IS TOPIRAMATE TOPS?

Topiramate Monotherapy in Newly Diagnosed Epilepsy in Children and Adolescents. Glauser TA, Dlugos DJ, Dodson WE, Grinspan A, Wang S, Wu SC; EPMN-106/INT-28 Investigators. *J Child Neurol* 2007;22(6):693–699. A double-blind, dose-controlled study evaluated topiramate as monotherapy in 470 patients with newly diagnosed (3 months) epilepsy or epilepsy relapse in the absence of therapy. In addition to having at least 2 lifetime-unprovoked seizures, patients had 1 or 2 partial-onset seizures or generalized-onset tonic-clonic seizures during a 3-month retrospective baseline. The trial included a large cohort (N = 151, 32%) of children and adolescents 6 to 15 years of age. Eligible patients were randomized to treatment groups in which topiramate was titrated to target maintenance dosages of either 400 mg/day (n = 77) or 50 mg/day (n = 74). Patients were followed for at least 6 months. Based on Kaplan-Meier analyses, the primary efficacy endpoint of time to first seizure favored the higher topiramate dose in both the overall population and the cohort of children/adolescents. The probability that children/adolescents remaining in the study were seizure free at 6 months was 78% in the 50-mg target dose group and 90% with the higher dose. At 12 months, the probability of being seizure free was 62% and 85%, respectively. The incidence of treatment-limiting adverse events was 4% in the 50-mg target dose group and 14% in the group assigned to 400 mg as a target dose. The most common adverse events, excluding typical childhood illnesses, were headache, appetite decrease, weight loss, somnolence, dizziness, concentration/attention difficulty, and paresthesia. As shown in this subset analysis, topiramate is effective and well tolerated as monotherapy in children and adolescents.

COMMENTARY

Topiramate is classified as a new antiepileptic drugs (AED), although in the near future, it will lose its patent protection and be available as a generic product. In spite of the fact that the drug has been in the clinical use for 10 years, much remains unknown about topiramate, such as how efficacious it is for new onset epilepsy as compared with other AEDs, especially for children. Most studies on drug efficacy for children are not performed until late in the drug's development; thus, information regarding use with children always lags behind that of adults. Furthermore, the number of child participants usually falls short of that required to adequately power a study to make a reliable assessment of the agent for this age group. In the study by Glauser and colleagues, the same problematic issues are evident. This trial is a "superiority design," or low-dose/high-dose paradigm, in which a low dose of the drug (50 mg) is compared to a high dose (400 mg); the design permits a relatively small sample size. The purpose generally is to show that the higher dose is more effective in controlling seizures than the lower dose or placebo for U.S. Food and Drug Administration (FDA) approval, as such data are required for the monotherapy labeling. Knowing that 50 mg is not as effective as 400 mg, still omits key data on whether 100, 200, or 300 mg doses are as effective; these data potentially could avoid an overdose while identifying an optimal response. A problem with this study design is that patients in the lower dose group cannot increase their dose if they fail; thus, the outcome is inherently biased against this group. The end point measure was time to first seizure; in other words, after one seizure the patient had to exit the study. However, if tolerability issues occurred in the high-dose group, patients were allowed to stay in the study but at a lower dose (reductions up to 100 mg)—again a potential study bias. While from clinicians' perspectives, the "noninferiority clinical trial design" is a more useful clinical trial design for new onset epilepsy, it does not satisfy FDA registration requirements—thus the present study's design. However, the question remains: do the findings provide information to successfully treat a child or adolescent with new onset epilepsy?

Glauser et al. had two subsets of patients—those with partial onset seizures and those with generalized tonic–clonic seizures. Analysis was not made as to a specific syndrome classification in the generalized group, however patients with EEGs characteristic of absences or myoclonic seizures were excluded. During a 3-month baseline period, for inclusion in the study, one to two seizures were permitted, but not more, although more seizures were allowed in the time prior to enrollment. After 6 months of treatment, 78% of the 50-mg children/adolescents group and 90% of the 400-mg children/adolescents group were seizure free, while by 1 year the percentages were 62% and 85%, respectively. The results are impressive and better than

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the adults assessed alone (i.e., without children/adolescents) for which only 70% were seizure free after 1 year on 400 mg/day (1). When the results were stratified into those patients with partial onset seizures and those with generalized tonic–clonic seizures, the findings then were similar, with 60% of patients in the partial group given 50 mg/day seizure free for a year and 81% in the 400 mg/day group. For the generalized tonic–clonic group, 63% were seizure free for 1 year in the 50 mg/day group and 88% seizure free in the 400 mg/day group.

The negative side effect profile for topiramate has stopped this drug from being used as a first-line therapy, particularly because of issues related to cognitive dysfunction. Indeed, in the Glauser et al. study, 20% of children/adolescents on the 400 mg dose compared with 8% at the 50 mg dose had cognitive problems. No child treated with 50 mg stopped the study because of cognitive side effects, whereas 7 on the 400 mg dose dropped out. Although patients were rated as having mild or moderate intensities of the adverse events, cognitive side effects, albeit mild, can make a significant difference in the life of a school-age child. Therefore, even if very effective, a 400-mg/day dose of topiramate cannot be a recommended starting dose for any child. In Europe, topiramate labeling indicates a starting dose as low as 100 mg; however, 50 mg is effective and may be a preferred initial dose for children, for whom reducing side effects, especially those influencing learning, is of great importance.

In all clinical trials, blood samples are taken to determine drug concentration but are not always disclosed. Therefore, it was a positive factor that Glauser et al. reported blood concentrations, with findings indicating that higher concentrations were associated with a better response to topiramate—indicating that the data could be used to determine optimal dosing. Therapeutic drug monitoring may be helpful, if low-dose topiramate is not effective.

The key points for clinicians from Glauser et al. trial include:

1. Topiramate can be effective at low doses; comparative trials indicate it is at least as good as other low-dose AEDs (2).
2. Low-dose topiramate produces fewer rates of and less intense side effects than higher doses. It is an appropriate initial low-dose treatment for a broad spectrum of seizure disorders, including partial seizures and generalized tonic–clonic seizures.
3. Children tend to respond more favorably than adults to topiramate.
4. Therapeutic drug monitoring of topiramate may be of value in determining the optimal dose, with the least side effects.

Unanswered questions include whether topiramate, or any of the other newer drugs, have antiepileptogenic effects or can prevent the development of refractory epilepsy. One way to assess these issues is to treat patients who become seizure free for 2 years, then randomize them to either stopping or continuing the drug to see if differences in relapse rates appear. Also, the newer AEDs need to be compared with each other so that useful information concerning the best choice of a first AED can be determined.

by Elinor Ben-Menachem, MD, PhD

References

1. Arroyo S, Dodson WE, Privitera MD, Glauser T, Naritoku DK, Dlugos DJ, Wang S, Schwabe SK, Twyman RE, EPMN-106/INT-28 Investigators. A randomized dose-controlled study of topiramate as first-line therapy in epilepsy. *Acta Neurol Scand* 2005;112:214–1222.
2. Glauser T, Ben-Menachem E, Bourgeois B, Cnaan A, Chadwick D, Guerreiro C, Kalviainen R, Mattson R, Perucca E, Tomson T. ILAE treatment guidelines: evidence-based analysis of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. *Epilepsia* 2006;47:1094–1120.

Does Increased Levetiracetam Clearance during Pregnancy Require Planned Intervention?

Pharmacokinetics of Levetiracetam During Pregnancy, Delivery, in the Neonatal Period, and Lactation. Tomson T, Palm R, Källén K, Ben-Menachem E, Söderfeldt B, Danielsson B, Johansson R, Luef G, Ohman I. *Epilepsia* 2007;48:1111–1116. PURPOSE: To study pharmacokinetics of levetiracetam (LEV) during pregnancy, delivery, lactation, and in the neonatal period. METHODS: Fourteen women with epilepsy receiving LEV treatment during pregnancy and lactation contributed with 15 pregnancies to this prospective study in which LEV concentrations in plasma and breast milk were determined. Trough maternal plasma samples were collected each trimester, and at baseline after delivery. Blood samples were obtained at delivery from mothers, from the umbilical cord, and from newborns during 2 days after delivery. LEV concentration was also determined in breast milk and in plasma collected from 11 of the mothers and their suckling infants after birth. RESULTS: The umbilical cord/maternal plasma concentration ratios ranged from 0.56 to 2.0 (mean 1.15, $n = 13$). LEV plasma concentrations in the neonates declined with an estimated half-life of 18 h ($n = 13$). The mean milk/maternal plasma concentration ratio was 1.05 (range, 0.78–1.55, $n = 11$). The infant dose of LEV was estimated to 2.4 mg/kg/day, equivalent to 7.9% of the weight-normalized maternal dose. Plasma concentrations in breastfed were approximately 13% of the mother's plasma levels. Maternal plasma concentrations during third trimester were only 40% of baseline concentrations outside pregnancy ($p < 0.001$, $n = 7$). CONCLUSIONS: Our observations suggest considerable transplacental transport of LEV and fairly slow elimination in the neonate. Plasma concentrations of LEV in nursed infants are low despite an extensive transfer of LEV into breast milk. Pregnancy appears to enhance the elimination of LEV resulting in marked decline in plasma concentration, which suggests that therapeutic monitoring may be of value.

COMMENTARY

Pregnancy may be associated with increased seizure frequency in close to 20% of women with epilepsy (1). The cause of the escalation in seizure frequency during pregnancy is likely multifactorial and may be related, in part, to a change in antiepileptic drug (AED) clearance and serum concentration. Lamotrigine, in particular, is considerably affected by pregnancy, with a substantial increase in clearance and a drop in serum levels (2,3). This finding is most pronounced in the second and third trimesters when lamotrigine clearance almost doubles (3). The decreased concentration of lamotrigine is accompanied by rising concentrations of its 2-*N*-glucuronide metabolite, suggesting increased metabolism by glucuronidation (2). Oxcarbazepine, another new AED whose metabolism involves glucuronidation, is similarly affected by pregnancy. A small study showed that the concentration of the active moiety during the second and third trimesters is less than half of the concentration after delivery (4). Valproate, which inhibits glucuronidation, reduces the effect of pregnancy on lamotrigine clearance (5). The amplified glucuronidation during the last two trimesters is most likely related to increasingly higher levels of estrogen, which is known to induce glucuronidation, thus reducing the concentration of drugs metabolized through this pathway (6).

Limited information is available regarding the effect of pregnancy on other new AEDs. Among them, levetiracetam is frequently used as an adjunctive treatment for partial and generalized epilepsy, and it recently received European approval as an initial monotherapy to treat partial-onset seizures. Favorable preliminary reports regarding the safety of levetiracetam during pregnancy are likely to encourage levetiracetam use in that setting (7). The current study by Tomson et al. found that levetiracetam clearance was consistently greater during the third trimester. In women whose dose of levetiracetam remained unchanged, the mean levetiracetam serum concentration in the third trimester was 40% of the mean concentration after delivery. Since levetiracetam is not metabolized through glucuronidation, it is not clear why its clearance is so greatly increased. To clarify the mechanism, a prospective study will need to be conducted to measure concentrations of levetiracetam, as well as its metabolites in plasma and urine, through the stages of pregnancy and after delivery.

An important issue is whether the altered clearance of levetiracetam during pregnancy requires intervention to maintain seizure control. Pregnancy-induced changes in lamotrigine clearance and serum concentration have been shown to be very clinically relevant. Several studies have demonstrated increased seizure frequency associated with declining lamotrigine serum levels (8,9). Lamotrigine dose adjustments are necessary after the first trimester and again following delivery (3). In a large study of seizure control during 1,956 pregnancies, women treated with oxcarbazepine and lamotrigine were the most likely to require dose adjustments. The study did not

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have enough patients taking levetiracetam to adequately power a separate analysis.

In the study of Tomson and colleagues, only two of seven women had a greater number of seizures during pregnancy, and both also were taking lamotrigine. In four women who took concomitant lamotrigine, the third trimester reduction in AED levels seemed more pronounced for lamotrigine than levetiracetam. While the clinical relevance of AED serum concentration is established for lamotrigine (10), it is not for levetiracetam. Levetiracetam efficacy is evident very early in titration (11), such that the initial target dose is likely to exceed the minimum effective dose for most treatment-responsive patients. The current study points to the need to study a larger cohort of patients to assess the effect of increased levetiracetam clearance during pregnancy on seizure control, but it does not currently provide enough evidence to support levetiracetam dose adjustment during pregnancy.

The study of Tomson and colleagues did not suggest adverse consequences from the extensive transfer of levetiracetam across the placenta and through breast milk. Even though the levetiracetam half-life in neonates was more than double that of adults, the levetiracetam plasma concentration declined rapidly after birth, with no evidence of accumulation. This finding is in accordance with a previous study (12) and should be reassuring to mothers who wish to provide their infants with the benefits of breast milk.

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References

1. The EURAP Study Group. Seizure control and treatment in pregnancy: observations from the EURAP epilepsy pregnancy registry. *Neurology* 2006;66:354–360.
2. Ohman I, Beck O, Vitols S, Tomson T. Plasma concentrations of lamotrigine and its 2-N-glucuronide metabolite during pregnancy in women with epilepsy. *Epilepsia* 2007; Dec 11 [Epub ahead of print].
3. Pennell PB, Peng L, Newport DJ, Ritchie JC, Koganti A, Holley DK, Newman M, Stowe ZN. Lamotrigine in pregnancy. Clearance, therapeutic drug monitoring, and seizure frequency. *Neurology* 2007; Nov 28 [Epub ahead of print].
4. Mazzucchelli I, Onat FY, Ozkara C, Atakli D, Specchio LM, Neve AL, Gatti G, Perucca E. Changes in the disposition of oxcarbazepine and its metabolites during pregnancy and the puerperium. *Epilepsia* 2006;47:504–509.
5. Tomson T, Luef G, Sabers A, Pittschieler S, Ohman I. Valproate effects on kinetics of lamotrigine in pregnancy and treatment with oral contraceptives. *Neurology* 2006;67:1297–1299.
6. Reimers A, Helde G, Brodtkorb E. Ethinyl estradiol, not progestogens, reduces lamotrigine serum concentrations. *Epilepsia* 2005;46:1414–1417.
7. Hunt S, Craig J, Russell A, Guthrie E, Parsons L, Robertson I, Waddell R, Irwin B, Morrison PJ, Morrow J. Levetiracetam in pregnancy: preliminary experience from the UK Epilepsy and Pregnancy Register. *Neurology* 2006;67:1876–1879.
8. de Haan GJ, Edelbroek P, Segers J, Engelsman M, Lindhout D, Devile-Notschaele M, Augustijn P. Gestation-induced changes in lamotrigine pharmacokinetics: a monotherapy study. *Neurology* 2004;63:571–573.
9. Vajda FJ, Hitchcock A, Graham J, Solinas C, O'Brien TJ, Lander CM, Eadie MJ. Foetal malformations and seizure control: 52 months data of the Australian Pregnancy Registry. *Eur J Neurol* 2006;13:645–654.
10. Hirsch LJ, Weintraub D, Du Y, Buchsbaum R, Spencer HT, Hager M, Straka T, Bazil CW, Adams DJ, Resor SR Jr, Morrell MJ. Correlating lamotrigine serum concentrations with tolerability in patients with epilepsy. *Neurology* 2004;63:1022–1026.
11. French J, di Nicola S, Arrigo C. Fast and sustained efficacy of levetiracetam during titration and the first 3 months of treatment in refractory epilepsy. *Epilepsia* 2005;46:1304–1307.
12. Johannessen SI, Helde G, Brodtkorb E. Levetiracetam concentrations in serum and in breast milk at birth and during lactation. *Epilepsia* 2005;46:775–777.

Cognitive Effects of Levetiracetam versus Topiramate

The Influence of Antiepileptic Drugs on Cognition: A Comparison of Levetiracetam with Topiramate. Gomer B, Wagner K, Frings L, Saar J, Carius A, Härle M, Steinhoff BJ, Schulze-Bonhage A. *Epilepsy Behav* 2007;10(3):486–494. Levetiracetam (LEV) and topiramate (TPM) are considered highly effective novel antiepileptic drugs (AEDs) in the treatment of focal epilepsies. To explore potential side effects, this study investigated their influence on cognitive functions comparatively by means of a standardized neuropsychological test battery assessing several cognitive domains. In this observational study, cognitive changes were explored in 30 consecutively recruited patients with focal epilepsy treated with LEV and in 21 patients treated with TPM, comparing functions assessed prior to gradual initiation and after reaching steady state of the individual target dosage. Before titration, patient groups did not differ significantly with respect to cognitive performance. Whereas the LEV group manifested no change in cognitive performance after AED titration, the TPM group worsened in the cognitive domains of cognitive speed and verbal fluency, as well as short-term memory. These findings suggest that TPM, unlike LEV, may impair frontal lobe functions. The lack of cognitive side effects related to LEV treatment may be relevant for treatment decisions.

COMMENTARY

The study by Gomer and colleagues compared the cognitive effects of levetiracetam (LEV) and topiramate (TPM) by examining changes in cognitive function beginning when the antiepileptic drug (AED) was started as an adjunctive therapy for patients with focal epilepsy. They found adverse cognitive effects were worse for TPM compared with LEV. Overall, patients were more likely to experience adverse cognitive effects with TPM, but some patients on TPM exhibited improvements in cognitive scores, and less than half of the patients on TPM deteriorated more than one SD on any measure—except one, block span. Limitations of the study include its observational, unblinded, nonrandomized, parallel design with relatively small sample sizes. Despite the limitations, these comparative findings are consistent with prior studies comparing TPM with other AEDs. TPM was shown to have slightly more adverse cognitive effects than valproate (1,2) and much greater adverse effects than lamotrigine (3). Since the cognitive effects of valproate are similar to carbamazepine (4) and both LEV and lamotrigine have fewer adverse cognitive effects than carbamazepine (5,6), it is not surprising that TPM would exhibit a much greater negative impact on cognitive functioning than LEV. In addition, a pattern of particular sensitivity to tasks involving frontal lobe function previously was reported to be associated with TPM (7), although TPM-induced deficits are not limited to those related to frontal lobe function (3). Gomer et al. note a lack of cognitive side effects related to LEV. The complete lack of effects in the present study probably is due to the small sample size and other study limitations. During other clinical trails, CNS-related adverse events have occurred, and mild adverse cognitive effects can be seen with an appropriate study design (5). Nevertheless, LEV is very well tolerated and has few cognitive side effects.

The study by Gomer et al. did not find that cognitive tasks were influenced by dosage for either TPM or LEV. The authors support their finding by stating that neither Huppertz et al. (7) nor Kockelmann et al. (8) demonstrated a "clear relationship between daily dosage and cognitive side effects." However, neither of these studies was conclusive in this regard, as they had limitations and reported some dose-dependent adverse events. The investigation by Huppertz et al. was a nonrandomized, open-label study with only 37 patients, and the authors specifically noted that adverse cognitive effects were decreased in a subset of patients whose doses were reduced 25–150 mg/day. The investigation by Kockelmann et al. was a nonrandomized, retrospective, cross-sectional study with just 42 patients, who received neuropsychological testing only once; however, the study did report significant correlations between TPM serum levels and verbal fluency, verbal memory span, as well as verbal memory (delayed recall and recognition). A recent study by Loring et al. examined dose-dependent cognitive effects of TPM in 183 cognitively normal adults, using a double-blind, placebo-controlled, parallel group, dose-ranging study of 24 weeks duration (9). Dosing was initiated at 32 mg (16 mg/bid) and increased to target doses of 64, 96, 192, or 384 mg/day. The investigators found that the neuropsychological impairment associated with TPM emerges in a dose-dependent fashion. Thus, the lack of a dosage effect in the Gomer et al. report likely is due to the sample size and other limitations of the study.

Gomer et al. state that Aldenkamp and coworkers: "proposed that gradual introduction of TPM could prevent cognitive side effects." Aldenkamp et al. actually stated that: "gradual

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introduction of TPM can reduce the extent of cognitive impairment" (1). Gomer et al. argue against a critical effect of the initial TPM titration, since their study started with a low dose, gradual titration, and testing was carried out under steady-state conditions. The titration rate used in this study was actually twice the recommended rate, and remarkably, there were no dropouts among the 51 consecutive patients, over approximately 4 months and two neuropsychological evaluations. While rapid titration increases the risk of cognitive side effects for virtually all AEDs, these effects are particularly prominent with TPM. For example, an investigation in healthy adults found that an acute dose of TPM at 2.8 mg/kg produces greater cognitive side effects than a slower titration over 4 weeks to a higher dose of 5.7 mg/kg (10).

Gomer et al. also state that: "Loring and Meador ascribed cognitive side effects of TPM to polypharmacy, higher dosages, and blood levels" (11). This sentence does not appear in the referenced article or in any articles by these authors. Indeed, a variety of factors affect the risk of adverse cognitive function by TPM as well as other AEDs, including polypharmacy, higher dosages, higher blood levels, rapid initiation, individual patient susceptibility, and the risk for the specific AEDs (4). Treatment-emergent adverse events, which are centrally mediated, typically are more frequent in adjunctive than monotherapy clinical trials. Dosage and blood level effects on cognition can be difficult to demonstrate within standard therapeutic ranges and may also be obscured if appropriate study design is not employed. Susceptibility to adverse cognitive effects in a patient is due to their individual pharmacokinetic and pharmacodynamic responses. Finally, there are differences across individual AEDs as demonstrated in the present study and prior investigations (4). Clinician awareness of these factors may help to reduce risks of adverse cognitive effects. Drug treatment often requires a balance between the risk of seizures and the risks posed by AEDs—including systemic side effects as well as cognitive function.

by Kimford J. Meador, MD

References

1. Aldenkamp AP, Baker G, Mulder OG. A multicenter, randomized clinical study to evaluate the effect on cognitive function of topiramate compared with valproate as add-on therapy to carbamazepine in patients with partial-onset seizures. *Epilepsia* 2000;41:1167–1178.
2. Meador KJ, Loring DW, Hulihan JF, Kamin M, Karim R CAPSS-027 Study Group. Differential cognitive and behavioral effects of topiramate and valproate. *Neurology* 2003;60:1483–1488.
3. Meador KJ, Loring DW, Vahle VJ, Ray PG, Werz MA, Fessler AJ, Ogrocki P, Schoenberg MR, Miller JM, Kustra RP. Cognitive and behavioral effects of lamotrigine and topiramate in healthy volunteers. *Neurology* 2005;64:2108–2114.
4. Meador KJ. Cognitive effects of epilepsy and of antiepileptic medications. In: Wyllie E, ed. *The Treatment of Epilepsy. Principles and Practices.* 4th ed. Philadelphia: Lippincott Williams & Wilkins, 2005:1185–1195.
5. Meador KJ, Gevins A, Loring DW, McEvoy LK, Ray PG, Smith ME, Motamedi GK, Evans BM, Baum C. Neuropsychological and neurophysiologic effects of carbamazepine and levetiracetam. *Neurology* 2007;69:2076–2084.
6. Meador KJ, Loring DW, Vahle VJ, Ray PG, Werz MA, Fessler AJ, Ogrocki P, Schoenberg MR, Miller JM, Kustra RP. Cognitive and behavioral effects of lamotrigine and topiramate in healthy volunteers. *Neurology* 2005;64:2108–2114.
7. Huppertz HJ, Quiske A, Schulze-Bonhage A. Cognitive impairments due to add-on therapy with topiramate. *Nervenarzt* 2001;72:275–280.
8. Kockelmann E, Elger CE, Helmstaedter C. Significant improvement in frontal lobe associated neuropsychological functions after withdrawal of topiramate in epilepsy patients. *Epilepsy Res* 2003;54:171–178.
9. Loring D W, Meador KJ, Williamson DJ, Wiegand F, Hulihan J. Topiramate dose effects on neuropsychological function: analysis from a randomized double-blind placebo-controlled study. *AES Abstracts* 2007;2:234. Available at: http://www.aesnet.org/go/publications/aes-abstracts/abstract-search/?mode=display&st=Loring&sy=2007&sb=Authors&startrow=1&id=7683.
10. Martin R, Kuzniecky R, Ho S, Hetherington H, Pan J, Sinclair K, Gilliam F, Faught E. Cognitive effects of topiramate, gabapentin, and lamotrigine in healthy young adults. *Neurology* 1999;52:321–327.
11. Loring DW, Meador KJ. Cognitive and behavioral effects of epilepsy treatment. *Epilepsia* 2001;42(suppl 8):24–32.

Intravenous Valproate for Status Epilepticus . . . An Effective, Yet Still Merely Empirical Alternative!

Valproate Is an Effective, Well-Tolerated Drug for Treatment of Status Epilepticus/Serial Attacks in Adults. Olsen KB, Taubøll E, Gjerstad L. *Acta Neurol Scand Suppl* 2007;187:51–54. OBJECTIVE: Status epilepticus (SE) and serial attacks (SA) represent neurological emergencies, and mortality rate for SE/SA is high, ranging from 3% to 25%, depending on cause and co-morbidity. As SE/SA become more refractory to treatment over time, rapid, appropriate treatment is extremely important. Here, we report a prospective registration of the effect of intravenous (IV) valproate (VPA) on SE/SA in a group of Norwegian patients. PATIENTS AND METHODS: Forty-one adult patients (18 males, 23 females) were included in the study. All had previously been unsuccessfully treated with diazepam. For 19, the main SE/SA seizure type was generalized tonic-clonic, while 16 had complex-partial seizures. Six had seizures that were difficult to classify. The treatment protocol recommended 25 mg/kg of VPA loading dose over 30 min, followed by continuous infusion of 100 mg/h for at least 24 h, then per oral administration. If seizures persisted after the loading dose, general anaesthesia (barbiturates/propofol/midazolam) was administered. RESULTS: No serious side effects were reported. In 76% of the cases (31 of 41), SE/SA stopped and anaesthesia was not required. Of the patients treated within 3 h, only 5% needed anaesthesia, whereas of those treated after 3–24 h, 38% needed anaesthesia. Of those who waited for more than 24 h before treatment, 60% required anaesthesia. Furthermore, 60% of the patients who needed anaesthesia were given loading doses below 2100 mg. CONCLUSIONS: VPA seems to be a safe, effective treatment of SE/SA, but efficacy is dependent on time lapse between symptoms and VPA treatment, and administration of a sufficiently high loading dose.

COMMENTARY

The Veterans Administration collaborative study (VACS) is the largest and most important study, to date, on the treatment of generalized convulsive status epilepticus (GCSE) (1). The investigators compared the safety and efficacy of four commonly prescribed antiepileptic drug (AED) regimens in 384 patients. The regimens included intravenous (IV) lorazepam, phenobarbital, and phenytoin given as monotherapy, and diazepam followed by phenytoin. Overt GCSE remitted in 64.9% randomized to lorazepam, 58.2% treated with phenobarbital, 43.6% of patients randomized to phenytoin, and 55.8% given diazepam followed by phenytoin. A switch to any of the other three treatment arms yielded seizure remission in only 10% of patients whose GCSE persisted after the initial AED trial. Since the publication of that study, other AEDs, not used in the VACS, have been evaluated in the management of status epilepticus (SE). They include IV valproate (VPA), high-dose oral topiramate, and more recently levetiracetam, as oral or IV preparations. IV VPA has been the AED most extensively studied.

Efficacy of IV VPA has been demonstrated in animal models of SE. For example, Martin and Pozo used an in vivo model of SE induced by intrahippocampal application of 4-aminopyridine; IV VPA was administered before or after the induction of SE (2). The intrahippocampal injection of 4-aminopyridine induced continuous epileptic activity without a clinical component and lasted more than 60 min. IV administration of 400–600 mg/kg VPA over a period of 100 s abolished the SE, and this effect persisted for more than 4 h. Of note, IV administration of 100–300 mg/kg VPA did not abolish previously induced SE, but prevented the appearance of SE when applied before the induction of SE. In contrast, the IV injection of 80 mg/kg phenytoin or carbamazepine did not abolish or prevent SE. In a separate study, Walton and Treiman tested the efficacy of IV VPA in a model of GCSE rats with cortical cobalt lesions; the animals were injected with homocysteine thiolactone to induce secondarily generalized tonic–clonic seizures (3). They found that seizure remission occurred at a median effective dose of 211.9 mg/kg, which yielded a serum concentration of 270 μg/mL at 30 min after the dose was given; all doses were administered intraperitoneally following the second generalized tonic–clonic seizure.

Recently, Trinka as well as Larch and Trinka presented the results of a systematic review of the literature on the efficacy of IV VPA in various forms of SE (4,5). The investigators identified 20 published studies (13 retrospective, 7 prospective) that together involved 533 adults and children. Seizure control was achieved within 20 min of the IV VPA infusion in three-quarters of patients, and the authors concluded that this AED was as effective as phenytoin in resolving SE in patients who had previously failed conventional first-line therapies, such as benzodiazepines. Unfortunately, most of the studies included in the review were uncontrolled trials, leaving open room to question whether the findings might be spurious.

In one of two randomized, open studies carried out thus far on GCSE, 68 patients were assigned to IV VPA or IV

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phenytoin, as first line therapies (6). Seizure remission was reached in 66% of patients administered VPA and 42% given phenytoin. Of note, these remission rates were almost identical to those yielded by GABAergic AEDs (e.g., lorazepam, phenobarbital, diazepam) in the VACS. For patients whose seizure activity persisted at the end of the initial AED trial, a switch to the other AED was carried out. Among patients switched to valproic acid, 79% became seizure-free, but this outcome occurred in only 25% of patients switched to phenytoin. Unfortunately, the study was underpowered to demonstrate superiority of VPA over phenytoin, and hence, the difference in efficacy was only suggestive (7). In the second randomized study on GCSE, 40 children with refractory SE were randomized to treatment with either IV VPA or IV diazepam (8). Seizure activity remitted in 80% of children given IV VPA and 85% on IV diazepam. The median time needed to control the refractory SE was significantly shorter with VPA (5 min) than diazepam (17 min).

In the VACS, only 10% of patients whose seizure activity persisted after administration of the initial trial remitted with one of the other three treatment alternatives (1). This low remission rate contrasts with the 79% remission rate found with use of IV VPA in patients who failed to respond to phenytoin (6). Whether the difference is meaningful is yet to be determined, since the VACS did not include IV VPA as one of the treatment arms. Yet, such high success has been reported in other studies in which SE failed to be controlled with benzodiazepines. The present study by Olsen et al. is a case in point: seizure activity stopped in 76% of 41 adults with SE ($n = 21$) or serial seizures ($n = 12$) treated with VPA. This entire group of patients had previously been unsuccessfully treated with IV diazepam. Do these data suggest that IV VPA is more effective than the first-line therapies used in the VACS? Or, is it possible that the therapeutic effect yielded by VPA was the result of an enhanced effect of the prior administration of diazepam. For example, is it possible that 76% of patients whose seizures failed to stop with benzodiazepines remitted with VPA, not only because of the latter's anticonvulsant effect, but also by a positive pharmacodynamic interaction between VPA and diazepam? By the same token, is it possible that the remission of SE with IV VPA in cases of unsuccessful prior trials with IV phenytoin can be explained as well by an increase in the free fraction of phenytoin, caused by its displacement from albumin receptors?

In addition to its successful treatment of GCSE, the efficacy of IV VPA has been observed in trials involving nonconvulsive SE with complex partial seizures, absence status, and in status myoclonicus (4,5), though each of the studies were based on open trials. Despite all of these promising data suggestive of the efficacy of IV VPA in the treatment of SE, at this point, there are no methodologically sound head-to-head comparison studies to suggest that VPA is superior in efficacy to any other AEDs.

With respect to its safety and tolerability, the profile of IV VPA appears to be very attractive, as it does not have the adverse events encountered with the benzodiazepines, phenobarbital, and phenytoin (8–10). Indeed, IV VPA rarely is associated with cardiovascular adverse events, such as hypotension or arrhythmia, even when administered at high doses with very rapid infusions, and it has not been found to cause respiratory depression. With such a profile, VPA would be the ideal first-line treatment of SE. . .if we only had methodologically sound data to support this indication! Unfortunately, difficulty with getting institutional review board approval to conduct head-to-head comparisons of drugs for SE (at least in the United States) poses significant obstacles to obtaining relevant data.

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References

1. Treiman DM, Meyers PD, Walton NY, Collins JF, Colling C, Rowan AJ, Handforth A, Faught E, Calabrese VP, Uthman BM, Ramsay RE, Mamdani MB. A comparison of four treatments for generalized convulsive status epilepticus. Veterans Affairs Status Epilepticus Cooperative Study Group. *N Engl J Med* 1998;339:792–798.
2. Martín ED, Pozo MA. Valproate suppresses status epilepticus induced by 4-aminopyridine in CA1 hippocampus region. *Epilepsia* 2003;44:1375–1379.
3. Walton NY, Treiman DM. Valproic acid treatment of experimental status epilepticus. *Epilepsy Res* 1992;12:199–205.
4. Trinka E. The use of valproate and new antiepileptic drugs in status epilepticus. *Epilepsia* 2007;48(Suppl. 8):49–51.
5. Larch J, Trinka E. Intravenous valproate in status epilepticus. A systematic review of the evidence. *Epilepsia* 2006;47:39.
6. Misra UK, Kalita J, Patel R. Sodium valproate vs phenytoin in status epilepticus: a pilot study. *Neurology* 2006;67:340–342.
7. Mehta V, Singhi P, Singhi S. Intravenous sodium valproate versus diazepam infusion for the control of refractory status epilepticus in children: a randomized controlled trial. *J Child Neurol* 2007;22:1191–1197.
8. Sinha S, Naritoku DK. (2000) Intravenous valproate is well tolerated in unstable patients with status epilepticus. *Neurology* 2000;55:722–724.
9. Limdi NA, Faught E. The safety of rapid valproic acid infusion. *Epilepsia* 2000;41:1342–1345.
10. Venkataraman V, Wheless JW. (1999) Safety of rapid intravenous infusion of valproate loading doses in epilepsy patients. *Epilepsy Res* 35:147–153.