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The Effect of Bromocriptine on the Liver of Immature Female Rats

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Abstract:
The present study was performed to determine the effect of bromocriptine (BRO) a dopamine agonist on the liver of immature female rats. Sixty-five immature rats (15 days old) weighing 20-25g were assigned into four groups (20 for each group except the first group of 5 animals), the first group was initial control sacrificed on day 1 of the experiment. The second group served as control and received vehicle (IP), the third and fourth group received BRO (IP) at 2.5 and 5 mg/kg BW respectively for two durations (7 days and 21 days). Five animals of each group were maintained for 1 month without treatment for recovery study. BRO treatment caused; i) a significant decrease in the body weight, ii) a significant increase in the weight of the liver, iii) a significant increase in serum levels of alkaline phosphatase in immature rats of both treated groups when compared to the control group. Histological changes in the liver were observed in both BRO treated groups of each duration indicating that BRO induced liver injury. From the present study, we conclude that despite the effect of BRO in the liver of immature female rats, a period of one month without treatment was sufficient for the recovery of BRO effects.

Keywords: Bromocriptine, immature rats, liver, Recovery.

INTRODUCTION

Bromocriptine, an ergot alkaloid derivative, structurally related to dopamine and suggested to be a dopamine D2 receptor agonist (Barbieri and Ryan, 1983). BRO is widely used clinically for the treatment of patients with microprolactinoma and macroprolactinoma. With this drug treatment, serum prolactin concentration usually dropped to the normal range and directly binds to pituitary dopamine D2 receptors and inhibits prolactin secretion through the inhibition of adenyl cyclase activity (Barbieri and Ryan, 1983). BRO directly activates lactotrope dopamine receptors, leading to the inhibition of spontaneous and TRH-induced release of prolactin (Schwartz, 2004). BRO is effective as long as its administration is continued (Thorner *et al.,* 1980). BRO has side effects with the doses required for prolactin suppression *viz*. nausea, vomiting, and postural hypotension with dizziness, drowsiness, fatigue, headache, indigestion, light-headedness, loss of appetite, nausea, stuffy or runny nose, weakness, etc., but these symptoms usually disappear within two to three days (Lancranjan, 1981). It has been reported that BRO is also a common drug for the therapy of Parkinson's disease (Ahlskog, 1994; Ogawa, 1998). Previous reports showed that BRO exerts pharmacological effects on the nervous system as it decreases the spontaneous firing rate of neurons in the cortex and the pars compacta of the substantia nigra (Bioulac *et al.,* 1978) and inhibited the tuberoinfundibular dopaminergic neuron activity (Demarest *et al.,* 1985). The side-effects of BRO on the cardiovascular system have also been investigated. Treatment with BRO decreases blood pressure and heart rate in both experimental animals and in humans (Hof and Hof 1984; Ageel *et al.,* 1987; Roquebert *et al.,* 1991; Schobel *et al.,* 1995). Meanwhile, the results of numerous studies indicated that BRO affects adrenal function in pigs (Klemcke *et al*., 1990). Moreover, it has been reported that BRO treatment in immature female rats delayed the onset of puberty and interfered with the follicular development and the ovarian activity which was evidenced by the reduction in the number of healthy follicles and increase in the number of atretic follicles (Ameen *et al.,* 2011).

Many studies reported that the usage of drugs has an adverse effect or a harmful and undesired effect on the body. Adverse effects may cause a reversible or irreversible change, including an increase or decrease in the susceptibility of the individual to other chemicals, foods or procedures, such as drug interactions (Green and Spencer, 1966). Drugs are important causes of liver injury, more than 900 drugs, toxins, and herbs have been reported to cause liver injury, and drugs account for 20-40% of all instances of fulminant hepatic failure (Mehta *et al.*, 2014). It has been reported that BRO induced acute hepatitis in Parkinson's disease patients (Liberato *et al.,* 1992) and hepatotoxicity and nephrotoxicity in mice (Adejoke *et al.,* 2014). Besides, a recent study categorized bromocriptine as a drug-induced liver injury (Bjornsson and Hoofnagle, 2016). Toxic effects on the kidneys related to medications are both common and expected. Any drugs have nephrotoxic potential and some of them can cause more than one pattern of injury (Zager, 1997).

There are no studies on the effects of BRO on the gross and histomorphology of the liver in immature female rats to date. Data on the effects of BRO on the liver function test *viz.* analysis of alkaline phosphatase is limited. Further, the reversible effect of BRO is not studied so far. Therefore, it is necessary to know the reversibility effects of BRO by the cessation of treatment. Hence, the study aimed at finding out; whether the administration of two different doses (2.5 and 5 mg/kg BW) of BRO for two durations (7 and 21 days) have any toxic effects on the liver in immature female rats? Whether or not the effects of BRO are reversible?

MATERIALS AND METHODS

Chemicals

Technical grade bromocriptine was kindly purchased from Sigma-Aldrich, St. Louis, USA.

Ethical approval

The protocols were approved by the Institutional animal ethics committee and the guidelines of CPCSEA, Govt. of India were followed for care and maintenance of animals.

Animals and treatment

Sixty-five immature female Wistar albino rats (15 days old) weighing 20-25g, originally obtained from an inbred population of Central Animal Facility, Department of Zoology, University of Mysore, India. The animals were housed in polypropylene cages (5 animals per cage) with husk as the bedding material and kept under natural photo thermal conditions. The animals were supplied with dry food pellets and water *ad libitum* during the period of the experiment. Bodyweight of each mouse was recorded before the commencement of the treatment (initial BW). Animals were divided into 4 groups; the first group served as initial control (5 rats) and the other three groups consisting of 10 rats each. The rats of the first group (initial control) were sacrificed on the first day of the experiment. The second group served as control and received intraperitoneal (IP) administration of the vehicle (0.1 ml distilled water /rat/day). The third group of the low dose received BRO (IP) (2.5mg/kg BW), and the fourth group of the high dose received BRO (5 mg/kg BW) for two durations i.e. 7 days and 21 days. Five rats of each group were sacrificed 24h after the last administration (22 and 36 days old respectively) and remaining five rats of each group of each duration were maintained for 1 month without treatment (52 and 66 days old) to study whether or not the effect of BRO were reversible. Bodyweight of each mouse during the whole study was also recorded.

Biochemical assay

Blood samples were collected and serum was separated and stored at -20 ºC for determining serum level of alkaline phosphatase (U/L) by the International Federation of finical chemistry method (IFCC) as an indicator whether the liver functions have been affected or not (Bowers and McComb, 1966).

Histology of the liver

At autopsy, the weight of the liver was recorded and later converted into relative weight. Liver organs were washed with saline to remove blood stain and fixed in Bouin's fixative, dehydrated with different grades of alcohol, cleared in chloroform, infiltrated with molten paraffin wax and embedded in paraffin wax. Sections of 5µm thickness were taken and stained with haematoxylin and eosin and evaluated under the light microscope (Bancroft and Gamble, 2008).

Recovery experiment

Five immature rats from each group (Control, low dose and a high dose of BRO) of each duration (7 and 21 days) were maintained without treatment for one month to study the reversibility effect of BRO. Rats were sacrificed after one month and weights of the body and liver were recorded. Blood samples were collected and serum was separated and stored at -20 ºC for determining serum level of alkaline phosphatase (U/L).

Statistical analysis

The mean values of each parameter were computed considering data from 5 rats per group and expressed as mean ± SE. One-way analysis of variance (ANOVA) followed by Duncan's new multiple range tests (DMRT) was used to determine significant differences among mean values. Mean values were judged significantly different if $P<0.05$.

RESULTS

Bodyweight

There was a significant decrease in the bodyweight of immature rats of low and high treated groups (2.5 and 5 mg/kg BW) respectively when compared to the control group. However, there was no significant difference in the bodyweight of immature female rats following treatment with low and high BRO doses one month after cessation of treatment compared to the control group (Figures 1 and 2).

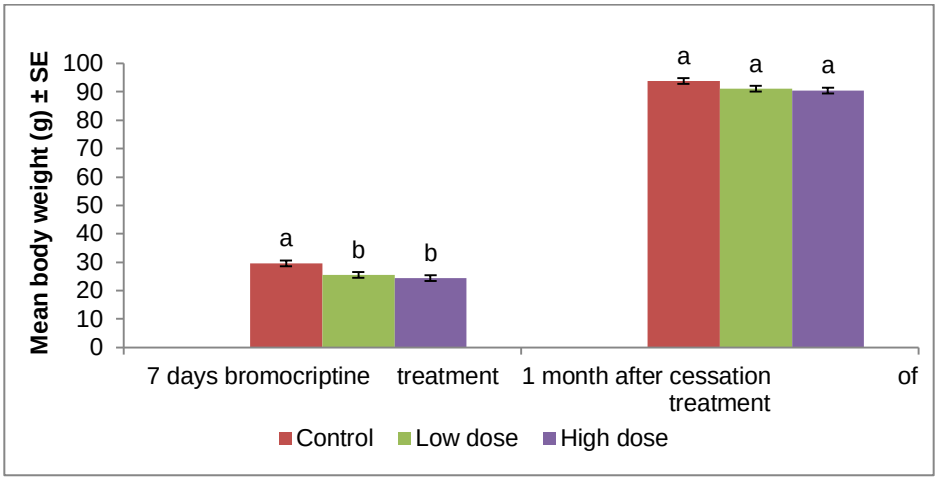

Fig. 1. Mean body weight of female immature rats of control, low dose, and high dose treated groups following 7 days treatment and 1 month after cessation of 7 days treatment. Bars with same superscript letters are not significantly different, whereas those with different superscript letters are significantly (P<0.05) different, as judged by ANOVA following Duncan multiple range test. Control:(0.1ml distilled water/day/rat), Low dose: (2.5 mg/kg BW), High dose: (5mg/kg BW).

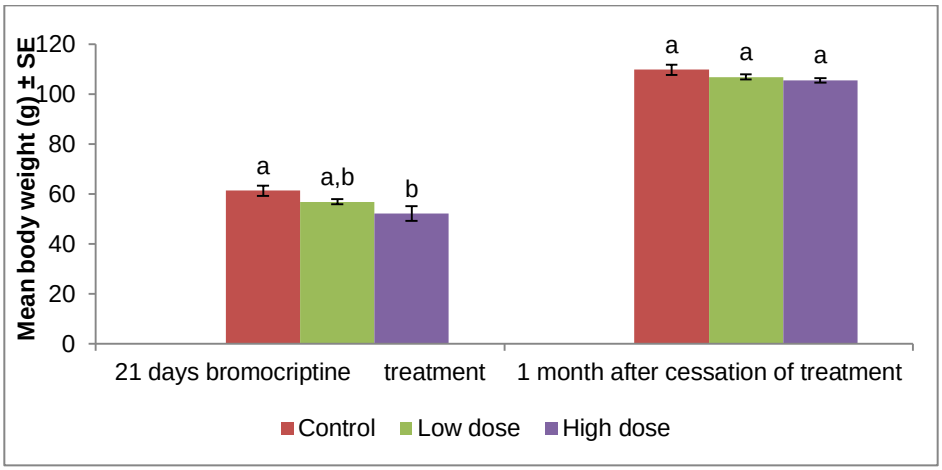

Fig. 2. Mean body weight of female immature rats of control, low dose, and high dose treated groups following 21 days treatment and 1 month after cessation of 21 days treatment. Bars with same superscript letters are not significantly different, whereas those with different superscript letters are significantly (P<0.05) different, as judged by ANOVA following Duncan multiple range test. Control: (0.1ml distilled water/day/rat), Low dose: (2.5 mg/kg BW), High dose: (5mg/kg BW).

Liver weight

There was a significant increase in the mean relative weight of the liver of immature female rats of low and high BRO treated groups (2.5 and 5 mg/day BW) respectively compared to the control group. There was no significant difference in the mean relative weight of the liver of low and high BRO treated immature female rats one month after cessation of BRO treatment when compared to the control group (Figures 3 and 4).

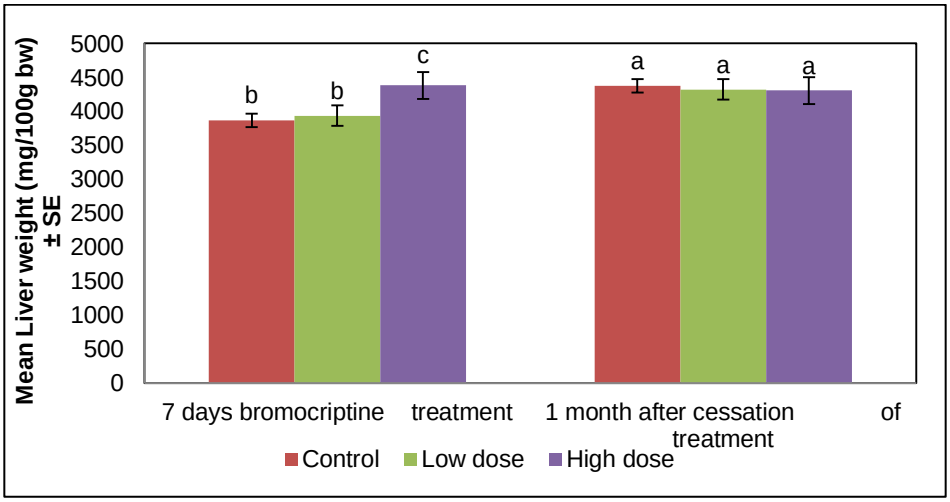

Fig. 3. Mean weight of the liver of female immature rats of control, low dose and high dose treated groups following 7 days treatment and 1 month after cessation of 7 days treatment. Bars with same superscript letters are not significantly different, whereas those with different superscript letters are significantly (P<0.05) different, as judged by ANOVA following Duncan multiple range test. Control: (0.1ml distilled water/day/rat), Low dose: (2.5 mg/kg BW), High dose: (5mg/kg BW).

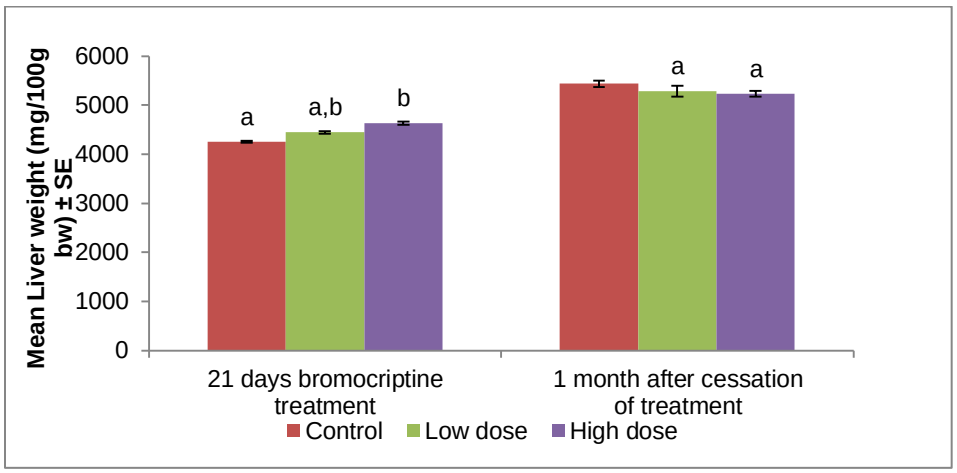

Fig. 4. Mean weight of the liver of female immature rats of control, low dose and high dose treated groups following 21 days treatment and 1 month after cessation of 21 days treatment. Bars with same superscript letters are not significantly different, whereas those with different superscript letters are significantly (P<0.05) different, as judged by ANOVA following Duncan multiple range test. Control: (0.1ml distilled water/day/rat), Low dose: (2.5 mg/kg BW), High dose: (5mg/kg BW).

Biochemical assay:

Serum Alkaline phosphatase level (U/L)

There was no significant difference in the mean of serum alkaline phosphatase level of the initial control and the controls of both durations. Whereas, there was a significant increase in the mean serum alkaline phosphatase level of low and high treated groups compared to the controls (Table 1). One month after cessation of 7 and 21 days treatment showed that there was no significant difference in the mean serum alkaline phosphatase level of both treated groups compared to the controls (Table 1).

Table 1. Mean serum alkaline phosphatase levels in immature female rats administered with bromocriptine for 7 and 21 days and one month after cessation of the treatment.

Groups	Mean serum alkaline phosphatase levels (U/L) ± SE			
	7 days of treatment (15-21 days old)	1 month after cessation of 7 days treatment (22-52 days old)	21 days of treatment (15-35 days old)	1 month after cessation of 21 days treatment (36-66 days old)
Initial control (15 days)	615.18 ± 31.17[a]	-	564.40 ± 20.29[a]	-
Control	695.2 ± 131.31[a]	316.6 ± 47.42[a]	636.20± 40.20[a]	341.6 ± 29.42[a]
Low dose	748.20 ± 93.90[b]	298.0 ± 29.98[a]	1091.2 ± 133.38[b]	331.20± 19.52[a]
High dose	792.40 ± 36.25[b]	292.4 ± 10.0[a]	1220.2 ± 193.46[b]	329.20± 26.95[a]
ANOVA F-value (df=3,16)	8.02 P<0.001	NS	4.36 P<0.05	NS

Note: Values with the same superscript letters are not significantly (P<0.05) different whereas those with different superscript letters are significantly (P<0.05) different. df= degree of freedom. F -values were compared using one way ANOVA.

Histological study of the liver

Sections of the liver of initial control and control rats showed normal histological architecture. It showed of hexagonal or pentagonal lobules with central veins and peripheral hepatic triads or tetrads embedded in connective tissue. Hepatocytes are arranged in trabeculae running radiantly from the central vein and are separated by sinusoids containing Kupffer cells. They are regular and contain a large spheroidal nucleus with a distinctly marked nucleolus and peripheral chromatin distribution (Figure 5). Histopathological changes in the cross-section of the liver of BRO treated groups following both durations were noticed. Liver sections showed that some hepatocytes were enlarged and contained empty vacuole-like spaces, degeneration, vacuolation, infiltration in the hepatocytes, infiltration of leukocytes and hemorrhage were also noted. These changes were more in higher doses (Figure 5 and 6). On the other hand, liver sections exhibit normal appearance one month after cessation of 7 and 21 days treatment when compared to the controls (Figure 6).

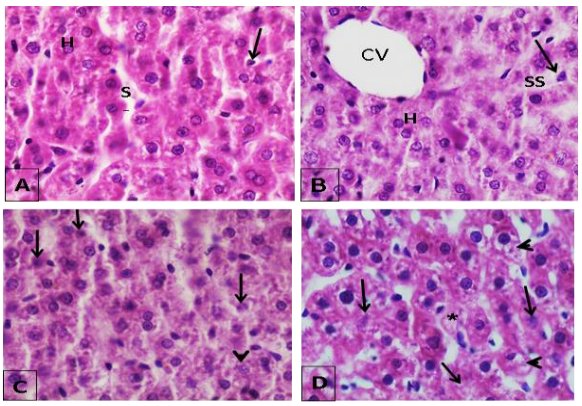

Fig. 5. Cross-section of the liver of rats of (A) initial control and (B) control showing normal appearance of the liver, normal hepatocytes (H), sinusoids (S), normal Kupffer cells (arrows), normal central vein (CV); (C) cross-section of the liver of immature rats treated with low dose of BRO for 7 days & (D) cross-section of the liver of immature rats treated

with high dose of BRO for 7 days showing some degenerated changes: necrosis of hepatocytes with degenerated nucleus (arrows), modest enlarged of hepatocytes with vacuolation changes (arrowheads), little bubbles of fat inside hepatocytes (asterisk). 400x, H & E.

Control: (0.1ml distilled water/day/rat), Low dose: (2.5 mg/kg bw), High dose: (5mg/kg bw).

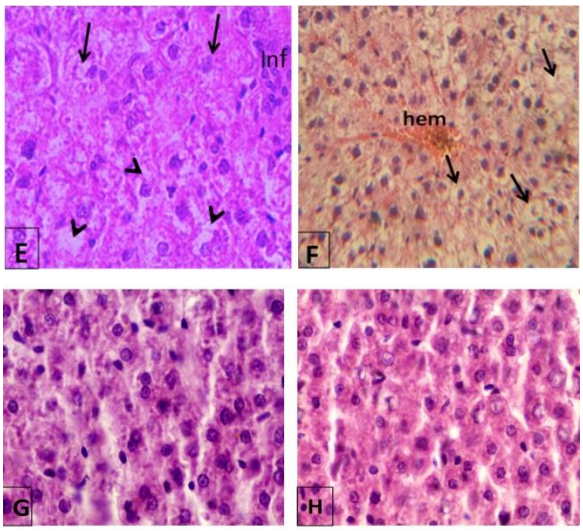

Fig. 6. Cross-section of the liver of rats of (E) cross-section of the liver of immature rats treated with low dose of BRO for 21 days showing degenerated (arrows) and vacuolation of hepatocytes (arrowheads) and an infiltration of leukocytes (inf); (F) cross-section of the liver of immature rats treated with high dose of BRO for 21days showing high degree of degenerated and vacuolation of hepatocytes (arrows) beside a hemorrhage (hem). Cross-sections of immature rats in (G), one month after cessation of 21 days treatment of low dose group, and in (H), one month after cessation of 21 days treatment of high dose group, showing healthy-looking, more or less like control rats liver sections with less degenerated changes. 400x, H & E.

Control: (0.1ml distilled water/day/rat), Low dose: (2.5 mg/kg bw), High dose: (5mg/kg bw).

DISCUSSION

The present study reveals that the treatment of low and high doses of bromocriptine either for 7 or 21 days in immature female rats caused a significant reduction in the mean body weight which attributed to the reduction in food intake in immature female rats. Our finding is in agreement with some other studies demonstrated either on animals (Eiscmann *et al.,* 1984; Cincotta and Meier, 1989) or human (Meier and Cincotta, 1992) who also reported reduction in the bodyweight following bromocriptine treatment which might be due to its actions as a dopamine agonist which is necessary for regulating body's energy expenditure and also its actions on hepatic triglycerides (Ingram *et al.,* 2000). The mean relative weight of the liver in immature female rats has been increased significantly following treatment with bromocriptine when compared to the control group which might be attributed to the increase in the inflammatory cell, infiltration of mononuclear cells from the blood vessels and haemorrhage in liver tissues which attributed with some of the founded histopathological changes.

The liver is the largest organ and one of the most important organs in the body. The liver regulates the level of most of the biomolecules found in the blood and acts with the kidneys to clear the blood from drugs and toxic substances. The liver metabolizes these products, alters their chemical structure, makes them water-soluble, and excretes them in bile. Some liver function tests such as alkaline phosphatase tests are used to determine if the liver has been damaged or its function impaired. Elevations of these markers for liver injury or disease indicate that something is interrupted with the liver (Burtis, 1999). Literature reviews revealed the availability of poor data that deal with the effect of bromocriptine on the liver in immature mammals. It has been reported that the effects of bromocriptine on the liver of women showed that small group of hyperprolactinemic patients treated with bromocriptine have a transient asymptomatic increase in serum alkaline phosphatase (Gillam *et al.,* 2006). On the other hand, Mahmood et al. (2010) found that treatment with bromocriptine in women showed no abnormality in the liver function test. Whereas, data on the effect of bromocriptine on liver function test, for instance, serum alkaline phosphatase levels in immature females are not

available. Therefore, the present study showed for the first time that there was a significant increase in the serum level of alkaline phosphatase following treatment with low and high doses of bromocriptine either following 7 or 21 days treatment. In accordance with the elevation in serum level of alkaline phosphatase following bromocriptine treatment, marked histological changes were noticed in liver tissues in immature female rats which revealed degeneration, vacuolation, infiltration in the hepatocytes, an infiltration and hemorrhage which were more clear in higher dosage either following 7 or 21 days of treatment. Our finding is in agreement with other studies that showed that bromocriptine treatment in humans-caused liver injury (Liberato *et al.,* 1992; Livertox, 2013; Adejoke *et al*., 2014). On the other hand, some studies on BRO showed that it has no adverse effects on the histology of the liver whereas it causes significant increase in the biochemical parameters of the liver as this elevation was mild and still situated within a normal limits of these parameters in hyperprolactinemic women (Mahmood *et al.,* 2010).

One of the objectives of the present study was to investigate the reversibility effects of bromocriptine treatment in immature female rats. Rats were examined one month after cessation of treatment to find out whether each of the parameters studied in the present study was restored to normalcy or not. The serum level of alkaline phosphatase showed noticeable progress. It restored to normalcy in low and high dose treated rats though they were normalized one month after cessation of treatment. Hence, the result of the present study also reveals for the first time that treatment with bromocriptine (2.5 and 5 mg/kg BW) has side effects on the liver in immature female rats through increasing the level of alkaline phosphatase in serum following treatment with low and high dose of bromocriptine either after 7 or 21 days treatment. Interestingly, it has been found that bromocriptine exerts a reversible effect in the liver of immature female rats. This indicates that a period of one month was sufficient for the recovery of BRO toxic effect which might be attributed to the ability of hepatocytes in immature female rats to regenerate itself during a period of one month. The present study reported that a period of one month was sufficient for the recovery of the toxic effect of bromocriptine on the liver of immature female rats. Hence, the important contribution of the present study is, despite the effect of BRO on the liver of immature female rats, BRO confirms that it has a reversible effect one month after cessation of treatment.

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CONFLICT OF INTEREST

The authors declare no potential conflict of interest with respect to the research, authorship, and/or publication of this article.

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