

Renewed Interest in Calcium Channel Blockers as Antimania Agents in the Third Millennium

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Abstract

The calcium channel blocker verapamil has been extensively studied for the treatment of mania, with the evidence suggesting that verapamil is effective for controlling mania. Nimodipine has also shown specific utility in patients with rapid cycles. Clinicians faced with a patient with mania who does not respond to other antimania agents may consider using verapamil as an adjunctive therapy. This article reviews the reasons for a surge of interest in these drugs and their underutilisation in clinical practice. Renewed investigation and more research to assess their efficacy and safety are warranted in the third millennium.

Key words: *Bipolar disorder, Calcium channel blockers, Nimodipine, Verapamil*

Introduction

For the past 2 decades, there has been a search for an effective treatment for the 20% to 40% of patients with classic mania who do not respond to treatment with lithium.¹ In addition, some patients cannot tolerate the side effects of lithium.² The need for regular monitoring of serum lithium concentrations, a narrow therapeutic range, and problems with compliance further complicate long-term treatment with lithium. Lithium is generally not prescribed for pregnant women.³ Certain diagnostic subtypes (e.g., dysphoric mania, rapid cycle) have shown a poor response to lithium. This situation has necessitated the availability of both adjunctive and alternative treatment options to lithium, some of which have been borrowed from other medical specialties.⁴ The relatively incisive and specific affect-modulating action of lithium has instigated a surge of interest in the role of other cations — particularly calcium — in the pathogenesis and therapy of mood disorders. Clinical trials have also generated interest and shown that calcium channel blockers have maintained their role in the treatment of mania.^{5,6}

Two classes of calcium channel blockers have been extensively studied to elucidate their role in mood disorders. These compounds include widely recognised phenylalkylamines such as verapamil and dihydropyridine types such as nifedipine, isradipine, and nimodipine. These 2 types of calcium channel blockers differ from each other in their biochemical and physiological effects on cardiac cells and neurones. Phenylalkylamines gain access to the calcium channel less rapidly than dihydropyridine types. Dihydropyridines are highly lipid-soluble and associated with dopamine overflow in the nucleus accumbens, whereas phenylalkylamines lack these characteristics.

Mood Disturbances with Altered Calcium Metabolism

Mood disorder is a frequent complication of a primary disorder of calcium metabolism. Manic illness may arise from disorders in calcium-regulated functions. Calcium metabolism has been reported to be disturbed in various forms of affective disorders. In a study in which calcium metabolism was measured in 29 patients with unipolar disorder, 14 with bipolar depression, 11 with mania, and 10 healthy controls, it was found that the plasma calcium level was lower in patients with unipolar disorder and mania than in the controls.⁷ Patients with unipolar and bipolar disorders also showed different types of disturbances in calcium metabolism. Altered intracellular calcium homeostasis in the blood cells of patients with bipolar disorder has been studied.⁸ Data suggest that storage-operated calcium channels may be the source of the elevated intracellular calcium level in platelets and lymphocytes of patients with bipolar disorder.

Anger and lethargy occur, almost universally, in hypercalcaemic disorders such as hyperparathyroidism⁹ or

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hypervitaminosis D.¹⁰ Extreme cycles of mood and activity have been described in various hypocalcaemic conditions, which may be idiopathic or induced by surgery, or which may occur with pseudohypoparathyroidism.¹¹ Prompt resolution of mood symptoms usually follows medical and surgical restoration of normal calcium metabolism.¹² Reduction within the physiological range of calcium concentration surrounding neurones in the central nervous system (CNS) may modify their general function. Reduction in extracellular calcium level can disinhibit post-synaptic membrane-bound enzymes such as acetylcholinesterase.¹³

Several other observations are consistent with the speculation that calcium concentration within cells may be elevated in mania. Intraerythrocytic and intracellular sodium levels are elevated in patients with mania.¹⁴ Since levels of calcium within cells generally tend to be parallel to those of sodium,¹⁵ calcium ion concentration within cells might be increased. Although direct measures of intracellular calcium have not been performed, a strong correlation has been observed between mood and intraerythrocytic calcium adenosine triphosphatase activity in patients with mood disorders.¹⁶

Biological Hypothesis of Calcium Dysregulation in Affective Disorders

Calcium dysregulation has long been implicated in the potential pathophysiology of different phases of affective disorders.¹⁴⁻¹⁶ A hypothetical model of the role of intracellular calcium ions in affective disorders has been proposed.¹⁷ Increased intracellular levels of calcium ions resulting from increased influx through calcium channels opened by depolarisation of the presynaptic neurones or resulting from mobilisation of excessive intracellular stores by normal influx might stimulate both increased synthesis and exocytosis of neurotransmitters. At the post-synaptic receptor site, increased intracellular calcium may stimulate the membrane phosphorylase. This increased enzyme activity may enhance receptor sensitivity to norepinephrine, thereby resulting in a heightened response to the same amount of neurotransmitter.

Some actions of lithium-like inhibition of norepinephrine release from brain synaptosomes are reversed by increased calcium ion concentrations — a phenomenon that is characteristic of compounds that block calcium entry into cells or compete with calcium at intracellular sites. The effect of lithium on serum and cerebrospinal fluid (CSF) calcium levels has generated interest in elucidating the intracellular role of calcium in bipolar disorders. A review of numerous studies correlating changes in serum and CSF calcium with changes in mood, motor activity, psychotic agitation, and mania has also been reported.¹⁸ The role of calcium in mood disorders is further supported by the following factors:

- calcium-related endocrinopathies are associated with mood disorders
- abnormal levels of calcium have been found in blood and

- spinal fluid in association with mood dysregulation
- abnormalities in intracellular calcium level have been documented in studies of blood elements of patients with unipolar and bipolar mood disorders^{19,20}
- preliminary data indicate that calcium-active treatments may be therapeutically effective.²¹

Thus, calcium acts between cells in different ways by activating a wide range of enzymes, and lithium seems to alter many calcium-dependent processes. It may be proposed that affective disorder is a result of disturbances in calcium-regulated functions. Patients with affective disorders who respond favourably to lithium treatment showed a rise in calcium levels in their blood during the first 4 months of treatment.²² Those who did not respond to lithium showed unaltered calcium levels. Irregularities in calcium's signal-sending actions within cells may explain bipolar disorder. Lithium and other mood-stabilising treatments seem to work by regulating calcium ion hyperactivity. Given these considerations, the hypothesis emerges that calcium antagonists could be alternative pharmacological agents for the treatment of mania.

Calcium Channel Blockers in Affective Disorders

The psychopharmacological profile of calcium channel blockers is unique. Although these agents are generally used for the treatment of cardiovascular disorders, they have been shown to be effective in a number of psychiatric disorders.²³⁻²⁵ Verapamil is accepted as an effective potential therapeutic agent for mania. Nifedipine (in combination with an antipsychotic agent) has been reported to be effective for the treatment of refractory schizoaffective disorder and bipolar mania.²⁶

Nimodipine may be more effective than verapamil for treating bipolar disorders because of its anticonvulsant properties, high lipid solubility, and good penetration into the CNS.²⁷ In preliminary studies, nimodipine was effective in ultra-rapid cycling patients and had augmenting effects when combined with lithium, carbamazepine, or other anticonvulsants.^{28,29} A recent consensus survey of psychiatric experts classified nimodipine as an alternative treatment and nimodipine and other calcium channel blockers as adjuncts to other mood stabilisers for treatment-resistant mania.^{30,31} Clinicians treating a patient with resistant mania not responding to other antimania drugs, either alone or in combination, might consider verapamil as an adjunctive treatment. Given the safety and relative lack of side effects of calcium channel blockers and their potential efficacy in the treatment of mania, it is proposed that they may be an alternative choice to lithium.

Nimodipine shows special promise for rapid and ultra-rapid cycling patients.^{32,33} The low rate of teratogenic effects of calcium blockers may make them preferable to standard mood stabilisers during pregnancy and breastfeeding.^{34,35} Verapamil and nimodipine have successfully controlled symptoms of mania in pregnant women.^{3,36}

Clinical Trials of Calcium Channel Blockers

In clinical trials, calcium channel blockers have shown promising results for the treatment of mania. Verapamil has been reported to be comparable to lithium and superior to placebo for the management of acute mania in anecdotal series, small case series, and a few small double-blind trials. The first report of the use of calcium channel blockers for the treatment of mania was a double-blind placebo-controlled trial of verapamil 240 mg/d in a single patient.³⁶ It was reported that remission of mania occurred with verapamil treatment; however, when a placebo was substituted, the patient's symptoms returned to the previous level. In an open uncontrolled study, verapamil 160 to 320 mg was given to 6 patients with mania and improvements in symptoms were reported during 2 to 3 weeks.³⁷ Beneficial effects of verapamil in rapidly cycling bipolar disorders and antidepressant-induced hypomania have been reported.³⁸

Partially controlled studies, usually involving the substitution of placebo for the active drug,³⁹ and controlled trials have been performed. In a controlled trial, verapamil has been compared with lithium and placebo. Verapamil was found to be superior to placebo on several measurements but not to lithium.⁴⁰ This may have been because an insufficient dose of verapamil 240 mg was used in this trial. The majority of trials include verapamil at a dosage of 120 to 360 mg/d. The results of these trials are mixed but encouraging in many aspects.

In a comparative trial of 12 men with the *Diagnostic and Statistical Manual of Mental Disorders-III* criteria for a manic episode, the antimanic effects of verapamil, lithium, and placebo were evaluated. The patients received verapamil 320 mg/d during the first 30 days. They were then switched to a glucose placebo for a 10-day period, which served as a washout phase. During the last 30 days, each patient received lithium 900 to 1800 mg, resulting in serum levels of 0.84 to 1.26 mEq/L.⁴¹ The results suggested that verapamil possesses antimanic effects that compare favourably to those of lithium.

In a double-blind crossover study of 20 patients with bipolar mania, the effect of verapamil 240 mg/d was compared with that of lithium during 6 months. Verapamil was reported to be more effective than lithium as a mood stabilising agent.⁴² A double-blind randomised trial comparing verapamil and lithium was performed in 12 patients with acute mania, for whom the Peterson Mania Scale, Brief Psychiatric Rating Scale, and Clinical Global Impression scores were administered before treatment and weekly for 4 weeks. The verapamil dose was titrated from 80 mg twice a day on the first day, 80 mg 3 times a day for the next 2 days, and then 80 mg 4 times a day for the remainder of the trial.⁴³ The lithium levels were maintained in the range of 0.75 to 1.5 mEq/L. Both groups improved significantly and there was no significant difference between the 2 modes of treatment.

In an inclusive sequential series of female outpatients with bipolar disorders, some of whom were pregnant, verapamil was prescribed.⁴⁴ The criterion of 50% reduction in scores of the Mania Rating Scale was used to define the response for women who were treated for an acute episode. One hundred percent of women with acute mania responded to verapamil, while a response rate of 77% was seen for women with mixed states. This study concluded that further research is required into the efficacy of verapamil and sex-specificity in bipolar disorders.⁴⁴

Underutilisation of Calcium Channel Blockers

Clinicians tend to act according to their training by senior doctors, and their attitudes about the effectiveness of antimania agents are variable. In general, especially in public hospitals, lithium is preferred to other mood stabilisers, either because it is well studied or because of its availability in most hospitals. Psychiatrists in clinical practice are generally reluctant to try innovative treatments, even for resistant patients.

Pharmaceutical companies have a role to play in the use of a particular agent, as they usually promote agents that are good from a commercial point of view. In developing countries, the negative attitude of pharmaceutical companies towards promoting older inexpensive products has had an effect on research priorities.

Calcium channel blockers have not been studied extensively in developing countries. Research into these antimania agents is still in its infancy, yielding no definite conclusion about their place in the pharmacotherapy of mania.

During the past decade, the pharmaceutical industry has launched a number of new mood stabilisers, especially anticonvulsant drugs in different compositions. These newer molecules come with a substantial number of studies supporting their use. This further reduces the potential role of calcium channel blockers in the treatment of mania.

Conclusion

Although use of calcium channel blockers has been investigated for several years, the number of published reports has been sparse. One important reason could be that the pharmaceutical industry has not pursued efficacy studies to obtain a drug application for a new indication. Mania is the major psychiatric indication studied for calcium channel blockers and is the one that reaps the most benefit. Recent research data on calcium channel blockers are highly promising and, in many clinical trials, response rates are favourably comparable to those for other mood stabilisers. Although the research results are promising, more evidence is still warranted to firmly establish their safety and efficacy both as adjunctive medications and monotherapeutic alternatives to lithium. Patients with typical mania as well as those with refractory forms of this illness deserve the benefit of further clinical trials and experimentation with these drugs.

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