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Full Length Research Paper

The Effects of Oral Intraperitoneal and Inhaled Methamphetamine on some Biochemical Parameters using Wistar Albino Rats

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Abstract

Abuse of hard drugs has become a norm for an increasing number of young people globally with methamphetamine currently the second most abused in Nigeria. The need for people to know as much as it is consumed was what inspired this research. With the oral, inhaled and intraperitoneal as the three routes of administration to be investigated, the animals were sequestered into seven groups of five each. Besides the control group, the other six were used to investigate effects of administering low and high doses of methamphetamine. Doses 0.57mg/kg and 14.28mg/kg were administered to the test animals via inhalation, oral and intraperitoneal means for 21 days while their weights were taken four times in a five day interval before sacrifice and biochemical analysis. The highest reductions in weight were recorded in groups orally administered 14.28mg/kg with a reduction percentage of 24.4% while those intraperitoneally administered 14.28mg/kg showed a 15.9% increase in weight. Groups orally and intraperitoneally administered 14.28mg/kg showed significant (p<0.05) elevations in AST levels when compared to the control group. The ALT levels increased significantly (p<0.05) in all test groups when compared to the control. Significant increase (p<0.05) in serum urea levels was recorded in groups intraperitoneally administered as well as those administered 0.57mg/kg via inhalation while all test groups administered 14.28mg/kg showed significant (p<0.05) rise in serum urea levels. Also, the creatinine levels showed significant increase (p<0.05) in groups intraperitoneally administered 14.28mg/kg. The results summarily suggest that the substance; both in low and high doses, can cause serious perturbations to vital organs and expose patrons to a host of health complications notwithstanding route of administration.

Keywords: Methamphetamine, Abuse, Oral, Intraperitoneal Inhalation, Doses, Route

INTRODUCTION

Dependence and abuse of drugs are among the most prevalent and life-threatening maladies accosting young people globally. Dependence and addiction; being the inability to quit using a substance irrespective of the harm it causes (Felman, 2021), is fast becoming an epidemic among teenagers and young adults at the peak of reproductive age (Comer *et al.,* 2001). Among the most abused of substances in the world are hard drugs and psycho-stimulants like opiates, cocaine, and cannabis (Rehm *et al.,* 2010).

Methamphetamine is one of the notorious psycho-stimulants; a central nervous system stimulant (United Nations Office on Drug and Crime, 2007) whose abuse is on the rise under different street names such as speed, ice, meth crystal (Radfar and Rawson 2014). It is commonly called 'mkpuru mmiri' by the Igbos in theSouth-East of Nigeria, because its physical appearance is similar to those of ice pebbles. Nigeria has emerged over the past decade as a significant producer of methamphetamine (Mouhamadou, 2019), and although the abuse; especially in eastern Nigeria, has become critical, the presence of factories thus discovered by the National Drug Law Enforcement Agency (NDLEA) in Asaba, Delta State and in Enugu reveal the height of negligence exhibited by the patrons of such substance (Jatau *et al.,* 2021).

The rate of methamphetamine abuse is on the ascendancy in Nigeria, whereas exhaustive information of its effects; especially on the vital organs responsible for its metabolism, remain elusive. Therefore there is need to evaluate its effect on some biochemical parameters. Some drugs like desoxyne possess methamphetamine as an active ingredient; therefore it becomes even more imperative to investigate what such a prescription might herald. Knowledge of the effects of methamphetamine on the vital organs will go a long way to educate patrons, abusers, law enforcement agencies on the dangers and hazards of the drug and similarly provide further empirical data for counselors. This is possible by properly profiling some hepatic and renal toxicity parameters of the exposed wistar rats, then publishing the results.

Materials and Methods
Materials
Glass distilled water was used in the preparation of all solutions and all the chemicals and reagents used were purchased from British Drug House (BDH) products, and are of analytical grade. The equipments used were; 3015 Single Chamber Water-jacketed Laboratory Incubator, Spectrophotometer (KJ – 721G China), Centrifuge (PEC – MEDICAL USA), Micro-hematocrit Centrifuge, Electronic Weighing Balance (Model: Adam AFP 800L), Randox test kits

Methods
Site of Study: The study was carried out at Applied Biochemistry Laboratory of Nnamdi Azikiwe University Awka, Anambra state.

Duration of Study: The study was completed in five weeks for the *in vivo* assay, collection of results and statistical analysis.

Collection of Sample and Identification: Crystal methamphetamine (10g) was acquired from the National Drug Law Enforcement Agency (NDLEA) Anambra state command.

Preparation of Methamphetamine Stock Solution: Stock solutions 0.08mg/ml and 2mg/ml were prepared for the low and high dose administrations respectively. The first stock solution (0.08mg/ml), was prepared by

dissolving 8mg (0.008g) of crystal methamphetamine in 100ml of distilled water; while 2mg/ml stock solution was prepared by dissolving 20mg (0.02g) in 10ml of distilled water.

Purchase, Acclimatization and Feeding of Animals

A total of 62 animals were purchased and allowed to acclimatize for seven days while being fed and given water *ad libitum.* Thirty eight animals were utilized for acute toxicity studies via intraperitoneal route using modified Lorke's method (Lorke, 1983) while twenty five were tested.

Ethical Approval

All experimental protocol was approved by AREC, Nnamdi Azikiwe University Awka, Anambra state, Nigeria. The approval number obtained is NAU/AREC/2023/00064

Administration

Syringes were used to administer 0.57mg/kg (1.5% of the LD_{50}) and 14.28mg/kg (38% of the LD_{50}) of methamphetamine orally and intraperitoneally. However, a digestion flask, pipe, a bunsen burner and a partially airtight box was used to administer the substance via inhalation. Measured volumes of the stock solution were poured into the digestion flask and then cocked with a pipe channeled into the container where the animals were kept. As heat is applied to the digestion flask, the contents vaporize into the chamber where the animals breathe them in.

Acute Toxicity Study

The median lethal dose (LD_{50}) was determined using modified lorke's method as described by Sani *et al.* (2020). It was carried out in three phases; the initial phase had four groups of three rats each and these were administered 0.07, 0.21, 0.36 and 0.57mg/kg of the methamphetamine sample. The animals were monitored within the first four hours for signs of toxicity such as sniffing, restlessness, hyperactivity, leaking of paws, defecation, stretching and protrusion of the eye balls, calmness, and death. The symptoms highlighted above were nonexistent so the study proceeded into the second phase. In this phase, four groups with three rats each were employed and administered 1.14, 2.14, 3.57 and 5.0mg/kg of the sample. The signs highlighted were also absent so the study proceeded into the third and final phase with five groups of three rats each. These were administered 8.57, 14.29, 28.57, 35.7, and 50.0mg/kg of the methamphetamine sample and monitored. Casualties were recorded and the LD_{50} was calculated by obtaining the geometric mean of the Highest Non Lethal Dose and the Lowest Lethal Dose that caused death.

$$LD50 = (Highest\ Non\ Lethal\ Dose\ \times Least\ Lethal\ Dose)^{1/2}$$

Grouping

The rats were divided into seven groups of five rats each. A total of thirty five rats were used for this study, and for the duration of 28days. Group A was the control; group B were orally administered 0.57mg/kg, group C were orally administered 14.28mg/kg, group D were intraperitoneally administered 0.57mg/kg, group E were intraperitoneally administered 14.28mg/kg; group F inhaled 0.57mg/kg, group G inhaled 14.28mg/kg methamphetamine.

Indices of growth parameters measured

The initial weights of the animals were taken after acclimatization. The weights were taken again four more times in a five days interval, before sacrifice.

Sacrifice and blood collection

The animals were anaesthetized with chloroform and blood samples were collected via closed cardiac puncture. The

blood samples were collected using universal bottles.

Biochemical Analysis
Liver Function Tests

The blood samples were centrifuged at 4000rpm for 15mins and used for the subsequent assay.

The Aspartate Aminotransferase (AST) was determined by monitoring the concentration of oxaloacetate hydrazone formed with 2,4-dinitrophenylhydrazine at 546nm. According to Limdi and Hyde (2003), an aliquote of the serum (0.1ml) was mixed with 0.5ml of Randox AST R1 buffer containing 100mmol phosphate buffer, 100mmol L-aspartate and 2mmol α-oxoglutarate. This was allowed to stand for 30mins at room temperature followed by the addition of 0.5ml of 2mmol 2, 4-dinitrophenylhydrazine. After 20mins, 5ml of 0.4M NaOH was added and the absorbance was taking at 546nm after 5min. the concentration of AST in the serum was calculated from the standard values given by Randox.

The Alanine Aminotransferase (ALT) was determined by monitoring the concentration of pyruvate hydrazone formed with 2, 4-dinitrophenylhydrazine at 546nm. As reported by Limdi and Hyde (2003), an Aliquote of the serum (0.1ml) was mixed with 0.5ml of Randox ALT R1 buffer containing 100mmol phosphate buffer, 200mmol L-alanine and 2mmol α-oxoglutarate. This was allowed to stand for 30mins at room temperature followed by the addition of 0.5ml of 2mmol 2,4-dinitrophenylhydrazine. After 20mins, 5ml of 0.4M NaOH was added and the absorbance was taking at 546nm after 5min. the concentration of ALT in the serum was calculated from the standard values given by Randox.

Alkaline phosphatase (ALP) hydrolyses p-nitrophenylphosphate to producephosphate and p-nitrophenol. In the assay conducted using the method reported by Limdi and Hyde (2003), 20µL of the serum was mixed with 1ml of 10mmol/L p-nitrophenylphosphate in 1mol/l Diethanolamine buffer. The initial absorbance was read immediately with Axiom 752 UV-VIS spectrophotometer at 405nm, and then the absorbance was taken again after a minute, 2minutes and 3minutes. The ALP activity was calculated as follows: ALP (U/L) = $2760\Delta A_{405}$nm/min. Where ΔA_{405} = change in absorbance at 405nm.

The albumin test was conducted using the method reported by Limdi and Hyde (2003). This is based on its quantitative binding to the indicator 3, 3', 5, 5'-tetrabromo-m cresol sulphone phthalein (bromocresol green, BCG). The albumin-BCG-complex absorbs maximally at 578 nm, the absorbance being directly proportional to the concentration of albumin in the sample. An Aliquote of the serum (10µL) was mixed with 3ml of BCG reagent. This was allowed to stand for 5mins at 30°C. The absorbance was read at 578nm.

Total protein was determined using Biuret method (Tonog and Lakhkar 2022). The serum (0.1ml) was dilute in 0.9ml of normal saline. Blank Biuret reagent (5ml) was added to samples and were mixed well and allowed to stand for 20 min at room temperature 27°C. Absorbance was read for one test and standard against a blank at 540 nm.

Renal Toxicity Assay

The blood was centrifuged at 4000rpm for 15mins and the serum was used to assay for the renal function enzymes.The renal toxicitytest was determined spectrophotometrically according to the method of Limdi and Hyde (2003). The

kidney function parameters assayed were serum creatinine and serum urea.

Creatinine was determined based on its reaction with picric acid to form a coloured complex. The amount of the complex formed is directly proportional to the creatinine concentration. An aliquot of the serum (50µL) was mixed with 0.5ml of randox reagent containing 35mmol/l picric acid and 0.32mol/l NaOH. This was read with autoanalyzer and the concentration of creatinine displayed on the machine was recorded.

Results
The findings are presented in tables after being analyzed with SPSS (Statistical Package for Social Sciences) version 25 to facilitate interpretation.

Acute Toxicity Test
The result of a 24 hour acute toxicity test of intraperitoneally administered methamphetamine is shown in Table 1. The groups administered 0.07, 0.21, 0.36 and

As the urea in the serum is hydrolyzed to ammonia in the presence of urease, the ammonia librated is measured photometrically by Berthelot's reaction. An aliquot of the serum (5µL) was mixed with 50µL of Randox reagent containing 116mmol/L sodium nitroprusside and 6mmol/L urease. It was allowed to stay for 10mins at 37ºC after which 1.25ml of 120mmol/l phenol and 27mmol/l sodium hypochlorite was added and allowed to stay for 15mins at 37ºC. The concentration of urea was then recorded with auto analyzer.

0.57mg/kg did not show any signs of toxicity. So also did the groups administered 1.14, 2.14, 3.57, 5.0, 8.57, 14.29 and 28.57 mg/kg; not show any signs of toxicity. The groups administered 35.7mg/kg reported a 67% mortality rate within 24 hour while those administered 50.0 mg/kg showed 50% mortality. The lethal dose (LD_{50}) of methamphetamine was calculated and found to be 37.8mg/kg (2645.8 mg/70kg).

Table 1: Result of the acute toxicity study (LD_{50}) of the aqueous solution of methamphetamine administered intraperitoneally

	Dose (mg/kg)	No of Death	% Mortality	Remark
1	0.07, 0.21, 0.36, 0.6	0	0	Normal
2	1.14, 2.14, 3.57, 5.0	0	0	Normal
3	8.57, 14.29	0	0	Normal
4	28.57	0	0	Mildly toxic
5	35.70	2	67	Toxic
6	50.0	1	50	Toxic

Body Weight Profile
The average body weights of the rats administered (0.57mg/kg and 14.28mg/kg doses)of methamphetamine via Inhalation, oral and intraperitoneal routes are exposed in Tables 2 and 3.
The results show that there were no significant alterations ($p > 0.05$) in the weight of the animals administered 0.57mg/kg of the solutions via Inhalation, oral and

intraperitoneal routes. However, bar those orally administered 14.28mg/kg of methamphetamine which showed significant decrease ($p < 0.05$) in days 3 and 4 when compared to day2, the results show no significant alteration ($p > 0.05$) in the body weight of the animals administered 14.28mg/kg of the methamphetamine solution via the three routes.

Table 2: Weight profile of rats administered 0.57mg/kg and 14.28mg/kg b.w. of the aqueous solution of methamphetamine via oral, intraperitoneal (IP) and nasal routes (IH).

Groups	Day 1	Day 2	Day 3	Day 4
Control	104.6 ± 24.10	118.1 ± 25.0^{d}	$104 \pm 23.5^{d,e}$	$94.45 \pm 21.3^{d,e,f}$
Oral 0.57mg/kg	115.5 ± 20.27	128.7 ± 22.48^{d}	$106.7 \pm 19.69^{d,e}$	$115.4 \pm 23.03^{d,e,f}$
Oral 14.28mg/kg	147.85 ± 26.66	158.6 ± 25.99^{d}	$131.7 \pm 21.25^{d,b}$	$111.7 \pm 14.4^{d,e,f}$
IP 0.57mg/kg	158.8 ± 40.75	159.01 ± 35.91^{d}	$144.37 \pm 32.87^{d,e}$	$124.3 \pm 40.76^{d,e,f}$
IP 14.28mg/kg	125.17 ± 17.69	135.12 ± 20.77^{d}	$138.16 \pm 22.95^{d,e}$	$145.15 \pm 21.22^{d,e,f}$
IH 0.57mg/kg	132.33 ± 29.30	132.16 ± 29.97^{d}	$133.21 \pm 28.76^{d,e}$	$133.06 \pm 32.73^{d,e,f}$
IH 14.28mg/kg	128.36 ± 35.00	129.855 ± 34.7^{d}	$131.01 \pm 33.60^{d,e}$	$139.9 \pm 32.44^{d,ef}$

The table shows result of mean ± Standard deviation of the body weight profile of the animals before, during and after administration of methamphetamine [a] Significant difference when compared to Day 1, [b] Significant difference when compared to Day2, [c] Significant difference when compared to Day3, [d] No Significant difference when compared to Day 1, [e] No Significant difference when compared to Day 2, [f] No Significant difference when compared to Day 3.

Table 3: Percentage Difference on Day 4 when compared to Day 1

SN	Control	ORAL 0.57mg	ORAL 14.28mg	IP 0.57mg	IP 14.27mg	IH 0.57mg	IH 14.28mg
	9.7%	0.09%	24.5%	21.7%	15.9%	0.6%	8.99%

%Percentage Decrease when compared to Day 1
%Percentage Increase when compared to Day 1

Effects of Methamphetamine on the Hepatic Parameters of Rats

The liver function parameters of the wistar rats which include the Aspartate transaninase (AST), Alanine Transaminane (ALT), Alkaline Phosphatase (ALP), Total Protein (TP) and Serum Albimin (ALB) are shown in Table 4.

The result shows no significant effect (p>0.05) in the aspartate aminotransferase (AST) levels across the test groups when compared to the control. The substance therefore showed no effect on the AST levels when compared to the control.

All test groups showed varying increases in the alkaline phosphate (ALP) levels when compared to control but only those orally and intraperitoneally administered 14.28mg/kg of the substance (groups C and E) were significant (p<0.05). The highest value of 4.35 ± 0.74 was obtained for the group E (14.28mg/kg intraperitoneal). This means that the substance affected the ALP

levels especially when intraperitoneally administered high doses.

The results show a significant (p<0.05) increase in the ALT levels of all the test groups when compared with the control. The highest value among the test groups of 31.70 ± 2.60 (U/L) was obtained for group C (14.28mg/kg orally) while the least value of 18.83 ± 1.79 (U/L) was obtained for group F (0.57mg/kg inhalation). This shows that the substance has the most pronounced effect on the ALT when orally administered high doses.

The total protein (TP) test result revels no significant (p>0.05) difference in the total protein concentration of the test groups when compared with control. Therefore, the substance did not affect the TP levels when administered at any dose via any of the three routes.

The albumin levels of the test groups administered 0.57mg/kg and 14.28mg/kg of methamphetamine via all routes showed no significant (p<0.05) difference when

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compared with the control group as shown in table 4.

Table 4: The effect of administering different doses methamphetamine and via different routes on the liver function parameters

Groups	AST (U/L)	ALT (U/L)	ALP (U/L)	TP (mg/dl)	ALB (mg/dl)
Control	6.98 ± 1.0	1.70 ± 0.79	0.25 ± 0.19^b	7.05 ± 0.87	3.59 ± 0.36
Oral0.57mg/kg	7.18 ± 0.99^b	21.64 ± 2.95^a	1.07 ± 0.22^b	7.09 ± 0.86^b	4.13 ± 0.59^b
Oral14.28mg/kg	7.60 ± 0.86^b	31.70 ± 2.60^a	2.72 ± 0.32^a	7.06 ± 0.52^b	3.70 ± 0.35^b
IP 0.57mg/kg	7.13 ± 0.81^b	20.24 ± 0.44^a	1.42 ± 0.07^b	6.90 ± 0.36^b	3.77 ± 0.47^b
IP14.28mg/kg	6.81 ± 0.58^b	26.73 ± 2.02^a	4.35 ± 0.74^a	6.86 ± 0.75^b	4.30 ± 0.24^b
0.57mg/kg (IH)	5.88 ± 0.24^b	18.83 ± 1.79^a	1.19 ± 0.26^b	6.98 ± 0.55^b	4.66 ± 0.80^b
14.28mg/kg (IH)	5.90 ± 0.43^b	24.92 ± 1.96^a	1.34 ± 0.11^b	7.04 ± 0.62^b	4.14 ± 0.29^b

The table shows the mean ± Standard deviation [a] Significant difference when compared to Control, [b] No Significant difference when compared to Control.

The Effects of Methamphetamine on some Kidney Function Parameters

The results of the urea levels show a significant increase ($p<0.05$) in the groups administered 0.57mg/kg intraperitoneally and via inhalation when compared to control. Also, significant ($p<0.05$) increases were also recorded in the urea levels of all the groups administered 14.28mg/kg of the solution when compared to control. The highest value among the test groups with a value of 24.47±1.99 was obtained for group E (14.28mg/kg intraperitoneal), while the lowest value of 15.31 ± 1.29 was obtained in group B (0.57 oral).

The creatinine levels of all the groups administered 0.57mg/kg of the methamphetamine solution showed no significant difference when compared to the control group. Among groups administered high doses, only the creatinine levels of the groups intraperitoneally administered 14.28mg/kg showed a significant ($p<0.05$) increase when compared to the control group. Among the test groups, the highest value of 5.67 ± 1.17 was obtained for group E (14.28mg/kg intraperitoneal) while the lowest value of 0.83 ± 0.29 was obtained for group F (0.57mg/kg inhalation). This shows that intraperitoneal administration at high doses has the most effect the creatinine levels.

Table 5: Renal Function Parameters after Methamphetamine Administration

Groups	Urea (mg/dl)	Creatinine (mg/dl)
Control	12.48 ± 0.39	0.67 ± 0.29
Oral (0.57mg/kg)	15.31 ± 1.29^a	1.00 ± 0.00^b
Oral (14.28mg/kg)	23.42 ± 1.11^a	1.33 ± 0.58^b
IP (0.57mg/kg)	21.79 ± 2.87^a	1.67 ± 1.15^b
IP (14.28mg/kg)	24.47 ± 1.99^a	5.67 ± 1.17^a
IH (0.57mg/kg)	23.25 ± 0.56^a	0.83 ± 0.29^b
IH (14.28mg/kg)	21.96 ± 1.89^a	1.17 ± 0.77^b

Values are mean ± Standard deviation [a] Significant difference when compared to Control, [b] No Significant difference when compared to Control.

Discussion

The consensus is that addicts and abusers of methamphetamine, like every other hard drug, are liable to the allure of crime and many other social vices; vulnerable to psychosis and several psychological

maladies. However, its effects on some biochemical parameters remain to be thoroughly investigated.

The acute toxicity study revealed the median lethal dose to be 37.8mg/kg via intraperitoneal administration. The LD_{50} result contradicts Funahashi *et al.* (1988) with a lethal dose report of 95mg/kg for orally administered methamphetamine. The discrepancy might be as a result of the difference in the route of administration, and the significance of first pass effect. The first pass effect is a phenomenon of drug metabolism that causes a reduction in the concentration of the active drug, specifically when administered orally (Maheshwari *et al*., 2018). Therefore a higher oral dose is needed to illicit the same effects when compared to other routes of administration that bypasses the first pass phenomenon. Substances with an LD_{50} value below 5g/kg are declared toxic whereas those with an LD_{50} above are said to be nontoxic (Lorke, 1983), so it can be said that methamphetamine is toxic at high doses. Richards and Lawin (2023) maintain that high doses of methamphetamine can lead to severe acute toxicity, resulting in hyperthermia (elevated temperatures), cardiovascular collapse and convulsions. They insist that these effects can be life threatening and may contribute to mortality. Histopathology and biochemical analysis are recommendations to evaluate the extent of damage to the organs when toxic levels of methamphetamine are administered, and also to know the biochemical state of the animals during acute toxicity.

The reduction percentage in weight was highest in groups administered high oral doses (14.28mg/kg) at 29.6%. The reduction is statistically significant confirming that the oral route reduced the weights more than did other routes. The animals in group C (oral 14.28mg/kg) were noticed to consume less and less amount of feed each day unlike the other groups. This observation agrees with Yasaei and Saadabadi (2022) who states a gross reduction in the weight of methamphetamine users as one of the long term effects of methamphetamine consumption. According to American Addiction Centers Editorial Staff (2023), methamphetamine users experience a severe loss of appetite and a sped up metabolism leading to significant weight loss. This agrees with Rusyniak (2011) who reports that chronic oral methamphetamine use may result in weight loss due to its appetite-suppressing effects. The result however disagrees with McCarty and Avent (2020) who is of the opinion that intravenous use of methamphetamine may potentially have a more significant impact on body weight due to the rapid and potent delivery of the drug. From the study, the groups administered via inhalation and intraperitoneal routes showed no loss in appetite but rather, these gained weight because of a sped up metabolism. Therefore unlike those orally administered, the most probable conjecture is that the appetites of the animals in the other groups were not affected.

Methamphetamine has also shown to be able affect organ-system functions. Although the Aspartate Transaminase (AST), Albumin levels and Total Protein (TP) levels remained normal, the Alkaline Phosphatase (ALP), and Alanine Transaminase (ALT) levels showed significant differences when compared to the control. According to Lala *et al,* 2022, abnormal levels of ALP in the blood might be a sign of a wide range of health maladies, including liver disease, chronic kidney disease and bone disorders. Therefore the significant increase noticed in groups administered 14.28mg/kg might be attributed to the onset of one of those health conditions. Recall that it was only the oral and intraperitoneal routes that showed the significant difference in ALP levels. Although Hassan *et al.* (2018) reports

that the normal Alanine Transaminase (ALT) range for rats is 10U/L to 30U/L, the ALT levels of the samples remained significantly ($p<0.05$) high when compared to the control group. This results agrees with Kerrigan *et al.*(2016) who reports that methamphetamine abuse increased ALT and AST levels. Also, Lasker *et al.* (2019) noted the normal ALT levels to be 6U/L to 8U/L in his yogurt syndrome and oxidative stress induced experiment with stressed ALT levels at 17U/L. AST, ALP and ALT are enzymes found mainly in the liver (Curtis and Sivilotti, 2015) therefore the elevated levels recorded in the serums of the treatment groups are evidences of liver perturbation. Also according to Vargas and Bamhill (2023), mild to moderate elevation in liver enzymes; especially ALT, often means there is some type of inflammation within the liver. According to Halpin *et al.* (2013); who performed histology studies on the livers of experimental animals exposed to methamphetamine using an electron microscope, methamphetamine induced hyperthermia contributes significantly to persistent liver damage. In summary it can be hypothesized that methamphetamine stresses the liver and if prolonged, might damage them irrevocably.

Significant increase in renal toxicity parameters observed especially in groups administered high doses (14.28mg/kg) show that the kidney is affected when the substance is consumed. The significant increase seen in the blood urea levels of all the test groups when compared to the control is indicative of renal toxicity. This finding agrees with Kala *et al.* (2007) who reports an increase in urea levels of chronic methamphetamine abusers when compared to the control subjects. According to Bishop *et al* (2010), elevated serum levels of byproducts of protein metabolism such as urea and creatinine; signals the onset of uremia. According to Cheriyedath (2023), the liver produces and releases urea into the bloodstream which carries it to the kidney concentrated as urine for excretion by the kidney. High serum urea levels indicate therefore that the kidney is not working correctly leading to impaired kidney function. This signifies that; since methamphetamine administration elevates serum urea levels especially among groups intraperitonealy administered high doses, it impairs kidney function. Only groups intraperitoneally administered 14.28mg/kg displayed a statistically significant ($p<0.05$) elevation in the serum creatinine level when compared to the control group. Therefore high intravenous or intraperitoneal administrations pose the most threat against the kidney; especially in high doses. This is partly in agreement with the report of Torrecilla *et al.* (2018) who recorded increases in the creatinine levels of exposed test groups when compared to the control group. According to Wu *et al.* (2023), creatinine is the waste product of creatine, which the muscles use to make energy and it travels in the blood to the kidneys, where it leaves the body in the urine. Therefore, high levels in the blood might indicate that the kidneys are not working correctly. However, the result also affirms that the least nephrotoxic route is via oral administration because low doses did little to significantly alter the kidney function parameters. This gives a benign nod to those drugs like Desoxyn, Adderall, Vyvanse, Ridlin and Concerta which is are methamphetamine and amphetamine hydrochloride tablets. A renal biopsy on a patient with no medical history, except years of oral and intravenous methamphetamine abuse, vascular and glomerular changes consistent with thrombotic microangiopathic injury and advanced glomerulosclerosis were noticed (Baradhi *et al.*, 2019). According to Baradhi *et al.* (2019) these illustrate

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methamphetamine-induced renal disease which leads to end-stage renal disease.

Histopathological examinations of both organs are a recommendation to further evidence the damage methamphetamine inflicts on the kidney and liver of methamphetamine users.

Conclusion

The results show that methamphetamine is able to cause a loss in the body weight especially if orally administered and in high doses, so users and abusers can be identified with such. The substance causes significant increases in biochemical parameters indicating serious perturbations to essential organs such as the kidney and liver. It can be assumed that if abuse is prolonged, the substance can and will damage either organs, or both. Although low doses administered orally showed the lowest nephrotoxic effect, it would be prudent to remind that the scope of this research does not accommodate effects of prolonged usage. Therefore, prescription drugs with methamphetamine active ingredients like dexoxyne should remain strictly regulated. However, from observing and sacrificing the animals that were exposed to the substance for a period of 21 days, this research reveals that notwithstanding reason, consumption of methamphetamine does more to harm the body than it does to aid it.

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