Research article
Ερευνητική εργασία

Low dosage lithium augmentation in venlafaxine resistant depression: An open-label study

B. Alevizos, E. Alevizos, A.A. Leonardou, I.M. Zervas

1st Department of Psychiatry, University of Athens, Eginition Hospital, Athens, Greece

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Lithium augmentation is one of the best studied strategies for resistant depression. The lithium dosage usually given is around 900 mg/day and plasma level is maintained in the range of 0.5–0.8 mEq/L. However, the administration of lithium in this dosage necessitates monitoring of plasma concentration and increases the risk of toxicity and side effects. Since it has been shown that low lithium levels increase serotonin turnover and enhance serotonin neurotransmission, we thought it of interest to assess the efficacy of low dosage lithium augmentation for patients with resistant depression. Fifty one patients suffering from severe unipolar or bipolar depression who had failed to respond to treatment with venlafaxine 300–375 mg/day were included in the study and treated as outpatients. Patients had previously been exposed to unsuccessful treatment with various antidepressants, mostly SSRIs. After a washout period for previously administered antidepressants of one week, the dosage of venlafaxine was rapidly titrated to 300 or 375 mg/day, corresponding to about 5 mg/kg. The dose remained stable during the next six weeks. Additional antipsychotic medication was allowed to treat psychotic symptoms. Forty seven severely depressed patients who failed to respond to 300–375 mg/day venlafaxine were, in addition, given lithium carbonate in low dosage (300–450 mg/day). The Clinical Global Impression Improvement scale was used as the treatment outcome. A score of 1 or 2 was considered as non-response. All patients gave informed consent to participate in the study. Ratings were performed at baseline and after 1,2 and 5 weeks. Lithium plasma concentration measurements were performed after 1 and 4 weeks. After 5 weeks of augmentation, 51% of the patients were rated as "much" or "very much" improved. Bipolar patients showed a better response than unipolar (64.3% *vs* 45.5%, $p<0.038$). Most patients (76%) showed a rapid response (up tp 7 days), and only 2 patients (4.6%) responded after more than 2 weeks The mean lithium plasma level was 0.33±0.09 mEq/L. No significant differences were found in treatment response with regard

to sex, family history, psychotic symptomatology and suicidal ideation. No troublesome side effects were reported. Our results show that treatment augmentation with low lithium dosage may be as effective as augmentation with higher dosage, is well tolerated and does not necessitate monitoring of plasma level. Hence, an initial trial of augmentation at low dosage lithium may be the preferred first choice in non-emergent situations. The low dosage also minimizes the risk of side effects and drug-drug interactions. Prospective controlled studies to confirm our findings are needed as are larger scale comparisons with therapeutic dose lithium augmentation.

Key words: Resistant depression, severe depression, venlafaxine, lithium augmentation.

Introduction

Many case reports, open trials, placebo-controlled studies, reviews and meta-analyses of these studies concluded that, there is significant evidence to support the efficacy and utility of lithium augmentation.[1–4] Lithium may cause severe adverse effects[5] and increases the risk of toxicity,[6] but is well tolerated when lower doses are used. Moreover, lithium administration necessitates careful monitoring of plasma concentration and also requires multiple daily dosing. For these reasons, although lithium augmentation is the treatment option of first choice in refractory depression, it has lost popularity and is not widely used. It is a common practice to maintain serum lithium concentrations in the range of 0.5 to 0.8 mmol/L. However, some studies have shown that low lithium dosage may be beneficial as augmentation strategy with plasma level ranging between 0.15 and 0.40 mEq/L.[7–9] The present study was designed to evaluate the efficacy of low lithium dosage augmentation in venlafaxine resistant patients. With low dosage, troublesome adverse effects, toxicity and possible drug-drug interactions are avoided and treatment compliance may be enhanced.

Material and method

Fifty one patients suffering from severe unipolar or bipolar depression who had failed to respond to treatment with venlafaxine 300–375 mg/day were included in the study and treated as outpatients. Patients had previously been exposed to unsuccessful treatment with various antidepressants, mostly SSRIs. After a washout period for previously administered antidepressants of 1 week, the dosage of venlafaxine was rapidly titrated to 300 or 375 mg/day, corresponding to about 5 mg/kg. The dose remained stable during the next 6 weeks. Patients who did not respond were administered lithium carbonate at a single evening dose as low as 300–450 mg/day and this was continued for 5 weeks. Additional antipsychotic medication was allowed to treat psychotic symptoms. The severity of depressive episode was assessed using the Clinical Global Impression-Severity of Illness (CGI-S).[10] The Clinical Global Impression- Improvement Scale (CG-I) (7-points) was used as the main outcome measure. A score of 1 or 2 was considered as non-response. All patients gave informed consent to participate in the study. Ratings were performed at baseline and after 1.2 and 5 weeks. Lithium plasma concentration measurements were performed after 1 and 4 weeks. Vital signs, blood pressure and unwanted effects were recorded at each visit. Differences in demographic and clinical variables between groups were analyzed by independent t-tests or x^2 tests. The changes from baseline in CGI scores were analyzed with paired t-tests.

Results

Forty seven patients (30 women, 17 men) received lithium augmentation and were included for analysis. Thirty three were diagnosed with unipolar depression and 14 with bipolar affective disorder, currently depressed, according to DSM-IV criteria. Nineteen patients suffered from psychotic major depression. Twenty (44.7%) had suicidal ideation

and 8 (17%) had a history of attempted suicide in the current episode. Four patients discontinued during the augmentation period. Table 1 summarizes the demographic and clinical characteristics of patients, lithium dosage and plasma level. The mean lithium dosage was 353.3±85.5 mg/day and the mean plasma concentration 0.33±0.09 mmoL/L. Five patients (10.6%) scored 7 (very severely ill) in CGI-S scale, 34 patients (72.3%) scored 6 (severely ill) and 8 patients (17.0%) scored 5 (markedly ill). The mean CGI-S score decreased from 5.91±0.62 at baseline to 3.49 (±...) at the end of 5th week (t=11.2, p-0,000). Twenty four patients (51%) scored 1 or 2 "very much" or "much improved" in CGI-I scale, and 23 patients (49%) scored at least 3 at week 5. Bipolar patients showed a better response than unipolar (64.3% *vs* 45.5%, x^2=6.87, p<0.038). Four bipolar patients (28.6%) recovered in comparison with 1 unipolar (3.0%) (x^2=4.68, p<0.03). Most patients (76%) showed a rapid response (up to 7 days), and only 2 patients (4.6%) responded after more than 2 weeks. None of the bipolar patients switched to mania or hypomania during the treatment period. No significant differences were found in treatment response with regard to sex, family history, psychotic symptomatology and suicidal ideation. The most common adverse effects with venlafaxine were nausea, sweating and headache. No additional adverse effects were reported with venlafaxine plus lithium.

Table 1. Study patients profile

No of patients	47
Sex (male: female)	17:30
Age (y)-(Range)	43.6±16.3 (20–69)
Diagnosis N(%)	
Unipolar	33 (70.2)
Bipolar I	6 (12.8)
Bipolar II	8 (17.0)
With psychotic symptoms	19 (40.4)
Without psychotic symptoms	28 (59.6)
Lithium dosage (mg)	353.3±85.5
Lithium plasma level	0.33±0.09
CGI Severity score	5.91±0.62
Mean venlafaxine dose (mg)	305 (300–375)

Discussion

Of our patients (N=47), 51% obtained a positive response and 72.3% had at least a partial response. This response rate was higher than that of Hpencamp et al[11] and Bertschy et al[11] who found a 35% and a 38.4% response respectively in venlafaxine-resistant patients treated with lithium augmentation. Mean lithium plasma levels in these studies were 0.66±0.19 mEq/L and 0.81±0.22 mEq/L, respectively. The overall 51% response rate in this study is similar to that reported in previous studies 2–3 where higher lithium dosage was used. We also found a 10.6% rate of complete remission in comparison with 9% of the study of Hoencamp et al[11] and 23% of the study of Bertschy et al.[12] No patient withdrew for adverse effects due probably to the low dosage of lithium. All patients were severely depressed and had failed to respond to previous trials with various antidepressants. A better response to lithium augmentation of patients with more severe depression was found by Bschor et al,[13] who found that severity of depression was a predictor of response to lithium augmentation.

The low lithium dosage we used was well tolerated and the venlafaxine-lithium combination did not cause additional adverse affects other than those caused by venlafaxine. Patients with rapid and dramatic response (5) had lower, but not statistically significant plasma level (0.3 *vs* 0.4 mEq/L). Similarly, Thase et al[4] found lower plasma level in patients who showed a rapid (within 3 days) and complete recovery. Bipolar patients responded better than unipolar patients to lithium augmentation (p<0.03). The results in the literature are contradictory. Similarly to Rybakowski and Matkowski[14] we found a better response when improvement occured during the first week than later.

Our results show that plasma lithium levels above 0.5 mEq/L are not necessary to obtain treatment response in refractory depressive patients. This is consistent with several studies showing a good response with low lithium levels. Kushnir et al[7] reported a 100% response rate with plasma levels ranging

between 0.15 mEq/L and 0.40 mEq/L in a geriatric population. Fava et al[8] reported that lithium augmentation of fluoxetine (20–40 mg/day) was effective with dosage 300–600 mg/day and plasma 0 levels 21±0.11 mEq/L.

Lithium acts through multiple pathways to inhibit glycogen synthetase kinase-3 beta (GSK3 beta). This enzyme phosphorylates and inhibits nuclear factors that turn on cell growth and protection programs, including the nuclear factor of activated T cells (NFAT) and WNT/beta-catenin. In animals, lithium upregulates neurotrophins, including brain-derived neurotrophic factor (BDNF), nerve growth factor, neurotrophin-3 (NT3), as well as receptors to these growth factors in brain. Lithium also stimulates proliferation of stem cells, including bone marrow and neural stem cells in the subventricular zone, striatum, and forebrain. The stimulation of endogenous neural stem cells may explain why lithium increases brain cell density and volume in patients with bipolar disorders. Lithium also increases brain concentrations of the neuronal markers n-acetyl-aspartate and myoinositol. Lithium also remarkably protects neurons against glutamate, seizures, and apoptosis due to a wide variety of neurotoxins.[15]

It has been proposed that in depression lithium augmentation may promote improvement via an increase of central serotonergic function.[14] This may indicate that low dose lithium may further increase serotonergic function to produce a therapeutic effect, while higher doses may cause adverse effects via serotonergic stimulation. It has been shown that low plasma levels of lithium (0.1 mEq/L) increase the turnover of serotonin neurons and enhance serotonergic neurotransmission.[16]

Our results indicate that low dosage lithium augmentation is an effective and well tolerated treatment for the more severely depressed patients who are refractory to venlafaxine with a response rate of at least 50% after a period of 2–3 weeks. The low dosage makes the lithium-antidepressant combination safe, user friendly, not necessitating monitoring of plasma lithium concentration and practically without risk of toxicity and drug interactions. Prospective controlled studies to confirm our findings are needed.[17] In addition larger scale studies comparing therapeutic to subtherapeutic lithium augmentation or perhaps sequential treatment, initially with subtherapeutic and then with therapeutic does in bipolar versus unipolar non-responders would be useful for algorithm treatment of depression.

Ενίσχυση με χαμηλή δόση λιθίου της αγωγής με βενλαφαξίνη στην ανθεκτική κατάθλιψη: Μια ανοιχτή μελέτη

Β. Αλεβίζος, Η. Αλεβίζος, Α.Α. Λεονάρδου, Ι.Μ. Ζέρβας

Α' Ψυχιατρική Κλινική Πανεπιστημίου Αθηνών, Αιγινήτειο Νοσοκομείο, Αθήνα

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Η ενίσχυση της αντικαταθλιπτικής αγωγής με λίθιο είναι μία από τις καλύτερα μελετημένα στρατηγικές για την ανθεκτική κατάθλιψη. Η δοσολογία λιθίου συνήθως είναι περίπου 900 mg/ημέρα και το επίπεδο του πλάσματος διατηρείται στην περιοχή του 0,5–0,8 mEq/L. Ωστόσο, η χορήγηση του λιθίου σε αυτή τη δοσολογία απαιτεί την παρακολούθηση της συγκέντρω-

σης στο πλάσμα και αυξάνει τον κίνδυνο της τοξικότητας και άλλων ανεπιθύμητων ενεργειών. Δεδομένου ότι έχει αποδειχθεί ότι τα χαμηλά επίπεδα του λιθίου αυξάνουν την ανακύκλωση της σεροτονίνης και την ενίσχυση της νευροδιαβίβασης με σεροτονίνη, σκεφτήκαμε ότι παρουσιάζει ενδιαφέρον για την αξιολόγηση της αποτελεσματικότητας της ενίσχυσης με χαμηλή δοσολογία λιθίου για ασθενείς με ανθεκτική κατάθλιψη. Πενήντα ένας ασθενείς που έπασχαν από σοβαρή μονοπολική ή διπολική κατάθλιψη και που δεν ανταποκρίθηκαν στη θεραπεία με βενλαφαξίνη 300–375 mg την ημέρα συμπεριελήφθησαν στη μελέτη ως εξωτερικοί ασθενείς. Οι ασθενείς είχαν προηγουμένως εκτεθεί σε ανεπιτυχή θεραπεία με διάφορα αντικαταθλιπτικά, ως επί το πλείστον SSRI. Μετά από μια περίοδο έκπλυσης μίας εβδομάδας για προηγουμένως χορηγηθέντα αντικαταθλιπτικά, η δόση της βενλαφαξίνης ταχέως τιτλοποιήθηκε σε 300 ή 375 mg/ημέρα, δόση που αντιστοιχεί σε περίπου 5 mg/kg. Η δόση παρέμεινε σταθερή κατά τη διάρκεια των επόμενων έξι εβδομάδων. Πρόσθετα αντιψυχωσικά φάρμακα επιτρεπόταν να χορηγηθούν για τη θεραπεία των ψυχωσικών συμπτωμάτων. Σε 47 σοβαρά καταθλιπτικούς ασθενείς οι οποίοι απέτυχαν να ανταποκριθούν σε 300–375 mg/ημέρα βενλαφαξίνης χορηγήθηκε στη συνέχεια ανθρακικό λίθιο σε χαμηλές δόσεις (300–450 mg/ημέρα). Η CGI χρησιμοποιήθηκε για να αξιολογήσει το αποτέλεσμα της θεραπείας. Ο βαθμός 1 ή 2 θεωρήθηκε ως μη απάντηση. Όλοι οι ασθενείς έδωσαν συγκατάθεση για τη συμμετοχή στη μελέτη. Βαθμολογήσεις πραγματοποιήθηκαν κατά την έναρξη και μετά από 1, 2 και 5 εβδομάδες. Μετρήσεις της συγκέντρωσης του λιθίου πλάσματος έγιναν μετά από 1 και 4 εβδομάδες. Μετά από 5 εβδομάδες, το 51% των ασθενών βελτιώθηκε «πολύ» ή «πάρα πολύ». Διπολικοί ασθενείς ανταποκρίθηκαν καλύτερα από τους μονοπολικούς. Το μέσο επίπεδο του λιθίου στο πλάσμα ήταν 0,33±0,09 mEq/L. Δεν βρέθηκαν σημαντικές διαφορές στην ανταπόκριση στη θεραπεία σε σχέση με το φύλο, το οικογενειακό ιστορικό, την ψυχωτική συμπτωματολογία και τον αυτοκτονικό ιδεασμό. Δεν αναφέρθηκαν σημαντικές ανεπιθύμητες ενέργειες. Τα αποτελέσματά μας δείχνουν ότι η ενίσχυση της θεραπείας με χαμηλή δόση λιθίου μπορεί να είναι εξίσου αποτελεσματική με την ενίσχυση με μεγαλύτερη δοσολογία. Η χαμηλής δόσης ενίσχυση είναι καλά ανεκτή και δεν απαιτεί παρακολούθηση των επιπέδων πλάσματος. Ως εκ τούτου, μια πρώτη δοκιμή της αύξησης σε χαμηλές λιθίου δόση μπορεί να είναι η προτιμώμενη πρώτη επιλογή σε μη ανταποκρινόμενες καταθλίψεις. Η χαμηλή δοσολογία ελαχιστοποιεί τον κίνδυνο ανεπιθύμητων ενεργειών και αλληλεπιδράσεων μεταξύ φαρμάκων. Χρειάζονται μελέτες με ομάδες ελέγχου για να επιβεβαιώσουν τα ευρήματά μας, καθώς και μεγαλύτερα δείγματα ασθενών με εν συνεχεία αύξηση της δόσης του λιθίου στους μη ανταποκρινόμενους στη χαμηλή δόση ασθενείς.

Λέξεις ευρετηρίου: Ανθεκτική κατάθλιψη, σοβαρή κατάθλιψη, βενλαφαξίνη, ενίσχυση με λίθιο.

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Corresponding author: B. Alevizos, Associate Professor of Psychiatry, University of Athens, Athens, Greece
Tel: (+30) 210-72 36 028
e-mail: valeviz@med.uoa.gr