Superiority of Lithium Over Verapamil in Mania: A Randomized, Controlled, Single-Blind Trial

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Background: Both case reports and small controlled studies suggest the efficacy of verapamil in the treatment of mania.

Method: Forty patients with DSM-IV mania were studied in a 28-day randomized, controlled, single-blind trial of either lithium or verapamil.

Results: The patients receiving lithium showed a significant improvement on all rating scales (Brief Psychiatric Rating Scale [BPRS], Mania Rating Scale [MRS], Global Assessment of Functioning [GAF], and Clinical Global Impression [CGI]) compared with those receiving verapamil. The mean MRS score at Day 28 in the lithium group was significantly lower than that in the verapamil group (17.47 vs. 24.43, respectively; $F = 6.17$, $df = 1$, $p = .018$). A similar pattern was seen with the BPRS (12.68 vs. 20.57; $F = 10.69$, $df = 1$, $p = .002$), CGI (2.31 vs. 3.33; $F = 6.05$, $df = 1$, $p = .019$), and GAF (43.52 vs. 52.31; $F = 4.36$, $df = 1$, $p = .044$) (ANCOVA).

Conclusion: This study suggests that lithium is superior to verapamil in the management of acute mania.

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Lithium is the standard treatment for acute mania. However, the mood-stabilizing effects of lithium are delayed and often incomplete.[1] Not only this, but a large proportion of patients (20%–40%) are unable to tolerate lithium or do not respond at all.[2,3] There is, therefore, a need for alternatives and adjuncts to lithium.[4] Recently, there has been interest in the calcium channel blockers, in particular verapamil, in the treatment of acute manic episodes. The calcium channel blockers are indicated primarily for the treatment of cardiovascular disease, including angina, supraventricular arrhythmias, and hypertension.

Verapamil shares several pharmacologic properties with lithium: they are both cations and are thought to interfere with sodium calcium counterexchange.[5] They decrease spontaneous sinoatrial depolarization and are both capable of inhibiting thyroid stimulating hormone (TSH) release, inhibiting antidiuretic hormone (ADH), and blocking adenyl cyclase activity.[6] Neither has sedative nor hypnotic effects.[7] Verapamil is also known to antagonize dopamine and to act as an anticonvulsant.[4] It may block central serotonergic receptors and potentiate the antinociceptive effects of morphine.[8] A major advantage of verapamil is that it is well known to be safe and well tolerated, even with long-term administration.[9,10]

Case reports regarding the antimanic effects of verapamil were the first to appear in the literature.[11,12] These were followed by uncontrolled studies.[13,14] Several formal studies have reported that verapamil has equivalent antimanic activity with lithium.[1,6,7] Others have shown verapamil to be superior to placebo in reducing manic symptomatology,[10,15] and a trial comparing verapamil with clonidine found that verapamil was superior.[16] In general, where effects of verapamil were seen, they were at doses between 120 and 480 mg daily and were noted within an average of 2 weeks of treatment.[5]

However, an open study of 14 manic patients who were unresponsive to lithium showed that none of the 8 patients treated for acute mania or hypomania showed improvement on verapamil therapy.[3] Of greater concern is that the only placebo-controlled trial showed no benefit of verapamil over placebo.[17]

In most studies, numbers of patients have been small,[1,3,6,10,13] trials have been brief, and patients have been only moderately ill.[18,19] Most studies have been handicapped by the use of concomitant medications, e.g., antipsychotics, lithium, antidepressants, and anxiolytics, and greater use of concomitant medications in the verapamil group in some studies.[1,9] Other methodological limitations in the literature include diagnostic limitations,[7] open designs,[3,13] and crossover designs.[10,16]

Taking this into consideration, it is still difficult to come to any definitive conclusions about the use of verapamil in mania. We decided to compare the efficacy of lithium versus verapamil in the treatment of severely manic inpatients, using a larger sample size than had been used in previous studies.

METHOD

Study Group

The study was conducted at a lockup psychiatric facility with 840 beds and a high patient turnover. The sample population was 40 consecutive new admissions between April 1, 1995, and September 30, 1995, who met the DSM-IV[20] criteria for acute mania on structured interview. The patients were between 18 and 65 years of age and were assigned consecutively to lithium or verapamil in a randomized, controlled fashion. The two groups were matched in terms of illness severity. Eighteen patients completed the trial in each group. Three patients did not complete the trial in the verapamil group (N = 21) and 1 in the lithium group (N = 19). Data were analyzed on an intent-to-treat basis. Informed consent was obtained from patients or their relatives, and the study was passed by an institutional ethical review board.

Exclusion Criteria

Patients with abnormal liver function, thyroid function, or hematologic findings were excluded from the study, as well as those who had had a depot antipsychotic preparation in the last month. We excluded those who displayed an acute systemic medical disorder or those who had a medical disorder requiring frequent changes in medication. Patients who displayed substance dependence according to DSM-IV and those with preexisting cardiac disease were also excluded. Electrocardiograph examinations were done before patients entered the study.

Measurement

The patients were assessed at admission by a structured interview to confirm that they displayed acute mania according to DSM-IV criteria. Physical and neurologic examinations were completed. The patient's psychiatric condition was measured on Day 1 (the first day of treatment) using the Brief Psychiatric Rating Scale[21] (BPRS), the Mania Rating Scale[21] (MRS), the Global Assessment of Function[20] (GAF) scale, the Clinical Global Impression[21] (CGI) scale, and the Simpson-Angus Neurologic Rating scale.[21] These scales were repeated by the same investigator (S.A.W.) on Day 3, Day 10, Day 21, and Day 28 of the study for each patient. Routine blood tests including full blood count, urea and electrolytes, thyroid functions, syphilis serology, and urine cannabis were performed.

Study Procedure

Any existing psychotropic medication was discontinued prior to the first day of the study. All men were admitted to a single lockup ward with 40 beds and all women to another lockup ward with 40 beds. All patients were treated with verapamil 230 to 360 mg daily or lithium carbonate 500 to 1000 mg daily. The medication was given orally. Lithium was started at 250 mg three times a day (t.i.d.) and adjusted according to blood level. This, unfortunately, unblinded the study, leaving it single-blind only. The mean daily lithium dose was 832.3 mg and the mean lithium level was 0.51 mmol/L. Verapamil was started at 40 mg t.i.d. for 2 days and then increased to 80 or 120 mg t.i.d. Four patients were then maintained on 80 mg t.i.d. and 14 patients on 120 mg t.i.d. Lorazepam, intramuscularly or orally, was prescribed on an as needed basis for the control of agitation. No other psychotropic medication was permitted during the course of the study. Seclusion, when necessary, was also permitted.

Statistical Analysis

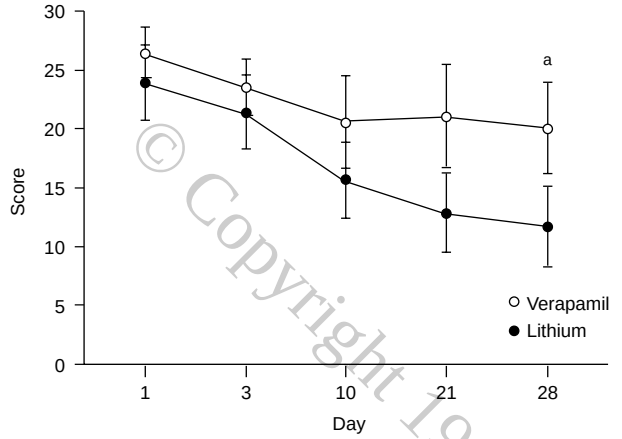
Data were analyzed using analysis of covariance (ANCOVA) for repeated measures to control for baseline values as the primary statistical method. Analysis of variance (ANOVA) for single measures was also used. All data were analyzed on a last-observation-carried-forward basis.

RESULTS

The study sample consisted of 21 patients on lithium therapy (Group 1) and 19 on verapamil therapy (Group 2). One patient in the verapamil group ended the study on Day 24 and was included in the analysis. Four patients were early discontinuations from the study. Two men in the verapamil group withdrew consent on Days 5 and 9, respectively. One woman in the verapamil group was withdrawn from the study on Day 3, and 1 woman taking lithium was withdrawn on Day 5, both owing to behavioral difficulties.

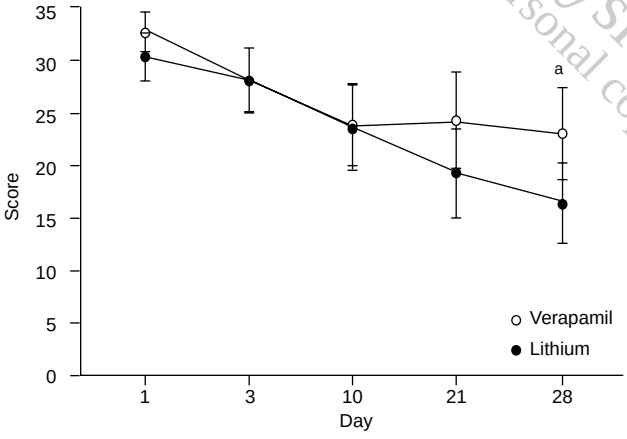
The two groups were matched in age (Group 1 mean = 36.2 years, Group 2 mean = 33.2 years), ratio of men to women (Group 1 = 10 men, 8 women; Group 2 = 12 men, 6 women), race, marital status, and level of education. The two groups had the same amount of employed and unemployed patients (employed = 4, unemployed = 14 in each group). The patients in each group had similar numbers of previous admissions. Urine cannabis was positive in a similar number of patients: 3 in Group 1 and 7 in Group 2, and is unlikely, therefore, to account for a difference in outcome. Antipsychotic medication was given at the end of the trial to 11 patients in Group 1 and 15 in Group 2. There were no significant differences in any of the four rating scales between the two groups at baseline (ANOVA). All patients were acutely manic, as evidenced by their scores on the rating scales.

Figure 1. Brief Psychiatric Rating Scale Scores: Verapamil Versus Lithium



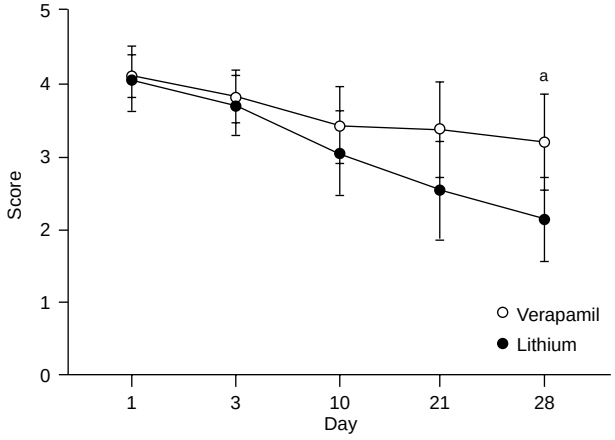
[a]p = .002.

Figure 2. Mania Rating Scale Scores: Verapamil Versus Lithium



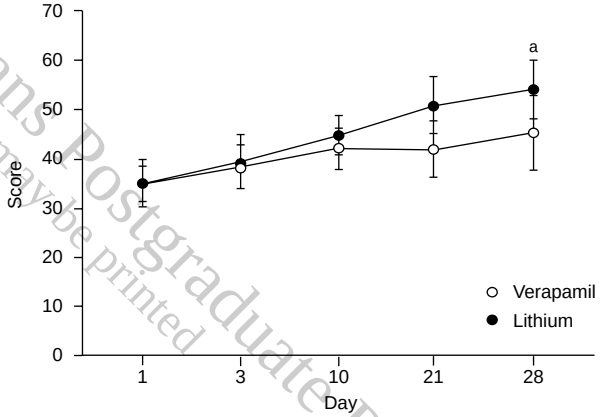
[a]p = .018.

Figure 3. Clinical Global Impression Scale Scores: Verapamil Versus Lithium



[a]p = .019.

Figure 4. Global Assessment of Function Scale Scores: Verapamil Versus Lithium



[a]p = .044.

The patients receiving lithium showed a significant ($p < .05$) improvement on all rating scales (BPRS, MRS, GAF, and CGI) compared with those receiving verapamil. The mean BPRS score at Day 28 (12.68 vs. 20.57; $F = 10.69$, $df = 1$, $p = .002$) in the lithium group was significantly lower than in the verapamil group (Figure 1). A similar pattern was seen with respective scores from the MRS (17.47 vs. 24.43; $F = 6.17$, $df = 1$, $p = .018$; Figure 2), CGI (2.31 vs. 3.33; $F = 6.05$, $df = 1$, $p = .019$; Figure 3), and GAF (43.52 vs. 52.31; $F = 4.36$, $df = 1$, $p = .044$; Figure 4) (ANCOVA). At Day 21, the difference between the groups on the BPRS ($F = 4.46$, $df = 1$, $p = .043$) and GAF ($F = 4.80$, $df = 1$, $p = .036$) was significant, whereas the MRS had not yet reached significance ($F = 1.86$, $df = 1$, $p = .128$).

No patients on verapamil treatment reported side effects, while 4 taking lithium experienced mild tremor. The Simpson-Angus scale revealed no differences between the two groups, since neither group had extrapyramidal side effects except for mild tremor. The amount of lorazepam that was given to the patients on an as needed basis for agitation or aggression was not significantly different between the two groups; those in the lithium group received a mean dose of 140.86 mg and those in the verapamil group, a mean dose of 164.94 mg over 28 days. The mean hours of seclusion for each patient over 28 days similarly did not differ between the two groups (lithium, 12.6 hours; verapamil, 18.5 hours).

DISCUSSION

To our knowledge, this is the largest trial that has been done comparing verapamil and lithium in the treatment of acute mania. All patients were acutely ill at the time of admission. The lithium and verapamil groups were matched in terms of demographic data as well as baseline

scores. In this study, lithium was shown to be significantly superior to verapamil on all measures used. This finding is contrary to the results of most of the studies done on verapamil in acute mania. This difference may reflect the relative severity of illness in this group and methodological limitations of certain other studies, the most important being sample size, as the small sample size in other studies may have obscured intergroup differences.

There were methodological limitations to this study, the main one being that it was single-blind. While doses of lithium were toward the low end of the spectrum, this did not impair the efficacy of the lithium limb of the trial. The randomization procedure should have helped equalize the influence of confounding variables such as positive urine cannabis results. However, it seems that the efficacy of verapamil in acute mania needs to be questioned, and further studies need to be done. Other calcium channel agents may differ in their psychotropic profile and clinical utility. Last, the issue of maintenance treatment with verapamil is unanswered.

Drug names: clonidine (Catapres), lorazepam (Ativan and others), verapamil (Calan and others).

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