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Research Article

Risk Assessment of Co-treatment with Rifampicin and Tenofovir on Renal Function Indices of Albino Rats

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Background: Tuberculosis is one of the comorbid infections commonly associated with human immunodeficiency virus which could necessitate the concurrent use of tenofovir and rifampicin (TDF-RIF). These drugs are individually associated with renal toxicity; hence concurrent use might be detrimental to renal function.

Objectives: This study, comparatively evaluated the toxicological effects of treatments with tenofovir, rifampicin and tenofovir- rifampicin combination on renal function of male albino rats.

Materials and Methods: Healthy adult male albino rats used for this study were divided into five (5) groups of sixteen animals (16) each. Animals in group A (placebo control) and group B (solvent control) were treated orally with water and arachis oil respectively. Animals in groups C-E were treated orally with 80mg/kg of rifampicin, 32 mg/kg of tenofovir and tenofovir-rifampicin combination for 1-8 weeks respectively. Animals were weighed and sacrificed at the end of drug treatment, blood samples were collected, centrifuged and serum extracted for creatinine, urea, uric acid, albumin, total protein and glucose evaluation. Animals were dissected kidneys were collected and weights determined.

Results: Treatment with tenofovir-rifampicin combination did not produce significant (p>0.05) effects on body and relative kidney weights, albumin, total protein and glucose levels when compared to their individual doses. Furthermore, insignificant (p>0.05) and time-dependent increases in serum creatinine, urea and uric acid levels were obtained in animals treated with combined doses of TDF-RIF when compared to their individual doses.

Conclusion: These results showed that concurrent use of tenofovir and rifampicin in the management of human immunodeficiency virus and tuberculosis co-infection may not be associated with synergistic renal toxicity at the dose levels used.

Keywords: Renal, Toxicity, Co- treatment, Tenofovir, Rifampicin, Rats

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1. Introduction

Tenofovir is an acyclic nucleotide phosphonate diester analog of adenosine monophosphate. Similar to many Nucleoside Reverse Transcriptase Inhibitors (NRTIs) tenofovir inhibits HIV-1 reverse transcriptase by competing with the natural substrate deoxyadenosine 5′-triphosphate, which is part of the nucleotide pools used by virus in generating cDNA (Lyseng-Williamson et al, 2005; Vivet-Boudou et al, 2006). It is an orally bioavailable prodrug that is widely prescribed due to its potency, convenient dosing, and a favorable safety and tolerability profile. It was approved for use in adults and adolescents as preferred first-line nucleotide reverse transcriptase inhibitors in combination with other antiretroviral drugs for the management of Human Immunodeficiency Virus (HIV) infection (WHO, 2012). When administered, tenofovir is eliminated by active tubular secretion and glomerular filtration with predominant accumulation in proximal renal tubular

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cells (Sax et al, 2011). The use of tenofovir could be associated with proximal tubular dysfunction with or without decreased renal function. Renal impairments, characterized by acute renal failure, interstitial nephritis and Fanconi's syndrome, have been reported with the use of tenofovir in humans and animals (Viread, 2006; Adikwu et al, 2013). In addition alterations in kidney architecture characterized by proximal tubular necrosis, chronic tubulointerstitial scarring, and ultrastructural mitochondrial abnormalities could occur with the use of tenofovir (Kohler et al, 2009; Parazella et al, 2010; Herlitz et al,2010).

Rifampin is a large lipid soluble semisynthetic macrocyclic antibiotic produced from *Streptomyces mediterranei*. It is a first-line drug mostly used in combination with isoniazid, ethambutol and pyrazinamide in the treatment of all forms of tuberculosis caused by organisms with known or presumed sensitivity to the drug. It has activity against organisms that are dividing rapidly (early bactericidal activity) and against semidormant bacterial populations, thus accounting for its sterilizing activity. It acts by binding to β subunit of bacterial DNA-dependent RNA polymerase in prokaryotic, but not in eukaryotic cells thereby inhibiting RNA synthesis (Geo et al, 2010; Peters and Chike, 2013). Rifampicin is said to be safe, but it has been associated with adverse reactions such as nephrotoxicity sometimes resulting in acute renal failure (Jover-Saenz et al, 2006). Also, deterioration in renal function, associated with acute tubulointerstitial nephritis and/or acute tubular necrosis, typically appears in patients receiving intermittent rifampicin therapy. In addition, some authors have reported cases occurring during continuous rifampicin therapy (Warner, 1975; Salih et al, 2008; Aminiafshar et al, 2009; Min et al, 2013).

Despite the fact that rifampicin and tenofovir are individually associated with renal toxicity these drugs are usually co-administered in the management of human immunodeficiency virus/ tuberculosis co-infection (Pozniak et al, 2011). The direct exposure of the kidney to co-administered TDF-RIF could be associated with overlapping renal toxicity that may alter the anatomical structure of the kidney thereby impairing its physiological functions. The kidney is an essential organ required for several important functions including the maintenance of homeostasis, detoxification, and excretion of toxic metabolites and drugs (Ferguson et al, 2008). This makes the kidney to be frequently subjected to high concentrations of potentially toxic drugs and their metabolites especially with concurrent use of medications which could lead to a variety of nephrotoxic effects (Aronson, 2003; Asangansi et al, 2005). Therefore, this study was designed to investigate the effect of co-treatment with tenofovir- rifampicin on renal function of adult male albino rats.

2. Materials and Methods

2.1 Drugs

Rifampicin used for this study was manufactured by Mancare Pharmaceuticals, India while pure sample of tenofovir disoproxil fumarate was purchased from Shijiazhuang Aopharm Import & Export Trading Co., Ltd. Shijiazhuang, China. All other chemicals used for this study were of analytical grade. The doses of rifampicin and tenofovir disoproxil fumarate used for this study are 80mg/kg and 32 mg/kg respectively (CDC, 2003; Viread, 2013). Rifampicin was dissolve in water while tenofovir powder was suspended in arachis oil (Adikwu et al, 2015).

2.2 Animals

Eighty (80) adult male albino rats of average weight 330 ±5 g were used for this study. The animals were obtained from the animal house of the Department of Pharmacology and Toxicology, Madonna University, Elele, Rivers State. The animals were allowed to acclimatize for 14 days and had free access to food and water *ad libitum*.

2.3 Experimental Design

Animals were group into five groups A- E of 16 animals per group. Animals in each group were further sub divided into four groups of four animals each. Animals in group **A** (placebo control) were treated with water, while animals in group **B** (solvent control) were treated with arachis oil. Animals in groups **C-E** were treated with 80 mg/kg of RIF, 32 mg/kg of TDF and a combination of TDF- RIF orally for 1-8 weeks respectively.

2.4 Collection of Sample for Analysis

At 1, 2, 4 and 8 weeks, after overnight fast, 2mls of blood samples were collected from the rats by cardiac puncture under diethyl ether anesthesia. The blood was collected and transferred into a non- heparinized sterile sample container and allowed to clot; serum was then separated by centrifugation at 1200 rmp for 15 min and used for the evaluation of renal function parameters.

2.5 Evaluation of Serum Renal Function Parameters

Serum urea, uric acid and creatinine levels were determined as described by Prabu et al, 2010. Total protein and albumin were evaluated as reported by Ogbuehi et al, 2014. Blood glucose level was evaluated with the aid of one touch basic meter (lifescan, Inc., 2001 Milpitas, CA 95035, USA) (Tende et al, 2011)

2.6 Determination of Relative Kidney Weight

At sacrifice, the weights of the kidneys were determined using a top loader sensitive balance (Mettler Toledo, Germany) and the relative organ weight (%) was calculated from the body weight at sacrifice and the absolute weight of the kidney as follows:

$$\text{Rel. Organ Weight} = \frac{\text{Absolute organ weight (g)}}{\text{Body weight at sacrifice (g)}} \times 100$$

2.7 Statistical Analysis

Data are expressed as mean values ± SEM. Analysis of data was performed with one-way analysis of variance (ANOVA). Statistical significance was set at $p < 0.05$.

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2.8 Ethical Considerations

All animals used for this study were handled in accordance with the international, national and institutional guidelines for care and use of laboratory animals in biomedical research as promulgated by the Canadian Council of Animal Care (2009).

3. Results

Animals treated with TDF, RIF and a combination of TDF and RIF did not show significant (p>0.05) changes in body and relative kidney weights, serum albumin, total protein and glucose levels when compared to the control (**Table 1**).

Table 1: Effects of tenofovir and rifampicin on body, relative kidney weights, serum total protein, albumin and glucose levels of albino rats

Drug	WK1	WK2	WK4	WK8
Body weight (g)				
Control	330±7.10	337±6.15	345±4.41	376±7.26
TDF 80mg/kg	325±5.00	333±8.20	341±6.05	361±9.10
RIF 32mg/kg	330 ±8.21	335±7.50	347±8.00	364±5.52
TDF/RIF	327±8.11	330±6.35	345±7.27	358±6.48
Relative kidney weight (%)				
Control	0.20±0.07	0.22±0.05	0.19±0.02	0.17±0.03
TDF 80mg/kg	0.22±0.04	0.19±0.03	0.20±0.07	0.19±0.05
RIF 32mg/kg	0.22±0.03	0.20±0.06	0.23±0.01	0.18±0.09
TDF/RIF	0.23±0.07	0.25±0.01	0.21±0.04	0.22±0.06
Serum Albumin (g/dL)				
Control	3.31±003	3.23±0.11	3.30±0.06	3.45±0.02
TDF 80mg/kg	3.34±0.03	3.30±0.01	3.28±0.05	3.47±0.07
RIF 32mg/kg	3.30±0.01	3.31±0.04	3.29±0.06	3.41±0.05
TDF/RIF	3.28±0.06	3.35±0.02	3.30±0.03	3.43±0.02
Serum total protein (g/dL)				
Control	6.41±0.07	6.53±0.03	6.50±0.06	6.51±0.02
TDF 80mg/kg	6.39±0.05	6.55 ±0.02	6.45±0.01	6.43±0.04
RIF 32mg/kg	6.35±0.09	6.57±0.04	1.42±0.07	6.54±0.02
TDF/RIF	6.32±0.01	6.65±0.08	6.58±0.03	6.59±0.04
Serum Glucose (mg/dL)				
Control	50.4±1.07	53.7±2.00	56.2±3.76	56.9±2.16
TDF 80mg/kg	52.3±1.63	55.5 ±3.11	54.7±2.59	55.6±3.75
RIF 32mg/kg	50.5±3.26	51.7±1.75	50.5±1.32	52.4±1.72
TDF/RIF	51.2±2.95	56.1±0.49	53.9±0.99	53.5±1.74

However, time-dependent increases in serum creatinine levels to 1.50±0.05, 1.62±0.01, 1.74 ±0.04 and 2.73±0.03 mg/dL at 1-8 weeks respectively were obtained in TDF treated animals while increases in a time-dependent manner to 1.41±0.03, 1.55±0.06, 1.71±0.01 and 2.51±0.04 mg/dL at 1-8 weeks respectively were obtained in RIF treated animals. These increases were significant (p<0.05) only at week 8 when compared to the control.

Time dependent increases in creatinine levels to 1.47±0.02, 1.69±0.09, 1.78±0.05 and 2.81±0.12 mg/dL at week 1-8 respectively were also obtained when TDF-RIF were co-administered, but these increases were insignificant (p>0.05) when compared to their individual doses (**Table 2**).

Serum urea levels were also increased in a time-dependent manner in animals that received individual doses of TDF and RIF with significance (p<0.05) observed at week 8 when compared to the control. A combination of TDF and RIF further increased serum urea levels in a time-dependent manner, but increases were insignificant (p>0.05) when compared to their individual doses of TDF and RIF (**Table 2**).

Furthermore**,** uric acid levels were insignificantly (p>0.05) increased in a time-dependent manner in animals treated with individual doses of TDF and RIF when compared to the control. Uric acid levels were further increased in a time-dependent manner with combined doses of TDF-RIF, but increases were insignificant (p>0.05) when compared to what were obtained with their individual doses (**Table 2**).

Table 2: Effects of tenofovir and rifampicin on serum creatinine, urea and uric acid levels of albino rats

Drug	WK1	WK2	WK4	WK8
Serum creatinine (mg/dL)				
Control	1.24±0.01	1.27±0.03	1.32±0.02	1.29±0.05
TDF 80mg/kg	1.50±0.05	1. 62±0.01	1.74±0.04	2.73±0.03*
RIF 32mg/kg	1.41±0.03	1.55±0.06	1.71±0.01	2.51±0.04*
TDF/RIF	1.47±0.02	1.69±0.09	1.78±0.05	2.81±0.02*
Serum urea (mg/dL)				
Control	30.3±0.20	30.4±2.23	32.6±1.14	31.4±1.31
TDF 80mg/kg	32.7±1.21	35.0 ±3.13	37.3±2.11	43.5±0.03*
RIF 32mg/kg	31.6±0.13	35.7±1.23	38.1±1.23	41.3±0.11*
TDF/RIF	34.97±1.00	36.21±0.12	36.4 ±2.21	46.7±1.12*
Serum uric acid (mg/dL)				
Control	1.51±0.01	1.53±0.03	1.50±0.02	1.52±0.07
TDF 80mg/kg	1.57±0.03	1.60±0.04	1.65±0.05	1.77±0.04
RIF 32mg/kg	1.54±0.08	1.57±0.09	1.60±0.02	1.67±0.02
TDF/RIF	1.59±0.06	1.65±0.05	1.68±0.03	1.79±0.08

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4. Discussion

Toxic effects on the kidney related to medications are both common and expected, given the kidney's roles in plasma filtration and maintenance of metabolic homeostasis. Renal dysfunction and injury secondary to medications can present as subtle injury and/or overt renal failure. Some drugs perturb renal perfusion and induce loss of filtration capacity while others directly injure vascular, tubular, glomerular and interstitial cells (Choudhury and Ahmed, 2006). The present study comparatively evaluated the toxicological effects of treatments with tenofovir, rifampicin, and tenofovir-rifampicin combination on the renal function of adult male albino rats. Effects were evaluated on creatinine, urea, uric acid, albumin, total protein and glucose because they are clinical end points that mark renal function (Adikwu et al, 2016). The effects of these agents were also evaluated on body and relative kidney weights because effects of a drug on organ or body weights are indices for toxicological assessment (Michael et al, 2007). In this study, treatments with these agents did not produce changes in body and relative kidney weights. Also, co-treatment with TDF-RIF did not produce synergistic effects on serum creatinine, urea, uric acid levels, albumin, total protein and glucose levels. Observation in this study showed that co-therapy with TDF-RIF in HIV/TB co-infection may not be associated with synergistic renal toxicity.

The present study observed time-dependent increases in serum creatinine, urea, and uric acid levels with no effects on total protein and albumin levels in animals treated with individual doses of TDF and RIF. These observed changes suggest signs of renal toxicity (Antoniou et al, 2005; Patel et al, 2010). The observed changes in serum creatinine, urea, and uric acid levels in tenofovir treated animals are consistent with the work of Adaramoye and others who treated rats with 50mg/kg of TDF for 4 weeks (Schleenvoigt et al, 2011; Adaramoye et al, 2012). These observations are also in agreement with the work of Abraham and others who treated rats with 600mg/kg of TDF for 5 weeks (Abraham et al, 2013).

Furthermore, increases in creatinine, urea and uric acid levels observed in rifampicin treated animals are in agreement with previous reports (Opromolla et al, 1992; Rekka et al, 2005; Havey et al, 2012; Shabana et al, 2012 Rosati et al, 2013; Peters et al, 2013). In this study, observed increases in creatinine, urea and uric acid in animals treated with these agents could be attributed to the induction of oxidative stress by these agents in the kidneys of treated animals which might have decreased glomerular filtration rate (Ramamoorthy et al, 2011). Studies suggest that free radical-induced oxidative stress via mitochondrial damage could be one of the possible mechanisms of TDF associated renal toxicity (Kohler et al, 2009; Lebrecht et al, 2009). Studies have also implicated oxidative stress via increase in kidney lipid peroxidation indices and decrease in antioxidants status as a possible mechanism of RIF associated renal toxicity (Mohmoud et al, 2015). Furthermore, scholars have acknowledge that oxidative stress can induce cell membrane permeability, loss of functional capacity of the kidney (Recknagel et al, 1989), and stimulate vasoactive mediators which can induced renal vasoconstriction and reduce glomerular filtration capacity (Garcia-Cohen et al, 2000).

5. Conclusion

Based on the findings in the present study, the concurrent use of tenofovir and rifampicin in the treatment of human immunodeficiency virus and tuberculosis co-infection may not be detrimental to renal function.

Conflict of Interest Declaration

The authors declare no conflict of interest.

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