Effects of Hydrochlorothiazide on Tenofovir Disoproxil Fumarate-Induced Nephrotoxicity in Rats

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Abstract

Tenofovir disoproxil fumarate, a nucleotide reverse transcriptase inhibitor utilized for the treatment of hepatitis B virus and human immunodeficiency virus infections; and is now one of the most widely used antiretroviral drug. However, tenofovir disoproxil fumarate can induce nephrotoxicity, which may be attributed to the interaction between such drug and the organic anion transporters (hOAT1, and OAT3) with consequent changes in levels of some parameters that may have a role in nephrotoxicity. Thiazide diuretics have high to intermediate potency of inhibition of OAT1s and OAT3; thus, it may possess nephroprotective effects. This study was designed to investigate whether hydrochlorothiazide has nephroprotective effects on tenofovir disoproxil fumarate-induced nephrotoxicity in rats.

Twenty eight healthy adult male albino rats weighing 180-200g were utilized in this study for duration of 5 weeks (35 days) treatment. Rats were randomly divided into four groups (7 animals each). Group I: Negative control (orally given distilled water) by gavage tube; Group II: Rats orally received 600 mg/kg/day tenofovir disoproxil fumarate by gavage tube; Group III: Rats orally administered hydrochlorothiazide alone at a dose (10 mg/kg/day) by gavage tube, and Group IV: Rats orally administered hydrochlorothiazide at a dose (10 mg/kg/day) plus tenofovir disoproxil fumarate 600 mg/kg/day by gavage tube. On day 36 of the study, after euthanization of each animal by diethyl ether, 3.5ml of blood samples were collected from each rat by an intra-cardiac puncture, then centrifuged at 3000 rpm for 15 minutes to obtain serum, which was then transferred into suitable plain tubes and preserved at -20 °C; and it was utilized for the estimation of cystatin C and IL-10 level.

Rats administered tenofovir disoproxil fumarate for 5 weeks (group II) produced a significant - elevation (P<0.05) in serum cystatin C level and – reduction in serum IL-10 levels compared to negative control group (group I); similarly, administration of hydrochlorothiazide alone to rats (group III) produced a significant -elevation (P<0.05) in serum cystatin C level and – reduction in serum IL-10 levels compared to negative control group (group I); also, rats administered combination of hydrochlorothiazide plus tenofovir disoproxil fumarate to rats for 5 weeks (group IV) produced significant elevation (P<0.05) in serum level of cystatin C, and a significant reduction (P<0.05) in IL-10 serum level in treated rats compared to the corresponding levels of negative control animals (group I); beside that in (group IV) rats there were significant reduction (P<0.05) in serum level of both cystatin C, and IL-10 in treated rats compared to the corresponding levels compared to TDF-treated (group II). In conclusion, treatment with hydrochlorothiazide plus tenofovir disoproxil fumarate in an attempt to prevent nephrotoxicity induced by tenofovir disoproxil fumarate is not attained.

Key words: Nephrotoxicity, Tenofovir, Hydrochlorothiazide, Cystatin C, IL-10.

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58
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It has been shown that after oral administration, TDF can be metabolized to tenofovir (TFV), which, in turn, can intracellularly be phosphorylated to the active moiety, tenofovir diphosphate (TFV-DP). However, higher circulating plasma levels of TFV have been associated with both renal and bone adverse effects of the prodrug (TDF) (11, 12).

Yang, Y. et al (2016) have been reported numbers of agents that including some clinical drugs may possess renoprotective effects in acute kidney injury (AKI) models (3).

Thiazide diuretics have high to intermediate potency of inhibition of organic anion transporters, OAT1s and OAT3 (14). Thiazides are sulfonamide-related organic acids that are secreted into the proximal tubule by an organic secretory mechanism; they act to increase the excretion of Na\(^+\) and Cl\(^-\) by inhibiting the Na\(^+\)/K\(^+\)/2Cl\(^-\) symporter in the distal convoluted tubule. Natriuresis may be accompanied by some loss of potassium and bicarbonate.

Moreover, thiazides can enhance Ca\(^2+\) reabsorption in the distal convoluted tube by increasing the Ca\(^2+\)/Na\(^+\) exchanger. Thiazides can also reduce the urinary excretion of Ca\(^2+\) and actively transported into the renal proximal tubule cells (10). Authors reported that, TDF-associated nephrotoxicity may primarily result in proximal tubular injury; where, severe acute tubular necrosis was seen in 33 (77%) of 43 biopsy-proven cases of TDF nephrotoxicity (10).

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Moreover, thiazides can enhance Ca\(^2+\) reabsorption in the distal convoluted tube by increasing the Ca\(^2+\)/Na\(^+\) exchanger. Thiazides can also reduce the urinary excretion of Ca\(^2+\) and
therefore can be employed in the treatment of kidney stones and may also be useful for treating osteoporosis \(^{(15)}\). The aim of this study is to investigate whether hydrochlorothiazide has nephroprotective effects on tenofovir disoproxil fumarate-induced nephrotoxicity in rats.

**Methods**

**Drugs**

Tenofovir disoproxil fumarate (TDF) tablet (300 mg) was purchased from Cipla, India. Hydrochlorothiazide tablet (25 mg) was purchased from T and D Pharma GmbH, Germany.

**Animals**

Twenty eight healthy adult male albino rats weighing 180-200g were utilized in this study; they were obtained from and maintained in the Animal House of the College of Pharmacy, Baghdad University, under conditions of controlled temperature. Animals were fed commercial pellets and tap water ad libitum throughout the experiment period. The study was approved by the Scientific and the Ethical Committees of the College of Pharmacy/University of Baghdad.

**Experimental protocol**

Healthy rats were randomly divided into four groups (7 animals/group) as follows:

**Group I** - Rats orally administered distilled water by gavage tube for 5 weeks. This group served as negative control.

**Group II** - Rats orally administered 600 mg/kg/day of tenofovir disoproxil fumarate (TDF) by gavage tube for 5 weeks \(^{(16)}\).

**Group III** - Rats orally administered hydrochlorothiazide alone at a dose of 10 mg/kg/day by gavage tube for 5 weeks \(^{(17)}\).

**Group IV** - Rats orally administered hydrochlorothiazide at a dose of 10 mg/kg/day plus tenofovir disoproxil fumarate 600 mg/kg/day by gavage tube for 5 weeks.

**Preparation of serum samples**

Twenty-four hour after the end of the treatment duration (i.e. at day 36), each animal was euthanized by diethyl ether. Blood samples were collected (3-5 ml from each rat) by an intra-cardiac puncture, then centrifuged at 3000 rpm for 15 minutes to separate serum, which was then transferred into suitable plane tubes and preserved at -20 °C. The serum of each rat was used for the estimation of cystatin C and IL-10 level.

**Statistical analysis**

Data were expressed as mean±standard error of the mean (SEM). The statistical significance of the differences among various groups was determined by one-way analysis of variance (ANOVA). Differences were considered statistically significant for P<0.05.

**Results**

Table 1 and figure 1 summarize the effect of different treatments on cystatin C level in serum of rats’ groups. Cystatin C was significantly elevated (P<0.05) in serum of rats that were orally administered TDF for 5 weeks (group II) compared to negative control group (group I); where, the mean ± SEM values were 0.45±0.017 ng/ml and 0.19±0.02 ng/ml, respectively. Furthermore, there was a significant elevation (P<0.05) in cystatin C level in serum of rats in hydrochlorothiazide-treated group (group III) compared to negative control group (group I), the mean±SEM value was (0.24±0.015 ng/ml); moreover, in group of rats treated with hydrochlorothiazide plus TDF (group IV), mean± SEM serum cystatin C levels was significantly elevated compared to the corresponded serum level in negative control rats (P<0.05); where, the mean±SEM values were (0.39±0.01 ng/ml) compared with negative control group (0.19±0.02ng/ml).

Moreover, table 1 and figure 1 showed that there were significant elevations (P<0.05) in serum cystatin C level among rats in groups II (orally administered TDF (600mg/kg), III (orally administered hydrochlorothiazide (10mg/kg), and IV (administered hydrochlorothiazide (10 mg/kg) plus TDF (600 mg/kg)]).

In addition rats treated with hydrochlorothiazide plus TDF (group IV), the mean±SEM serum cystatin C levels was significantly reduced compared to the corresponded serum level in TDF-treated rats (group II) (P<0.05); where, the mean±SEM values were (0.39±0.01 ng/ml) compared with TDF-treated group (0.45±0.17ng/ml).

**Table 1. Effect of different treatments on cystatin C level in serum of rats’ groups.**

| Group / Treatment                  | Mean serum cystatin C level (ng/ml) |
|-----------------------------------|-------------------------------------|
| Group I/ negative control (distilled water) | 0.19±0.02                          |
| Group II/ TDF (600 mg/kg)         | 0.45±0.017* A                       |
| Group III/ hydrochlorothiazide (10 mg/kg) | 0.245±0.015 * B                    |
| Group IV/ hydrochlorothiazide (10 mg/kg) plus TDF (600 mg/kg) | 0.392±0.01 * C                    |

Data expressed as mean± Standard error of mean (SEM).

*: P<0.05: Significant difference compared to negative control group.

Values with non-identical Capital letters (A, B, and C) are considered significantly different (P<0.05).

TDF, tenofovir disoproxil fumarate.
Hydrochlorothiazide on tenofovir-induced nephrotoxicity in rats

Figure 1. Effect of different treatments on cystatin C level in serum of rats’ group.
(a): Indicate a significant difference (P<0.05) compared to negative control group.
(b): Indicate a significant difference (P<0.05) compared to tenofovir disoproxil fumarate treated group.

Table 2 and figure 2 summarize the effect of different treatments on serum interleukin-10 (IL-10) level of rats’ groups. There was a significant reduction (P<0.05) in interleukin-10 level in serum of -TDF-treated group (group II) [the mean±SEM value was (20.341± 0.45pg/ml)], - hydrochlorothiazide-treated group (group III) [mean±SEM value was (16.991± 0.412 pg/ml)], and -in group of rats administered hydrochlorothiazide plus TDF (group IV) [mean±SEM value was (13.655±0.512 pg/ml)] compared to the corresponding levels in negative control group (group I) [mean±SEM value was (28.846± 0.56 pg/ml)]. Additionally rats treated with hydrochlorothiazide plus TDF (group IV), the mean±SEM serum interleukin-10 levels was significantly reduced compared to the corresponding serum level in TDF-treated rats (group II) (P<0.05); where, the mean±SEM values were (13.655±0.512 pg/ml) compared with TDF-treated group (20.341± 0.45 pg/ml).

Furthermore, table 2 and figure 2 showed that there was a significant reduction (P<0.05) of interleukin-10 level in serum among rats of group II, III, and IV.

Table 2. Effect of different treatments on interleukin-10 level in serum of rats’ groups.

| Group / Treatment | Mean serum IL-10 level |
|-------------------|------------------------|
| Group I/ negative control (distilled water) | 28.846± 0.56 |
| Group II/ TDF (600 mg/kg) | 20.341± 0.45 *A |
| Group III/ hydrochlorothiazide (10 mg/kg) | 16.991± 0.412* A |
| Group IV/ hydrochlorothiazide (10 mg/kg) plus TDF (600 mg/kg) | 13.655±0.512* B |

Data expressed as mean± Standard error of mean (SEM).

*: P<0.05: Significant difference compared to negative control group.
Values with non-identical Capital letters (A and B) are considered significantly different (P<0.05).
TDF, tenofovir disoproxil fumarate.

Figure 2. Effect of different treatments on interleukin-10 level in serum of rats’ groups
(b): Indicate a significant difference (P<0.05) compared to negative control group.
(c): Indicate a significant difference (P<0.05) compared to tenofovir disoproxil fumarate-treated group.

Discussion
The widespread introduction of highly active antiretroviral therapy (HAART) in the mid-1990s dramatically altered the course of human immunodeficiency virus (HIV) infection, with improvements in survival and reductions in the incidence of AIDS-defining illnesses. Although, antiretroviral therapy has been shown to reduce the incidence of both AIDS-defining and non-AIDS conditions, long-term exposure to HAART may also be associated with significant toxicity (18).

Tenofovir disoproxil fumarate (TDF) is an orally bioavailable pro-drug of TFV (19). The renal proximal tubule (PT) is the main target of TFV toxicity (20). Animal studies have revealed that TFV can cause proximal tubular (PT) damage in mice (21), rats (22, 23), and non-human primates (24), furthermore, numerous case reports and case series illustrated that
Fanconi Syndrome (FS) or acute kidney injury (AKI) in HIV-infected patients was produced by TFV (25, 26). Moreover, most studies considered creatinine clearance (CrCl) as a marker of renal function for the assessment of TDF-induced nephrotoxicity. However, creatinine clearance (GCl) was reported to be a weak indicator for evaluation of kidney function for TDF-induced nephrotoxicity (27); in addition to that, creatinine is derived from skeletal muscle and HIV-infected patients can have abnormal muscle mass, these are important considerations when interpreting studies (28).

Horberg M. et al (2010) showed that TDF-exposed patients had greater development of proximal tubular dysfunction over time, reduced GFR, and had greater risk of medication discontinuation, especially as renal function worsened and serum creatinine were also reported to be significantly elevated among TDF-exposed patients compared with TDF-sparring patients (29). Thus, in the current study, serum level of cystatin C as a marker for tubular damage was measured instead of serum creatinine.

The results of this study showed that there was significant elevation (P<0.05) in serum level of cystatin C in rats orally administered TDF for 5 weeks (group II) compared to the corresponding levels in negative control (group I) and this coincide with that founded by Horberg M. et al (2010) from the point of the effect.

Cystatin C is a non-glicolized protein with small molecular weight (13.3 kDa), a hundred times bigger than creatinine. It is produced at a constant rate by all the nucleated cells, and is freely filtered by glomeruli and minimally linked to proteins, and is not reabsorbed in the systemic circulation after the filtering (30). Furthermore, it has shown promise as a replacement for serum creatinine in estimation of glomerular filtration rate (GFR). It has been reported that after glomerular filtration, cystatin C is fully catabolized in the proximal renal tubule and is not returned to blood. Moreover, the concentration of serum cystatin C is not affected by gender, age, race, protein intake, and muscle mass, unlike serum creatinine. When GFR reduced, cystatin C level begin to rise proportionately (31).

Moreover, the results of the present study revealed that there were significant elevations (P<0.05) in cystatin C level in serum of rats group administered hydrochlorthiazide (10mg/kg) alone (group III) compared to negative control rats (group I) or hydrochlorthiazide (10 mg/kg) plus TDF (600 mg/kg) (group IV) compared to the corresponding levels in -TDF-treated rats (group II) and -negative control (group I). Thus, results of this study concerning the effects of hydrochlorthiazide on kidney are coincide with that of Wadei H.M, et al at 2008 who reported that low kidney function and glomerular and tubular injury can be more commonly manifested in thiazide-treated rats (32).

Furthermore, in the current study, it was found that there was statistically a significant (P<0.05) reduction in serum IL-10 level of TDF-treated rats (group II) compared to the corresponding level in negative controls (group I). Moreover, treatment of rats with hydrochlorthiazide (10 mg/kg/day) alone (group III), and with hydrochlorthiazide (10 mg/kg/ day) plus TDF (600 mg/kg) (group IV) produced significant (P<0.05) reduction in serum IL-10 level compared to TDF-treated rats (group II) and negative control (group I), respectively.

Interleukin-10 (IL-10) is an anti-inflammatory cytokine produced by a number of activated immune cells like monocytes/macrophages, and T helper-1 (Th1) cells (33). Moreover, it has been reported that such cytokine is a potent inhibitor of inflammation and immune responses to infections and antigens (34, 35). Furthermore, pretreatment of human peripheral blood mononuclear cells (PBMCs) with TDF caused a reduction in levels of IL-10, and strongly reduced the induction of IL-10 (36).

Moreover Farkhondeh N and Ali D. A. (2012) showed that, clinically relevant concentration of hydrochlorthiazide could elevate the secretion of the proinflammatory cytokine IL-1β by the peripheral blood mononuclear cells (PBMCs), and might result in aggravation of inflammatory processes in vascular wall and worsen the condition in long-term (37). To our knowledge, the current study is the first that study the effect of hydrochlorothiazide on IL10, thus we could not have a chance to compare the results obtained from this study with others concerning this respect.

Conclusion

It could be concluded that hydrochlorothiazide had no nephron-protective effect against tenofovir disoproxil fumarate-induced renal damage.

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