Adverse Effects of Memantine

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Abstract

The current study covers key issues related to memantine’s toxicity (0.36 mg/kg, P.O. once daily) and its effect on liver, kidney, blood and antioxidant enzymes for three weeks. Then tissue and blood samples were collected at the 1st, 2nd and 3rd weeks post-treatment. Our results indicated that Memantine has hepato-nephrotoxicity and elevation of liver enzymes (ALT, AST and ALP), creatinine, urea and uric acid. Obvious decline in all blood parameters with respectable decline in antioxidant enzyme like CAT, SOD, GPX and a significant increase in MDA. Histopathology revealed hepatic steatosis and increase the apoptotic and necrotic cells mostly within the centrolobular, as. Also, tubular basophilia and interstitial nephritis were observed. Therefore, Memantine should be used with caution with hepatic or people with kidney problems.

Keywords: Memantine, Alzheimer’s Disease, Dementia, CBC, Antioxidant enzymes.

Introduction

Memantine, is previously included in a novel class of Alzheimer’s sickness medications acting on the glutameric framework by closing the N-methyl D-aspartate (NMDA) receptors. Because continuous raised level of glutamate in the brain of demented patients are sufficient to counter the voltage-dependent block of NMDA receptors by Mg²⁺ ions and allow a continuous entering of Ca²⁺ ions into cells, ultimately resulting in neuronal degeneration. Excitotoxicity is the morbid disease by which nerve cells are deteriorated by exaggerated excitation by neurotransmitters such as glutamate. This happens when receptors for the provocative neurotransmitter glutamate (glutamate receptors) such as the NMDA receptor is overactivated by glutamatergic storm. Excitotoxins like NMDA which are bound to these receptors, as well as pathologically high levels of glutamate, can lead to excitotoxicity by allowing excess levels of calcium ions (Ca²⁺) to enter into the cell [1]. Ca²⁺ influx into cells enhance a number of enzymes, including phospholipases, endonucleases, and proteases. These enzymes lead to break cell structures such as components of the cytoskeleton, membrane, and DNA. Memantine does its action through uncompetitive NMDA receptor antagonist, attaching preferentially to the NMDA receptor-operated cation channels. Memantine binds more effectively than Mg²⁺ ions at the NMDA receptor, and thereby effectively blocks this prolonged influx of Ca²⁺ ions through the NMDA channel. Thus, it protects against chronically elevated concentrations of glutamate [2]. Also, Memantine has the ability to block nicotinic acetylcholine receptors at the cellular level [3]. Memantine has antagonistic effects at the 5HT3 receptor [4] and enhancing histaminergic receptor action [5] both of which could possibly contribute towards synergistic effects in cognitive enhancement. It is most effective when more channels are open (which is maximized under pathological conditions of excess glutamate), which suggests that Memantine is more effective at blocking the channels in cases of moderate or severe neurodegenerative disease severity rather than during milder stages [6]. In addition, the uncompetitive nature of the Memantine’s mechanism of action makes its antagonistic activity more potent in areas with massive activation of NMDA receptors. Besides it was found to prevent neuronal death induced via excitotoxic mechanisms.

The main targeted organs of toxicity are the kidneys, and livers. The kidney is recognized to be the most common organ exposed to drug toxicity and environmental chemicals. Its increased liability could be attributed to high

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renal blood flow in addition to its individual possession of renal tubular epithelium in concentrating urine and its ingredients, including drugs and chemicals [7]. Nephrotoxicity is a disease whose primary feature is impairment of the normal function of the kidney which is ranged from mild reduction in renal function to severe progressive toxicity culminating in end stage of renal disease as hematuria, proteinuria and urolithiasis [8]. Liver has a central role in transforming and clearing chemicals and is susceptible to the toxicity of these agents. Certain medicinal agents, when taken in overdoses and sometimes even when introduced within therapeutic ranges, may injure the organ. More than 900 drugs have been involved in causing liver injury [10] and it is the most common reason for a drug to be outgoing from the market. Hepatotoxicity and drug-induced liver injury also account for a fundamental number of compound failures, highlighting the need for drug screening assays, such as stem cell-derived hepatocyte-like cells, that are capable of detecting toxicity early in the drug development process [11]. Adverse effects of Memantine on liver contained hepatic failure [12].

Materials and Methods

Drugs and chemicals

Memantine (Namenda®) was supplied by Forest Laboratories, Inc., H. Lundbeck, Merz Pharma, Memantine was prepared in saline immediately before use.

Animals

Forty adult female albino rats (150-200 g) were purchased from local breeder and were permitted free access to standard laboratory chow and tap water throughout the acclimatization and experimental periods. Animals were preserved under standard condition of temperature about 30°C and dampness (60 ± 10%) with uniform 12 h light/12h dark cycle. All experimental steps qualified in this study abided by the ethical principles and guidelines for the care and the use of laboratory animals adopted by the “Research Ethics Committee”, Faculty of Veterinary Medicine, Zagazig University, Egypt.

Experimental design

Forty animals were randomly allocated into 2 groups (n=20/group). Group I (control): rats were received saline. Group 2 (Memantine): rats were received Memantine (0.36 mg/kg/day, P.O.) once daily for 21 successive days. The animals were monitored weekly.

Preparation of serum sample and tissue sample

At the end of the experiment (12 hrs. after the last dose), rats were sacrificed and the following samples were collected: Blood was collected and allowed to clot for 30 minutes at 25 ºC. Thereafter, they were centrifuged at 2000g for 10 min, and the top yellow layers of serum were pipetted off without distributing the white buffy layer. Serum was stored at -20 ºC and thawed just before use for the determination of liver and kidney enzymes. Livers and kidneys were excised and suspended in a physiological saline containing heparin (0.016mg/ml) to prevent blood clots.

Biochemical markers of liver and Kidney injury:

Determination of biochemical markers of liver as serum alanine aminotransferase (ALT), aspartate aminotransferase (AST) activities were done [13,14]. Determination of serum alkaline phosphatase (ALP) activity was done according to Tietz et al., [15]. Evaluation of creatinine, urea and uric acid were done according to Pagana [16]. These Biochemical markers were evaluated by using commercial kits from Spectrum Diagnostics (Cairo, Egypt).

Hepatic and Nephro histopathological evaluation:

Liver and kidney tissues were fixed in 10% neutral buffered formalin solutions for 24h. Then, tissue processing and paraffin blocks preparation were done. Masson’s trichome and hematoxylin-eosin stains were used to evaluate fibrotic areas and necroinflammation activity according to the method of Ishak et al. [17].

Biochemical markers of antioxidant activity:

Determination of catalase activity (CAT), superoxide dismutase activity (SOD), glutathione peroxidase activity (GPX) and malondialdehyde activity (MDA) by method according to the principle of Aebi, [18],
Nishikimi et al., [19], and Paglia and Valentine, [20] respectively.

**Hematological testing:**

Include methodologies and sources of error for blood cell counts, hematocrit and hemoglobin determinations, white blood cell count, platelet count, basophil, eosinophil and lymphocyte. Formulae for calculating indices (MCV, MCH and MCHC) according to Jacob et al., [21].

**Statistical analysis**

Data in the present study were analyzed using prism version 6. Statistical assessments of the results, unless the histopathological results, were completed by using methods of one way and two-way analysis of variance (ANOVA) according to Tamhane and Dunlop, [22]. Duncan’s test was carried which considered statistically significant when P< 0.05.

**Results**

*Effects of Memantine (0.36 mg/kg, P.O. once daily for 21 successive days) on biochemical markers of liver injury on ALT*

There was gradual significant increase in level of serum ALT, but a high significant increase was observed in the second week (85.33±11.40 U/L) when compared with third week (147.55±63.12 U/L). In the first week a significantly raised serum AST activity (85.33±11.40 U/L) was more than (34.33±1.18 U/L) for the control group, a week later there was an obvious increase in serum AST activity (96.34±20.97 U/L) compared with (34.33±1.18 U/L) for the control group. In the third week there was a significant increase in serum AST activity (147.55±63.12 U/L) compared with (34.33±1.18 U/L) for the control group (Figure 1).

*Effects of Memantine (0.36 mg/kg, P.O. once daily) on ALT*

ALT activity (75.36±17.98 U/L) compared with (32.60 ±2.70 U/L) for the control group (Fig 1).

There was gradual increase in level of serum AST, but a significant increase was observed in the second week (85.33±11.40 U/L) when compared with third week (147.55±63.12 U/L). In the first week a significantly raised serum AST activity (85.33±11.40 U/L) was more than (34.33±1.18 U/L) for the control group, a week later there was an obvious increase in serum AST activity (96.34±20.97 U/L) compared with (34.33±1.18 U/L) for the control group. In the third week there was a significant increase in serum AST activity (147.55±63.12 U/L) compared with (34.33±1.18 U/L) for the control group (Figure 1).
Effect of time-point treatment with Memantine on liver parameters (AST, ALT and ALP) of rats treated with memantine for successive 21 days.

Figure 1: Effect of time-point treatment with Memantine on liver parameters (AST, ALT and ALP) of rats treated with memantine for successive 21 days.

*Effects of Memantine (0.36 mg/kg, P.O. once daily) on total serum proteins*

There was gradual significant decrease in level of total serum proteins when compared 1-week pt. result (6.17±0.23 g/dl) with the second (5.41±0.49g/dl) and third week (4.79±0.14g/dl). Decrease in total protein activity was observed 1-week pt. (6.17±0.23 g/dl) compared with (6.73 ±0.03 g/dl) for the control group, in the second there was a significant decrease in total protein activity (5.41±0.49g/dl) compared with (6.73 ±0.03g/dl) for the control group. In the third week there was a significant decrease in total protein activity (4.79±0.14g/dl) compared with (6.73 ±0.03 g/dl) for the control group.

*Effect of Memantine (0.36 mg/kg, P.O. once daily) on serum total bilirubin*

There was gradual increase in level of serum total bilirubin, but a significant increase was seen when compared 1-week pt., result (0.17±0.01 mg/dl) with the third week (0.21±0.02 mg/dl) and second week result (0.19±0.03 mg/dl) and third week (0.21±0.02 mg/dl). First week pt., there was an increase in direct bilirubin activity (0.17±0.01 mg/dl) comparing with (0.14±0.01mg/dl) for the control group, meanwhile in the second week there was a significant increase in direct bilirubin activity (0.19±0.03 mg/dl) comparing with (0.14±0.01mg/dl) for the control group. In the third week there was a significant...
increase in direct bilirubin activity (0.21±0.02 mg/dl) compared with (0.14±0.01 mg/dl) for the control group. The effect of Memantine (0.36 mg/kg, P.O. once daily) on successive 21 days: there was gradual decrease in level of serum total bilirubin was observed, meanwhile a significant increase was seen when compared First week pt., result (3.67±0.25 g/dl) with the third week (2.81±0.31 g/dl).

First week pt., there was a decrease in albumin activity (3.67±0.25 g/dl) comparing with (4.01±0.24 g/dl) for the control group, meanwhile an obvious decline in albumin activity was seen in second week (3.1±0.08 g/dl) comparing with (4.01±0.24 g/dl) for the control group. Significant decrease in albumin activity was observed in the third week (2.81±0.31 g/dl) when compared with (4.01±0.24 g/dl) for the control group.

The effect of Memantine (0.36 mg/kg, P.O. once daily) on serum globulin

There was gradual increase in level of serum globulin, but a significant increase was seen when compared 1-week pt., result (2.94±0.20 g/dl) with the third week (3.18±0.18 g/dl) and second week result (2.96±0.08 g/dl) with third week (3.18±0.18 g/dl). First week pt., there was an increase in globulin activity (2.94±0.20 g/dl) comparing with (2.30±0.21 g/dl) for the control group, but a significant raise in globulin action was seen in the second week (2.96±0.08 g/dl) comparing with (2.30±0.21 g/dl) for the control group. In the third week there was an obvious increase in globulin activity (3.18±0.18 g/dl) comparing with (2.30±0.21 g/dl) for the control group.

Effect of Memantine (0.36 mg/kg, P.O. once daily) on serum creatinine

There was gradual increase in level of serum creatinine was observed, but a significant increase was observed when compared First week pt., result (0.76±0.05 mg/dl) with the third week (0.98±0.07 mg/dl). An increase in creatinine activity was observed 1-week pt. (0.76±0.05 mg/dl) contrasted with (0.60±0.05 mg/dl) for the control group, but a presumed increase in creatinine activity resulted after 14 days of administration (0.90±0.10 mg/dl) comparing with (0.60±0.05 mg/dl) for the control group. Significant increase in creatinine activity (0.98±0.07 mg/dl) compared with (0.60±0.05 mg/dl) for the control group was seen in the third week (Figure 2).

The effect of Memantine (0.36 mg/kg, P.O. once daily) on serum uric acid

There was gradual increase in level of serum uric acid was observed, but a significant increase was seen when compared 1-week pt., result (3.58±0.60 mg/dl) and second week (3.81±0.54 mg/dl) with the third week (3.98±0.43 mg/dl). First week pt., there was an increase in uric acid activity (3.58±0.60 mg/dl) comparing with (2.25±0.14 mg/dl) for the control group, meanwhile after two weeks of administration there was a significant raise in uric acid action (3.81±0.54 mg/dl) comparing with (2.25±0.14 mg/dl) for the control group. Significant increase in uric acid activity (3.98±0.43 mg/dl) comparing with (2.25±0.14 mg/dl) for the control group was observed in the third week (Fig 2).

Effect of Memantine (0.36 mg/kg, P.O. once daily) on serum urea

There was gradual increase in level of serum urea was observed, meanwhile a significant increase was seen when compared 1- week pt., result (25.84±4.96 mg/dl) and second week (35.47±5.03 mg/dl) with the third week (47.82±7.85 mg/dl). First week pt., there was an increase in urea activity (25.84±4.96 mg/dl) comparing with (17.82±0.34 mg/dl) for control group, but an obvious raise in urea activity was observed in the second week (35.47±5.03 mg/dl) comparing with (17.82±0.34 mg/dl) for the control group. In the third week there was a significant increase in urea activity (47.82±7.85 mg/dl) comparing with (17.82±0.34 mg/dl) for the control group (Figure 2).
Figure 2: Effect of time-point treatment with Memantine on kidney parameters (creatinine, uric acid and urea) of rats treated with Memantine for successive 21 days.
Effects of Memantine (0.36mg/kg, P.O. once daily) on biochemical markers of antioxidant enzymes.

Effect of Memantine (0.36 mg/kg, P.O. once daily) on CAT: there was bit-by-bit decrease in level of CAT was observed, but a significant decrease was seen when compared 1-week pt., result (0.16±0.09U/ml) with the third week (0.08±0.05U/ml). First week pt., there was a decrease in catalase activity (0.16±0.09U/ml) comparing with (0.22±0.03U/ml) for the control group, meanwhile a significant decrease was seen after 14 days of Memantine administration (0.11±0.03U/ml) comparing with (0.22±0.03U/ml) for the control group. Significant decrease in catalase activity (0.08±0.05U/ml) comparing with (0.22±0.03U/ml) for the control group was observed in the third week (Fig 3).

Effect of Memantine (0.36 mg/kg, P.O. once daily) on SOD: there was bit-by-bit decrease in level of SOD, meanwhile a significant decrease was seen 1-week pt., result (0.16±0.09U/ml) with the second week (0.13±0.06 U/ml) and with third week (0.08±0.05U/ml). First week pt., a decrease in SOD activity was observed (0.18±0.01U/ml) comparing with (0.21±0.03U/ml) for the control group. In the second week, there was an obvious decline in SOD action (0.13±0.06 U/ml) comparing with (0.21±0.03U/ml) for the control group. Significant decline in SOD action (0.09±0.04U/ml) comparing with (0.21±0.03U/ml) for the control group was seen in the third week (Figure 3).

Effect of Memantine (0.36 mg/kg, P.O. once daily) on GPX

There was bit-by-bit decrease in level of GPX, meanwhile a significant decrease was seen when compared 1-week pt., result (0.20±0.04U/ml) with the third week (0.10±0.05U/ml). First week pt., there was a decrease in GPX activity (0.20±0.04U/ml) compared with (0.25±0.03U/ml) for the control group. An obvious decrease in GPX activity (0.14±0.06U/ml) compared with (0.25±0.03U/ml) for the control group was seen in the second week. Significant decrease in GPX activity (0.10±0.05U/ml) comparing with (0.25±0.03U/ml) for the control group was observed in the third week(Figure 3).

Effect of Memantine (0.36 mg/kg, P.O. once daily) on MDA: there was gradual significant increase in level of MDA was observed (0.22 ±0.07mm/L), (0.38 ±0.10mm/L) and (0.48±0.05mm/L). First week pt., there was an increase in MDA activity (0.22 ±0.07mm/L) comparing with (0.14±0.07mm/L) for the control group, but a significant increase in MDA activity was seen in the second week (0.38 ±0.10mm/L) comparing with (0.14±0.07mm/L) for the control group. In the third week there was a significant increase in MDA activity (0.48±0.05mm/L) comparing with (0.14±0.07mm/L) for the control group (Figure 3).
Histopathological findings of liver

Liver of control animal sacrificed at the 7th day pt., showed normal periportal area with normal round to oval hepatocytes with normal vesicular nucleus, (Figure 4-A). Scarification of Memantine-treated animal in the 7th day pt. showed that centrolobular hypertrophy of the hepatocytes of liver and periportal vacuolation of hepatocytes. (Figure 4-B). Liver of control animal at the 14th day pt., showed normal hepatocytes around the central vein (Figure 4-C). Liver of Memantine-treated animal in the 14th day pt., showed numerous apoptotic cells associated with hepatic vacuolation (Figure 4-D). Liver of control animal at the 21st day pt., showed normal hepatocytes around the central vein (Figure 4-E). Liver of Memantine-treated animal at the 21st day pt., showed hepatic steatosis and increase the apoptotic and necrotic cells mostly within the centrolobular area (Figure 4-F).
Histopathological findings of kidney

Kidney of control animal sacrificed at the 7th day pt., showed normal renal glomeruli and tubules (Figure 5-G). Kidney of Memantine-treated animal at the 7th day pt., showed focal necrosis of the medullary renal tubules associated with leukocytic infiltration (Figure 5-H).

Kidney of control animal at the 14th day pt., showed normal renal glomeruli and tubules (Figure 5-I). Kidney of Memantine-treated animal at the 14th day pt. showed tubulo—interstitial nephritis represented by marked mononuclear cell infiltration (Figure 5-J).

Kidney of control animal at the 21th day pt., showing normal renal glomeruli and tubules (Figure 5-K). Kidney of Memantine-treated animal at the 21th day sacrifice, showed interstitial nephritis (Figure 5-L).
Figure 5 G: Kidney of control animal sacrificed at the 7th day showing normal renal glomeruli (arrow) and tubules (arrowhead), H&E, X200. H: Kidney of Memantine-treated animal (7th day sacrifice) showing degeneration of renal tubular with attempt of regeneration of the lining epithelial cells of the renal tubules (arrow), also periglomerular and peritubular few inflammatory cell infiltrations was noticed, H&E, X200. I: Kidney of control animal sacrificed at the 14th day showing normal renal glomeruli (arrow) and tubules (arrowhead), H&E, X200. J: Kidney of Memantine-treated animal (14th day sacrifice) showing tubule—interstitial nephritis represented by marked mononuclear cell infiltration, H&E, X200. K: Kidney of control animal sacrificed at the 21st day showing normal renal glomeruli (arrow) and tubules (arrowhead), H&E, X200. L: Kidney of Memantine-treated animal (21st day sacrifice) showing tubular basophilia (arrow), H&E, X200.

Discussion

The kidney is recognized as one of the most common target organs of toxicity of the drugs and environmental chemicals. A number of drugs, chemical, and heavy metals have been shown to alter its structure and function [23]. Some drugs lead to severe damage to the kidney with marked tubular damage. Also, liver is the remarkable organ as it is dealing with the physiological activities in the human body. It plays an important role in regulating various physiological processes in the body. It is involved in several vital functions, such as metabolism, secretion, and storage; liver has a great capacity to detoxicate toxic substances and synthesize useful principles.

Liver injury biomarkers as ALT, AST, and ALP are biomarkers enzymes which show the functional integrity of the liver cells [24]. These biomarkers are usually increased in
acute hepatotoxicity and hepatocellular damage [25]. Memantine is one of the drugs which are approved by the FDA for the treatment of moderate to severe Alzheimer’s disease lead to liver damage.

This present study was prepared to show the venomous effect of memantine also protective effects of antioxidant Vit.E against side effects of Memantine on liver and kidney of rats. In this study, memantine is used in a dose (0.36mg/kg, P.O. once daily for successive 21 days) to encourage oxidative stress in rat organs like liver and kidneys, as evidenced by high significant decline in antioxidant enzyme activities CAT, SOD and GPX and high significant rise in MDA production. Memantine significantly produced nephrotoxicity and hepatotoxicity as evidenced by rising in the action of ALT and AST beside elevation in levels of total bilirubin, direct bilirubin, and urea.

Our results suggested that administration of memantine increases kidney parameters like creatinine, urea, and uric acid compared to control group. In addition, our histopathological results in the 1-week pt., showed focal necrosis of the medullary renal tubules associated with leukocytic infiltration. In the second week, the result showed tubule-interstitial nephritis represented by marked mononuclear cell infiltration and in the third week, tubular basophilia and interstitial nephritis were noticed.

Our results are in harmony with the results reported by Ferguson et al., [26] who found that the public techniques that lead to renal damage involve exchange in glomerular hemodynamics, tubular cell damage, inflammation, deposition of crystals, rhabdomyolysis, and thrombotic microangiopathy. Our results suggested that the activities of serum ALT, AST and ALP were obviously increased following memantine administration, especially in third week.

Our histopathological results in the First week pt., the liver showed centrilobular hypertrophy of the hepatocytes and periportal vacuolation of hepatocytes. In the second week showed numerous apoptotic cells, hepatic steatosis and single cell necrosis and diffuse hepatic vacuolation and hepatic steatosis and increased the apoptotic and necrotic cells mostly within the centrilobular area were noticed in the third week. These results coincided with those obtained by Micuda et al., [27] who found that rats administered memantine induced a significant elevation in hepatic markers (ALP, ALT, and AST).

Our results suggested that the administration of Memantine (0.36mg, P.O. once daily for successive 21 days) have showed significant decrease on hemoglobin, red blood cell count (RBC), white blood cell (WBC), hematocrit (HCT), platelets count (PLT), lymphocyte, mean corpuscular hemoglobin (MCH), mean corpuscular volume (MCV) and mean corpuscular hemoglobin concentration (MCHC). Tanashyan et al., [28] reported that It was investigated the effect Memantine in patients with cerebrovascular disorders. In vitro studies showed that Memantine, exhibited antiplatelet activity. Kahlfuß et al., [29] reported that NMDAR antagonists have profound effects on T-cell function.

**Conclusion**

In conclusion, Memantine has some adverse effects on liver and kidney of rats. Therefore, Memantine should be used with caution in people with liver or kidney problems.

**Conflict of interest**

The authors declare that they have no conflict of interest.

**References**


الملخص العربي

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تم إجراء هذه الدراسة لبيان الآثار الضارة للميمانتين وهو دواء لعلاج مرض الزهايمر وذلك عن طريق إعطائه للجرذان بجرعة (٣٦ مجم/كم من وزن الجسم) عن طريق الفم لمدة ثلاثة أسابيع متتالية. تم أخذ عينة الدم من كل جرد اسبوعيا وتم فصل المصل وذلك لقياس انزيمات الكبد والكلى وانزيمات الأكسدة وكذلك بعض من مكونات الدم وأخذ نسخة من الكبد والكلي وذلك للفحص الهيستوبائلوبيوجي وقد أظهرت النتائج ارتفاع واضح في انزيمات الكبد والكلي وانخفاض في مستوي الهيموجلوبين بعد كرات الدم الحمراء والبيضاء والصفائح الدموية وكذلك انخفاض في مستوي مضادات الأكسدة وارتفاع في مستوي الالدُندي. وبالنسبة لنتائج الهيستوبائلوبيوجي قد أظهرت تلف في الكبد والتهاب في الكلي. لذلك يجب مراعاة الجرعة لدى مرضى الكبد والكلى.