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Evaluation of selected parameters of rat liver and kidney function following repeated administration of yohimbine.

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Abstract

The effects of administration of yohimbine, an aphrodisiac on some functional parameters of rat liver and kidney were investigated. White male albino rats weighing between 200-250g were grouped into two such that one group was orally administered with 14mg/kg body weight on daily basis for 15days while the control received an appropriate volume of sterile distilled water on daily basis for the same period. Bilirubin concentration in the test showed a significant decrease ($P<0.01$) when compared with the control, with an interruption of a significant increase only on day 5 of administration ($P<0.01$). Sodium ion concentration showed significant increase only on the first and the last days when compared with the control ($P<0.01$). The serum albumin content and K^+ displayed significant increase throughout the experimental period ($P<0.01$) while serum content of urea and creatinine decreased significantly throughout the period of administration ($P<0.01$). The results suggest that yohimbine administration has adverse affect on the functional capacities of the liver and the kidney.

Key words: Functional parameters, Kidney, Liver, Yohimbine

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INTRODUCTION

There is no known condition more devastating to a man's ego than impotence. It annihilates his very essence of masculinity[1]. Impotence or erectile dysfunction is the persistent inability to achieve or maintain an erection of the male copulatory organ sufficient for the purpose of a satisfactory sexual performance[2]. It is not a disease in itself, but a symptom of an underlying disease in 80% of all occasions[3].The disorder which is age associated is with an estimated prevalence rate of 5% among men 40 years old and 15% among those 70 years old[4].

The complex nature of human sexual response and penile physiology makes erectile dysfunction to have many different causes. Common causes include psychological, endocrine abnormalities, systemic illness, radiation treatment for prostate cancer, side effect of drugs, life style and aging. The mainstay of erectile dysfunction treatment include psychotherapy, diet, testosterone supplementation, intraurethral pellets (MUSE), vacuum device, penile injections, penile implants, surgery, phytotherapy and oral therapy such as viagra, yohimbine[3,5,6,7,8].

Yohimbine is the principal indole alkaloid derived from the bark of the Yohimbe Tree (*Pausinystalia yohimbe* = *Corynanthe yohibi*) (Family, Rubiaceae). It is also found in *Rauwolfia serpentine* and the dried bark of *Aspidosperma quebracho*[9]. The evergreen forest tree is native to southwestern Nigeria, Cameroon, Gabon and the Congo. Yohimbe bark contains up to 6% indole alkaloids, 10-15% of which are yohimbine; also α-yohimbine, *allo*-yohimbine(dihydroyohimbine), yohimbinine, α-yohimbane, yohimbenine and corynatheine[10]. The main alkaloid is yohimbine. It is a monoamine oxidase inhibitor[11]. It is a true aphrodisiac since it increases arousal in sexually inexperienced male rats, facilitates copulation in sexually naïve males and increases sexual activity in males that were previously sexually inactive[5]. It has been used as a possible treatment for organic, psychogenic and substance induced erectile impotence and other male sexual dysfunctions. Its effect on male sexual performance is possibly related to its peripheral autonomic nervous system effects[12]. It increases blood flow to erectile tissues and may increase testosterone levels[13]. Currently, it is assumed that Yohimbine exerts its erectogenic effect through a central action[14]. Side effects include elevated blood pressure and heart rate, irritability, headache and dizziness[14].

Studies have shown the effect of pH and binding of ten physiologically active compounds including yohimbine on the molecular structure of human serum albumin[15], and the effect of clonidine on sodium and potassium excretions after previous administration of prozasin and yohimbine into the ventromedial nucleus of hypothalamus of conscious rats[16], but information on its effect of administration on selected functional indices of rat kidney and liver appears to be scanty. This work is therefore set out to provide information on the effect, if any, of repeated administration of yohimbine at the required therapeutic dose of 14mg/kg body weight on selected functional indices of rat liver and kidney. This was evaluated by monitoring some function tests for the rat liver and kidney.

MATERIALS AND METHODS

Animals and Assay Kits

A total of twenty-five male, white albino rats(*Rattus novergicus*) weighing between 200-250g were obtained from the small Animal Breeding Unit of the Department of Biochemistry, University of Ilorin, Ilorin, Nigeria. Yohimbine was supplied by MLO Product, Fairfield, U.S.A. The albumin and bilirubin assay kits were obtained from Randox Laboratories, Ltd., United Kingdom while the urea and creatinine assay kits were supplied by Quinica Clinica Applicada, S. A., Spain. Other reagents used were of analytical grade and were prepared in all glass-distilled water.

Animal Groupings and Drug Administration.

The rats which had been maintained on normal rat chow and water *ad libitum* were allowed to acclimatize for seven days after which they were randomly grouped into two: (i) Group A- which consisted of 5 rats received orally 1ml sterile distilled water on daily basis. This served as the control. (ii) Group B- which consisted of 20 rats received orally appropriate volume corresponding to the therapeutic dose of 14mg/kg body weight of yohimbine preparation on daily basis. This served as the test group. Five rats each in group A were sacrificed 24hours after 1, 5, 10

and 15 daily doses of yohimbine while the remaining five rats in the control group were sacrificed 24hours after the 15 daily doses of sterile distilled water[17].

Serum Preparation

The rats were anaesthetized using cotton wool soaked in chloroform vapour. When they became unconscious, they were quickly brought out of the jar. The neck area was cleared of fur and skin to expose the jugular veins. These veins were then cut sharply with sterile scapel blade and the rats were held head downwards and allowed to bleed into clean dry corked test tubes, allowed to clot and left for 10mins at room temperature for serum formation[18]. The serum was collected using Pasteur pipette after centrifugation at 3000rpm for 5minutes[19], kept frozen and used for the various liver and kidney function analyses within 12hours of collection.

Determination of Biochemical Parameters

Serum albumin concentration was determined based on its quantitative binding to the indicator 3, 3', 5, 5'-tetrabromo-m-cresol sulphonaphthalein (bromocresol green, BCG) which absorb maximally at 578nm[20] while the method of Evelyn and Malloy[21] was used to determine the serum bilirubin content of the samples. Sodium and potassium ions concentrations in the serum were measured using the flame photometer as described by Bassir[22]. Concentration of creatinine was determined using the method of Tietz *et al*[23] while the method of Kaplan[24] was employed to determine the serum urea concentration.

Statistical analysis

Values obtained were subjected to test of statistical significance using the student's t-test[25].

RESULTS

Tables 1 and 2 depict the effect produced on selected functional indices of rat liver and kidney respectively following the repeated administration of yohimbine. Yohimbine administration resulted in an initial significant decrease in serum content of bilirubin ($P<0.01$) and by the fifth day, the concentration has increased significantly when compared with the control ($P<0.01$) (Table 1). The bilirubin concentration compared favourably with the control by the tenth day of administration, a trend which was not sustained beyond that day as there was significant reduction in bilirubin concentration of about half the control value ($P<0.01$) (Table I). The serum albumin concentration displayed a general pattern of significant increase right from the start of the drug administration and was sustained throughout the experimental period ($P<0.01$) (Table I).

There was an initial significant increase in Na^+ concentration ($P<0.01$) which was not sustained beyond the first day as the values thereafter compared favourably with the control ($P>0.01$). This was thereafter followed by another significant increase in Na^+ concentration by the end of drug administration ($P<0.01$) (Table II). In contrast, K^+ concentration increased significantly right from the start of drug administration and this trend was sustained throughout the experimental period ($P<0.01$). Compared with the control, yohimbine administration produced significant reduction in the serum concentration of urea and creatinine throughout the experimental period ($P<0.01$), with the reduction being about half the control value in the urea and creatinine concentration by the end of drug administration ($P<0.01$).

DISCUSSION

The biochemical indices evaluated in this study are useful parameters to indicate impairment in functional capacities of the organs. However, there is no single test for measuring liver function, because all the functions of the liver are not equally or simultaneously affected in hepatobillary disorder. Consequently, a battery of tests assessing a variety of hepatic functions has to be simultaneously performed. The concentration of the proteins, bilirubin and albumin in the serum can indicate the state of the liver and can be used to ascertain different types of liver damage.

The non-definite pattern of serum bilirubin concentration observed in the first five days of administration (Table 1) may be attributed to various attempts by the tissue to adapt to the effect of the drug[17,26], which was eventually achieved by the tenth day of administration (Table 1). Further attempt at complete adaptation to the adverse effect of yohimbine failed, leading to reduction in concentration of half its control value by the end of administration (Table 1). Consequently, the

Table 1: Effect of daily administration of yohimbine (14mg/kg body weight) on some rat liver function parameters

Days after Administration	Albumin (g/L)	Total Bilirubin (umol/L)
Control	19.00±0.71	7.20±0.07
1	24.40±1.14**	5.40±0.86**
5	26.00±1.00**	10.30±1.50**
10	23.00±1.00**	6.56±2.75*
15	25.00±0.71**	3.90±0.07**

*Statistical significance were tested using Student's t-test; compared with control values, *p>0.01; **p<0.01, ±SD, n=5.*

Table 2: Effect of daily administration of yohimbine (14mg/kg body weight) on some rat kidney function parameters

Days after Administration	Na^+ (mmol/L)	K^+ (mmol/L)	Creatinine (mmol/L)	Urea (mmol/L)
Control	122.00±0.71	5.30±0.07	330.00±0.71	18.30±0.07
1	148.00±2.00**	5.84±0.38**	232.00±12.21**	13.16±0.71**
5	119.00±5.00*	11.38±2.57**	226.00±17.29**	12.62±0.95**
10	127.00±7.00*	8.70±0.60**	200.00±20.00**	11.24±0.95**
15	128.00±0.71**	6.56±0.09**	187.00±0.71**	10.40±0.07**

*Statistical significance were tested using Student's t-test; compared with control values, *p>0.01; **p<0.01, ±SD, n=5*

hypobilirubinemia is an indication of impairment of the tissue's functional capacity as extensive liver damage may lead to decrease serum levels of bilirubin[27].

Liver is the exclusive site of synthesis of albumin. The observed hyperalbuminemia (Table 1), although, a rare occurrence could be attributed to severe dehydration[28]. It may also be adduced to increased rate of hepatic synthesis of albumin without a proportionate increase in the rate of its catabolism. Consequently, the amino acid pool will no longer be maintained within normal limits. The hyperalbuminemia may adversely affect the transportation of a wide variety of ligands to the organs and tissues for their utilization or excretion. It may also lead to hyper-osmotic pressure[28]. The observed hyperalbimnemia throughout the drug administration may be an indication that the increase in albumin synthesis is dependent only upon initial drug administration and not the duration.

The functional capacity of the kidney can be measured by the dye excretion tests, clearance test, concentration and dilution tests and method for examination of blood concentrations of excretory and electrolyte constituents. Furthermore, renal function tests are required either to demonstrate the presence or absence of active lesion in the kidney, or to assess the normal functioning capacity of different parts of the functioning unit, nephron[29]. Inorganic

electrolytes occur in large quantities in both extracellular and intracellular fluids. Due to their ability to dissociate readily into their constituent ions or radicals, they comprise the single most important factor in the transfer and movement of water and electrolytes between three divisions of the extracellular and intracellular compartment[30]. The initial profile of serum Na^+ concentration (Table 2) may be adduced to attempt at counteracting the effect of the drug[26]. By the end of the experimental period, the functional capacity was compromised by the nephron with significant increase in Na^+ concentration (Table 2), probably resulting from excessive loss of Na^+ pool body fluids. It may also be due to either increase production of aldosterone and other mineralcorticoids which will in turn increase the tubular reabsorption of Na^+ or decreased production of either antidiuretic hormone or decreased tubular sensitivity to the hormone[23]. Hypernatraemia could in a way serve as an indicator of liver disease[31]. Potassium ions play an important role in the way in which nerve impulses are propagated along the nerve cells and transmitted to receptor cells. The sodium pump maintains the intracellular K^+ concentration of 140mM as against the extracellular K^+ concentration of 5mM[32]. The hyperkalaemia observed in the first ten days of administration (Table 2) suggests a possible adverse effect on the pump that maintains the constancy of its extracellular concentration. Hyperkalaemia is a more dangerous condition because of its effect on the heart, but it rarely occurs unless renal function is depressed. It may result in the paralysis of the atria and ventricular arrhythmias may develop. The muscle fibres may eventually become unexcitable, and the heart stops in diastole[33]. However, the no significant difference from the control value by the end of drug administration may be that the system has successfully combated the adverse effect of yohimbine, an indication that it may be of low toxicity to the monovalent ion.

Urea is the major nitrogen-containing metabolic product of protein catabolism. The significant reduction in serum urea concentration throughout the experimental period may be attributed to impairment of the urea cycle leading to reduced production of the metabolic product. Since biosynthesis of urea could be divided into four stages of transamination, oxidative deamination of glutamate, ammonia transport and reactions of the urea cycle[34] and since it has been evaluated by this same set of authors that yohimbine administration resulted in reduction in serum transaminases (Glutamate oxaloacetate transaminase and Glutamate pyruvate transaminase), it seems logical that the aphrodisiac may be affecting the transamination stage of the urea cycle. This is an indication of abnormality in the physiological excretion of urea caused by a non-renal factor[35]. Consequently, since urea synthesis converts toxic ammonia to non toxic urea, defects in urea synthesis as observed in this study (Table 2) may result in ammonia intoxication.

The significant reduction in creatinine, another product of protein metabolism from the start of drug administration to half the control value by the end of drug administration may be an indication of compromise of the renal function. Yohimbine might have adversely interfered with the metabolism of creatinine leading to its observed reduction, an indication of partial loss of its functional capacity of tubular excretion[30].

The various alterations in the functional indices of the tissues and their values which do not compare favourably with their control values are clear manifestation of adverse effects of the functional parameters evaluated following the daily administration of the aphrodisiac. This study suggests that repeated administration of yohimbine has some deleterious effect on the basic functions of the liver and kidney investigated.

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