Lithium, Carbamazepine and Valproate in Acute Mania

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ABSTRACT:
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Objective: Mood stabilizers are frequently used in the management of acute mania. Lithium has been used for this indication since Cade first described its effectiveness in psychotic excitation in 1949. Carbamazepine and valproate are also accepted as effective antimanic agents. Whether one of these agents is more effective than others is still a matter of discussion. Our aims have been to clarify this issue and to see which one has a faster onset of action. **Methods:** We compared the clinical efficacy of lithium, carbamazepine and valproate in 30 inpatients with acute mania. Diagnoses were made according to DSM-IV criteria. There were 10 patients on each arm. Clinical efficacy was assessed weekly by Bech-Rafaelsen Mania Scale, Brief Psychiatric Rating Scale, and Clinical Global Impressions Scale for six weeks. Serum levels of study drugs were obtained weekly in order to maintain recommended serum levels. We referred to neuroleptics for excitation when really necessary, and the amount used was recorded as chlorpromazine equivalents. **Results:** During weekly assessments and at the end of the study, none of the drugs was superior to each other neither in antimanic efficacy nor in the week the efficacy began at. All of study drugs reduced assessment scale scores significantly at the end of third week. The amount of neuroleptics used was not different among the patient groups. **Conclusions:** Lithium, carbamazepine and valproate are efficacious antimanic agents that have no superiority on each other in treatment of acute mania, but these findings need to be replicated in larger studies.

Key words: acute mania, mood stabilizers, lithium, carbamazepine, valproate, efficacy

Bull Clin Psychopharmacol 2001;11:90-95

ÖZET:
AKUT MANİ TEDAVİSİNDE LİTYUM, KARBAMAZEPİN VE VALPROAT

Amaç: Duygudurum düzenleyicileri akut mani tedavisinin vazgeçilmez ilaçlarıdır. Lityum psikotik eksitasyonda etkili olduğu, 1949 yılında Cade tarafından bildirildiğinden beri kullanılmaktadır. Karbamazepin ve valproat da lityumun alternatifleri olarak görülmektedirler. Bu ilaçlardan hangisinin akut manide daha etkili olduğu henüz yanıtı tam olarak verilemeyen bir soru olarak klinisyenleri meşgul etmektedir. Bu açık çalışma akut manili hastalarda lityum, karbamazepin ve valproatın etkinliğini ve etkinin ortaya çıkma süresini karşılaştırmak için yapılmıştır. **Yöntem:** Çalışmaya tanıları DSM-IV sınıflandırmasına göre konulmuş, akut manili, yatan 30 hasta alınmıştır. Her bir grupta 10 hasta yer almış, altı hafta izlenen hastalara haftalık olarak Bech-Rafaelsen Mani Ölçeği, Kısa Psikiyatrik Değerlendirme Ölçeği, Klinik Global İzlenim Ölçeği uygulanmış ve ilaçların kan düzeyleri ölçülmüştür. Sadece zorunlu oldukça kullanılan nöroleptikler klorpromazin eşdeğeri olarak kaydedilmişlerdir. **Bulgular:** Üç ilacın etkinliği ve etki hızı benzer bulunmuştur. Her üç grupta da klinik iyileşme üçüncü haftada başlamış, çalışma boyunca kullanılan nöroleptiklerin miktarı istatistiksel açıdan anlamlı bir farklılık göstermemiş ve altı haftalık çalışma tamamlandığında hastalardaki iyileşme benzer bulunmuştur. **Sonuçlar:** Lityum, karbamazepin ve valproat akut maninin tedavisinde etkili ilaçlardır. Çalışmamızda bu ilaçların hiçbirisi, diğer ikisinden daha üstün bulunmamıştır.

Anahtar sözcükler: akut mani, duygudurum düzenleyicileri, lityum, karbamazepin, valproat, etkinlik

Klinik Psikofarmokoloji Bülteni 2001;11:90-95

INTRODUCTION

Bipolar disorder is a severe, highly prevalent disorder, which has an episodic nature, and is characterized by manic or depressive episodes followed by symptom-free periods (1). Although an untreated manic episode generally lasts from 2 to 8 months (2), unwanted events that may complicate the patient's life necessitates an effective and also quick treatment.

Lithium is drug of choice in bipolar disorder treatment (3) since its antimanic (originally antipsychotic) activity has been described by Cade in 1949 (4). In spite of the fact that patients described as having classic mania are being treated well by lithium (5), it is now accepted that belonging to any of three diagnostic subgroups that is, dysphoric manic/mixed states, rapid cycling, or comorbid substance abuse is associated with a lower response rate to lithium (6). Approximately 20-40% of patients with acute mania fail to respond to lithium (7). For those, carbamazepine and valproate may be effective

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Kabul tarihi: 26 Ocak 2001

alternatives. Although lithium and valproate have been approved by Food and Drug Administration for treatment of mania in the United States, efficacy of carbamazepine in acute mania is also well documented (1).

Emerging questions are whether one of these is more effective or has a faster onset of action in acute treatment of mania. This study was performed to test whether the clinical effectiveness and the time for onset of action of lithium, carbamazepine and valproate in acute mania is different or not. The patients involved in this study will also be followed for five years during maintenance treatment. This will enable us to evaluate the prophylactic efficacious of lithium, carbamazepine and valproate.

METHODS

The study was designed as an open label, clinical comparative study with inpatients. Acutely ill manic patients were hospitalized at Mood Disorders Unit of Psychiatry Department of Turgut Ozal Medical Center, in Malatya, one of eastern provinces of Turkey. Diagnoses were made according to Diagnostic and Statistical Manual of Mental Disorders (8) (DSM-IV) criteria. The study was approved by the Ethical Comittee of Inonu University.

Inclusion and exclusion criteria were as follows: patients who were between 18-65 years and meeting DSM-IV criteria for manic episode; that were without substance abuse history in the previous year and who had not been treated with any psychotropic agent during the previous month entered the study. Rapid cycling patients and patients with mixed episode were also excluded.

After initial evaluation and informed consent, Bech-Rafaelsen Mania Scale (9) (BRMS), Brief Psychiatric Rating Scale (10) (BPRS) and Clinical Global Impressions Scale-Severity Subscale (CGI) scores were obtained before institution of any pharmacological treatment. Patients were randomized in the following rank: the first patient was in lithium group, the second in carbamazepine, the third in valproate group, the fourth patient was again in lithium group and so on. There were 10 patients on each treatment arm.

Study drugs were 300 mg capsules of lithium carbonate, 200 and 400 mg tablets of carbamazepine, and 200 and 500 mg tablets of sodium valproate. Daily dosage was between 900-1500 mg for lithium, 600-1000 mg for carbamazepine and 750-1500 mg for valproate. Total daily dosage was divided into two or three, and was administered orally. Serum levels of drugs were obtained weekly, beginning within the end of the first treatment week. Targeted serum levels were between 1.0-1.4 mmol/L for lithium and 4-12 mg/ml for carbamazepine and 50-150 mg/ml for valproate. Intramuscular injections of neuroleptics were administered in cases of excitation. The amount of neuroleptics administered to each patient was recorded as chlorpomazine equivalents. BRMS, BPRS and CGI scores were obtained repeatedly at the end of each week until the end of the 6 weeks study period. Wilcoxon and Kruskal-Wallis tests were used for statistical analyses.

RESULTS

Demographic data: There were 10 patients on each treatment arm. Two of 30 patients were experiencing their first manic attacks, while the remaining had had previous manic attacks. Mean age was 36.60±11.49, and mean number of episodes was 2.70±0.82 in the lithium group. Mean age was 30.50±16.07 and mean number of episodes was 4.80±2.34 in the carbamazepine group. Mean age was 38.00±12.20 and mean number of episodes was 3.70±2.58 in the valproate group. (Table 1)

Tablo 1. Demographic data

	N	Age (mean±SD)	# of episodes
Lithium	10	36.60±11.49	2.70±0.82
Carbamazepine	10	30.50±16.07	4.80±2.34
Valproate	10	38.00±12.20	3.70±2.58

Efficacy data: Mean BPRS score in the lithium group was 31.20±7.83 before treatment, 17.70±4.74 at the end of week 1, and 1.20±3.16 at the end of week 6. Mean BPRS score in the carbamazepine group was 28.40±5.91 before treatment, 19.30±8.10 at the end of week 1, and 4.80±6.60 at the end of week 6. Mean BPRS score in the valproate group was 31.80±10.69 before treatment, 18.50±8.92 at the end of week 1, and 0.60±1.90 at the end of week 6. The difference among these values was statistically not significant ($p>0.05$). (Table 2)

Mean BRMS score in the lithium group was 29.80±3.82 before treatment, 18.70±5.29 at the end

Tablo 2. Brief Psychiatric Rating Scale (BPRS) scores (mean±SD)

	Lithium n=10	Carbamazepine n=10	Valproate n=10	P
Pre-treatment	31.20±7.83	28.40±5.91	31.80±10.69	p>0.05
1. week	17.70±4.74	19.30±8.10	18.50±8.92	p>0.05
2. week	10.20±4.76	12.10±8.53	8.80±9.24	p>0.05
3. week	5.70±4.76	8.10±7.17	4.40±6.75	p>0.05
4. week	3.20±5.41	5.00±7.12	3.60±5.93	p>0.05
5. week	2.80±6.20	5.90±7.59	1.10±3.14	p>0.05
6. week	1.20±3.16	4.80±6.60	0.60±1.90	p>0.05

Tablo 3. Bech-Rafaelsen Mania Scale (BRMS) scores (mean±SD)

	Lithium n=10	Carbamazepine n=10	Valproate n=10	P
Pre-treatment	29.80±3.82	29.40±4.06	27.80±5.73	p>0.05
1. week	18.70±5.29	19.40±8.15	19.40±8.98	p>0.05
2. week	11.70±4.69	13.30±8.47	9.70±7.72	p>0.05
3. week	6.80±6.61	9.10±8.89	5.00±6.90	p>0.05
4. week	2.90±4.65	6.70±9.90	5.00±6.85	p>0.05
5. week	2.70±4.55	6.60±7.82	1.90±4.01	p>0.05
6. week	1.50±4.06	4.90±8.62	1.00±2.49	p>0.05

Tablo 4. Clinical Global Impressions Scale-Severity Subscale (CGI) scores (mean±SD)

	Lithium n=10	Carbamazepine n=10	Valproate n=10	P
Pre-treatment	5.40±0.70	5.10±0.74	5.30±0.67	p>0.05
1. week	4.10±0.88	4.20±1.03	4.00±0.94	p>0.05
2. week	3.20±1.03	3.10±1.37	2.70±1.16	p>0.05
3. week	2.20±1.32	2.30±1.57	2.00±1.15	p>0.05
4. week	1.50±0.85	1.90±1.52	1.80±1.03	p>0.05
5. week	1.40±0.84	1.60±0.97	1.20±0.63	p>0.05
6. week	1.30±0.67	1.60±1.26	1.10±0.32	p>0.05

of week 1, and 1.50±4.06 at the end of week 6. Mean BRMS score in the carbamazepine group was 29.40±4.06 before treatment, 19.40±8.15 at the end of week 1, and 4.90±8.62 at the end of week 6. Mean BRMS score in the valproate group was 27.80±5.73 before treatment, 19.40±8.98 at the end of week 1, and 1.00±2.49 at the end of week 6. The difference among these values was statistically not significant (p>0.05). (Table 3)

Mean CGI score in the lithium group was 5.40±0.70 before treatment, 4.10±0.88 at the end of week 1, and 1.30±0.67 at the end of week 6. Mean CGI score in the carbamazepine group was 5.10±0.74 before treatment, 4.20±1.03 at the end of week 1, and 1.60±1.26 at the end of week 6. Mean CGI score in the valproate group was 5.30±0.67 before treatment, 4.00±0.94 at the end of week 1, and 1.10±0.32 at the end of week 6. The difference among these values was statistically not significant (p>0.05). (Table 4)

Although the difference between week 0 and week 1 BPRS scores was statistically significant (p=0.0051) for each drug, there was not a statistically significant difference (p=0.29) when the differences between week 0 and week 1 scores on BPRS, among three treatment groups were compared. This statistically non-significant difference state among three groups was observed for BRMS (p=0.70) and CGI (p=0.61), too. Though the differences between week 0 and week 1 were significant for both BRMS score (p=0.0051) and CGI score (p=0.01). We found similar results in comparison of week 0 and week 6 BPRS, BRMS and CGI scores. These results and all weekly comparisons of scores are also outlined in tables.

Dosage and serum levels: Mean daily dosage for treatment drugs were 1147.00±91.62 for lithium,

Tablo 5. Daily dosages (mg) and serum levels of study drugs (mean±SD)

	Lithium n=10	Carbamazepine n=10	Valproate n=10
Dosage	1147.00±91.62	959.30±92.88	982.70±18.37
Serum level	0.89±0.12 mmol/L	8.90±0.87 mg/ml	84.99±4.82 mg/ml

Tablo 6. Daily neuroleptic dosage as chlopromazine equivalents (mean±SD)

	Lithium n=10	Carbamazepine n=10	Valproate n=10	P
1. week	284.28±76.92	265.71±101.00	247.86±108.28	p>0.05
2. week	202.14±93.38	207.86±113.76	189.29±130.46	p>0.05
3. week	70.00±58.69	105.00±113.29	82.14±114.50	p>0.05
4. week	10.00±31.62	51.43±73.06	43.57±121.24	p>0.05
5. week	5.00±15.81	39.29±124.23	24.29±76.80	p>0.05
6. week	0.00±0.00	39.29±124.23	10.00±31.62	p>0.05

959.30±92.88 for carbamazepine and 982.70±18.37 for valproate. Mean serum levels were 0.89±0.12 mmol/L for lithium, 8.90±0.87 mg/ml for carbamazepine and 84.99±4.82 mg/ml for valproate. (Table 5)

Neuroleptic dosage: The difference in mean daily dosages for neuroleptics were statistically not significant in any treatment week among the patient groups as shown in the tables. (Table 6)

We could not see any side effect severe enough to cause a dropout.

DISCUSSION

We compared antimanic efficacy of lithium, carbamazepine and valproate in 30 acutely ill manic patients. There were 10 patients on each treatment arm. Two of 30 patients were experiencing their first manic attacks, while the remaining had had previous manic attacks. But, none of the patients in our study was rapid cycle (four or more episodes in a year) and none of them was experiencing a mixed episode. We could not find any statistically significant difference among the acute antimanic efficacious of lithium, carbamazepine and valproate among patient groups. The amount of neuroleptics used on each treatment arm was not different as the time for the onset of antimanic efficacy was not either. We could not see any side effect severe enough to cause a dropout.

To our knowledge there is not a study that has ever compared three of these agents in the same research cite and sample in adult bipolar patients. So, we can only discuss the results of this study with those comparing either two agents with each other and/or one or two of them with placebo. Although there is some controversy, both valproate and carbamazepine have generally been effective alternatives in treatment of mania (11-15). Carbamazepine has been superior to placebo (16), while it has been found less effective than lithium in a comparison study (17), but equally effective in the study by Small et al (18). Okuma et al (19) has reported effectiveness of carbamazepine in 60% of patients-equally effective to chlorpromazine-a proportion close to the efficacy of lithium.

Valproic acid and its enteric-coated derivative, divalproex sodium are effective antimanic agents (20). In a comparison study of a 3 week treatment with either valproate or placebo, valproate has been more effective than placebo, and antimanic efficacy of valproate has been apparent on the fourth day of treatment (12), and over the first 3 days of treatment in another study with divalproex oral loading (14). The time course of response to carbamazepine is between 1 to 2 weeks (21). We did not look for the efficacy parameters before the end of first treatment week. All of the drugs were similarly effective at the end of first treatment week, in our study.

Freeman et al (22) found that lithium was effective in 92% and valproate was effective in 63% of manic patients, but this difference was statistically not significant. Bowden et al (23) reported that both divalproex and lithium were significantly more effective than placebo in reducing the symptoms of acute mania. Reported later, a detailed subanalysis (24) of that trial (23) revealed a similar overall efficacy of lithium and divalproex in acute mania, but a better response to lithium in classic mania, and to dival-

proex in mixed mania. Divalproex was effective in rapid-cycling manic patients, too.

In fact, the true prevalence of rapid cycling is uncertain and lithium is still argued to have value in this group. The claim that anticonvulsants are more effective than lithium in rapid cycles has not been supported so far by comparative investigations (5). Another important point is the mentioned ineffectiveness of lithium in patients with rapid cycling is generally during a maintenance period, not in an acute period. The recent suggestion that the proportion of patients with rapid cycling diminished from the 1970s through 1990s, probably because of more conservative use of antidepressants, (25) is remarkable.

A retrospective study by Okuma (26), one of the earliest advocates of the use of carbamazepine in bipolar disorder, found that rapid cycling is a predictor of a poor response to that drug as well as to lithium consistent with the current opinion from Maj (27) of poor outcome in this diagnostic subgroup is independent of treatment. Another view is different presentations in phenomenology of mania, an important issue that may have an impact on the efficacious of antimanics. Dilsaver et al (28) report that manic episodes can be naturalistically classified as classic (predominately euphoric), dysphoric, or depressed. Indeed, subjects meeting criteria for mixed states differ from those with classic mania regarding elevated hypothalamic-pituitary-adrenocortical axis function (29).

Lithium has antimanic and antidepressant properties and decreases the number and/or frequency of episodes in a substantial proportion of patients. It is thus, to date, the only compound that satisfies full criteria as a mood stabilizer (5). Although carbamazepine and valproate are often referred to as mood stabilizers, they do not share the same properties with lithium at least clinically and in terms of outcome.

The effectiveness of both dopamine D_2 receptor antagonists and carbamazepine in acute manic period and their relative ineffectiveness in maintenance period (1,2,13,15,30-32) suggest that the mechanism of action of dopamine D_2 receptors and carbamazepine in bipolar disorder may be different when increasing data supporting the protein kinase C (PKC) inhibition as the mechanism of efficacy of lithium and valproate during acute and prophylactic treatment (33). The preliminary findings that tamoxifen citrate, a relatively selective PKC inhibitor, may be effective in the treatment of acute mania (34) should be considered as an important contribution in explaining the mood stabilizing effect. Another finding related to mechanism of action of lithium and valproate was presented by Silverstone et al, recently (35). The results of their study suggest that both lithium and valproate may work through a common mechanism of action involving the phosphoinositol-cycle.

We recently reported preliminary results of 15 acutely ill patients with mania (36). Those and the results presented in this article suggest a similarity between the antimanic efficacy of lithium, carbamazepine and valproate in at least acute period of the disorder. We continue to evaluate the patients prospectively in order to see the long-term efficacy. At the same time the acute period study is going on. Whether the results change, when the sample size is larger, is still a remaining question.

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