



HEPATORENAL-TOXICITY EVALUATION OF ATIKPA®: A COMMERCIAL POLYHERBAL POISON ANTIDOTE IN NIGERIA

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ABSTRACT

The consuming public considers herbal medicines safe and uses them without caution. Atikpa® is a popular herbal preparation used traditionally as a purgative in the treatment of ingested poisons. This work used animal models to investigate the safety of Atikpa® on the kidney and liver. The preparation was dispersed in 2 % crystalline methylcellulose and administered to albino rats at doses of 100, 125 and 150 mg/kg. The mean body weight, food and water intake and gross behavior of the animals as well as some biochemical indices of liver and kidney toxicity were monitored. The results of the study showed that the herbal preparation did not significantly [$P > 0.05$] increase mean body weight. Differences in food and water intake between the treated and control animals were not dose-dependent. Acute toxicity study showed that the herbal preparation is moderately toxic [$LD_{50} = 224.9$ mg/kg]. Biochemical findings also revealed that the preparation induced a dose-related elevation of liver enzymes, SGPT and SGOT. The elevation was significant [$P < 0.001$] at 150 mg/kg. There was also a significant [$P < 0.05$] increase in serum urea level at 150 mg/kg. These results indicate a hepatic and renal toxic potential of Atikpa® when used for treatment of health subjects. This study highlights the need for pre-clinical toxicity assessment as well as post-marketing surveillance of the numerous herbal preparations used in our ethno medicine.

KEYWORDS- Atikpa®, Hepatic toxicity, Polyherbal medicine, Renal toxicity

INTRODUCTION

Herbal medicines are commonly considered safe and free from toxicity [1, 2]. The World Health Organization defines herbal medicines to include herbs, herbal materials, herbal preparations and finished herbal products that contain as active ingredients parts of plants, or other plant materials,

or combinations [3]. A number of herbal products are considered food or food supplements. Although some of these herbal products are registered or "listed" with government regulatory agencies, most of them have not been subjected to pre-clinical and clinical safety and testings. Toxicity issues

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associated with conventional drugs could also contribute to the renewed interest in herbal medicine. A number of patients seek help in alternative natural treatments, believing them to possess little or no side effects. Consequently, herbal medications continue to gain more attention from those who may have been disappointed by orthodox medicines [1, 4]. Herbal medicines have been established to be toxic [5-7]. There may be need for pre- and post-marketing toxicity testing of these products to ensure their safety.

Atikpa® is a popular herbal preparation marketed in Nigeria, which can be procured from State Herbal Medical Boards. It is indicated for the treatment of poison. It is composed of plant materials from *Fagara zanthoxyloides*, *Rauwolfia vomitoria* leaves, *Olox subscorpiodea* and also claimed to contain slices of flesh of dried vulture, cock and tortoise. Atikpa® is usually mixed or suspended in coconut oil and about 30 ml is administered twice daily for up to 5 days to induce vomiting and "defecation of poison". Although the product is patronized by many, there are no previous reports or data on the safety or efficacy of this product.

In this preliminary study, we set out to investigate the toxic potential of Atikpa® on the liver and kidney.

MATERIALS AND METHODS

Source of herbal preparation

The herbal preparation under study was obtained from Enugu State Herbal Medical Board, Enugu State, Nigeria.

Preparation of test material

The test sample was prepared by suspending the powdered drug mixture in 2 % crystalline methylcellulose in water.

Study animals

Albino mice (15-25 g) were used for acute toxicity test and Wistar rats (110 – 160 g) were used for the hepato-renal toxicity screening. Mice and rats of both sexes were obtained from the animal house of the Department of Pharmacology and Toxicology, University of Nigeria, Nsukka. The animals were housed in standard laboratory conditions and fed with rodent feed (Guinea Feed Nigeria Ltd), and allowed free access to water.

All procedures concerning animal treatments and experimentations in this study were reviewed and approved by the local Ethics Committee at University of Nigeria.

Acute toxicity test

Doses of 75, 150, 300, 600 and 900 mg/kg were administered to 5 groups of mice (n=4) respectively. Percentage death was recorded and converted to probit values. From the regression equation of the plot of probit versus log dose, the LD50 was calculated [8].

Administration of test drug

A total of 16 rats were used for this part of the study. The animals were divided into 4 groups (n=4). Groups I, II and III were injected daily intra peritoneal 100, 125 and 150 mg/kg respectively of the herbal preparation suspended in 2 % crystalline methylcellulose for 8 days. Group IV was injected daily intra peritoneal 0.2 ml of 2 % crystalline methylcellulose in water for 8 days. The animals were observed for death and any overt toxicity throughout the period of the study.

Food and water intake

The body weights, as well as the quantity of food and water consumed over the 8-day period of study were determined. An amount of food and water in excess of the need of the animal was provided. After 24 h the amount of food or water left unconsumed were determined. The difference from the initial amount was taken as approximately the food or water intake.

Biochemical and histological evaluation

Sample collection: Blood was collected into heparinized test tubes at the end of the study. The blood was centrifuged at 3000 rpm for 10 min and the plasma used for the biochemical evaluations. Determination of some biochemical parameters Serum urea, serum glutamine oxaloacetate transferase (SGOT) and serum glutamine pyruvate transferase (SGPT) were determined. SGOT and SGPT were determined using Kone-Pro device and Bio-Merieux reagents.

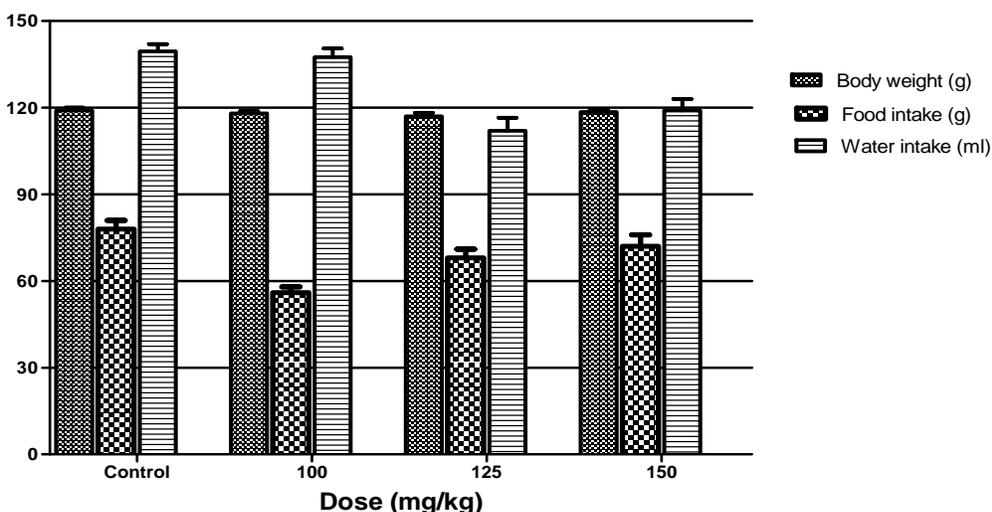


Figure 1: The effect of herbal product, Atikpa® on body weight, food and water intake. The figure shows a dose-dependent variation in the food and water intake. However, there were no significant differences between the body weights of the control and treated groups

Statistical Analysis

Data obtained were analyzed by SPSS version 11 using one way ANOVA and subjected to Fischer LSD post hoc tests and expressed as mean \pm SEM. Differences between means were considered significant at $P < 0.05$.

RESULTS

The LD50 was found to be 224.9 mg/kg (Table 1). No change in behavior or of overt toxicity in the animals was observed in the 8-day period.

There were dose-dependent variations in the food and water intake. While the food intake increased with increasing dose of the herbal formula, the water intake decreased with increasing doses of the same. At the end of the study, there were no significant differences between the body weights of the control and treated groups (Figure 1).

The herbal preparation elevated the serum urea, SGOT and SGPT as the dose administered increased (Figure 2). However, at 150 mg/kg dose, there was a drop in the values of the above parameters below those of the control group.

Discussion

Irrespective of the public opinion that herbal medicines are safe, previous studies have demonstrated that herbal medicine can be toxic [9, 10]. Several herbs have been reported to be hepatotoxic [11] and nephrotoxic [12-14].

Our study showed that Atikpa® elevated SGPT and SGOT, which are intracellular enzymes that leak from the cytoplasm of liver cells into the blood stream in response to injury. The extent of leakage is usually considered to be equivalent to the extent of damage to the cell [15, 16]. Although the herbal preparation under this study did not show elevation of liver enzymes above the normal range, the observed dose – dependent increase in liver enzymes found in treated rats is an indication that prolonged use especially at high doses may result in hepatotoxicity. Excretion of increasing levels of nitrogen – based waste products like urea is one of the cardinal signs of nephrotoxicity [17]. The elevation of serum creatinine and serum urea by Atikpa® could be due to accumulation of toxic components in the kidney.

It may not be easy to identify the exact compounds responsible for the observed toxicity. A single herbal medicine usually contains a variety of pharmacologically active ingredients that act through several mechanisms. The number of these

ingredients increases when the herbal formula contains more than one herb or herbal extracts. It thus becomes difficult to associate the observed toxicity to a particular chemical entity. Most naturally occurring purgatives that are safe and gentle for general use contain anthraquinones [18]. Cases of rare hepatic inflammation, possibly induced by anthraquinone derivatives have been reported and may be dose – related [19, 20]. Some stimulant laxatives, which contain anthraquinones e.g. Senna and Cascara sagrada have been associated with liver reaction [19, 21]. Our preliminary phytochemical

investigation of the herbal preparation, however, did not show the presence of anthraquinones but rather increased amounts of alkaloids. Alkaloids, particularly, pyrrolizidine alkaloids have been associated with the hepatic effects of most herbs observed in experimental animals [22-25].

However, whether the alkaloids found are responsible for the observed elevation of liver enzymes or not need to be investigated further. Degradation of protein materials present in the herbal medicine could generate amines and ammonia, which may further complicate the hepatic impairment [26].

Table 1: Results of the LD50 determination of the herbal preparation

Treatment [mg/kg]	No of animals	No of deaths	Percent death	Log Dose	Probit
75	4	0	0	1.875	0
150	4	1	25	2.176	2.5
300	4	3	75	2.477	7.5
600	4	4	100	2.778	10
900	4	4	100	2.954	10

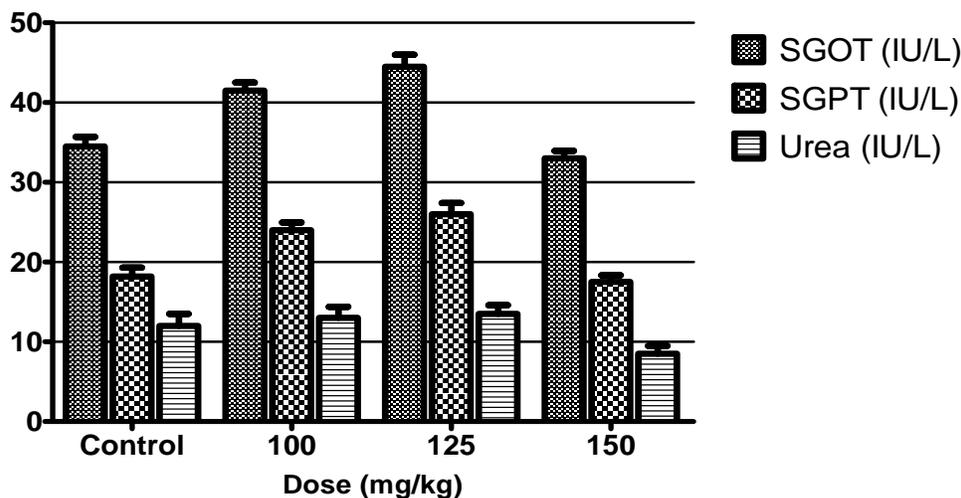


Figure 2: The effect of herbal product, Atikpa® on SGOT, SGPT, and serum urea. Fig. 2 shows that the herbal preparation elevated the serum urea, SGOT and SGPT as the dose of the administered herb increased

CONCLUSION

Our results show that Atikpa® may be toxic to the liver and kidney. This study, thus, highlights the need for both pre-clinical toxicity assessments and post-marketing surveillance of the numerous herbal preparations found in our drug market.

DISCLOSURE STATEMENT

The authors have no conflict of interest to declare

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