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An Interaction Study of Beta-Blockers with Lithium in Albino Rabbits

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ABSTRACT

Introduction- Hypertension and bipolar disorder are both very common clinical disorders. Lithium remains the mainstay of therapy of bipolar disorder and beta-blockers continue to be used frequently for hypertension. Co-administration of both the drug groups are a possibility and how they affect each other is valuable to know.

Method: Five groups of albino rabbits (n=10 each) were included in this study. One group fed with gum tragacanth served as control. Four groups were treated orally with lithium carbonate (50mg/kg), three groups out of them were co-administered with propranolol (15mg/kg), metoprolol (10mg/kg) & atenolol (10mg/kg) respectively. The blood drawn from the marginal ear vein of rabbits was used for estimation of serum lithium, sodium, and potassium levels by flame photometry. The effect of drug treatment on heart rate was recorded using a transducer connected to a polygraph machine.

Result: The administration of lithium to the rabbits caused an insignificant reduction in heart rate and in serum potassium concentration but raised serum sodium concentration (140.2±3.83 to 146.78±4.21). When propranolol was added the lithium concentration was found to be significantly raised from 0.47±0.02 to 0.63±0.06, and there was a marked reduction in the heart rate (246.56±6.69 to 206.3±8.98). The co-administration of lithium along with metoprolol & atenolol didn't show any significant change in either the heart rate, serum lithium or the sodium & potassium concentration.

Conclusion: It may be unsafe to co-administer lithium and beta-blockers. However in case of extreme necessity a cardioselective beta-blocker is to be preferred over a non-selective one.

Keywords: Lithium, propranolol, atenolol, metoprolol, bipolar-disorder.

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INTRODUCTION

Lithium is the mainstay of treatment for acute and prophylactic treatment of manic depressive psychosis although 60% of patients do not respond to it alone. Therefore, management of acute mania and prophylaxis for manic depressive psychosis is by simultaneous use of anticonvulsants, antipsychotics, hypnotics, calcium channel blockers and anti-adrenergic drugs. Beta-blockers are known to be useful in treating aggression in psychiatric patients including those suffering from bipolar disorders [1]. Beta adrenergic antagonists maintain their place a major drug group for management of hypertension by major international bodies [2,3]. Also, they are used commonly for cardiomyopatheis, prevention of ischemic heart disease and migraine. In psychiatric practice, besides its use in mania alongwith lithium, combination of beta blockers and lithium is found potentially useful in the treatment of dysthymia, pathological aggression in children and adolescents[4], behavioral disorder with mental retardation, disruptive behavior in organic mental syndrome and Alzheimer's disease[5]. The coexistence of manic depressive psychosis and hypertension is well documented in clinical medicine [6]. Under these circumstances concurrent administration of lithium salts and beta-blockers is quite likely. The effect of the newer beta-blockers on serum lithium concentration and thus any clinical toxicity are not well documented in literature.

Keeping this in mind the present study was undertaken to investigate the effect on serum lithium concentration when beta-adrenergic blockers are co-administered in albino rabbits. Simultaneously, the pulse rate, serum sodium and potassium concentration were also studied following administration of lithium per se and co-administration with beta-blockers.

Materials and Methods

Animals: In this study albino rabbits of either sex weighing approximately 2.5-3 kg, maintained on standard laboratory diet were used. The animals were fed orally with lithium carbonate, propranolol, atenolol and metoprolol. Blood was withdrawn from the marginal ear vein of the animals for estimation of serum lithium, sodium and potassium by flame photometry.

Acute Studies

Animals: Five groups of rabbits (n=10 each group) were used as given following.

Group I - Animals fed with gum tragacanth.

Group II -Animals fed with lithium carbonate 50mg/kg body wt which acts as control.

GroupIIl -Animals fed with lithium carbonate and Propranolol (15mg/kg).

GroupIV -Animals fed with lithium carbonate and Atenolol (10mg/kg).

Group V -Animals fed with lithium carbonate and Metoprolol (10mg/kg).

Blood sampling for estimation of lithium, sodium, potassium and recording of heartbeat was done exactly after 24 hours.

Chronic studies

The control and treatment groups were the same as given above for acute studies. The animals were fed orally with the drugs daily at 10 AM for ten days and on eleventh day the blood samples were collected for estimations.

Drugs

Propranolol, metoprolol and atenolol were obtained as free gift samples from

Cipla, Astra IDL and Kopran Ltd., respectively. Lithium carbonate was purchased from Universal Chemical Corporation, Mumbai. Propranolol and atenolol were administered orally as a suspension with gum tragacanth and metoprolol was administered as a solution in water. Lithium carbonate was dissolved in minimum possible hydrochloric acid and diluted with water for administration.

Statistical analysis

All data were expressed as mean±SEM. The results were analyzed by Students' 't' test (unpaired). $p<0.05$ was considered statistically significant.

RESULTS

Acute Studies

No significant changes were observed in serum lithium, sodium and potassium concentration when propranolol, metoprolol and atenolol respectively were co-administered with lithium. The heart rate as expected was reduced due to the beta blockade (Table 1.)

Chronic Studies

On chronic administration of lithium, the serum sodium was observed to increase but serum potassium was not affected (Table 2). When propranolol was co-administered (15mg/kg) the serum lithium level was increased significantly ($p<0.02$) and a marked reduction was noted in heart rate($p<0.05$).

When atenolol(10mg/kg) and metoprolol(10mg/kg) were added the rise in serum lithium and decrease in heart rate was marginal. Insignificant increase in serum potassium was noted with all the three test drugs and serum sodium was not affected. Increased mortality (11%) was also observed in the propranolol group.

Group	Heart rate (beats/min)	Serum sodium (mEq/L)	potassium Serum (mEq/L)	Serum lithium (mEq/L)
Gum tragacanth (Group I)	250.4±9.3	139.5±3.32	3.95±0.42	
Lithium+gum tragacanth (Group II)	248.4±7.5	137±4.36	3.69±0.35	0.04±0.01
Lithium+ Propranolol (Group III)	236.7±7.97	136.2±4.35	4.04±0.28	0.03±0.01
Lithium+ Atenolol (Group IV)	246.4±8.00	135±4.16	3.84±0.28	0.02±0.00
Lithium+ Metoprolol (Group V)	240.9±6.71	134.8±4.12	3.98±0.2	0.02±0.00

All values are mean±SEM

Table 1: Acute studies

Group Treated	Heart rate (beats/min)	Serum sodium (mEq/L)	Serum potassium (mEq/L)	Serum lithium (mEq/L)
Gum tragacanth (Group I)	250.2±7.14	140.2±3.83	3.71±0.42	
Lithium+gum tragacanth (Group II)	246.56±6.69	146.78±4.21	3.84±0.37	0.47±0.02
Lithium+ Propranolol (Group III)	206.3±8.98**	143.3±3.49	4.22±0.28	0.63±0.06***
Lithium+ Atenolol (Group IV)	235±7.92	145.3±3.72	4.31±0.27	0.48±0.04
Lithium+ Metoprolol (Group V)	241.75±7.71	142.11±3.56	4.01±0.23	0.49±0.03

All values are mean±SEM ** $p<0.05$ *** $p<0.02$

Table 2: Chronic studies

DISCUSSION

In the present study, an attempt has been made to investigate the effect of co-administration of some common beta-blockers on serum lithium level along with potassium and sodium concentrations also. The dose used for lithium carbonate was 50 mg/kg orally through a feeding tube. The dosage used was similar to one used by previous workers [7].

The beta blockade chosen for the study, propranolol, metoprolol and atenolol are very commonly prescribed drugs. Propranolol has been used to treat tremors caused by lithium therapy[8]. However the doses used are much less than what is recommended for anti-hypertensive effects. Therefore in our study we chose dosage which are in the higher range and as is likely in case of treatment of hypertension. For propranolol, metoprolol and atenolol it was 15 mg/kg, 10 mg/kg and 10 mg/kg respectively.

In the acute studies, lithium alone caused slight reduction in heart rate, serum sodium and potassium. When the treatment was continued for ten days during the chronic phase of the study, the heart rate fell further. The serum sodium increased and potassium levels remained the same. The decrease in heart rate by lithium in experimental animals and human beings is known [9]. First degree AV block and T wave inversion has also been observed in patients with plasma concentration at upper limits of the therapeutic range. Lithium induced bradycardia observed in our study therefore is in agreement with previous workers.

When beta-blockers were co-administered with lithium, we recorded a further fall in heart rate with all the drugs, however the fall was significant in case of propranolol only. This could be due to the synergistic effect of both the drugs on heart rate via different intracellular mechanisms. Propranolol caused a significant increase in serum lithium levels and this could explain the enhanced bradycardia and increased mortality in case of propranolol treated rabbits. Slight increases in lithium levels have been reported by earlier workers [10]. However in our study the effect is

more marked which might be due to the higher dose range chosen. The changes were same in case of metoprolol and atenolol but the alteration from control group was marginal. The reason for this difference could be that propranolol may be increasing lithium retention via a mechanism other than beta-receptor blockade. The relative selectivity of atenolol and metoprolol for beta-1-receptors could explain their relative safety on co-administration with lithium.

From the present study if can be summarized that it may be unsafe to use propranolol, a non selective beta-blocker along with lithium specially at higher dosage as required for treatment of hypertension. Smaller doses as needed for treatment of tremors may be safe. In case of extreme necessity, it may be advisable to use beta selective adrenergic blockers like atenolol and metoprolol when co-administration with lithium is required. However, this being an animal study, further confirmation of our findings is needed in case of human beings.

REFERENCES:

1.Nevels RM, Dehon EE, Alexander K, Gontkovsky ST. Psychopharmacology of aggression in children and adolescents with primary neuropsychiatric disorders: a review of current and potentially promising treatment options. Exp Clin Psychopharmacol. 2010;18(2):184-201

2. Evidence-Based Guideline for the Management of High Blood Pressure in Adults. Report from the panel members appointed to the eighth Joint National Committee (JNC 8). JAMA. 2014; 311(5):507-520

3. World Health Organisation (WHO)/International Society of Hypertension (ISH) statement on management of hypertension. J Hypertens 2003; 21:1983-1992

4. Fava M. Psychopharmacologic treatment of pathological aggression: Psychiat Clin North America 1997;20(2): 427-51.

5. Malleta G J: Treatment of behavioural symptomatology of Alzheimer's disease with aggression: current clinical approaches. Int Psychogeriatr 1992; 4 Suppl 1:117-30.

6. Douste - Blazy P et al: ACE inhibitors and lithium treatment, (letter): Lancet 1986; 1:1448

7. Awasthi PK, Garg HK, Srivastava VK et al: Effect of oral lithium on the action of various CNS active drugs: Indian J Physiol Pharmacol 1996: 40(3):241-244

8. Gelenberg AJ, Jefferson JW. Lithium tremor. J Clin Psychiatry. 1995; 56(7):283-7.

9. Dubovsky SL, Franks RD, Allens. Verapamil; a new antimanic drug with potential interactions with Lithium. J Clin Psychiatry 1987; 48: 371-372.

10. Sadock BJ, Sadock VA. Lithium: in Kaplan and Sadock's Synopsis of Psychiatry. Eds. Sadock BJ, Sadock VA Lippincott, William and Wilkins 10th ed; 2007.Vol2 Chapter 36.20