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Effect of Benzodiazepine on Liver and Kidney Functions Parameters

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Abstract

A benzodiazepine; often abbreviated "BZD" is a psychoactive drug with a core chemical structure of a benzene ring and a diazepine ring. Benzodiazepines enhance the effect of the neurotransmitter gamma-aminobutyric acid (GABA) at the GABA receptor, resulting in sedative, hypnotic (sleep-inducing), anxiolytic (anti-anxiety), anticonvulsant and muscle relaxant properties. The present study investigates the effect of long-term administration of diazepam on liver and kidney function parameters using adult male rats. The rats were grouped into five groups (GI – GV) of five rats each. GI served as normal control, GII, GIII, GIV and GV were administered with 0.25g/kg, 0.50g/kg, 0.75g/kg and 1.0g/kg body weight respectively for twelve weeks. The animals were euthanized 24 hours after the last diazepam administration, blood samples were collected for assessment of liver and kidney function indices. A significant ($p<0.05$) increase in liver enzymes (ALT, AST and ALP), Urea and Creatinine with a significant decrease ($p<0.05$) in Albumin in a dose dependent pattern compared to the normal control. The study established that long term usage of benzodiapine drugs could lead to liver and kidney failure and it should be used with caution.

Keywords: Benzodiazepine, Liver, Kidney, Rats, Function, Indices, Toxicity

1. Introduction

Diazepam is commonly used to treat a wide range of conditions, including anxiety, panic attacks, insomnia, seizures, muscle spasms, restless legs syndrome and alcohol withdrawal. It may also be used before certain medical procedures (such as endoscopies) to reduce tension and anxiety, and in some surgical procedures to induce amnesia. It may be used to hasten the onset of intravenous (IV) anesthesia while reducing dose requirements or as the sole agent when IV anesthesia is not available or is contraindicated [1]. It possesses anxiolytic, anticonvulsant, hypnotic, sedative, skeletal muscle relaxant, and amnestic properties [2]. The pharmacological action of diazepam enhances the effect of the neurotransmitter GABA by binding to the benzodiazepine site on the GABA receptor (via the constituent chlorine atom) leading to central nervous system depression [3]. Adverse effects of diazepam include anterograde amnesia (especially at higher doses) and sedation, as well as paradoxical effects such as excitement, rage, or worsening of seizures in epileptics. Benzodiazepines can also cause or worsen depression, particularly after extended periods of use. Long-term effects of benzodiazepines such as diazepam include tolerance, benzodiazepine dependence, and benzodiazepine withdrawal syndrome upon dose reduction. After cessation of benzodiazepines, cognitive deficits may persist for at least six months and longer than six months may be needed for recovery from some deficits [4].

The current study was conducted to investigate the effect of long-term administration of diazepam liver and kidney function parameters in adult male rats.

2. Materials and Methods

2.1 Study Animals

Male rats weighing 120g were obtained from Department of Biological Sciences, Bayero University Kano. Animals were housed in colony cages at an ambient temperature and relative humidity. The animals had free access to standard palletized grower feed and drinking water. The principles of laboratory animal care and guidelines were followed during experimentation [5, 6].

2.2 Administration of Benzodiazepine Drugs in Experimental Animals

Variable doses of Benzodiazepine drug were administered orally. The dose was repeated daily for three months. The volume of Benzodiazepine administered was determined by the weight of the rat according to the following relationship according to Muhammad *et al* [7].

$$\text{Volume to be administered (cm3)} = \frac{\text{Weight of rats (kg)} \times \text{Dose (g/kg)}}{\text{Concentration of Benzodiazepine (g/ml)}}$$

2.3 Grouping of Experimental Animals

A total of 25 rats were grouped into five groups of five rats each:

Group [1]: control group, Animals serve as a non-treated control group.

Group [2]: administered orally with 0.25g/kg body weight of Benzodiazepine

Group [3]: administered orally with 0.50g/kg body weight of Benzodiazepine

Group [4]: administered orally with 0.75g/kg body weight of Benzodiazepine

Group [5]: administered orally with 1.0g/kg body weight of Benzodiazepine

At the end of the experimental period, the rats were sacrificed, blood samples were collected for the Biochemical analysis of Kidney function parameters (urea, creatinine and uric acid) and Liver function parameters (Bilirubin, ALT, AST, and alkaline phosphatase).

2.4 Statistical Analysis

Results were expressed as mean ± standard deviation and analyzed using ANOVA, with p value <0.05 considered significant, a component of GraphPad Instat3 Software version 3.05 by GraphPad Inc.

3. Results and Discussions

3.1 Results

Table 1 shows liver function indices of rats administered with varying doses of Benzodiazepine.

Table 1: liver Function Parameters of rats administered with varying doses of Benzodiazepine

	Group I	Group II	Group III	Group IV	Group V
Weight of Liver (g)	$57.00\pm7.55^{a,b}$	57.5 ± 7.78	65.6 ± 3.88	76 ± 7.16^{a}	82.6 ± 8.21^{b}
ALT (U/L)	$46.00\pm4.00^{a,b,c}$	56.00 ± 4.00^{a}	63.00 ± 4.00^{b}	70.00 ± 2.00^{c}	88.00 ± 6.00^{d}
AST (U/L)	$39.00\pm6.00^{a,b,c,d}$	48.00 ± 6.00^{a}	56.00 ± 3.00^{b}	68.00 ± 3.00^{c}	82.00 ± 4.00^{d}
ALP (U/L)	$48.00\pm7.00^{a,b,c}$	54.00 ± 9.00	64.00 ± 4.00^{a}	70.00 ± 2.00^{b}	71.00 ± 5.00^{c}
T-Bilirubin (mg/dl).	$0.33\pm0.02^{a,b,c,d}$	0.39 ± 0.014^{a}	0.43 ± 0.14^{b}	0.44 ± 0.035^{c}	0.46 ± 0.017^{d}
D-Bilirubin (mg/dl).	0.03 ± 0.01	0.03 ± 0.008	0.038 ± 0.007	0.03 ± 0.014	0.03 ± 0.009
T-Protein (g/dl)	7.1 ± 0.37^{a}	6.96 ± 0.40	6.64 ± 0.43	6.74 ± 0.58	6.46 ± 0.34^{a}
Albumin (g/dl)	$4.20\pm0.21^{a,b}$	4.18 ± 0.45	4.00 ± 0.06	3.90 ± 0.14^{a}	3.04 ± 0.41^{b}
Globulin (g/dl)	2.88 ± 0.16	2.78 ± 0.44	2.64 ± 0.47	2.84 ± 0.69	3.06 ± 0.42
A/G ratio	1.46 ± 0.03	1.54 ± 0.30	1.56 ± 0.29	1.47 ± 0.38	1.14 ± 0.20

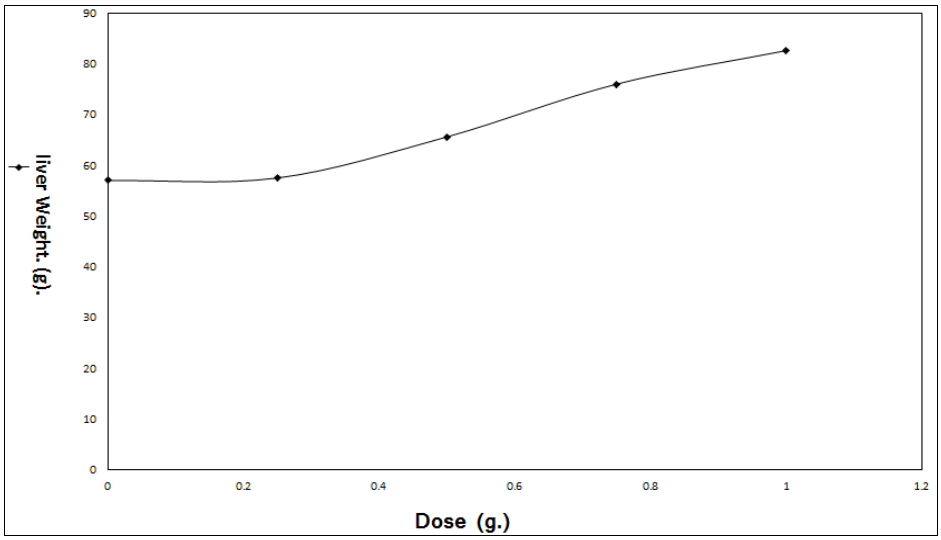

Fig 1: Effect of benzodiazepine doses on liver weight

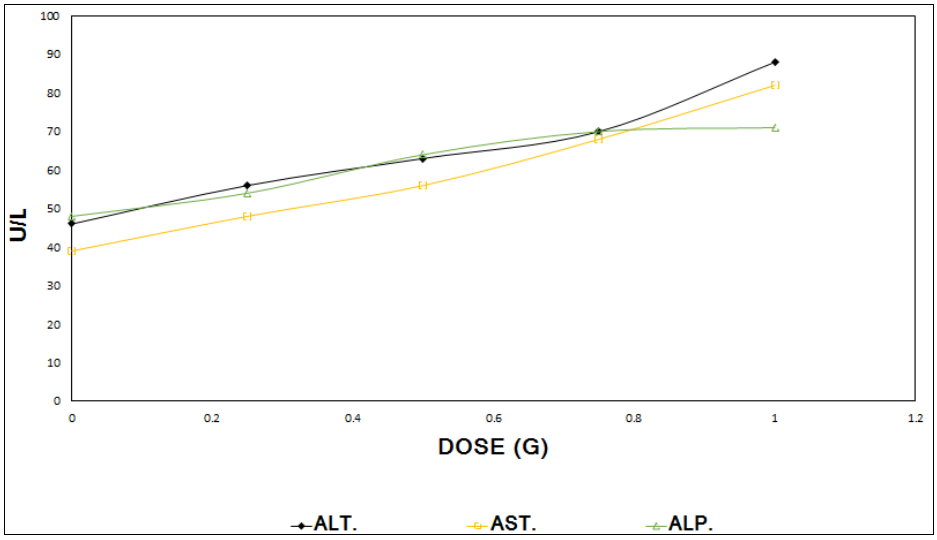

Fig 2: Effect of benzodiazepine doses on ALT, AST and ALP

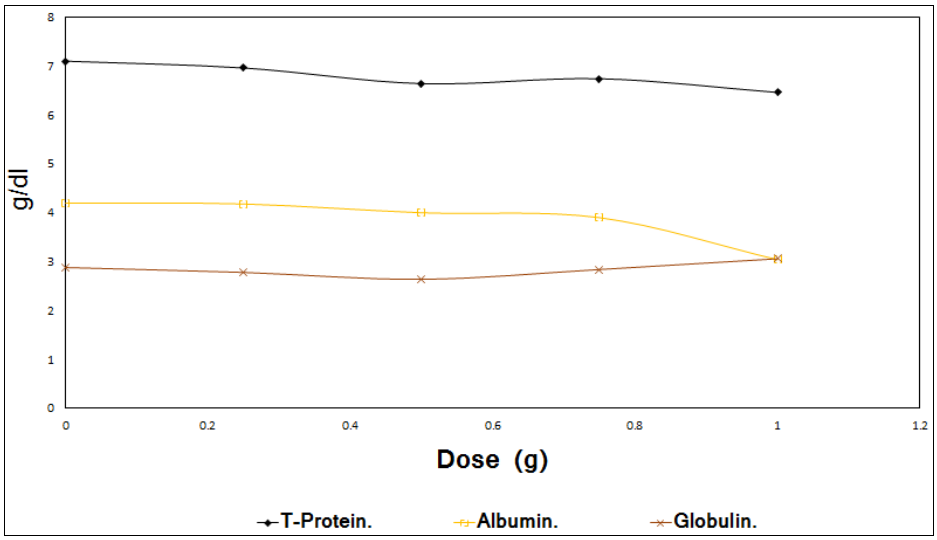

Fig 3: Effect of benzodiazepine doses on T-protein, Albumin and Globulin

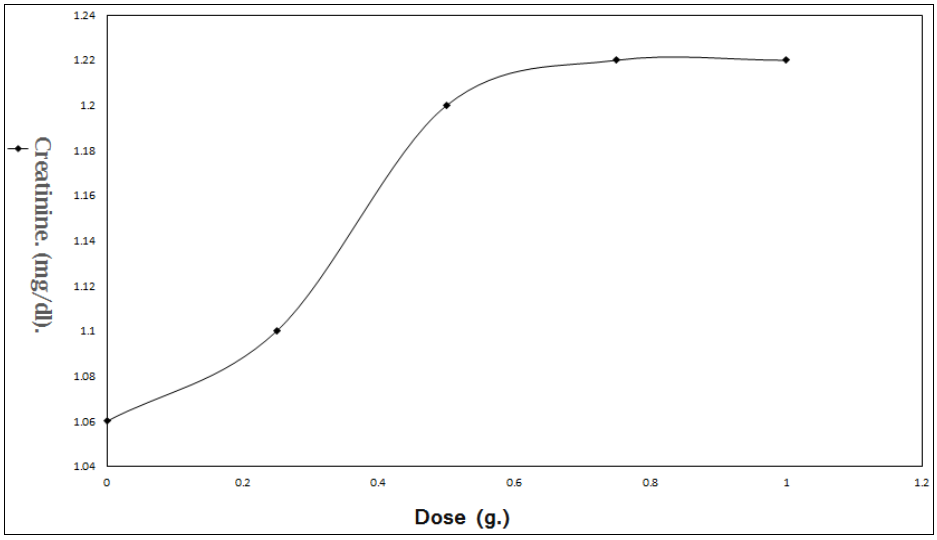

Fig 4: Effect of benzodiazepine doses on Creatinine

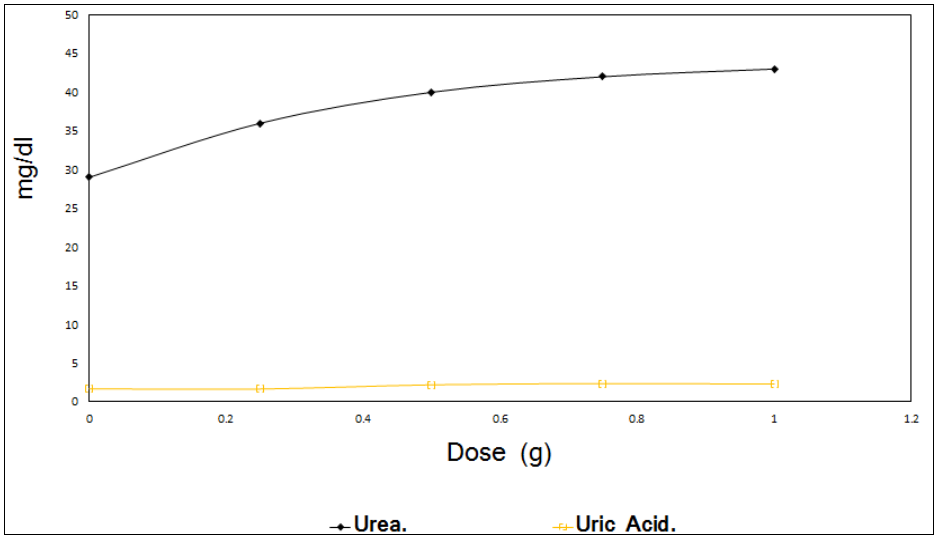

Fig 5: Effect of benzodiazepine doses on Urea and Uric acid

Fig 1 shows effect of diaziapine administration on liver weight, an increase in liver weight was observed in a dose dependent pattern compared with normal control.

Fig 2 and 3 shows effect of diaziapine administration on liver function indices, a significant increase ($P<0.05$) in ALT, AST ALP was observed compared to normal control rats. Although slight variation in other parameters were detected, it is not statistically significant.

Fig 4 and 5 presents the effect of administration on kidney function parameters. A significant increases in serum creatinine and urea level was observed compared to normal control. No significant variation in serum uric acid was detected.

3.2 Discussion

Benzodiazepines drugs are reported to be safe and effective in the short term, although cognitive impairments and paradoxical effects such as aggression or behavioral disinhibition occasionally occur [8]. Long-term use of Benzodiazepines drugs is controversial due to concerns about adverse psychological, Biochemical and physical effects [9]. Some reported symptoms of a benzodiazepine overdose may include; drowsiness, slurred speech, nystagmus, hypotension, ataxia, coma, respiratory depression, and cardiorespiratory arrest [10].

Liver is an important body organ and actively involved in different metabolic functions [11]. Hepatic damage caused by chemicals or infectious agents is associated with distortion of these metabolic functions and may lead to progressive liver fibrosis and ultimately cirrhosis and liver failure. The observed rise in serum activities of ALT, AST and ALP in Benzodiazepines administered groups indicates induction of liver. The enzymes were reported to be higher than normal levels in the blood when there is necrosis of the parenchymal cells of the liver as in viral or toxic hepatitis [12, 13]. This was supported by decrease in the level of albumin. i.e the damaged liver cannot synthesized albumin and thus fall in its level. A possible mechanism for the toxicity may be that at higher concentration the ability of the liver to metabolize and excrete the extract has exceed its threshold thereby leading to damage to the liver probably due to over burden the hepatocytes [14].

Kidneys are the major organs in eliminating toxic compound metabolized by the liver. It receives about 1200 ml of blood per minute containing a lot of chemical compounds [15]. Therefore, damage to the kidneys can be determined by measuring the level of urea, uric acid and creatinine in blood as an indicator of kidney damage. The reported high level of urea and uric acid indicates possible kidney damage as a result of long-term exposure to benzodiazepines.

4. Conclusion

The study reveals that administration of diazepam significantly altered biochemical parameters associated with liver and kidney function. It is therefore recommended to be used it caution under medical attention.

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