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INFLUENCE OF HIGH FAT DIET ON STEADY STATE BIOAVAILABILITY OF LITHIUM CARBONATE IN MANIC DEPRESSIVE PATIENTS- A PRELIMINARY REPORT

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SUMMARY

The effect of high fat food in the steady state bioavailability of lithium carbonate (900 or 1200mg daily, in divided doses) was studied in three patients of manic-depressive psychosis in a self-control cross-over design. Serial blood samples were collected by venepuncture until 8 hours following drug administration and lithium was assayed by flame photometry. The results indicated a reduction in the extent of bioavailability of lithium by the high fat food as compared to standard normal diet, in all the three patients studied. Caution should be exercised in regard to lithium administration along with food rich in fat content.

INTRODUCTION

Lithium carbonate has been the mainstay of therapy in manic-depressive psychosis (MDP) and the very low therapeutic index of the drug necessitates careful monitoring of the serum concentrations (Baldessarini, 1991). Some of our patients who were duly controlled and stabilized with lithium subsequently presented with recurrence of symptoms with less than adequate serum lithium levels, although no obvious reason for this was discernible. While poor compliance was the first possibility that came to our mind, we explored other possible reasons too.

The influence of food on the bioavailability of drugs is well recognized (Toothaker & Welling, 1980). Various constituents of food alter the pharmacokinetic profiles of drugs in different ways. A higher fat content in food has been shown to increase the bioavailability of griseofulvin (Crounse, 1961) and to reduce that of tetracycline (Welling, 1977). Lithium carbonate is completely and readily absorbed from the gastrointestinal tract. The clinical effectiveness of lithium is said to be increased when it is administered with food (Toothaker & Welling, 1980), in terms of reduced gastrointestinal irritation and local side effects. Besides, most patients tend to take drugs just prior to, along with or right after food in order to ensure compliance. The food habit of people in the northern part of India is different from that elsewhere in the country, to the extent that the fat content is relatively high. It seemed thus possible, that in our patients, high-fat meals could alter the absorption kinetics of the drug. In the present preliminary study, therefore, the possible influence of a high-fat breakfast on the steady-state bioavailability of lithium carbonate was assessed in three patients with Manic depressive psychosis (MDP) who were adequately controlled and stabilized with 900 to 1200 mg of lithium per day.

CASE PROFILES

Patient No.1: PKG, 20 yr old male, 56 kg, 176 cm, non-smoker, non-alcoholic, MDP circular currently manic, presented with a four month history of irritability, hyperactivity, euphoria, grandiosity and transient cognitive deficits. A past history of depression in 1987 (3 months) and mania in 1989 (6 months) for which no detailed history of treatment was available; no family history. Laboratory investigations (renal function tests, Liver function tests, haemogram and electrocardiogram) were within normal limits; He was treated with lithium carbonate (Licab R) Tab 1200 mg daily in divided doses under direct supervision, i.e., 300 mg each at 7.00 a.m., 3.00 p.m. and 600 mg at 11.00 p.m. Other treatment for control of manic symptoms (haloperidol, carbamazepine, lorazepam) was stopped a week prior to the bioavailability study.

Patient No.2: DA, 19 yr old male, 55 Kg, 173 cm, non-smoker, non-alcoholic, MDP circular currently manic, presented with a four month history of hyperactivity, restlessness, pressure of speech, elated mood and grandiose ideation. A past history of 2 manic and 1 depressive episode in two years, with an average duration of 2 months each; details of treatment not available. History of MDP (mania) in father; no other concomitant disease present. Laboratory investigations were (RFT, LFT, haemogram and EKG) within normal limits; He was treated with lithium carbonate (Licab^{R}) Tab 1200 mg daily in divided doses under direct supervision, i.e., 300 mg each at 7.00 a.m., 3.00 p.m. and 600 mg at 11.00 p.m. for $1^{1/2}$ months. Other treatment for control of manic symptoms (carbamazepine and lorazepam) and for neuroleptic malignant syndrome (bromocriptine) were stopped a week prior to the bioavailability study.

Patient No.3: PS, 47 yr old male, 67 Kg, 178 cm, non-smoker, non-alcoholic, MDP circular currently manic, presented with a three month history of irritability, talkativeness, psychomotor agitation and impaired insight; There was a past history of 3 episodes in last 3 years (2 manic and 1 depressive) which were treated with neuroleptics and antidepressants. No other concomitant disease present; All laboratory investigations (RFT, LFT, haemogram and EKG) were within normal limits. He was treated with lithium carbonate 900 mg daily in three divided doses under direct supervision, i.e., 300 mg each at 7.00 a.m., 3.00 p.m. and 11.00 pm for 1 month. Other treatment for control of manic symptoms (chlorpromazine and nitrazepam) were withdrawn a week prior to the bioavailability study.

METHOD

Following an overnight fast, a standard breakfast (SB: comprising of 4 slices of bread, 15 grams of jam and 200ml of orange juice) and after a gap of 2 days a high fat breakfast (HFB: comprising of 4 slices of bread, 15gms of jam, 200ml of orange juice 200ml and 50 gms of butter, Verka^{R}) were given to each patient at 6.50 am and the morning dose of lithium was given under direct supervision at 7.00 a.m. as usual, along with 200 ml of water. All the patients thus served as their own controls.

Blood samples were collected by venepuncture in heparinized tubes on both occasions at 0, 1.5, 3, 5 and 8 hours following lithium administration. The samples were processed and serum lithium was assayed by flame photometry.

The area under the plasma concentration curve (AUC 0-8) was calculated using trapezoidal rule. The peak serum concentration (C max), time to reach the same (t max), and the minimum serum concentration (C min) were taken from the actual observed values.

RESULTS

The Table shows the values of various kinetic parameters.

Lithium kinetic variables in the study subjects

Patients	AUC 0-8 (meq/l*hr)		C max (meq/L)		C min (meq/L)		Tmax (hr)	
	SB	HFB	SB	HFB	SB	HFB	SB	HFB
PKG	8.28	6.93	1.25	1.00	0.90	0.70	1.50	3.00
DA	4.58	3.69	0.70	0.60	0.40	0.35	3.00	3.00
PS	8.93	7.81	1.25	0.95	0.75	0.70	3.00	3.00

SB = standard breakfast; HFB = high-fat breakfast

In all three patients, the AUC 0-8 was lowered when lithium was administered with the high-fat breakfast (HFB) as compared to the standard breakfast (SB). The HFB also lowered the Cmax and Cmin in all three patients as compared to the SB control values. However, in two patients, the Tmax values were same with either SB or HFB but in the third (PKG), the Tmax increased to 3.0 hours from its SB control value of 1.5 hours.

DISCUSSION

The results suggest that high fat content in the diet can reduce the extent of bioavailability of lithium carbonate. To the best of our knowledge, an interaction of this kind has not been reported earlier. While understanding the underlying mechanism for such an interaction is beyond the scope of the present preliminary study, it is tempting to speculate that the high-fat diet possibly lowered the absorption kinetics of lithium. Nevertheless, since lithium carbonate is a drug of very low therapeutic index, such interaction could pose serious and sudden therapeutic problem to a patient with Manic Depressive Psychosis who has been otherwise controlled and stabilized with lithium carbonate. Though, carried out only in three patients, on the basis of this preliminary report the authors suggest that when lithium levels are below the therapeutic range, the physician, in addition to probing into possible compliance failure, should also enquire from his patient about any change in the dietary practice in the recent past.

REFERENCES

Baldessarini, R.J. (1991) Drugs and the treatment of psychiatric disorders. In Goodman & Gilman's *The Pharmacological Basis of Therapeutics*, (eds. A.G.Gilman, T.W. Rall, A.S.Nies & P.Taylor), Vol.I, 8th edition, pp.417. Maxwell MacMillan Publishing Co.

Toothaker, P.D. & Welling, P.G. (1980) The effect of food on drug bioavailability. *Annual Review of Pharmacology and Toxicology*, 20, 173-99.

Crounse, R.G. (1961) Human pharmacology of griseofulvin: the effect of fat intake on gastrointestinal absorption. *Journal of Investigative Dermatology*, 37, 529.

Welling, P.G. (1977) Bioavailability of tetracycline and doxycycline in fasted and nonfasted subjects. *Antimicrobial Agents and Chemotherapy*, 462.

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