EFFICACY AND WEIGHT EFFECTS OF VALPROATE AND LAMOTRIGINE

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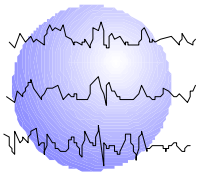

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ABSTRACT

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 zonegran. 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 Group[1] 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 Gates[2], 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 Dinesen[3], 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.

REFERENCES

1. Brodie, MJ, Yuen AWC, 105 Study Group. Lamotrigine substitution study: evidence for synergism with sodium valproate? Epilepsy Research 1997;26:423-432.
2. Gates JR, Mulligan KA, Penovich PE, Moriarty GL. Efficacy of valproate and lamotrigine therapy in patients with medically intractable epilepsy. Epilepsia (40)7:143, 1999.
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 Mean Age		72.9 Avg		75.9 Avg	91.8 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 Mean	65.7 Mean	309.6 Mean	13.6 Mean	5.2 Mean	2.2 Mean ($p < .03$)	

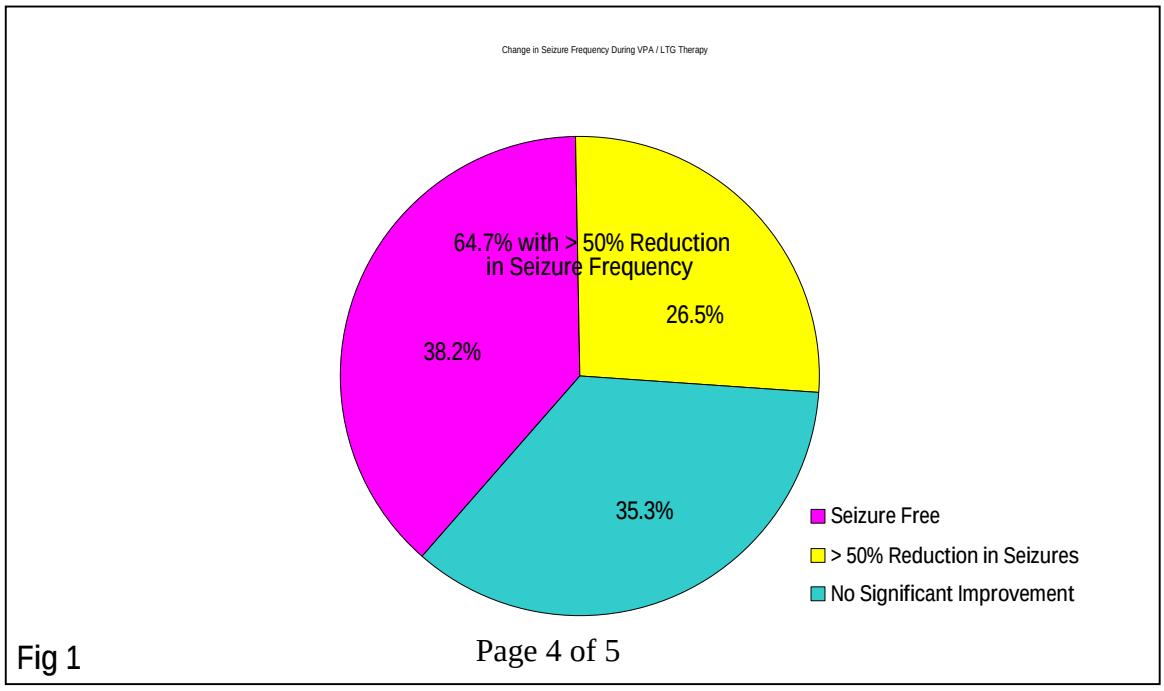

Fig 1

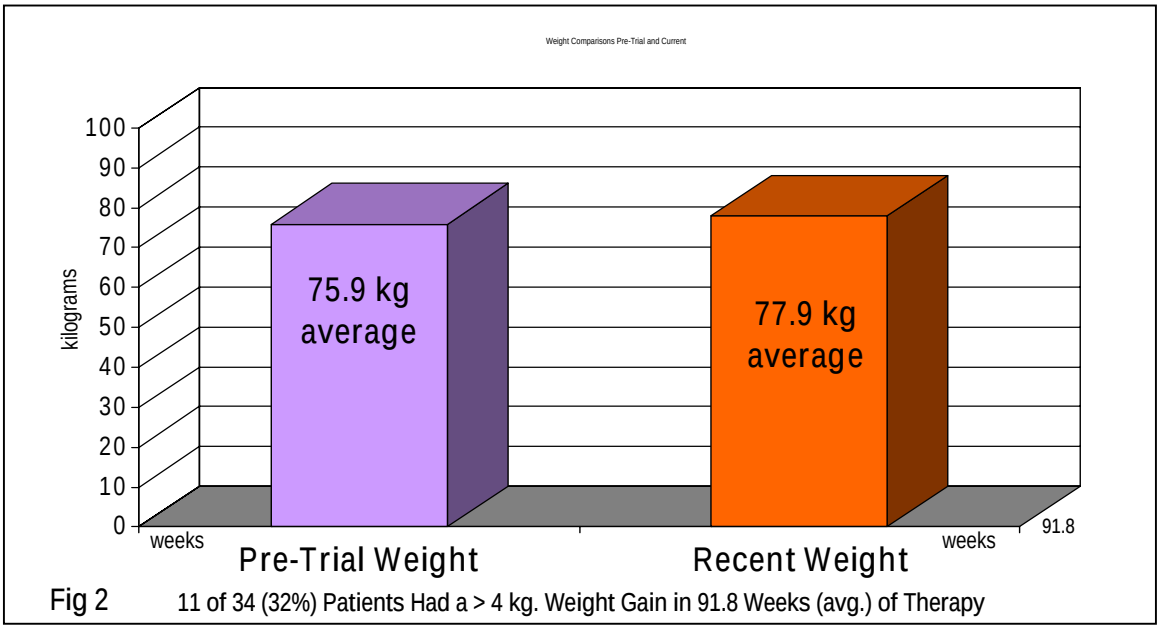

Fig 2 11 of 34 (32%) Patients Had a > 4 kg. Weight Gain in 91.8 Weeks (avg.) of Therapy

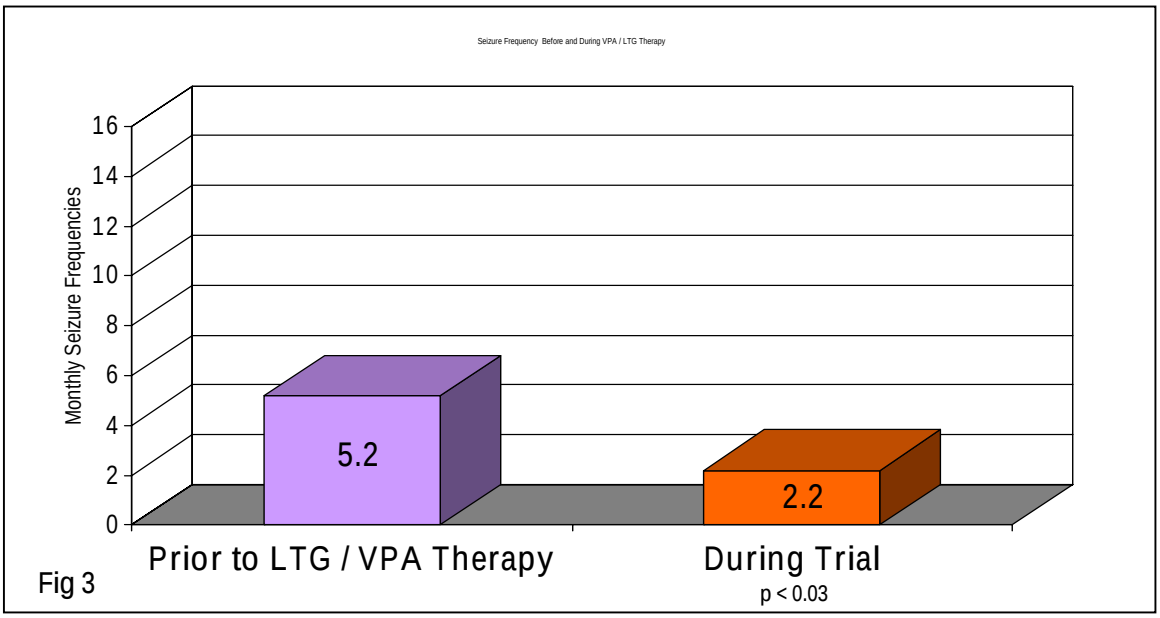

Fig 3