Alterations In Biochemical Parameters Of Wister Rats Administered With Sulfadoxine And Pyrimethamine (Fansidar®)

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Abstract: Sulfadoxine and pyrimethamine (Fansidar®) is commonly prescribed for the treatment of malaria in Owerri, Imo State Nigeria. This study examined the biochemical effect of Fansidar on the hepatic and renal function of wistar rats. Different concentrations of Fansidar® (50, 100 and 150mg/kg body weight) were administered to three groups of six wistar rats per group for 14 days. The fourth group of another six wistar rats received distilled water which served as control. Results showed that the Fansidar® treated groups exhibited a significant increase in mean serum urea and creatinine levels when compared with the control group. This study also revealed that the administration of Fansidar® caused pronounced increase in serum aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase as well as bilirubin levels. This study suggests that acute administration of Fansidar may probably affect both renal and hepatic function in humans.

Keywords: Fansidar®, hepatic function, renal function, malaria

Introduction

Fansidar® is an antimalaria agent each tablet contains 500mg sulfadoxine and 25mg pyrimethamine [1]. The drug combination Fansidar® (sulfadoxine-phyrinmethamine) acts synergistically by sequential blockade of two enzymes involved in the biosynthesis of folinic acid in the parasites [2]. A single dose therapy eliminates trophozoites and schizonts from the blood. According to world health organization (WHO) Fansidar is used for the prophylaxis or treatment of chloroquine resistant plasmodium facipharum [3]. The clinical treatment with Fansidar® is often accompanied by serious side effect such as allergic reactions including skin eruptions, toxic epidermal necrolysis, vriticaria, serum sickness, pruritus, and allergic myocardiatis that could be fatal [1]. Nosten et al [4] reported an increasing number of serious complication of antimalaria drug. This has raised some doubt about the safety of Fansidar®. In the same vein, serious concern has been raised concerning the uncontrolled use of these drugs in Owerri, Imo State Nigeria, as they are one of the most common and cheap drugs to combat malaria with. However, the use of this drug should be controlled and restricted to proven multi drug resistance on severe malaria in order to preserve their efficacy [5]. In this part of the world, Owerri, Imo State Nigeria in which malaria is highly endemic, self medication is highly common
and purchase of antimalaria tablets in the open market is rampant and cannot be controlled. Hence, the possibility of administering overdose and misuses of this antimalaria drug are very common. It has been revealed that drugs that are effective in malaria treatment can cause damage to some organs of the body [6]. It is necessary for drugs to be avoided and only to be safely administered when necessary. However, not much investigations have been documented on the effect of Fansidar® on liver and kidney as they are important organs of metabolism and excretion of drugs. Therefore, this study was carried out on the biochemical parameters of liver and kidney on wistar rats administered with Fansidar®.

Materials and Methods

The drug: Fansidar® (Swipha) were purchased from a standard pharmacy shop in Owerri, Imo State Nigeria. The tablets were dissolved in distilled water according to the required concentrations required for administration to the Wister rats on the basis of their body weight.

Experimental Animals: The Wister albino rats weighing between 150 and 220g, ages (8-10weeks) were used in the study. These animals were obtained from the Animal House of College of Medicine and Health Sciences, Imo State University, Owerri Nigeria. They were kept under standard laboratory conditions, fed with commercial growers mash, product of Tops Feeds Ltd, Sapele, Nigeria. Water and feed were provided ad libitum. The animals were left for two weeks to acclimatize and then divided into groups for experimentation.

Experimental Design: The animals were randomly assigned to four experimental groups (n = 6 x 4 group). The fourth group of animals which served as control were given distilled water. Group I, II, and III were given 50mg/kg, 100mg/kg and 150mg/kg body weight for 14days. In all groups the drug was administered through oral route using a feeding tube attached to a 5ml syringe. All animals were allowed free access to food and water throughout the experiment.

Blood Collection: Twenty four hours after the last doses were administered, the animals were anaesthetized with chloroform vapor, quickly brought out of the jar and sacrificed. Whole blood was collected by cardiac puncture from each animal into clean dry test tubes. The blood were allowed to stand for about 15minutes to clot and further spun in a Westerfuge centrifuge (model1384) at 10,000g for 5minutes. Serum was separated from the clot with Pasteur pipette into sterile sample tubes for the measurement of the biochemical parameters.

Biochemical Analysis: The serum bilirubin was determined by the method of Jendrassic and Groff method [7]. Serum AST and ALT were assayed by the method of Reitman and Frankel [8]. ALP was determined by the method of king and king [9]. Also, serum urea and creatinine were determined by the method of Urease Berthlot and Jaffe alkaline picrate method [10].

Statistical analysis: The results were expressed as mean ± standard deviation. The statistical evaluation of data was performed by using one-way ANOVA (Analysis of variance) followed by Duncan’s multiple range test [11].
Results

Table 1: Mean values of serum Bilirubin, AST, ALT, urea and creatinine levels in experimental and control groups.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Control</th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilirubin(µmmol/l)</td>
<td>4.16±1.3</td>
<td>6.37±2.6</td>
<td>7.2±4.3</td>
<td>7.5±6.4</td>
</tr>
<tr>
<td>AST(iu/l)</td>
<td>15.28±1.7</td>
<td>19.20±2.0</td>
<td>24.11±2.6</td>
<td>29.82±3.9</td>
</tr>
<tr>
<td>ALT(iu/l)</td>
<td>11.71±2.4</td>
<td>16.51±2.8</td>
<td>19.83±2.5</td>
<td>23.60±2.7</td>
</tr>
<tr>
<td>ALP(iu/l)</td>
<td>62.11±5.1</td>
<td>84.66±5.9</td>
<td>89.15±5.3</td>
<td>96.11±5.5</td>
</tr>
<tr>
<td>Urea(mmo/l)</td>
<td>3.33±0.50</td>
<td>4.12±0.58</td>
<td>5.0±0.62</td>
<td>7.32±0.76</td>
</tr>
<tr>
<td>Creatinine(µmmol/l)</td>
<td>61.28±2.9</td>
<td>68.49±3.2</td>
<td>90.26±6.4</td>
<td>104.10±6.9</td>
</tr>
</tbody>
</table>

The changes in the mean value of serum bilirubin and liver enzymes as well as urea and creatinine levels in all the groups are shown in Table I. There was a significant increase in the levels of bilirubin concentration, AST, ALT and ALP activities in Fansidar treated groups when compared with control (P < 0.05). Also serum urea and creatinine were significantly elevated in all the Fansidar treated groups when compared with the control. Two animals died in the 150mg/kg dose group while no death was recorded in 50mg/kg and 100mg/kg Fansidar treated groups.

Discussion

The serum bilirubin, AST, ALT and ALP are the most sensitive biochemical markers employed in the diagnosis of hepatic dysfunction. While urea and creatinine are important biochemical parameters for the diagnosis of renal impairment [12-13]. The results obtained from this study showed that Fansidar might have harmful effects on the liver and kidney of wistar rats. It has been observed that liver enzymes are usually elevated in acute hepatic toxicity but tend to decrease with prolong intoxication due to damages to the liver cells [14]. The increase activities of bilirubin concentration, AST, ALT and ALP in serum levels of wistar rats observed in this study indicates Fansidar induced liver impairment. This was confirmed by an earlier study of Nwanjo et al [15] in which hepatic markers were reportedly elevated. Other antimalaria halofantrine and chloroquine are also reported to induce liver damages [16-17]. The current investigations could probably suggest impairment of the liver cells of the wistar rats. The findings in this study agree with the work of Adams et al [18] and Price [19]. The liver cell damage may be associated with the generation of free radicals by Fansidar which are also partly responsible for their anti-malarial effects. Therefore, the harmful effects were considered to be caused by free radicals produced during peroxide formation. The level of hydroxyl and peroxide radicals induced by Fansidar treatment may be responsible for the hepatic impairment in wistar rats. Voznessensky and Schenkenman [20] reported that antimalaria pretreatment enhances the levels of Nicotinamide Adenine Diphosphate (NADPH) Cytochrome C reductase and cytochrome Gs, both enzymes being involved in the metabolism of endogenous and exogenous compounds. Therefore, the enhancement of these 2 enzymes system will lead to accumulation of free radicals oxygen species since these enzymes have been shown to generate superoxide radicals [21].
This may partially explain the elevated bilirubin in wistar rats manifested in the Fansidar induced hepatic impairment. Furthermore, it was observed from the study that administration of Fansidar caused a pronounced increase in serum urea and creatinine levels when compared with the control. This was in agreement with the work of Orjiako and Nwanjo [22] in which administration of drugs that inhibit prostaglandin synthesis like paracetamol, ibuprofen exacerbate renal failure. Colletti, et al [23] reported that in people with decreased blood volume or circulation problems, the kidney depends on the dilating effect of prostaglandins on renal blood vessels for maintenance of renal blood flow. However, when prostaglandin synthesis is inhibited at this stage, a problem results. In conclusion, these observations in wistar rats may be applicable to humans. It is hence suggested that the drug Fansidar be prescribed with caution in patients with hepatic and renal impairment; and even to the general populace especially as the drug is highly consumed by malaria patients as a second line drug after administration of the artemisinin combination therapy (ACTS) which have a very high recrudescence rate in our locality. Fansidar and its other brands are among the most common antimalaria drugs in Owerri Nigerian markets; hence, self medication associated with Fansidar should be discouraged as this may lead to overdose.

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