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RESEARCH ARTICLE

AN EXPERIMENTAL STUDY ON THE EFFECT OF FELODIPINE ON SERUM ELECTROLYTESAND LITHIUM CONCENTRATION IN ALBINO RABBITS

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ABSTRACT

Objectives: To study the effect of felodipine, a calcium channel blocker, on concurrent administration with lithium carbonate on serum electrolytes and lithium in Albino rabbits.
Material and Methods: Albino rabbits weighing 2.5 – 3 kg were divided in three group of ten each and were administered lithium carbonate and/or felodipine in suspension made of gum tragacanth daily for eight days. Blood was drawn from marginal ear vein after 24 hours of first dose and then at 28th day of drug/s administration for acute and chronic effects respectively. Serum was separated out and supernatant was decanted after centrifugation at 3000 rpm. Serum sodium, potassium and/or lithium were estimated using flame photometry. Heart rate was measured by heart transducer and polygraph. Mortality was observed till a week after last dose administration in this study.
Results: Acute effects of co-administration of felodipine and lithium resulted in highly significant decrease in heat rate but no fall in serum potassium and insignificant increase in sodium levels from the baseline values. On chronic co-administration, significant decrease in heat rate was maintained without any significant change in serum electrolytes and lithium levels from base line. No mortality was observed in the group treated with felodipine and lithium simultaneously.
Conclusions: Felodipine with lithium co-administration minimally affect the serum electrolytes and lithium concentration and thus appears relatively safe for co-administration.
Key words: Bipolar-disorder, Felodipine, Hypertension, Lithium

INTRODUCTION

Bipolar affective (maniac-depressive) disorder is a frequently diagnosed and a very serious psychiatric disorder. It is the second most common disorder after unipolar major depression.[1] It constitutes a major percentage of psychiatric morbidity amongst younger age group of childhood and adolescence as well as older age group of psychiatric patients too. Episodes of mood swings characteristics of this disease are generally unrelated to life events. Since the exact pathophysiology of the disorder is not well known, it poses a perpetual challenge to the treating physician. The clinical and therapeutic distinction of bipolar disorders prompted many researchers to find effective therapy for this condition.[2]

Lithium carbonate is often referred to as an "anti-maniac" drug, but in many parts of the world it is also considered as "mood stabilizing" agent too because of its primary action of preventing mood swings in patients in patients with bipolar affective (maniac-depressive) disorder.[3,4] Lithium salts were introduced into psychiatry in 1949 for the treatment of mania.[4] However, its use was based on incorrect hypothesis but extremely good fortune of choosing correct dosage.Since lithium salts were observed to have a very high toxicity and extremely low therapeutic index, when used as a substitute for sodium chloride in cardiac disease for which its use was discontinued for this purpose.[3,4] However after 1970, once there were convincing evidence for both the safety and efficacy of lithium in the treatment of mania and prevention of recurrent attacks of maniac-depressive disorders, again lithium surfaced in pharmacotherapy of bipolar disorders, prompted widespread use of lithium for these disorders.[3,5,6]

Of recent, since lithium therapy, which requires a careful monitoring of serum lithium levels and increasing awareness of the side effects of lithium therapy, the researchers are prompted to look for alternative anti maniac or mood stabilizing agents.[3, 7-9]

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However lithium salts remains, as main line of drug till an alternative drug with least side effects is made available for treatment of psychiatric patients suffering of bipolar disorders.[8, 10]

Hypertension remains one of the most important preventable contributors to disease and death. The first line drugs for treatment of hypertension are thiazide-type diuretic, calcium channel blockers (CCB), angiotensin converting enzyme inhibitors (ACEI), or angiotensin receptor blocker (ARB).[11]Presently CCBs are one of the commonly used drugs in management of hypertension, coronary heart diseases, and arrhythmias. Many new drugs in this group of CCBs were synthesized and now a days clinically available for use as amlodipine, diltiazem, felodipine, isradipine, lacidipine,lercanidipine, nicardipine, nifedipine, nisoldipine, verapamil,etc. CCBs promote vasodilator activity (and reduce blood pressure) by reducing calcium influx into vascular smooth muscle cells by interfering with voltage-operated calcium channels (and to a lesser extent receptor-operated channels) in the cell membrane.[12] Interference with intracellular calcium influx is also important in cardiac muscle, cardiac conduction tissue and gastrointestinal smooth muscle.[13]

The coexistence of maniac-depressive psychosis (MDP) or bipolar disorder and hypertension is well documented fact in clinical medicine.[14-16] Under such comorbid situations, co-administration of lithium carbonate with calcium channel blockers is fairly likely as both the drugs are well established and are forerunner in their respective fields.(16) However, many reports of adverse effects due co-administration are on record. Most of these reports have found that lithium toxicity gets precipitated in an otherwise stabilized patients whenever one of the CCBs were added to the regimen for control of hypertension.[3,4,17] Such observations led to rightful concern amongst the treating physicians while using these two drugs simultaneously. Also calcium antagonists may be an alternative choice in prophylactic treatment for bipolar illness, especially in patients who cannot be treated with lithium or carbamazepine.[17]

In view of the above, it was felt worthwhile to undertake a study to investigate possible effects of co-administration of lithium carbonate and a commonly used CCB (felodipine- a dihydropyridine) on serum lithium, sodium and potassium levels besides recording one of the cardiovascular parameters- heart rate.

MATERIALS AND METHODS

Healthy and adult albino rabbits of New Zealand strain weighing between 2.5 – 3.0 kg of either sex were used as experimental animals in this study after getting approval from Institutional Animal Ethics Committee. The rabbits were maintained on standard laboratory diet and water at libitum. They were divided into two groups of ten each. The drugs were administered orally in the morning at a fixed time i.e. 1000 hour after overnight fasting to eliminate the probability of food related or circadian variation. Pure lithium carbonate salt was first dissolved in minimal amount of hydrochloric acid and further diluted to make it to a working concentration of 30 mg/ml for administration to rabbits. Also, felodipine, a white crystalline compound, which is practically insoluble in water, was made into a suspension with 1% gum tragacanth, freshly prepared every day for administration to rabbits.

Equipment: A flame photometer model CL26D ELKON was used to estimate the serum electrolytes i.e. Na^+, K^+, Li^+. Apart from this, a transducer with polygraph was used to record heart rate.

Plan of study: Twenty rabbits were randomly divided into two groups of ten each. Group 1 was the control group which received only lithium carbonate while group 2 received both lithium carbonate and felodipine together. On day of beginning of the study, heart rate record was done using transducer and a polygraph. Also blood sample was drawn for baseline study from all the twenty animals from marginal ear vein and collected in dry and sterile test tube without undue frothing or disturbance.[18] Subsequently, the tubes were kept undisturbed for an hour at room temperature and then shifted into the refrigerator maintained at 4^0C overnight. Group 1 animals were administered first dose of Lithium carbonate in the dosage 50 mg/kg of body weight with gentle restraining in the cage and orogastric infant tube passed into stomach, taking due care, to ascertain that tube has not got into respiratory tract. Similarly, group 2 animals were administered both lithium carbonate 50 mg/kg and felodipine 1.5 mg/kg of body weight in 1% gum tragacanth suspension.

For acute effects, after 24 hours of first drug administration for both groups, the heart rate was recorded as well as the blood was collected to do estimation of serum electrolytes- Na^+& K^+ and Li^+. The drug administration was further continued for 28 days, group 1 with lithium carbonate and group 2 with co-administration of lithium carbonate and felodipine. On 28^{th} day, heart rate was recorded and blood was collected as before to do serum electrolytes- Na^+& K^+ and Li^+ estimation.

Blood samples was kept overnight in refrigerator at 4^oC and in morning was centrifuged at 3000 rpm. The supernatant was sequentially put through flame photometry with appropriate dilution as per the stock solution and sample was analyzed for sodium, potassium and where applicable for lithium concentration.Animals were observed for further 15 daysfor any mortality.

The data was analyzed statistically by student‘t’ test both paired and unpaired wherever applicable value. P value < 0.05 was considered significant.

RESULTS:

The mean serum levels of lithium were found to be dose dependent. Lithium carbonate produced mean serum concentration 0.19±0.04 mEq/L, 0.31±0.02 mEq/L and 0.58±0.02 mEq/L at doses of 25, 50 and 75 mg/kg respectively after 28^{th} day of oral treatment. Higher dosages of lithium - 75mg/kg produced 60% mortality. (Table 1) Since doses above 50 mg/kg were found toxic to animals, the dose of 50 mg/kg was chosen for subsequent interaction studies with felodipine.

Table 1: Effects of lithium carbonate on serum lithium concentration and mortality of albino rabbits:

Dose of oral lithium carbonate (mg/kg)	Serum lithium concentration (mEq/L)	Number of deaths
25	0.19±0.04	nil
50	0.31±0.02	nil
75	0.58±0.02	6

All values are mean ±SEM.

Effect of oral lithium carbonate and felodipine administration on heart rate of albino rabbits:

Baseline (pre-treatment) heart rate was 259 ± 2.22 beats per minute (bpm). Both lithium carbonateand felodipine on concurrent administration with lithium significantly decreased the heart rate from 259± 2.22 bpm to 244.80± 4.41 bpm and 250±2.14 bpm respectively after 24 hours of drug administration. Similarly both lithium carbonate and felodipine on concurrent administration with lithium decreased the heart rate from 259± 2.22 to 213.60± 3.45 bpm and 217±3.16 bpm respectively after 28th day of drug administration. This decrease was considered to be extremely statistically significant.

Table 2: Effect of oral lithium carbonate alone & oral lithium carbonate and felodipine administration on heart rate of rabbits:

	Baseline (pre-treatment)	**Lithium carbonate**		**Lithium carbonate and felodipine**	
		Acute effect (24hrs)	Chronic effect (28th day)	Acute effect (24hrs)	Chronic effect (28th day)
Heart rate (bpm)	259±2.22	242.80±4.40**	213.60±3.45***	250±2.14**	217±3.16***

All values are mean ±SEM
** P value = <0 .05; ** P value= < 0.01; *** P value = <0.001*

***Acute effect of oral lithium carbonate alone & oral lithium carbonate and felodipine administration on serum sodium and potassium*:**

The baseline serum sodium was 136.8 ± 1.40 mEq/L. After 24 hours of administration of lithium carbonate and felodipine on concurrent administration with lithium the sodium concentration was found to be 135.80±1.84 mEq/L and 134±1.65 mEq/L respectively which is statistically insignificant reduction (Table 3).

The baseline serum potassium was 3.44 ± 0.05 mEq/L. After 24 hours of administration of lithium carbonate and felodipine on concurrent administration with lithium, the potassium concentration was found to be 3.44±0.07 mEq/L and 3.32±0.04 mEq/L respectively which is statistically insignificant change(Table 3).

Table 3: Acute effect of oral lithium carbonate alone & oral lithium carbonate and felodipine administration on serum sodium and potassium:

	Baseline (pre-treatment)	**Lithium carbonate**	**Lithium carbonate and felodipine**
		Acute effect (24hrs)	Acute effect (24hrs)
Sodium conc (mEq/L)	136.8±1.40	135.80±1.84	134±1.65
Potassium conc (mEq/L)	3.44±0.05	3.44±0.07	3.32±0.04

All values are mean ± SEM
* P value = <0 .05; ** P value= < 0.01;*** P value = <0.001

Chronic effect of oral lithium carbonate and felodipine administration on serum sodium and potassium:

The baseline serum potassium was 3.44 ± 0.05 mEq/L. On 28th day of drug administration, there was in-significant increase of serum potassium levels with lithium carbonate and felodipine on concurrent administration with lithium, from 3.44± 0.05 mEq/L(baseline) to 3.52± 0.04 mEq/L and 3.55±0.02 mEq/L respectively (Table 4).

The baseline serum sodium was 136.8 ± 1.40 mEq/L. On 28th day of drug administration, serum sodium concentration was also marginally raised from 136.8 ± 1.40 mEq/L (baseline) to 139.20 ± 3.52 mEq/L and 141±2.14 mEq/L with lithium carbonate and felodipine on concurrent administration with lithium respectively(Table 4).All electrolyte changes essentially remained statistically in-significant.

Table 4: Chronic effect of oral lithium carbonate alone & oral lithium carbonate and felodipine administration on serum sodium and potassium:

	Baseline (pre-treatment)	**Lithium carbonate**	**Lithium carbonate and felodipine**
		Chronic effect (28th day)	Chronic effect (28th day)
Sodium conc (mEq/L)	136.8±1.40	139.20±3.52	141±2.14
Potassium conc (mEq/L)	3.44±0.05	3.52±0.04	3.55±0.02

All values are mean ± SEM
* P value = <0 .05; ** P value= < 0.01; *** P value = <0.001

Effect of oral lithium carbonate alone & oral lithium carbonate and felodipine administration on serum lithium concentration:

After 24 hours of drug administration, serum lithium levels was 0.31± 0.02 mEq/L with oral lithium carbonate alone and 0.40 ± 0.06 mEq/L with felodipine on concurrent administration with lithium. On 28th day the serum lithium concentration was 0.48±0.04 mEq/L and 0.51±0.03 mEq/L with oral lithium carbonate and felodipine on concurrent administration with lithium respectively (Table 5). The increment in serum lithium concentration with both group was statistically highly significant. Mortality was nil after 15 days of observation following 28 days of drug treatment.

Table 5: Effect of oral lithium carbonate alone & oral lithium carbonate and felodipine administration on serum lithium concentration:

	Lithium carbonate		**Lithium carbonate and felodipine**	
	Acute effect (24hrs)	Chronic effect (28th day)	Acute effect (24hrs)	Chronic effect (28th day)
Lithium conc (mEq/L)	0.31±0.02	0.48±0.04**	0.40±0.06	0.51±0.03***

All values are mean ± SEM
* P value = <0 .05; ** P value= < 0.01; *** P value = <0.001

DISCUSSION:

Lithium carbonate when given orally in increasing dose, increased the serum lithium concentration with mortality at higher dose i.e. 75 mg/kg. The therapeutic dose range of lithium in human being is between 0.6-1.25mEq/L. However in this study, blood concentration of 0.58mEq/L and above appeared to be toxic in albino rabbit. Serum lithium levels were found to be 0.31mEq/L in the control group. From these observations it seems that felodipine has virtually no effect on the same except for decrease in heart rate. In addition there was no mortality up to fifteenth day following drug therapy. These observations clearly indicate that felodipine appears to be safer.

Many workers have reported decrease in serum lithium levels due to concurrent administration of CCBs in humans and laboratory animals.[19]Some studies showed that lithium clearance were unaffected after CCBs administration.[4,6,14,20] The mechanism by which CCBs change the serum lithium levels is not clearly known. It has been postulated that lithium retention is related to the increase in sodium excretion associated with decreased aldosterone secretion induce by CCBs.[17,20,21] Any kind of volume depletion has also been implicated in precipitating lithium toxicity, since renal excretion of lithium depends on sodium balance. Thus diuretic effect of CCBs has also been implicated as a possible mechanism of this pharmacokinetic interaction.[17, 21, 22] Lithium reduces the production of cyclic adenosine monophosphate (cAMP) and inhibits the influx of calcium ion by limiting its channel opening, and these may interfere with SA and AV node function.[22, 23] There is also evidence that hypotensive and cardiac-depressant effects of lithium chloride are mediated by activation of adenosine triphosphate-sensitive potassium channels.[24] Concomitant use of diuretics, angiotensin-converting enzyme inhibitors, calcium channel antagonists or non-steroidal anti-inflammatory drugs has been associated with lithium toxicity through pharmacokinetic interactions.[25,26] A few workers have postulated that patient receiving long term lithium treatment may be dependent on an intact thirst mechanism to maintain a euhydrated state, since such prolong therapy has been said to produce nephrogenic diabetes insipidus, which is otherwise compensated by increased oral intake of water and sodium.[27] However, it is postulated that CCBs by some mechanism may be altering stimulus to thirst and drinking behavior and consequent lithium toxicity. In this study, however, no effort has been made to elucidate the nature or mechanism or the interaction between CCBs and lithium. Because lithium alters intracellular calcium ion dynamics and lowers platelet [Ca2+] in affectively ill patients but

not controls, drugs whose primary action is to modulate [Ca2+] in hyperactive cells have been used as antimanic agents.[28-30]There have been many reports of lithium toxicity in patients co-administered thiazide diuretics or angiotensin converting enzyme inhibitors.[31]CCBs are usually well tolerated and may be useful for a number of other psychiatric, neurological and medical conditions.

CONCLUSION:

From this study, it may be concluded that as far as possible use of CCB should be avoided but in case of unavoidable circumstances, it appears safe to use felodipine, a dihydropyridine group of CCB amongst all others. As this study was conducted in laboratory animals, more clinical studies are required before arriving at a definitive conclusion. Further study on this specific issue is needed to justify such off-label use of calcium channel blockers.

Conflicts of interest: Nil

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