

Research Article

Toxicological Assessment of Co-treatment with Rifampicin and Tenofovir on Serum Electrolytes and Kidney Histology of Albino Rats

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Background: Tenofovir and rifampicin have been individually implicated in renal toxicity characterized by electrolytes imbalance; hence concurrent use in human immunodeficiency virus/tuberculosis co-infection might induced synergistic electrolytes imbalance and kidney damage.

Objectives: This study comparatively evaluated the effects of treatment with tenofovir, rifampicin and a combination of tenofovir-rifampicin on serum electrolytes levels and kidney histology of male albino rats.

Methodology: 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) were treated orally with water while animals in group B (solvent control) were treated orally with arachis oil. 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. At the end of drug therapy the animals were sacrificed and blood samples collected. Serum was extracted from the blood samples and analyzed for chloride, sodium, calcium, potassium and bicarbonate levels. Animals were dissected, kidney collected and analyzed for histopathological changes.

Results: Treatment with a combination of tenofovir-rifampicin for 1-8 weeks did not produce significant ($p>0.05$) time-dependent effects on serum electrolytes when compared to treatment using individual doses of these agents. Kidneys of animals treated with these agents showed tubular necrosis, collapsed glomerular and collection of fibrous material on bowman's space.

Discussion and Conclusion: Treatment with a combination of tenofovir-rifampicin did not produce synergistic effects on serum electrolytes and kidney damage. The use of tenofovir – rifampicin combination in human immunodeficiency virus/tuberculosis co-infection may not be associated with electrolytes imbalance and kidney damage considering the dose level used for this study.

Keywords: Tenofovir, Rifampicin, Toxicity, Electrolytes, Kidney, Rats

Received: July, 2015

Published: October, 2015

1. Introduction

The kidney performs several excretory and regulatory functions including blood pressure control and maintenance of extracellular environment. It is responsible for the composition and volume of

circulating fluids with respect to water and electrolytes balance and acid-base status (Ferguson and Walker, 2012). Kidney damage by drugs and infections could lead to multiple disturbances of electrolytes metabolism and endocrine regulations (Peter, 1991). Serum electrolytes imbalance and altered mineral metabolism

which occurred due to drug treatment have been found to contribute to bone diseases, cardiovascular diseases and other clinical problems (Ugwuja and Eze, 2007). The high extent of delivery of materials including xenobiotics, via their passage through the tubular lumen may contribute to electrolyte imbalance and kidney damage (Hagos and Wolff, 2010).

The concurrent use of medications due to comorbidities could induce electrolytes abnormalities through interference with the absorption of electrolytes; alter hormonal responses affecting homeostasis, as well as direct impact on organ function responsible for maintaining electrolytes balance (Cruz et al, 2003; Buckley et al, 2010). One of the co-morbid conditions that necessitate concurrent use of medications is human immunodeficiency virus/tuberculosis (HIV/TB) infection. There are well established epidemiological and biological synergies between HIV and TB, influencing the distribution, progression and outcomes of both infections. The HIV epidemic is a key factor behind the resurgence in TB incidence worldwide (UNAIDS, 2013). The established relationship between HIV and TB infections has necessitates co-therapy with antiretroviral drugs and anti-tuberculosis drugs. These include cases of co-therapy with tenofovir containing regimes and rifampicin containing regimens (WHO, 2007).

Co-therapy with rifampicin and tenofovir containing regimes might be of therapeutic concern due to the individual nephrotoxic effects of rifampicin and tenofovir. Rifampicin is usually considered safe, but cases of rifampicin renal toxicity have been reported sporadically. Since the first description in 1971, there are more reported cases of renal toxicity characterized by acute tubulointerstitial nephritis and/or acute tubular necrosis, interstitial lesions, isolated or super imposed glomerular injury and electrolytes imbalance (Fenfield et al, 1999; Young and Killingworth, 2002; Yoshioka et al, 2002; Neugarten, 1983). Most cases of rifampicin-related renal failure are secondary to drug-induced haemolytic anaemia. Acute interstitial nephritis, rapidly progressive glomerulonephritis are usually characterized by proteinuria with acute onset deterioration of renal functions and light-chain proteinuria (Power et al, 1983; Prakash et al, 2001).

The use of TDF has been associated renal toxicity characterized by kidney histopathological changes. Large clinical studies and post-marketing data support a benign renal profile for tenofovir; numerous cases of kidney injury in humans raise concern for nephrotoxic potential. Animal studies show that tenofovir causes mitochondrial DNA depletion and mitochondrial toxicity (Herliz, 2010; Adikwu et al, 2014). Renal proximal tubules from HIV + transgenic mice exposed to tenofovir showed ultrastructural mitochondrial abnormalities (irregular shapes with sparse, fragmented cristae) and decreased mtDNA levels, which paralleled the ultrastructural mitochondrial abnormalities (Kholer et al, 2009). Also some reported cases of tenofovir-induced renal toxicity were characterized by serum electrolytes imbalance (Zimmerman et al, 2006; Turret et al, 2013; Patel et al, 2010; Kapitsinou and Ansari, 2008; Mathew and Kanus, 2006). Co-therapy with tenofovir and rifampicin may present important safety concerns on serum

electrolytes levels and kidney histology. This study was designed to comparatively evaluate the effects of treatment with rifampicin, tenofovir and a combination of tenofovir- rifampicin on serum electrolytes and kidney histology of albino rats.

2. Materials and Methods

2.1 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*.

2.2 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. Other chemicals used in this study were of analytical grade. The doses of rifampicin and tenofovir disoproxil fumarate used for this study were 80mg/kg and 32 mg/kg respectively (CDC, 2003; Viread, 2013). Rifampicin and tenofovir powder were suspended in arachis oil.

2.3 Grouping of Animals and Drug Administration

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 orally treated with water, while animals in group B (solvent control) were orally treated with Arachis oil. Animals in groups C-E were orally 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 under chloroform anesthesia, by cardiac puncture into sterile sample container and allowed to clot. Thereafter, serum was separated by centrifugation at 1200 rpm for 15 min and used for analysis. The animals were then killed by over dose of chloroform anesthesia; kidneys were dissected out, cleaned off the extraneous tissue, weighed and evaluated for histopathological changes.

2.5 Evaluation of Serum Electrolytes

Potassium and sodium were determined using flame photometric methods, while chloride and bicarbonate levels were determined using titrimetric methods.

2.6 Histopathological Analysis

The collected kidney tissues were fixed with 10% buffered formalin, dehydrated in ascending grades of ethanol, and cleared in xylene. The tissues were later embedded in paraffin wax and sections of 5 cm in thickness were prepared and stained with hematoxylin

and eosin. The stained sections were then examined under light microscopy and photomicrographs of the relevant stained sections were taken with the aid of a light microscope.

2.7 Statistical Analysis

This was done using Graph Pad Prism 5 statistical package and ANOVA for comparison of the means of the various groups. The means and standard errors were calculated and test groups results compared with that of the control groups. A p -value < 0.05 was considered significant.

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

Treatment with TDF for 1-8 weeks did not produce significant ($p>0.05$) time-dependent effects on serum electrolytes when compared to the control values. Also, serum electrolytes remained virtually normal without any significant ($p>0.05$) difference when compared to the control values following treatment with RIF for 1-8 weeks.

Furthermore, observations in this study show that treatment for 1-8 weeks with a combination of TDF-RIF did not produce significant ($p>0.05$) time-dependent effects on serum electrolytes when compared to the control values and when compared to treatment using individual doses of TDF and RIF (**Table 1**).

Table 1: Effects of treatment with tenofovir, rifampicin and tenofovir-rifampicin combination on serum electrolytes of male albino rats

Dose	WK1	WK2	WK4	WK8
Serum Sodium (mmol/L)				
Control	126.5±2.15	126.7±1.21	125.9±1.32	127.1±1.43
TDF 80mg/kg	127.1±1.20	126.1±2.11	126.3±1.15	128.5±1.40
RIF 32mg/kg	126.6±0.70	125.7±1.21	127.3±1.10	126.7±1.24
TDF/RIF	127.2±0.12	126.2±1.14	127.6±0.12	128.6±1.33
Serum Potassium (mmol/L)				
Control	3.49±0.07	3.47±0.03	3.50±0.04	3.48±0.01
TDF 80mg/kg	3.48±0.01	3.46 ±0.05	3.51±0.02	3.47±0.05
RIF 32mg/kg	3.51±0.06	3.48±0.01	3.50±0.04	3.49±0.03
TDF/RIF	3.50±0.07	3.53±0.03	3.52 0.02	3.48±0.04
Serum Chloride (mmol/L)				
Control	120.5±3.21	120.7±3.23	122.5±0.14	121.6±4.10
TDF 80mg/kg	121.3±2.21	123.2±1.20	119.7±3.14	124.1±0.25
RIF 32mg/kg	120.7±2.64	124.6±0.76	123.8±2.11	126.5±3.14
TDF/RIF	122.4±1.52	125.1±2.14	122.3±1.14	128.2±3.20
Serum Bicarbonate (mmol/L)				
Control	22.5±1.10	22.4±1.10	24.6±0.15	21.9±1.22
TDF 80mg/kg	22.4±0.22	22.0 ±0.13	22.1±0.01	19.9±0.03
RIF 32mg/kg	22.3±0.50	19.8±0.21	22.2±0.05	20.3±0.02
TDF/RIF	21.7±0.70	20.4±0.21	20.6± 0.32	21.0±1.00
Serum Calcium (mg/dL)				
Control	11.49±0.07	11.47±0.03	11.50±0.04	11.46±0.01
TDF 80mg/kg	11.50±0.21	11.48 ±0.05	11.51±0.02	11.60±0.15
RIF 32mg/kg	11.51±0.16	11.52±0.31	11.50±0.24	11.40±0.03
TDF/RIF	11.60±0.07	11.53±0.23	11.52 ±0.02	11.48±0.04

TDF: tenofovir, RIF: rifampicin.

Results are expressed as mean ± SEM, n= 4.

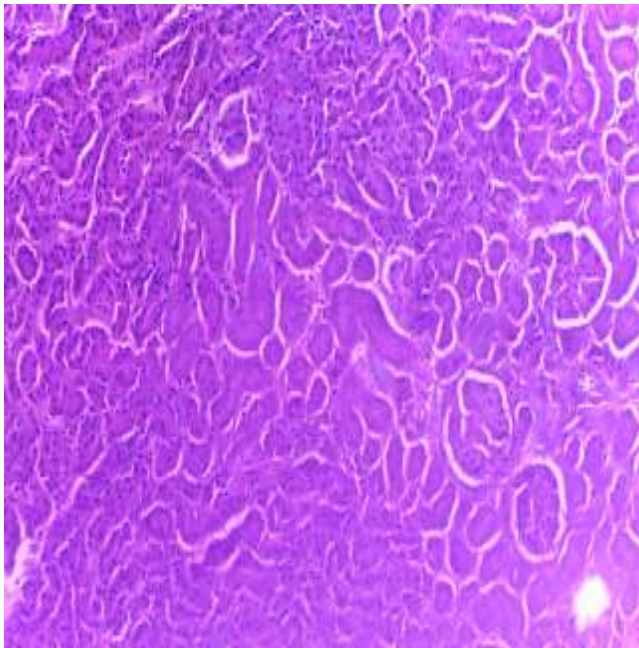


Figure 1: Photomicrograph of H and E stained section of the kidney of control rat treated with water for 4 weeks showing normal kidney histology. (x200)

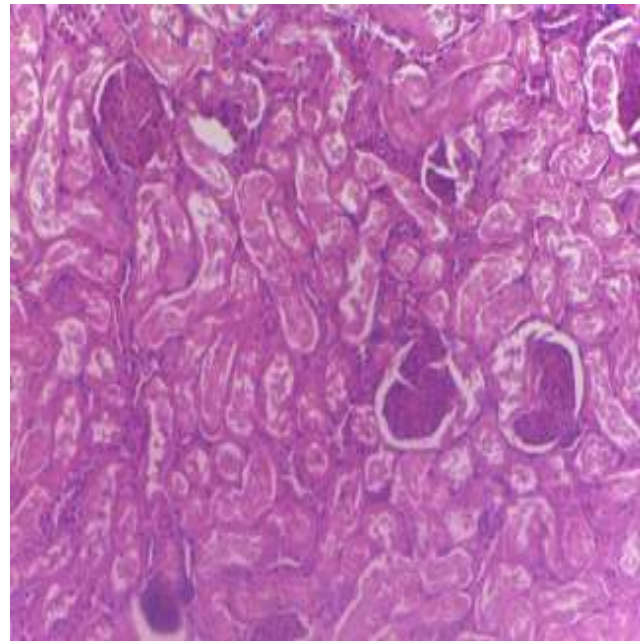


Figure 2; Photomicrograph of H and E stained section of the kidney of rat treated with 80mg/kg of rifampicin for 4 weeks showing sloughing of the epithelial cells of the tubules and collection of fibrous material on the Bowman's space (x200)

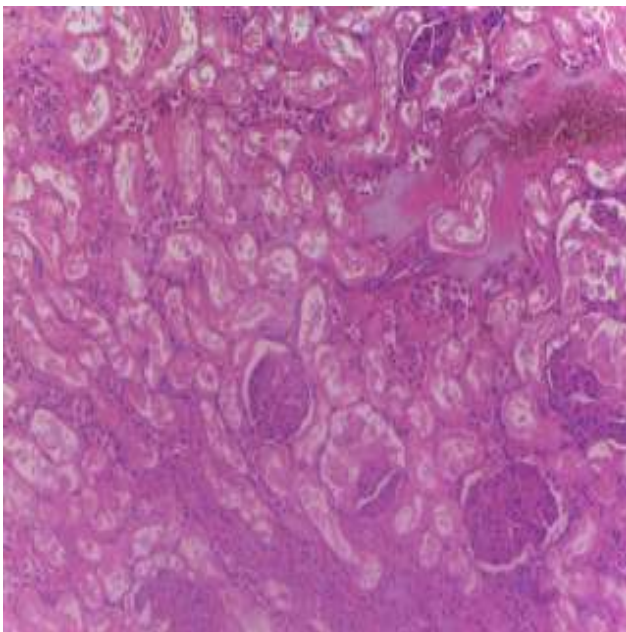


Figure 3; Photomicrograph of H and E stained section of the kidney of rat treated with 32mg/kg of tenofovir for 4 weeks showing tubular necrosis and collection of fibrous material on the Bowman's space (x200)

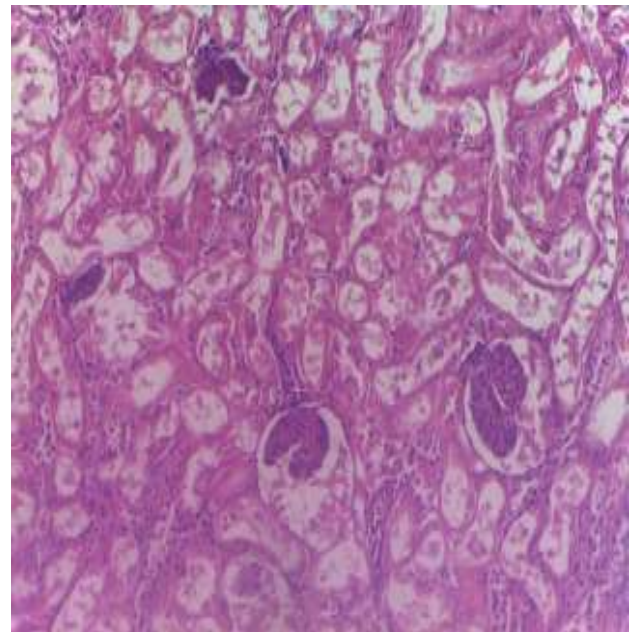


Figure 4: Photomicrograph of H and E stained section of the kidney of rat treated with 32mg/kg of tenofovir and 80 mg/kg rifampicin for 4 weeks showing tubular necrosis, collapsed glomerular and fibrous material on Bowman's space (x200)

Kidney of animals treated with tenofovir, rifampicin and a combination of TDF-RIF show various degrees of histopathological changes which include tubular necrosis, collapsed glomerular and collection of fibrous material on Bowman's space (**Figure1-4**).

4. Discussion

This study comparatively evaluated the toxicological effects of tenofovir, rifampicin and a combination of tenofovir-rifampicin on serum electrolyte and kidney

histology of albino rats. Effects on serum electrolytes evaluated include sodium (Na⁺), potassium (K⁺), calcium (Ca²⁺) chloride (Cl⁻) and bicarbonate (HCO₃) (Hall and Guyton, 2006; Buckley et al, 2010). Electrolytes play important role in intermediary metabolism and cellular function, including enzyme activities and electrical gradients (Bootman and Peter, 2001; Lobo, 2004; Meletis, 1990; Tripathi et al, 2011).

In this study, there was no electrolytes imbalance observed in animals treated with individual doses of tenofovir and rifampicin. Also treatment with a combination of tenofovir-rifampicin did not produce any additive or synergistic toxicological effect on serum electrolytes. Despite absence of electrolytes imbalance in animals treated with these agents, tubular necrosis, collapsed glomerular and collection of fibrous material on bowman's space were observed in the kidneys of animals treated with these agents. This may be due to the ability of the kidney to concentrate these agents as reported by some scholars (Lebretch et al, 2009; Cote et al, 2000). Observation in this study shows that co-therapy with tenofovir-rifampicin in human immunodeficiency virus/ tuberculosis co-infection may not be associated with fluctuations in serum electrolytes and kidney damage with respect to doses used for this study.

In this present study, lack of serum electrolytes imbalance observed in animals treated with tenofovir is at variance with the work of Ramamoorthy et al, 2012 who treated rats with 600mg/kg of tenofovir for 35 days and reported abnormalities in electrolytes. Observed variation may be due to higher doses of tenofovir used by these authors. Tenofovir has been reported to be associated with metabolic acidosis that occurs due to defective bicarbonate reabsorption in the proximal tubule which is at variance with our observation (Baum, 1993; Mukhyaprana et al, 2014).

Histopathological damage observed in the kidneys of tenofovir treated animals is in agreement with previous reports (Adaramoye et al, 2012; Liborio 2008; Rammoorthy et al, 2014; Shaaf et al, 2003). Histological alterations observed in the kidneys of animals treated with tenofovir may be due to accumulation in proximal renal tubular cells which can stimulate proximal tubule mitochondria damage leading to the production of oxidative radicals and the depletion of kidney antioxidants. Mitochondria are responsible for energy production and contain oxidative radicals which are released during mitochondria damage (Lebretch et al, 2009; Lewis et al, 2003; Cote et al, 2000; Tanji et al, 2009)

In this study, lack of electrolytes imbalance observed in animals treated with rifampicin contradicts the work of Peter and Chike, who treated rats with 1.10mg/120gBW and 0.55mg/120g BW of rifampicin for 20-60 days and reported electrolytes imbalance (Peter and Chike, 2013). Observation in this study is also at variance with reported cases of rifampicin-induced serum electrolytes imbalance by Min et al, 2013 and Rosati et al, 2013. Observed histopathological damage in the kidneys of rifampicin-treated animals is consistent with the work of Opromolla who reviewed cases of rifampicin associated renal failure and reported tubular necrosis as a common feature (Opromolla, 1992). Also, finding in

this study is in agreement with the work of Min and colleagues who reported a case of rifampin induced tubulointerstitial nephritis (Min et al, 2013) and Rosati et al who reported rifampicin-associated interstitial tubulopathy (Rosati et al, 2013). Also, some scholars have reported tubular necrosis as a common and pronounce feature of rifampicin nephrotoxicity (Deviese et al, 1983; Flyn et al, 1974; Feinfeld, 1999; Geo et al, 2010). Histological alterations observed in the kidneys of animals treated with rifampicin may be due to immune complex deposition with compliment fixation leading to glomerular endothelial swelling, obstruction of blood flow and tubular ischemia (Chan et al, 1975). This is supported by the work of Muthukumar and others who reported immune complex deposition in blood vessels or interstitium which caused glomerular endotheliosis leading to tubular injury (Muthukumar et al, 2002). Rifampicin nephrotoxicity may be associated with destruction and depletion of tubular mitochondria DNA which may result in the release of oxidative radicals and depletion of antioxidants.

5. Conclusion

Observations in this study show that treatment with tenofovir-rifampicin combination was not associated with synergistic toxicological effect on serum electrolytes. Tubular necrosis, collapsed glomerular and collection of fibrous material on bowman's space were observed in the kidneys of treated animals. These observations show that co-therapy with these agents in human immunodeficiency virus/tuberculosis co-infection may not be associated with electrolytes imbalance and kidney damage.

Conflict of Interest Declaration

The authors declare no conflict of interest.

Acknowledgements

The authors appreciate the technical assistance offered by Mr Eze Ihukwumere and Mr Charles Okeibunor of the Faculty of Pharmacy, Madonna University, Elele, Rivers State, Nigeria.

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