Infantile Spasms and Epilepsy Currents

The United Kingdom Infantile Spasms Study Comparing Vigabatrin with Prednisolone or Tetracosactide at 14 Days: A Multicentre, Randomised Controlled Trial

Lux AL, Edwards SW, Hancock E, Johnson AL, Kennedy CR, Newton RW, O'Callaghan FJ, Verity CM, Osborne JP

Lancet 2004;364:1773–1778

PURPOSE: Infantile spasms, a severe infantile seizure disorder, have a high morbidity and are difficult to treat. Hormonal treatments (adrenocorticotropic hormone and prednisolone) have been the main therapy for decades, although little evidence supports their use. Vigabatrin has been recorded to have a beneficial effect in this disorder. We aimed to compare the effects of vigabatrin with those of prednisolone and tetracosactide in the treatment of infantile spasms.

METHODS: The United Kingdom Infantile Spasms Study assessed these treatments in a multicenter, randomized controlled trial in 150 hospitals in the United Kingdom. The primary outcome was cessation of spasms on days 13 and 14. Minimum doses were vigabatrin, 100 mg/kg/day; oral prednisolone, 40 mg/day; or intramuscular tetracosactide depot, 0.5 mg (40 IU) on alternate days. Analysis was by intention to treat.

RESULTS: Of 208 infants screened and assessed, 107 were randomly assigned to vigabatrin ($n = 52$) or hormonal treatments (prednisolone, $n = 30$; tetracosactide, $n = 25$). None was lost to follow-up. Proportions with no spasms on days 13 and 14 were 40 (73%) of 55 infants assigned hormonal treatments (prednisolone, 21 of 30 [70%]; tetracosactide, 19 of 25 [76%]) and 28 (54%) of 52 infants assigned vigabatrin (difference, 19%; 95% CI, 1%–36%, $p = 0.043$). Two infants allocated tetracosactide and one allocated vigabatrin received prednisolone. Adverse events were reported in 30 (55%) of 55 infants receiving hormonal treatments and 28 (54%) of 52 infants receiving vigabatrin. No deaths were recorded.

CONCLUSIONS: Cessation of spasms was more likely in infants given hormonal treatments than in those given vigabatrin. Adverse events were common with both treatments.

COMMENTARY

By their very nature, infantile spasms are dramatic and are included as one of the catastrophic epilepsies of childhood. More than 50% of the affected children have underlying neurologic disorders, and many will have both physical and mental handicaps. Often this syndrome heralds the development of other seizure disorders, such as Lennox–Gastaut syndrome, or other neurologic disorders, such as autism. Even the treatment for infantile spasms is fraught with problems, as the drugs used are not universally effective, and all have serious side effects, some of which are irreversible.

The three most common drugs studied for infantile spasms are adrenocorticotropic hormone (ACTH), oral steroids, and vigabatrin. ACTH, administered as tetracosactide, must be given as an intramuscular injection and can cause anaphylactic reactions, sodium and water retention, hypertension, congestive heart failure, ulcers, growth retardation, and hyperglycemia—to name a few serious side effects. Mortality also is associated with the treatment. Prednisolone is given orally and can cause all the typical reactions connected to cortisone treatment. Vigabatrin also is given orally and, although it does not cause severe systemic reactions of prednisolone or ACTH, it does cause irreversible peripheral visual-field deficits, creating severe visual handicaps and precluding the option to drive.

A report by Chiron and colleagues indicates that most of the previous clinical trials on treatment of infantile spasms have been of very short duration, ranging from only 5 days to a maximum of 8 weeks (1). Furthermore, the mainstay treatment for infantile spasms, steroids or ACTH, has been subjected to few randomized clinical trials since their initial use in the 1950s, with six studies available for ACTH (2–7) and two for prednisone (2,5). Vigabatrin was introduced in the 1990s; four randomized controlled trials demonstrate its efficacy in children with infantile spasms (1,4, 8,9). Among the trials on infantile spasms, some evidence indicates that vigabatrin is more effective than hydrocortisone (1) or ACTH (4) for the patient group with tuberous sclerosis. In the Chiron study, 100% of the tuberous sclerosis patients became seizure free and EEG normal after being administered vigabatrin (1).

Patient numbers have been small in these studies, reducing the power of the results.

Therefore, the study by Lux and colleagues, which included 208 infants, began with ambitious aims. The main purpose

of the study was to see if patients with other causes of infantile spasms or cryptogenic infantile spasms responded better to prednisolone, ACTH, or vigabatrin. A secondary outcome was to evaluate which of the three drugs better controlled the hypsarrhythmias, as determined by EEG. The study was designed to have a statistical power of 90% and to show a difference of 20% between the drugs, which, theoretically, would demonstrate the superiority of one drug over another, thus producing more useful results than any of the previous trials. Disappointingly, it was very difficult to recruit patients among the 150 hospitals within the U.K. that participated in the study. Of the 250 patients needed for the statistical analysis, only 107 could be recruited, with 52 patients allotted to vigabatrin, 25 to tetracosactide, and 30 patients to prednisolone, resulting in a study that was equally as underpowered as the previous randomized controlled trials. In addition, protocol deviations were noted: 1 child in the vigabatrin group received prednisolone; 2 patients in the tetracosactide group received prednisolone; and 18 patients did not follow dosing as designated in the protocol.

Nonetheless, the study was able to demonstrate that tetracosaide was more effective than vigabatrin in the treatment of cryptogenic infantile spasms. The first end point, cessation of spasms after 14 days, was achieved in 76% of patients taking tetracosactide, 54% of the patients in the vigabatrin group, and 70% in the prednisolone group. No significant difference was found between the prednisolone and tetracosactide groups. The secondary measure, cessation of hypsarrhythmias, was achieved in 81% in the hormonal groups compared with 56% of the vigabatrin group. Side effects in the hormonal groups included an increase in blood pressure to 110/80 in 20% and higher than 120/90 in 15% of patients. No child needed to be treated for diabetes, and no deaths occurred. Adverse events in the vigabatrin group generally were milder compared with those in the hormonal groups and not of systemic consequence, with drowsiness and irritability being the most common events. Visual fields, of course, could not be tested in this group of young patients. In conclusion, the study found that hormonal treatment for infantile spasms not caused by tuberous sclerosis is more effective than vigabatrin and should be the first-line treatment. Lux et al. plan to report 1-year efficacy findings for both the hormonal therapy and vigabatrin groups, which importantly, will provide long-term results.

An evidence-based practice parameter developed by the American Academy of Neurology and the Child Neurology Society states that ACTH "is probably effective for the short-term treatment of infantile spasms," whereas vigabatrin is "possibly effective," and indicates that not enough evidence is available to determine the effectiveness of oral corticosteroids (10). Unfortunately, the Lux et al. study will not improve on these statements or increase confidence in them, as stated, primarily because of the low patient numbers and the short follow-up time. For the rare epilepsy syndromes, it may continue to be difficult to conduct large double-blind, randomized studies, leaving clinicians to sort out which treatment is best for each patient—based on available evidence regarding efficacy and side effect profile, the clinician must weigh treatment options in the context of the individual patient.

by Elinor Ben-Menachem, MD, PhD

References

1. Chiron C, Dumas C, Jambaque I, Mumford J, Dulac O. Randomized trial comparing vigabatrin and hydrocortisone in infantile spasms due to tuberous sclerosis. *Epilepsy Res* 1997;26:389–395.
2. Hrachovy RA, Frost JD Jr, Kellaway P, Zion TE. Double-blind study of ACTH vs prednisone therapy in infantile spasms. *J Pediatr* 1983;103:641–645.
3. Yanagaki S, Oguni H, Hayashi K, Imai K, Funatuka M, Tanaka T, Yanagaki M, Osawa M. A comparative study of high-dose and low-dose ACTH therapy for West syndrome. *Brain Dev* 1999;21:461–467.
4. Vigevano F, Cilio MR. Vigabatrin versus ACTH as first-line treatment for infantile spasms: A randomized prospective study. *Epilepsia* 1997;38:1270–1274.
5. Baram TZ, Mitchell WG, Tournay A, Snead OC, Hanson RA, Horton EJ. High-dose corticotropin (ACTH) versus prednisone for infantile spasms: A prospective, randomized, blinded study. *Pediatrics* 1996;97:375–379
6. Hrachovy RA, Frost JD Jr, Glaze DG. High-dose, long-duration versus low-dose, short-duration corticotropin therapy for infantile spasms. *J Pediatr* 1994;124:803–806
7. Dreifuss F, Farwell J, Holmes G, Joseph C, Lockman L, Madsen JA, Minarcik CJ Jr, Rothner AD, Shewmon DA. Infantile spasms: Comparative trial of nitrazepam and corticotropin. *Arch Neurol* 1986;43:1107–1110.
8. Appleton RE, Peters AC, Mumford JP, Shaw DE. Randomised, placebo-controlled study of vigabatrin as first-line treatment of infantile spasms. *Epilepsia* 1999;40:1627–1633.
9. Elterman RD, Shields WD, Mansfield KA, Nakagawa J. US Infantile Spasms Vigabatrin Study Group: Randomized trial of vigabatrin in patients with infantile spasms. *Neurology*. 2001;57:1416–1421
10. Mackay MT, Weiss SK, Adams-Webber T. American Academy of Neurology; Child Neurology Society: Practice parameter: medical treatment of infantile spasms: Report of the American Academy of Neurology and the Child Neurology Society. *Neurology*. 2004;62:1668–1681.