SAR Journal of Anatomy and Physiology

Abbreviated Key Title: *SAR J Anat Physiol*
Home page: https://sarpublication.com/journal/sarjap/home
DOI: https://doi.org/10.36346/sarjap.2025.v06i01.002

OPEN ACCESS

ISSN 2707-7713 (P)
ISSN 2709-6874 (O)

Original Research Article

Study the Effect of Different Doses of Methyldopa on Some Physiological Functions for Liver and Kidney of Male Mice

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Article History: | Received: 22.12.2024 | Accepted: 28.01.2025 | Published: 30.01.2025 |

Abstract: The Methyldopa (Aldomet) a medicine was classified under alpha-2 agonist category, which relaxes muscles and reduces blood pressure by targeting certain biochemical processes implicated in the development of hypertension. The objective of study was to detect the impact of methyl dopa on liver and kidney function. ***Methods*:** Fifteen male mice, whose weight ranged between (20-25 gm) and their age ranged between (4-6 weeks), the mice are gotten from the College of Science /University of AL-Kufa. They had been divided randomly and distributed into 3 group, with 5 in each group. The first group (T1) was gavaged with dose of 250 mg/kg B.W, the second group (T2) was gavaged at 500 mg/kg body weight, third control group (C) was gavaged by physiological solution (Normal saline) throughout the experiment by oral cavage method for 60 days. ***Result*:** A renal function test showed that the T1 and C groups for urea and cratinine concentrations differed significantly. The T2 group's higher urea and cratinine concentrations than the C group, indicated a significant difference ($p < 0.05$). Glutamate pyruvate transaminase levels (GPT) within T1 group were highest from C group, indicating a significant change within liver function test results. Additionally, the T2 and C groups differed significantly. Glutamic-Oxaloacetic transaminase (GOT) levels in the T1 compared with C group differed significantly. Additionally, T2 differed significantly from the C group. ***Conclusion***: The levels of creatinine and serum urea were markedly elevated by methyldopa. Caused the levels of the liver enzymes ALT and AST to rise noticeably as well. Methyldopa overdoses can cause liver damage. Increased transaminase levels attest to this injury. Excessive methyldopa dosage can cause kidney damage, which is confirmed by high urea and creatinine.

Keywords: ALT, AST, Ceratinine, Urea, Kidney, Liver, Methyl Dopa.

INTRODUCTION

The blood pressure is the power, push blood in vessels measured in millimetres of mercury, applied inside the body's major arterial system. It is conventionally categorised into systolic and diastolic measures. Systolic pressure represents the maximum blood pressure during ventricular contraction, whereas diastolic pressure indicates the minimum pressure recorded just before to the next contraction. It is influenced by several elements, including body posture, respiration, emotional condition, physical activity, and rest [1].

As antihypertensive drug, Methyldopa work centrally that had been used since 1970s and 1980s to management of hypertension. Currently, its use has mostly been supplanted as hypotension medication which with adverse effect; however, this drug remains utilised within underdeveloped nations owing to its affordability [2]. Generic methyldopa comes in tablets with 125, 250, or 500 mg of the drug [2]. Methyldopa, which is also known as α-methyldopa, is an antihypertensive and centrally acting sympatholytic [3]. Since it is a prodrug—a drug that needs to be biotransformed into an active metabolite in order to have therapeutic effects—It is a DOPA (3,4-hydroxyphenylanine) analogue. By acting as an agonist on alpha (α)-2 adrenergic receptors, it decreases vasoconstrictor adrenergic impulses and suppresses adrenergic neuronal output [4]. Methyldopa's drug-induced liver damage was discovered soon after it was first used in medicine in the 1960s. In 5% to 35% of

individuals, long-term methyldopa usage is linked to small, temporary increases in blood aminotransferase levels, which often go away even if the drug is continued. On the other hand, while hundreds of instances have been documented, methyldopa-induced liver damage that is clinically noticeable or substantial is rather rare. There are two known types of hepatotoxicity: acute hepatitis, which manifested between weeks and months after started of treatment, while in chronic inflammation, which manifests between months and years after starting of methyldopa medication [5].

Methyldopa often causes acute liver damage between two and twelve weeks after starting treatment. This damage is typically hepatocellular and is marked by moderate increases in alkaline phosphatase and large elevations in ALT and AST (5- to 100-fold). The symptoms, which include fever, headache, fatigue, anorexia, and nausea, are similar to those of acute viral hepatitis. Indications of hypersensitivity are uncommon except for fever. The damage might be serious and fatal [6].

Methyldopa-induced chronic liver damage often manifests six months after starting treatment, however it may sometimes show up years later. The more subtle start of this chronic hepatitis-like clinical picture is usually accompanied by minimal to no jaundice, weakness, and nausea. Spider angiomata and liver discomfort and enlargement are possible clinical symptoms. The clinical and laboratory pattern often mimics autoimmune hepatitis with moderate to marked elevations in ALT and AST, modest elevations in alkaline phosphatase, increases in immunoglobulin levels (particularly IgG), and high titers of autoantibodies such as smooth muscle antibody (SMA) and antinuclear antibody (ANA). A liver biopsy reveals varying degrees of fatty transformation and fibrosis along with persistent active hepatitis. Infiltrates of plasma cells might be seen. If the medication is used continuously, cirrhosis and end-stage liver disease may develop [7]. The condition goes away gradually but totally when methyldopa is stopped. It currently seems that the most prevalent kind of drug-induced liver damage caused by this agent is chronic liver injury. The two types of hepatic damage may have a shared aetiology, and some methyldopa-lead to liver damage within patients' exhibit characteristics of injury for both acute and chronic inflammation [8].

MATERIAL AND METHOD

Fifteen male mice had been used in this expermint, had been gotten from the University of Kufa's College of Science's animal house. Their weight extended between 20 - 30 gm and their ages were less than 5 weeks. Fifteen adult male mice were divided into three comparable groups, each of which include 5 male mice, Dosage duration is 60 days. The drug used in the study is methyldopa. Mice were placed in well-ventilated wire plastic cages and left for two weeks to acclimate and reared under controlled conditions of approximately 12-hour light and 12-hour dark with the temperature set at 20–25°C. The animals were given water and adequate food.

Methyldopa was taking form of commercial methyldopa in the form of coated tablets and concentration (250mg) produced by Kahira Pharm. & Chem.Ind. co. Cairo-Egypt. Each tablet was then melted in (12ml, 6ml) of normal saline solution (0.9%) to obtain the desired concentration in mg/ kg according to the method by [6]. The animals were orally administered methyldopa every day for 7 weeks.

When dosing period had finished, the animals had been dissected after anesthetizing them with ether and chloroform, then medical syringes with a 3 ml capacity were used to take blood straight from the heart by cardiac puncture. The blood was then collected in a gel tube to coagulate, put in centrifuge for 10 minutes within 3000 rpm to separate serum, then stored in a freezer at -20C for each usage [7].

RESULTS

Effect of Methyl Dopa on Levels of Serum Urea and Creatinine

The results of urea showed significant ($p < 0.05$) increase in T2 (54mg/dl), T1 (37mg/dl) compared with C group (15.80mg/dl) while there was significant difference between T1(37mg/dl), T2(54mg/dl).

There was a significant difference ($p<0.05$) between the T2 group's elevated creatinine level (0.84mg/dl) and the C group (0.31mg/dl), the table (1) revealed. Additionally, there was a notable variation marked by an increase in T1 (0.80mg/dl) with C group (0.31mg/dl).

Table 1: Effect of methyldopa on serum urea and creatinine in male mice dosed for 60 days orally, n=5

Kidney Function	Urea mg/dl mean ±SE	Creatinine mg/dL mean ±SE
Control (C)	15.80 ± 1.24 c	0.31 ± 0.022 b
T1 (250)	37. ± 0.67 b	0.80 ± 0.101 a
T2 (500)	54.00 ± 1.87 a	0.84 ± 0.024 a
LSD	3.9 *	0.156*

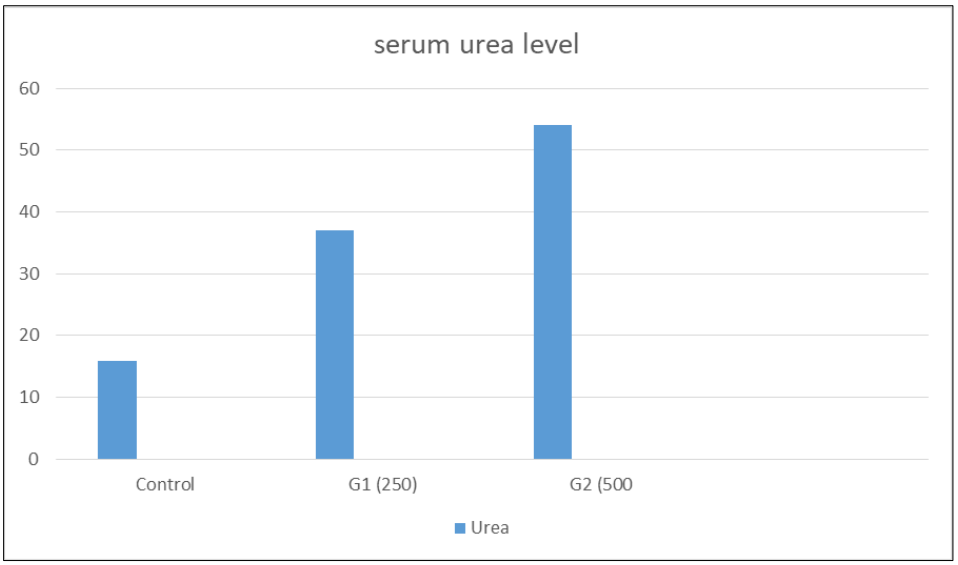

Figure 1: Effect of methyldopa on the serum urea in male mice treated for 60 days orally

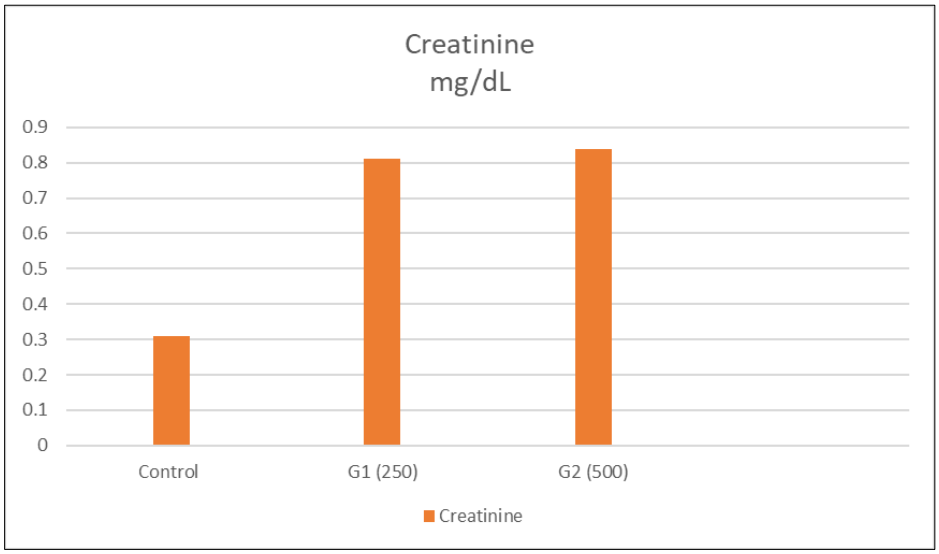

Figure 2: Effect of methyldopa on the serum creatinine in male mice treated for 60 days orally

Effect of Methyldopa on the Liver Functions Test (AST and ALT) in male mice

The table (2) showed there was significant difference ($p< 0.05$) represent by increase in GPT concentration in T2 group (85mg/dl) and T1 group (51.40mg/dl) compared with C group (43.20mg/dl).

The result of GPT in T2 group increased by 1.9, T1 1.1 times compared with C group.

The concentration of ALT increased with consumption of methyldopa.

Table (2) showed there was significant difference ($p<0.05$) represented by increase in GOT concentration in T2 (90.80mg/dl) and T1 group (76.60mg/dl) compared with C group (35).

The result in T2 group increased by 2.5 times, T1 2.1 upon C group.

Table 2: Effect of methyldopa on GPT and GOT levels

Liver function	**GPT U/L mean ±SE**	**GOT U/L mean ±SE**
Control (C)	43.20 ± 1.39 C	35.00 ± 1.703 C
T1 (250)	51.40 ± 1.40 B	76.60 ± 0.927 B
T2 (500)	85.00 ± 1.34 A	90.80 ± 1.020 A
LSD	3.53*	3.24*

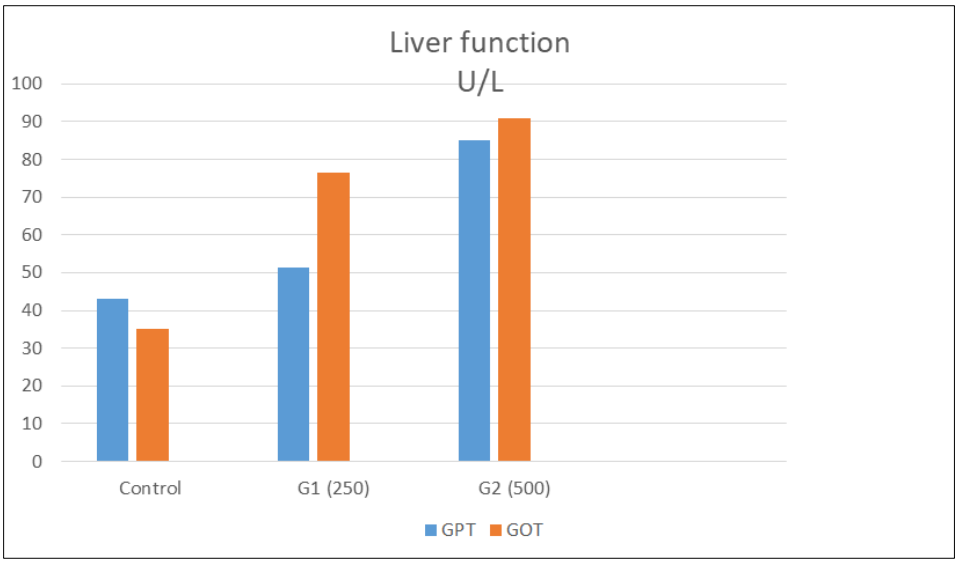

Figure 3: Effect of methyldopa on GPT and GOT levels

DISCUSSION

A significant difference ($p<0.05$) was seen within urea concentration, of T2 group exhibiting an increase compared to the C group. A notable difference was seen in the T1 group in comparison to the C group. While there was a significant difference between T1 and T2 group. This result were close to the a finding by [8], were caused increase in the creatinine clearance in female rats with concentration 400mg/kg/day. Table 1 shows that the urea in blood serum increased by 3.4 times in group T2, 2.3 times T1 compared to the C group.

The breakdown of proteins produces urea, the primary waste product of metabolism that contains nitrogen. It is almost completely eliminated from the body by the kidneys in urine, and for over 150 years, kidney function has been assessed clinically by measuring its content in urine and blood [9]. One component of the cycle that generates the energy required to contract muscles is creatine. The result of creatinine in blood serum in group T2 increasing by 2.7 times, T1 increasing by 2.5 upon C group. The body produces both creatine and creatinine at a rather steady pace. Blood levels are often a good sign of how well the kidneys are functioning since all of the body's creatinine is removed by the kidneys and released as urine [10]. Muscles produce creatinine as a metabolic byproduct when they break down the chemical creatine. The kidneys filter almost all of the creatinine in the circulation and remove it from the body via urine. The amount of creatinine in the blood and its excretion into the urine are measured by this test. This test measures the amount of creatinine present in blood or urine [11]. Administered of methyldopa have increased the concentration of liver enzymes (ALT and AST). These result was accepted with [12, 13], who established that the ALT and AST conc. had a significant increased by methyldopa administration. The table (2) directed to a significant differ ($p < 0.05$) as an increase in GPT concentration in the T2 group compared to the T1 group (51.40 ± 1.40) relative to the C group (43.20 ± 1.39). The GPT result in the T2 group grew by 1.9 times relative to the C group, while the T1 elevated at 1.1 when compared to the C group. The concentration of ALT increased following the use of methyldopa. AST and ALT are enzymes mostly located in the liver, but are also found in muscle tissue, heart cells, red blood cells, and other organs including the kidneys and pancreas [14].

ALT is an enzyme that catalyses the transfer of an amino group from the amino acid alanine to alpha-ketoglutaric acid, yielding glutamate and pyruvate. ALT is mostly located in the liver and kidneys, with lesser amounts seen in the heart and skeletal muscle Enhanced. Increased ALT activity is a more reliable indicator of liver damage than high aspartate aminotransferase (AST) [15].

In the other studies, the ALT activities in the ramipril-administered group were shown to be of low significance ($p < 0.05$) compared to the healthy control group, while exhibiting extremely high significance in the other pharmaceutical groups ($p < 0.0001$). The activities of AST and LDH in the hepatic tissue of animals treated with methyldopa, clonidine, rilmenidine, amlodipine, and ramipril were significantly elevated ($p<0.0001$) compared to the healthy control group. The AST activity in the groups of methyldopa, clonidine, rilmenidine, amlodipine, ramipril, and healthy control rats was assessed. Results are presented as the mean augmented by the standard error of the mean. **: $p < 0.0001$ [16].

Table (2) exhibited a significant difference ($p\leq0.05$) with an increase in GOT concentration in the T2 group (90.80 ± 1.020) and the T1 group (76.60 ± 0.927) relative to the C group (35.00 ± 1.703).

Aspartate aminotransferase (AST) is an enzyme that catalyses the transfer of an amino group from

aspartate to alpha-ketoglutarate, producing oxaloacetate and glutamate [17]. AST is present in most organs. The largest amounts, listed in descending order, are found in the liver, heart, skeletal muscle, kidney, brain, pancreas, lung, leukocytes, and erythrocytes. Because of its widespread tissue distribution, elevated AST levels demonstrate little specificity for any specific disease [18]. AST and ALT were formerly known as serum glutamic oxaloacetic transaminase (GOT) and serum glutamic pyruvate transaminase (GPT), respectively. AST or ALT values are mostly useful in diagnosing liver disease. While not exclusively indicative of liver illness, it may be used in conjunction with other enzymes to assess the progression of different hepatic conditions [19].

When body tissues or organs, such as the liver or heart, are afflicted or compromised, elevated quantities of AST and ALT are discharged into the circulation, resulting in increased enzyme concentrations. The levels of AST and ALT in the bloodstream are closely correlated with the degree of tissue damage [20].

CONCLUSION

Methyldopa caused a significantly increase of serum urea and creatinine. Also caused significant elevation of liver enzyme (ALT and AST) levels. Liver damage can occur do to overdoses of methyldopa. Elevated levels of transminase confirm this damage. Kidney damage can occur due to excessive dose of methyldopa and elevated urea and creatinine confirm this damage.

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