Pakistan J. Zool., vol. 43(6), pp. 1155-1160, 2011.

Adverse Effects of Withdrawal of Chronic Lithium Therapy On Liver—A Histological Study

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Abstract.- Effects of withdrawal of chronic lithium therapy have been investigated on liver. Lithium carbonate powder (34.2 mg/kg body weight) was administered daily by oral route in the form of capsule for four weeks to 15 adult male rabbits whereas a control group of 15 rabbits was given empty capsules and normal diet. Serum lithium levels were measured at the beginning of the experiment and thereafter checked weekly. After 4 weeks of consumption of drug, serum lithium levels increased significantly. The mean serum lithium levels gradually dropped after one week and significant fall was seen after 2 weeks of sudden withdrawal but it did not touch the baseline. After four weeks, 5 rabbits in each group were sacrificed and their livers were examined to see the effect of drug on them. Two other groups of 5 rabbits each were sacrificed one and two weeks after lithium withdrawal, respectively. Cholangitis (60%) and hepatitis (40%) were observed in both withdrawal groups. Cholangiocarcinoma (40%) was observed predominantly with chronic lithium therapy. This study highlighted the effect of chronic lithium therapy and its sudden withdrawal. It is suggested that once started, lithium therapy may be withdrawn gradually.

Key words: Chronic lithium, withdrawal effects, hepatitis, cholangiocarcinoma, pleomorphic.

INTRODUCTION

Lithium is the lightest alkali metal used effectively to treat manic disorders and in preventing recurring manic depressive episodes (Groleau, 1994; Sharma and Iqbal, 2005). But it has a narrow therapeutic range which makes blood serum lithium levels monitoring mandatory to avoid lithium intoxication (Dehpour *et al.*, 1998). Therapeutic serum lithium levels are usually maintained between 0.6-1.2 mEq/L whereas levels above 2.0 mEq/L are usually toxic (Groleau, 1994).

Lithium is well absorbed by the stomach and proximal small intestine with no absorption in the large intestine. After ingestion peak serum levels are seen after two and a half hours and completed within 6-8 hours (Goodman and Gillman, 1996). Lithium does not bind to plasma proteins but binds to some ligand (Clarke *et al*., 1998). As it moves slowly from extracellular compartment to intracellular space it may require 6-10-days to reach steady blood concentration and for the desired therapeutic responses (Groleau, 1994). Distribution of lithium in the human organs is almost uniform; it is concentrated in tissues like brain, kidney, thyroid, bone, liver and muscle cells against a concentration gradient. The body distribution of lithium is quite similar to that of sodium and greater part of it is contained in the cells probably at the expense of potassium (Javaid, 1985). It is excreted unchanged almost exclusively by the kidneys (Groleau, 1994). After glomerular filtration, 80% of lithium is reabsorbed by the proximal renal tubules. It is not reabsorbed in the distal part of nephron. In adult humans the 1/2 life of lithium is approximately 29 hours. Therefore serum levels would normally fall 20% within first 6 hours of discontinuation of therapy. Toxic effects of lithium may or may not be dose related (Javaid, 1985). Chronic lithium administration results in elevation of serum corticoids, lowering of serum glucose and altered induction of liver enzymes. It has been reported that lithium can alter the glucose metabolic set-point (Grier *et al.*, 1976) and inhibits the phosphoglucomutase (Csutora *et al*., 2005). Lithium ions cause an increase in hepatic glycogen (Bosch *et al.*, 2009) whereas a decrease in liver glycogen had been reported (Plenge, 1977; Lazarus, 1998) accompanied by an increase in skeletal muscle glycogen (Goodman and Gillman, 1996). An increase in fructose 2,6-bisphosphate levels had been observed with lithium treatment (Bosch *et al*., 2009) but it does not affect the concentration of cytochrome P-450 (Daniel and Netter, 1990).

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0030-9923/2011/0006-1155 $ 8.00/0

Chronic lithium treatment can produce significant inflammatory and congestive changes in different organs like kidney, liver, brain and spleen (Loghin *et al.*, 1999).

There are scarce studies on the effects of lithium therapy on the liver which is one of the vital organs. The present study, therefore, was undertaken to correlate the effects of chronic lithium therapy and its withdrawal on liver.

MATERIALS AND METHODS

Chemical

Lithium carbonate powder by Fluka Chemic AG. CH-9470 Buchs Company, made in Switzerland was obtained from the medical store of Postgraduate Medical Institute, Lahore and was used for the study.

Animals

Thirty adult male albino rabbits were used for the experiment. They were kept at the Animal House at Postgraduate Medical Institute, Lahore and were allowed 2 weeks for acclimatization in optimal light and temperature and had free access to water and seasonal vegetables.

Lithium carbonate administration

Animals were randomly divided into 2 main groups; control A and experimental B, each with further subgroups A1, A2, A3 and B1, B2, B3, each having 5 animals. Lithium carbonate powder was given orally in a dose of 17 mg/kg calculated from chronic oral consumption of 1200mg/day for an average of 70 kg given to man (Groleau, 1994). The weighed quantities of Li_2CO_3 in double the therapeutic dose 34.2 mg/kg body weight, once daily in capsules was given (Table I). The control group animals were given empty capsules. Serum lithium levels were recorded by using FP 10 and IT 20 Flame Photometer at the beginning of experiment and then weekly till the end of the experiment (Table I). The animals were sacrificed on different days and their livers were removed from the body for gross and histological study. 2 mm pieces were taken from different sites of liver and were processed in automatic processor, embedded in paraffin and sectioned at 5 µm by manual rotary microtome and stained with hematoxylin and eosin by standard procedure for light microscopy under different magnifications.

The results were analyzed using statistical variance appropriate to the experimental design.

RESULTS

Animals of control group (A) remained healthy and active with normal intake of food and water throughout the experiment. Animals belonging to experimental group B showed increase in body weight but a significant increase in body weight was observed after two weeks of sudden withdrawal.

No serum lithium levels were detected in control group animals as they did not receive lithium. The animals in experimental group who received double the therapeutic lithium dose for 4 weeks showed gradual mean increase in serum lithium levels of 0.54±0.07 m.mol/L from first to fourth week. Although the mean serum lithium levels gradually dropped after one week and significant decrease was seen after 2 weeks of withdrawal but it did not touch the baseline (Fig. 1).

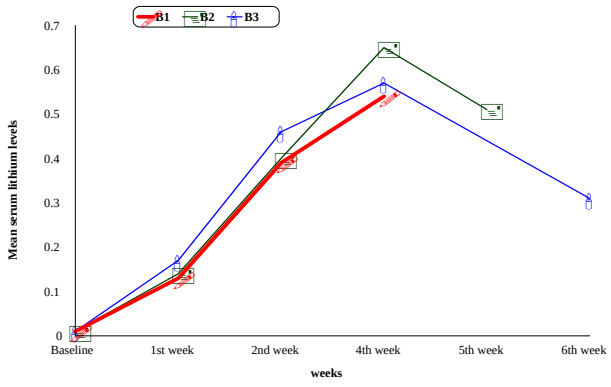

Fig. 1: Effect of withdrawal of chronic lithium therapy showing changes in mean serum lithium levels in different experimental subgroups (B_1, B_2, B_3).

No pathological changes were noticed on gross and microscopic examination of the livers of animals from control group (A) although mild venous congestion was observed in them (Fig. 2A).

Table I.- Lithium therapy administered to albino rabbits.

Groups	Subgroups	No. of rabbits	Treatment	Duration	Serum lithium level done & sacrificed
Group A	A 1	5	Normal diet and empty capsule	4 weeks	29th day
	A 2	5	Normal diet and empty capsule	4 weeks	After one week of withdrawal (36th day)
	A 3	5	Normal diet and empty capsule	4 weeks	After two weeks of withdrawal (43rd day)
Group B	B 1	5	Normal diet and lithium powder in capsule 34.2mg/kg	4 weeks	29th day
	B 2	5	Normal diet and lithium powder in capsule 34.2mg/kg	4 weeks	After one week of withdrawal (36th day)
	B 3	5	Normal diet and lithium powder in capsule 34.2mg/kg	4 weeks	After two weeks of withdrawal (43rd day)

Livers of all the animals belonging to experimental subgroups were reddish brown in color. Most of them showed circumscribed white spots, whereas hemorrhagic areas were observed predominantly after 2 weeks of withdrawal. Capsule of liver was intact.

Histological examination (Table II) revealed intact capsule and architecture. Dilation and congestion of central vein was observed in all experimental subgroups. Mild lymphocytic infiltration at portal areas especially around the bile ducts giving an appearance of cholangitis was observed in all subgroups but it was predominantly noticed after sudden withdrawal (Figs. 2B,C).

Table II.- Gross and microscopic findings of livers from experimental group.

Findings	B1 (n=5; %)	B2 (n=5; %)	B3 (n=5; %)
White spots	Present (n=1; 20%)	Present (n= 3;60%)	Present (n=4: 80%)
Architecture	Preserved	Preserved	Preserved
Central vein congestion	Present (+)	Present (++)	Present (+)
Cholangitis	Present (n=1; 20%)	Present (n=3; 60%)	Present (n=3; 60%)
Hepatitis	Present (n=1; 20%)	Present (n=2; 40%)	Present (n=2; 40%)
Fatty change	Absent	Absent	Present (n=4; 80%)
Cholangiocarcinoma	Present (n=2; 40%)	Present (n=1; 20%)	Present (n=1; 20%)

Lymphocytic infiltration was also observed in hepatic parenchyma which was not breaking the limiting plate and gave the appearance of chronic persistent hepatitis. The hepatocytes appeared normal but there was mild to moderate fatty change in cells after 2 weeks of withdrawal (Fig. 2D).

Bile duct proliferation was noticed in portal areas of some of the livers; these ducts were lined by hyperchromatic columnar epithelial cells with marked pleomorphism; these cells were forming papillary processes. A focal break in the basement membrane with invasion of stroma was also observed. It was diagnosed as well differentiated cholangiocarcinoma (Fig. 2E). Out of 15 experimental animals, 4 (26.6%) developed cholangiocarcinoma, predominantly seen after chronic lithium therapy (B1).

DISCUSSION

Since lithium is highly effective in controlling and preventing recurring manic depressive episodes, its use in psychiatry to rehabilitate patients continues despite its complications (Nciri *et al.*, 2009).

In the present study, daily lithium dose resulted in a gradual increase in serum lithium levels as was also observed by other workers (Javaid, 1985; Sharif *et al.*, 2003). It had been reported that after the withdrawal of the drug; the serum lithium level fell to about 20% within 6 hours of discontinuation (Groleau, 1994) and reached the base line in ten to fourteen days (Lapierre *et al.*, 1980; Simard *et al.*, 1989; Goodman and Gillman, 1996).

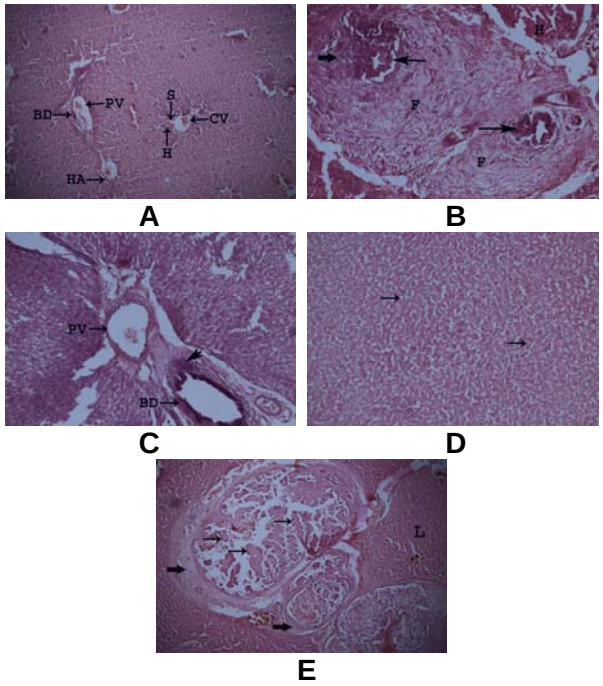

Fig. 2. Histological sections of liver; A, subgroup A_2 showing post-mortem changes caused by preterminal circulatory failure. There is dilated and congested central vein (CV) surrounded by radiating cords of hepatocytes (H), enclosing hepatic sinusoids (S); portal vein (PV), bile duct (BD) and hepatic artery (HA) are seen in portal area at the periphery of hepatic lobule; B, subgroup B_3 showing cholangitis characterized by bile ducts (thin arrows) surrounded by lymphocytes (thick arrow) and fibrosis (F); C, subgroup B_2 showing cholangitis characterized by dilated and congested portal vein (PV) and bile duct (BD) surrounded by lymphocytes (arrowhead); D, subgroup B_3 showing fatty change which is characterized by hepatocytes containing cytoplasmic vacuoles (thin arrows); E, subgroup B_1 showing cholangiocarcinoma which is characterized by proliferating bile ducts surrounded by fibrosis (thick arrow); these ducts are filled with hyperchromatic columnar epithelial cells forming papillary processes (thin arrows). H & E. X 100

However, our results indicated significant fall after 2 weeks of withdrawal, but the serum lithium level did not reach the baseline. Margo and McMahon (1982) and Delva *et al.* (1982) observed similar effect of withdrawal on the serum lithium levels (Margo and McMahon, 1982; Delva *et al.*, 1982). This prolonged excretion pattern may be related to tissue storage, particularly in bones (Laurence and Bennett, 1992; Birch, 1977) and its gradual release from there into blood (Laurence and Bennett, 1992). In another reported case (Sellers *et al.*, 1982) there was a post withdrawal rise in serum lithium levels, attributed to redistribution of lithium from its stored tissues like brain, kidney, liver and thyroid (Morton *et al.*, 1993).

The morphological examination of liver revealed that hepatic architecture was preserved in these experimental animals. The central veins were dilated and congested. Sharif reported congestive changes in kidney and thyroid gland in an animal study (Sharif *et al.*, 2003; Sharif and Raza, 2006). This finding might be explained on account of chronic passive congestion of liver developing with cardiac decompensation which is an element of preterminal circulatory failure as evidenced on postmortem examination (Kumar *et al.*, 1999).

Cholangitis was found to be increased after sudden withdrawal of lithium (20% in B1 whereas 60% each in B2 and B3). Hepatitis was noticed in all the experimental groups although increased frequency was observed after withdrawal ie; groups B2 and B3 (40% each) as compared to B1 (20%). The hepatocytes were normal except in group B3 which showed mild to moderate fatty change occurring two weeks after sudden withdrawal of lithium indicating reaction to cellular injury (Kumar *et al.*, 1999) implying that the withdrawal effects were more severe with abrupt rather than with slow withdrawal (Baldessarini *et al.*,1997). It had been noticed these changes usually occur after 1-2 weeks (Laurence and Bennett, 1992) but sometimes rebound phenomenon could take place even after 5 days of discontinuation of drugs (Lapierre *et al.*, 1980).

Withdrawal effects on various organs had been observed. In CNS, sudden withdrawal leading to early morbidity and suicidal behaviour had been reported (Baldessarini *et al.*, 1997). In thyroid, rebound hyperactivity leading to thyrotoxicosis (Rosser, 1976) caused by unmasking of disease in individuals with thyroid stimulated antibodies had been noted (Lazarus, 1998; Brownlie *et al.*, 1976). Sharif reported that 60% goiters showing rebound phenomenon either due to raised lithium ratio in

rabbits or due to marked iodine imbalance caused by sudden withdrawal of chronic lithium therapy (Sharif and Raza, 2006).

There was mild lymphocytic infiltration in portal areas but not breaking the limiting plate, thus giving the picture of hepatitis. The hepatotoxicity of lithium had been explained on the basis of two independent withdrawal mechanisms *i.e.* biotransformation of the drug in the liver with the formation of toxic metabolites or induction of an allergic hypersensitivity reaction (Kumar *et al.*, 1999). The former mechanism seems to be working in this experimental study rather than the other one as no allergic infiltrate like eosinophils was observed in liver parenchyma. Kumar *et al.* (1999) suggested that similar hepatic changes in laboratory animals could also be observed by dose dependent effect of directly acting therapeutic agents. Both inflammatory and congestive changes had also been reported in liver of lithium treated animal (Loghin *et al*., 1999).

In the present study, cholangiocarcinoma was observed in 40 % cases after 4 weeks of lithium therapy (B1) whereas 20 % was noticed in each of withdrawal subgroups (B2 and B3). These findings showed that risk of development of this carcinoma decreases after lithium withdrawal. The bile duct proliferation had been observed by Javaid (1985), however, such a carcinomatous change was never observed in earlier experiments. Laurence and Bennett reported that after withdrawal, there may be sustained effect on various tissues like liver in rabbits as compared to human (Laurence and Bennett, 1992).

CONCLUSIONS

The present study highlights the possibility of developing cholangiocarcinoma of intrahepatic biliary system with chronic lithium therapy, which is an irreversible change. This study, therefore, emphasizes the careful use of lithium carbonate. In addition, it is suggested that the course of cholangitis and hepatitis should also be studied with the period of withdrawal extended over a few more weeks, to find their correlation with cholangiocarcinoma and hepatocellular carcinoma, respectively. It is to be ensured that the withdrawal of lithium carbonate should be gradual and not sudden.

ACKNOWLEDGEMENTS

I am thankful to Dr. G. R Qureshi (Head of Pathology Department, CMH LM&DC) who helped us in diagnosing the histopathological slides and Dr. Asad Ahmed Shabbir (Demonstrator Pathology Department, CMH LM&DC) in photographing these slides. We are also indebted to Post Graduate Medical Institute for giving financial support for this project.

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(Received 26 July 2011, revised 20 January 2011)