily and 300 units total. While these doses are similar to those advocated from my own experience (JAMA, 1962) and doses currently employed by my colleagues (Drs Nordli, Stack, & Swisher) at Children's Memorial Hospital, Chicago, much larger amounts were favored by Snead in the US (1989) and by my colleagues (Drs Wilson & Brett, 1987) at the Hospital for Sick Children, Great Ormond Street, London. From a practical standpoint, the use of ACTH in the natural form in the US has become difficult because of short supply and price constraints (approx $1000 per vial). The synthetic form is thought to be more potent and toxic than the natural form, but controlled studies are lacking. In conclusion, ACTH can be an effective and relatively safe treatment for infantile spasms, when injections are initiated soon after diagnosis, doses are conservative, and the lowest effective amount is used for the shortest time. Toxicity may be minimized by close and frequent patient monitoring.

A symposium on West syndrome, edited by Fukuyama Y, Tokyo, Japan (Brain Dev 2001;23:624-648), included several papers on treatment. Hancock E et al, from the UK, in reviewing the literature on the effectiveness of vigabatrin compared to ACTH and predisone, concluded that the optimum therapy for West syndrome remains uncertain. Ito, M, reporting on practice in Japan, comments that non-hormonal treatments are tried before using ACTH. He adds that close monitoring of adverse effects, especially subdural hematoma, is important, even with low dose synthetic ACTH therapy. Riikonen R of Finland recommends low-dose ACTH as the first choice of treatment and preferable to vigabatrin, since side effects are well known, treatable, and reversible. Baram TZ of Irvine, CA, reviewing the reasons for differences regarding ACTH dosage among researchers, emphasizes the variability in ACTH preparations, their bio-availability, and possible genetic and environmental differences among patients that determine responsiveness to ACTH.

VIGABATRIN ASSOCIATED RETINAL PATHOLOGY

A prospective study of 29 children treated with vigabatrin (VGB) as add on therapy for epilepsy included ophthalmic examination before and at 6-month intervals for 6.5 years, at Sultan Qaboos University Hospital, Sultanate of Oman. Age of onset of seizures ranged from birth to 5 years (mean, 13 months). Of 21 fulfilling study requirements and follow-up, 6 had West syndrome, 3 had Lennox Gastaut syndrome, and the remainder, partial or mixed seizures. Eighty percent had psychomotor retardation. Dose of VGB was 25-114 mg/kg/day (mean 56 mg) and treatment duration was 6-85 months (mean 36 mos). Four (19%) taking 25-50