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The Effect of Bromocriptine on The Levels of Alkaline Phosphatase and Liver of Immature Male Rats

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ABSTRACT

Objectives: *The purpose of this investigation was to ascertain how bromocriptine (BRO) affected the livers of young male rats.* ***Method:*** *On the first day of experiments, the first group of five immature male rats (16 days old) weighing 25–30g was slaughtered. The remaining rats were divided into four groups, each consisting of 10 animals. The 3rd and 4th groups received BRO (IP) at 3 and 6 mg/kg BW, respectively, for two periods (9 days and 27 days), whereas the second group acted as the control and received the vehicle (IP). For the recovery trial, five rats from each group were kept for a month without receiving any therapy.* ***Results:*** *When compared to the control group, BRO therapy resulted in: A) a substantial loss in body the weight, B) significant rise in liver weight, and C) a significant increase in blood levels of phosphatase-alkaline in immature albino rats of both treated the groups.* ***Novelty:*** *The current investigation leads us to the conclusion that, even though BRO had an impact on the liver of young male rats, the effects of BRO may be recovered after a month of no treatment.*

INTRODUCTION

A semisynthetic ergot derivative, bromocriptine mesylate functions as a strong agonist and sympatholytic at both serotonin and post-synaptic dopamine D2 receptors (DRD2) [1], [2].

According to [3], it is frequently used to treat Parkinson's disease and hyperprolactinemia. By attaching itself to pituitary dopamine receptors, BRO suppresses the release of prolactin [4]. However, hepatotoxicity, hypotension, and nausea are among the adverse consequences linked to its usage [5].

BRO's function in metabolic control, especially its impact on hepatic lipid metabolism, has been highlighted by recent investigations [6]. Clinical settings have documented cases of BRO being associated with drug-induced liver damage (DILI) [7]. BRO's potential for hepatotoxicity in young animals is still little understood, despite its therapeutic advantages. This study examines how BRO affects immature male rats' livers and assesses recovery after therapy.

The chronic neuropsychiatric syndrome known as hepatic encephalopathy (HE) is characterized by an hepatics insufficiency that including either the hepatocellular-dysfunction, portal-systemic shunt's, liver cirrhosis, fulminant failure hepatic, acute injury liver, or a combination of these complicating that disrupts the central nervous system's ability to function [8], [9], [10]. Extrapyramidal symptoms or behavioral abnormalities in this illness may include changes in dopamine receptors as well as impairments in dopaminergic [11], [12].

BRO inhibits both spontaneous and TRH-induced prolactin production by directly activating lactotrope dopamine receptors [13]. BRO works as long as it is taken consistently [14]. When taken at the dosages required for prolactin suppression, the side effects of BRO, which include nausea, the vomiting, and hypotension postural with diaziness, drowsiness, fatigues, head-ache, indigastion, lightheadedness, weakness, etc., typically go away in two to three days [15]. According to reports, BRO is also frequently used as a medication to treat Parkinson's disease [16], [17]. Over 90% of the total ALP activity in normal serum is linked to liver and bone isoenzymes. The severity of the tissue injury from which the enzyme is derived is correlated with the relative ratio of each enzyme in serum. As a result, the relative rates of the various enzyme types in the patient's body cannot be predicted. According to [18], [19] an assessment of ALP activity from blood can identify anomalies in a number of medical illnesses, such as liver and bone diseases.

Research has also been done on BRO's adverse effects on the cardiovascular system. In people and experimental animals, BRO treatment lowers heart rate and blood pressure [20], [21], [22], [23] According to the findings of many research, BRO has an impact on pigs' adrenal function [24]. Additionally, BRO treatment has been shown to delay puberty in male immature rats and interfere with ovarian activity and follicular development, as evidenced by an increase in atretic follicles and a decrease in healthy follicles [25].

Numerous studies have shown that drug use has negative, damaging, and undesirable effects on the body. A person's sensitivity to other substances, foods, or procedures, such as medication interactions, may alter as a result of adverse consequences, either irreversibly or reversibly [26]. Approximately 20–40% of all cases of fulminant hepatic failure are caused by medications, and over 900 chemicals, poisons, and plants have been shown to induce liver damage [27]. BRO has been shown to cause hepatotoxicity and kidney damage in mice [28] as well as acute hepatitis in people with Parkinson's disease [29]. Furthermore, bromocriptine was classified as a drug-induced liver damage in a recent research [30]. It is normal and frequent for drugs to have toxic effects on the kidneys. All medications have the potential to be nephrotoxic, while certain of them can harm the kidneys in several ways [31].

To yet, no research has been done on how BRO affects the liver's gross and histological characteristics in male immature rats. There is little information on how BRO affects the alkaline phosphatase test, which measures liver function. Furthermore, no research has been done on BRO's reversible impact to far. As a result, it is essential to understand how BRO might be reversed by stopping medication. Therefore, the purpose of the study was to determine whether giving immature male rats two distinct dosages of BRO (3 and 6 mg/kg BW) over two different lengths of time (9 and 27 days) would have any harmful consequences on their livers. if the consequences of BRO can be reversed.

RESEARCH METHOD

Chemicals We gladly bought technical grade a bromocriptine from the Sigma-Aldrich in St. Louis, USA.

Ethical Approval

The study followed ARRIVE guidelines and was approved by the Institutional Animal Ethics Committee (IAEC/SU/2020/03).

Animals and treatment

An inbred colony of 35 male Wistar albino rats (16 days old) weighing 25–30g was first acquired from the Central of Animal Structure, Department of the Zoology, University of Kufa, Iraq. Five animals per cage were housed in plastic cages, which were naturally photothermally heated and furnished with husks as bedding. Throughout the trial, the animals were given dry food flakes and unlimited water. Each mouse's initial body weight (BW) was measured before to the start of the therapy. The animals were split up into four groups, with five rats serving as the initial control and ten rats each in the other three groups. On the first day of the experiment, the rats in the first group (the original control) were killed. The vehicles (0.1 ml distilled of water/rat/day) was administered intraperitoneally (IP) to the second group, which acted as a control. The fourth group got BRO (6 mg/kg BW) for two periods, namely 9 days and 27 days, whereas the third group received BRO (IP) at a dosage of 3 mg/kg BWTo determine if the effects of BRO were reversible, five rats from each group were killed 24 hours after the last dosage (at 25 and 43 days old, respectively), and the remaining five albino rats from each group of each period ware kept for a month without treatment (at 55 and 73 days the old). Throughout the whole investigation, the body weight of every mouse was also noted.

Biochemical and Histological Analysis

Using the International Association of Finical Chemistry technique (IFCC), blood sample ware collecte, serum was separated, and the serum was then stored at -20 ^{o}C to measure the serum leveling of alkaline-phosphatase (U/L), a measure of whether or not the function of the liver have been affected, Han et al.

The liver's weight was noted at autopsy and subsequently translated into relative weight. Following a saline wash to eliminate blood stains, the liver organs were fixed in Bouin's fixative, dehydrated using various alcohol grades. Haematoxylin and eosin-stained 5 µm-thick sections were obtained and examined under a light microscope, Baratta JL and et al.

Phase of treatment and recuperation**:**

To investigate the reversibility impact of BRO, five immature rats of each duration (9 and 27 days) from all groups (Control, low dosage, and high dose of BRO) were kept untreated for a month. After a month, the rats were slaughtered, and their carcass and liver weights were noted. The serum level of alkaline phosphatase (U/L) was measured by collecting blood samples, separating the serum, and storing it at -20 oC.

Analysis of Statistics

For every experimental group (n = 5), the data are shown as mean ± standard error (SE). One-way ANOVA and post-hoc Duncan's multiple range test were used for statistical comparisons across groups in order to pinpoint certain group differences. For every comparison, a probability value of $p < 0.05$ was deemed statistically significant.

RESULTS AND DISCUSSION

The Change in the Body and Liver Weight

When compared to the control group, body weight dropped considerably ($p<0.05$) in the BRO-treated groups (3 and 6 mg/kg BW), respectively. However, compared to the control group, the total body weight of immature male rats treated with low and high BRO dosages one month after treatment termination did not differ significantly, see Tables 1 and 2.

Table 1. The mean mass of male immature rats in the control, medium dose, and high dosage treatment groups after nine days of therapy and one month after the end of the nine-day treatment period is shown in this Table . 0.1 cc of distilled water per day per rat is the control; 3 mg/kg BW is the low dosage; and 6 mg/kg BW is the high dose.

9 Days Bromocriptine Treatment	Mean Body Weight (G) ±Se	One Month Following The End of Therapy
Control	47	93
Low dose	42	82
High dose	30	70
	significantly (P<0.05)	

Table 2. Male immature rats' mean body weights after 27 days of therapy and one month after stopping treatment for 27 days were compared for the control, low dosage, and high dose treated groups. 0.1 cc of distilled water per day per rat is the control; 3 mg/kg BW is the low dosage; and 6 mg/kg BW is the high dose.

27 Days Bromocriptine Treatment	Mean Body Weight (G) ±Se	One Month Following The End of Therapy
Control	82	130
Low dose	70	120
High dose	60	98
	significantly (P<0.05)	

In line with previous clinical findings, our investigation validates the hepatotoxic effects of BRO in male immature rats [5]. The findings on BRO-induced DILI are

consistent with the reversibility of liver injury [7]. Molecular processes such oxidative stress pathways should be investigated in future research [6].

Weight of the Liver When compared to the control group, the mean relative weight of the liver of immature male rats in the both low and high BRO treatment groups (3 and 6 mg/day BW) increased significantly. One month following the end of BRO therapy, the average compared weight of the livers of immature male rats treated with low and high BRO did not vary significantly from the control group, see Table 3.

According to other research, the tissue-unspecific (liver-bone-kidney) isozyme is the most common form of ALP enzymes in normal testis, accounting for approximately 95% of alkaline phosphatase. Placental-like alkaline phosphatase is the sole type that is present, Regidor et al. Following nefidipine medication therapy, elevated ALP levels are associated with increasing testicular architectural damage, Sulayman.

The majority of the biomolecules in the blood are regulated by the liver, which also works with the kidneys to rid the blood of toxins and medicines. These products undergo metabolization, chemical structural changes, water solubility, and excretion in bile by the liver. Alkaline phosphatase tests and other liver function tests are utilized to assess if the liver is currently injured or if its function has been compromised. Increases in these indicators of liver illness or damage suggest that there is a disruption in the liver, Burtis.

Table 3. Average weight of the liver of male immature rats in the control, low dosage, and high dose treatment groups after 9 and 27 days of therapy, as well as one month after stopping the 9 and 27-day treatment. 0.1 cc of distilled water per day per rat is the control; 3 mg/kg BW is the low dosage; and 6 mg/kg BW is the high dose.

Groups	9 days bromocriptine treatment		27 days bromocriptine treatment	
	Mean Liver weight (mg/100g bw) ±SE	1 month after cessation of treatment	Mean Liver weight (mg/100g bw) ±SE	1 month after cessation of treatment
Control	4100	5000	4200	5500
Low Dose	4500	4900	4800	5300
High Dose	5200	4800	5600	5200

ANOVA revealed that the differences were significantly ($P<0.05$).

Alkaline Phosphatase Level

Level of serum alkaline phosphatase (U/L) The mean serum alkaline phosphatase level of the first control and the controls of both durations did not differ significantly. In contrast, the mean serum alkaline phosphatase level of the low and high treated groups was significantly higher than that of the controls, see Table 4.

When compared to the controls, there was no discernible difference in the mean blood alkaline phosphatase level between the two treated groups one month after the 9. and 27-day treatment periods ended, see Table 4.

Table 4. Mean plasma alkaline phosphatase levels for male immature rats given bromocriptine for nine, twenty-seven, and one month after treatment ended.

Groups	9 Days of Treatment (16-24 Days Old)	1 Month After Cessation of 9 Days Treatment (25-55 Days Old)	27 Days of Treatment (16-42 Days Old)	1 Month After Cessation of 27 Days Treatment (43-73 Days Old)
Initial control (16 days)	515.18 ± 21.33		664.40 ± 80.29	
Control	595.2 ± 231.35	296.6 ± 37.42	736.20± 40.20	441.6 ± 39.30
Low dose	698.23 ± 93.90	301.0 ± 31.98	1191.2 ± 133.38	431.20± 29.72
high dose	711.30 ± 26.25	312.4 ± 11.0	1220.2 ± 193.46	429.20± 36.25
(df=3,16)	7.92 P<0.002	NS	5.36 P<0.05	NS

Note that df stands for degree of freedom. One-way ANOVA was used to compare the F-values.

Reviews of the literature showed that there is a dearth of information on the impact of bromocriptine on the liver in young animals. Research on the effects of bromocriptine on women's livers has revealed that a small percentage of hyperprolactinemic individuals treated with the drug have a brief, asymptomatic rise in blood alkaline phosphatase [5]. However, Mahmood et al discovered that women receiving bromocriptine medication did not exhibit any abnormalities in their liver function test results. However, there is little information on how bromocriptine affects liver function tests, such as blood alkaline phosphatase levels in male immature subjects. Thus, the current investigation demonstrated for the first time that therapy with low and high dosages of bromocriptine either after 9 or 27 days of treatment resulted in a substantial rise in the blood level of alkaline phosphatase. Significant histological changes were observed in the liver tissues of immature male rats in accordance with the increase in serum alkaline phosphatase levels after bromocriptine treatment. These changes included degeneration, vacuolation, infiltration in the hepatocytes, an infiltration, and hemorrhage, which were more obvious with higher dosages either after 9 or 27 days of treatment. Our results are consistent with prior research that shown that human liver damage was produced by bromocriptine medication, Liberato et al., Livertox, Adejoke et al. However, some research on BRO revealed that it has no negative effects on the histology of the liver, but it significantly raises the liver's biochemical parameters, though these measurements were mild and still within normal ranges in women with hyperprolactinemic syndrome, Mahmood et al. Examining the reversibility effects of bromocriptine therapy in immature male rats was one of the goals of the current investigation. To determine whether or not each of the parameters tested in this study had returned to normal, rats were checked one month after treatment ended. There was observable improvement in the serum level of alkaline phosphatases. Rats treated with

low and high doses returned to normal, but they were normalized a month after treatment ended. Therefore, the current study's results also show for the first time that bromocriptine treatment (3 and 6 mg/kg BW) causes liver side effects in immature male rats by raising the level of alkaline phosphatase in the serum after treatment with low and high doses of bromocriptine, either after 9 or 27 days of treatment. Remarkably, bromocriptine has been shown to have a reversible impact on the liver of young male rats. This suggests that a month was enough time for the BRO harmful impact to subside, which may be explained by the hepatocytes' capacity to self-renew in young male rats. According to the current study, bromocriptine's harmful effects on the liver of immature male rats might be recovered in just one month. Because of this, the study's key addition is that, while if BRO affects the liver of young male rats, it also shows that its effects are reversible a month after treatment ends.

CONCLUSION

Fundamental Finding : This study confirmed that bromocriptine mesylate (BRO), when administered to immature male rats at doses of 3 and 6 mg/kg body weight over 9 and 27 days, caused significant hepatotoxic effects. These were evident through reduced body weight, increased relative liver weight, and elevated serum alkaline phosphatase levels. Notably, after one month of drug cessation, most of these parameters returned to near-control levels, indicating that BRO-induced liver alterations may be reversible. **Implication :** The findings support clinical reports linking BRO with drug-induced liver injury (DILI) and suggest that early-stage hepatic damage induced by BRO could potentially be reversed if the drug is discontinued. This reinforces the need for cautious monitoring of liver function during BRO therapy, especially in pediatric or developmentally vulnerable populations. **Limitation :** The study was limited to male immature rats and did not explore detailed molecular mechanisms such as oxidative stress or inflammatory pathways. It also lacked assessment of long-term outcomes beyond the one-month recovery phase and did not include behavioral or neurological evaluations related to hepatic encephalopathy. **Future Research :** Future investigations should include molecular analyses to identify the pathways involved in BRO-induced hepatotoxicity, such as oxidative stress markers or cytokine profiles. Research on other age groups, female rats, and different organs such as the kidneys or brain could broaden understanding. Additionally, longer follow-up periods would help determine the full extent and permanence of recovery after drug withdrawal.

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