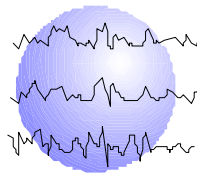


EFFICACY AND WEIGHT EFFECTS OF VALPROATE AND LAMOTRIGINE

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ABSTRACT

OBJECTIVE: To assess the effectiveness and side effect of weight gain associated with the combination of sodium valproate and lamotrigine for epilepsy.

BACKGROUND: Sodium Valproate (VPA) has been associated with significant weight gain in some patients who are on this drug. 57% gained > than 4kg in a series of 36 patients reported by Einesen, et al. A more recent study has reported the enhanced efficacy of VPA in combination with lamotrigine (LTG) (Gates, et al.). This study was designed to assess the efficacy of seizure treatment and whether the weight gain was a problem with the combination therapy as reported for VPA in monotherapy.

DESIGN/METHODS: The clinical charts of 34 adult patients, ages 21-64 (mean=39.5) on combination VPA and LTG therapy at Minnesota Epilepsy Group Clinic were reviewed for the period of 1984-2000. No other antiepileptic medications were administered while these patients were on valproate and lamotrigine combination therapy. All patients had partial seizures. Patients had previously failed 1-4 AED's (avg. 2.92) before study entry.

Average length on VPA/LTG therapy lasted 91.8 weeks (range 16-286). Mean blood level for VPA was 65.7 mcg/ml; mean blood level for lamotrigine was 13.6 mcg/ml. Mean dosages of VPA and LTG were 1136.0 mg/day and 309.6 mg/day, respectively.

RESULTS: The percentage of patients seizure free on this combination compared to baseline was 38.2%. The percentage of patients with > 50% reduction was 64.7%. Seizure frequency was reduced from an average of 5.2 seizures per month prior to initiation of dual treatment to 2.2 seizures per month ($p<.03$). Average weight before either VPA or LTG was started for the 34 patients was 72.9 kg. Average weight prior to VPA/LTG dual treatment was 75.9 kg. Eleven (32.4%) of the patients had a > 4 kg weight gain while on one of the two drugs. At an average of 91.8 weeks of dual therapy, the average weight was 77.9 kg. Eleven (32.4%) of the patients had a > 4 kg weight gain on the combination therapy. Two (5.9%) of the patients had a > 4 kg weight loss.

CONCLUSIONS: The combination of VPA and LTG demonstrates a remarkable efficacy (38.2% seizure free, 64.7% > 50% reduction), and is associated with a significant weight gain of > 4 kg in only 32.4% of patients.

INTRODUCTION

Several new antiepileptic medications have been released in the United States since 1993 when felbamate was the first in a series that has since included gabapentin, lamotrigine (LTG), levetiracetam, oxcarbazepine, topiramate, and zonisamide. There has been considerable interest in how these newer medications work with each other as well as with the more established medications. This study assesses the efficacy and the effects on body weight of LTG, in combination with valproic acid (VPA), both of which are broad-spectrum antiepileptic drugs for patients with medically refractory epilepsy. Interest in this combination is underscored by the previous work of Brodie, Yuen and the 105 Study Group¹ who demonstrated that when comparing combinations of LTG with carbamazepine, with phenytoin, and with VPA, the lamotrigine/valproate group dramatically improved for partial and tonic-clonic seizures. A more recent study by Gates², et al., reported enhanced efficacy of VPA in combination with LTG.

VPA has been associated with significant weight gain in some patients. 57% gained > than 4kg in a series of 36 patients reported by Dinesen³, et al. In addition to studying the efficacy of the LTG / VPA combination therapy, this study was designed to assess whether the weight gain as reported for VPA monotherapy was also a problem with this combination therapy.

CONCLUSION

The combination of VPA and LTG demonstrates a remarkable efficacy (38.2% seizure free, 64.7% > 50% reduction), and is associated with a significant weight gain of > 4 kg in only 32.4% of patients.

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3. Dinesen H, Gram L, Anderson T, Dam M. Weight gain during treatment with valproate. *Acta Neurol Scand* 1984; 70:65-69.

| Pt. # | Age | Pre-Drug Wt: | Date | Pre-combo Wt | Date | Recent Weight | Wks on LTG / VPA Therapy |
|-------|-----|-----------------|----------|-----------------|----------|------------------|-----------------------------|
| 1 | 28 | 67.6 | 09/08/97 | 68.5 | 07/19/99 | 81.5 | 51 |
| 2 | 52 | 77.0 | 02/27/90 | 73.0 | 04/27/95 | 77.1 | 234 |
| 3 | 40 | 66.7 | 01/01/11 | 66.7 | 07/08/96 | 75.2 | 180 |
| 4 | 23 | 79.1 | 01/06/99 | 80.8 | 03/23/99 | 82.6 | 37 |
| 5 | 50 | 55.9 | 03/14/89 | 53.8 | 03/21/99 | 58.7 | 20 |
| 6 | 51 | 79.0 | 02/21/96 | 73.0 | 09/04/97 | 81.6 | 144 |
| 7 | 47 | 77.5 | 09/04/87 | 89.9 | 03/05/99 | 89.9 | 18 |
| 8 | 41 | 78.0 | 08/13/86 | 90.3 | 11/24/98 | 90.8 | 84 |
| 9 | 27 | 66.4 | 01/15/91 | 66.1 | 09/06/94 | 77.8 | 286 |
| 10 | 27 | 52.3 | 12/17/94 | 64.0 | 05/26/98 | 69.0 | 60 |
| 11 | 62 | 72.0 | 06/15/95 | 73.0 | 10/16/97 | 75.6 | 134 |
| 12 | 61 | 81.1 | 07/30/96 | 83.5 | 05/24/99 | 80.7 | 43 |
| 13 | 42 | 67.1 | 11/27/91 | 76.3 | 06/26/95 | 87.7 | 248 |
| 14 | 44 | 78.5 | 05/06/98 | 75.4 | 08/02/98 | 72.2 | 99 |
| 15 | 21 | 85.4 | 03/10/99 | 81.7 | 04/15/99 | 79.3 | 49 |
| 16 | 30 | 52.8 | 11/11/97 | 56.3 | 11/04/98 | 57.8 | 88 |
| 17 | 40 | 92.2 | 06/05/95 | 102.9 | 08/16/96 | 101.9 | 188 |
| 18 | 38 | 68.2 | 08/12/96 | 72.2 | 10/15/97 | 66.6 | 136 |
| 19 | 42 | 88.6 | 09/25/92 | 83.9 | 05/25/96 | 84.3 | 194 |
| 20 | 21 | 57.6 | 12/28/98 | 65.3 | 07/13/99 | 71.0 | 46 |
| 21 | 61 | 85.0 | 09/23/97 | 85.9 | 12/27/97 | 85.9 | 26 |
| 22 | 28 | 69.0 | 05/01/89 | 82.1 | 03/01/98 | 82.4 | 56 |
| 23 | 28 | 82.4 | 06/02/97 | 76.8 | 04/01/98 | 82.7 | 82 |
| 24 | 56 | 78.5 | 05/05/99 | 78.5 | 10/05/99 | 79.5 | 23 |
| 25 | 53 | 77.3 | 11/13/92 | 88.3 | 05/05/99 | 89.9 | 17 |
| 26 | 22 | 62.9 | 01/29/99 | 65.0 | 06/01/99 | 62.7 | 54 |
| 27 | 40 | 55.4 | 08/09/92 | 2.4 | 10/11/96 | 53.2 | 64 |
| 28 | 57 | 70.0 | 05/03/90 | 71.4 | 07/24/95 | 64.7 | 118 |
| 29 | 38 | 73.5 | 02/01/97 | 75.7 | 04/29/98 | 71.9 | 84 |
| 30 | 49 | 92.7 | 12/12/96 | 94.4 | 06/10/99 | 99.6 | 32 |
| 31 | 35 | 64.0 | 04/30/84 | 80.1 | 02/12/99 | 79.7 | 16 |
| 32 | 28 | 70.5 | 01/01/92 | 70.3 | 05/01/95 | 72.5 | 22 |
| 33 | 28 | 80.5 | 07/28/93 | 91.1 | 03/01/97 | 89.9 | 98 |
| 34 | 32 | 73.6 | 02/13/95 | 73.5 | 07/01/95 | 73.9 | 90 |
| | | 39.5 | | 72.9 | | 75.9 | 91.8 |
| | | Mean Age | | Avg | | Avg | Weeks |

| Pt. # | Cur VPA Dose mg/day | Current VPA Level ug/ml | Cur LTG Dose mg/day | Cur LTG Level ug/ml | Sz Freq/Mo Prior to LTG/VPA Therapy | Sz Freq/Mo Last Visit on LTG/VPA Therapy | Comments re: Sz Freq: |
|---------------|---------------------|-------------------------|---------------------|---------------------|-------------------------------------|--|-----------------------|
| 1 | 1750 | 138.6 | 300 | 13.9 | 1.00 | 0.00 | Seizure free |
| 2 | 750 | 49.5 | 350 | 14.6 | 4.16 | 0.00 | Seizure free |
| 3 | 1750 | 74.5 | 300 | 10.3 | 6.00 | 0.90 | > 50% reduction |
| 4 | 625 | 64.0 | 225 | 11.2 | 14.17 | 0.00 | Seizure free |
| 5 | 750 | 63.2 | 200 | 14.3 | 0.30 | 0.25 | No change |
| 6 | 1750 | 98.9 | 250 | 16.2 | 41.00 | 4.50 | > 50% reduction |
| 7 | 1500 | 65.4 | 350 | 18.2 | 4.00 | 4.00 | No change |
| 8 | 2000 | 101.0 | 300 | 13.0 | 4.50 | 0.00 | Seizure free |
| 9 | 375 | 13.0 | 650 | 19.7 | - | 0.00 | Seizure free |
| 10 | 2125 | 91.9 | 400 | 21.7 | 3.00 | 11.79 | Increase in seizures |
| 11 | 375 | 43.6 | 175 | 10.8 | 1.50 | 1.00 | No change |
| 12 | 500 | 41.7 | 200 | 11.3 | 0.92 | 0.20 | > 50% reduction |
| 13 | 750 | 46.4 | 600 | 22.5 | 3.00 | 0.00 | Seizure free |
| 14 | 750 | 62.1 | 300 | 8.6 | 15.00 | 6.00 | > 50% reduction |
| 15 | 750 | 64.0 | 250 | 12.8 | 0.25 | 0.00 | Seizure free |
| 16 | 1000 | 70.4 | 325 | 17.1 | 16.50 | 17.70 | No change |
| 17 | 250 | 74.5 | 200 | 10.7 | 0.25 | 0.00 | Seizure free |
| 18 | 875 | 38.9 | 50 | 3.6 | 2.00 | 0.20 | > 50% reduction |
| 19 | 1500 | 63.0 | 300 | 11.0 | 0.08 | 0.00 | Seizure free |
| 20 | 1500 | 87.3 | 350 | 25.5 | 3.00 | 0.00 | Seizure free |
| 21 | 500 | 46.2 | 400 | 19.2 | 4.00 | 0.00 | Seizure free |
| 22 | 1500 | 58.0 | 250 | 11.0 | 0.00 | 0.00 | No change |
| 23 | 2000 | - | 200 | - | 1.50 | 0.00 | Seizure free |
| 24 | 1500 | 93.3 | 300 | 10.6 | 15.00 | 1.00 | > 50% reduction |
| 25 | 1000 | 32.2 | 25 | 2.1 | 1.00 | 0.25 | > 50% rduction |
| 26 | 375 | 24.9 | 75 | 2.5 | 2.50 | 4.50 | Increase in seizures |
| 27 | 1125 | 84.0 | 500 | 15.9 | 3.00 | 5.70 | Increase in seizures |
| 28 | 1000 | 38.9 | 200 | 9.2 | 2.20 | 4.50 | Increase in seizures |
| 29 | 1500 | 66.8 | 250 | 7.5 | 5.00 | 0.10 | > 50% reduction |
| 30 | 1500 | 86.1 | 350 | 9.2 | 2.00 | 1.00 | > 50% reduction |
| 31 | 1250 | - | 500 | - | 1.80 | 3.50 | Increase in seizures |
| 32 | 500 | 58.8 | 400 | 22.3 | 6.00 | 0.00 | Seizure free |
| 33 | 1000 | 78.4 | 500 | 19.9 | 2.00 | 3.10 | Increase in seizure |
| 34 | 2250 | 83.6 | 500 | 18.1 | 3.40 | 3.00 | No change |
| 1136.0 | 65.7 | 309.6 | 13.6 | 5.2 | 2.2 | | |
| Mean | Mean | Mean | Mean | Mean | Mean | Mean | (p < .03) |

