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Reference:
Dams Karolien, Burger David M., Weyler Jonas, Francque Sven, Jorens Philippe, Vanwolleghem Thomas.- A pharmacokinetic study to guide dosing of tenofovir disoproxil fumarate during different modalities of renal replacement therapy
Clinical biochemistry - ISSN 0009-9120 - 83(2020), p. 86-88
Full text (Publisher's DOI): https://doi.org/10.1016/J.CLINBIOCHEM.2020.05.015
To cite this reference: https://hdl.handle.net/10067/1693780151162165141
A pharmacokinetic study to guide dosing of tenofovir disoproxil fumarate during different modalities of renal replacement therapy.

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Short title: Dosing TDF in renal replacement therapy.

Conflict of interests: None declared
Ethical approval: Not required

Source of funding: This work was supported by Gilead Sciences Inc.; we received a grant for PK monitoring of TDF. At no time Gilead Sciences was involved in the interpretation or report of the data.
Introduction

Tenofovir disoproxil fumarate (TDF) is indicated for the treatment of chronic hepatitis B virus (HBV) infection. Elimination happens primarily by the kidneys. [1,2]. No data on pharmacokinetics of TDF in patients undergoing continuous renal replacement therapy (CRRT) have been published. We set up a prospective study to investigate the differences in tenofovir PK in different types of RRT, first continuous veno-venous hemofiltration (CVVH), followed by intermittent hemodialysis (IHD) and ultrafiltration (UF) only, in order to provide dosing guidance for this specific patient population.

Material and Methods:

Plasma samples were collected pre-dose and following administration of 300 mg TDF at frequent time points over 72 hours during CVVH, IHD and a UF session. (Fig. 1A).

Analysis of tenofovir concentrations in serum was performed using a validated LC-MS/MS technique, which was a modification of our previously published HPLC method [3]. The lower and upper limit of quantification of tenofovir was 0.015 – 1.5 mg/L. Accuracy ranged from 100.7 – 102.8% and precision from 1.8-5.3%. Pharmacokinetic parameters were calculated using WinNonlin software.

A 59-year-old patient with chronic HBV infection was admitted for acute on chronic renal failure, the creatinine clearance (CrCl) was 10.2 ml/min (24h urine collection). HBV was previously treated with lamivudine. The viral load progressively increased due to a YMDD mutation (L180M; M204V). Antiviral treatment was switched to tenofovir alafenamide (TAF), which was stopped on admission as oral intake was not feasible and no data on crushing TAF tablets were available. As TDF has been studied more extensively in this setting, more specifically the possibility to administer the drug via nasogastric tube, we switched treatment to TDF. (Fig. 1B) The disease course was complicated by septic shock and acute kidney injury stage 3, with a decrease of CrCl to 6.52 ml/min (24h urine collection), requiring vasopressor treatment and CVVH. The patient stabilized and finally, after 7 weeks of treatment in ICU, CVVH could be switched to IHD.
Results:

Fig. 1A illustrates the evolution of tenofovir PK. The previous dose of TDF was administered 96h before start of the study. Serum levels during CVVH were well above the accepted therapeutic window of 0.05-0.30 mg/L [4]. The peak concentrations were higher and it took up to 44 hours to bring the levels down to the therapeutic window. We performed a second sampling interval during IHD and UF. Suggested dosing interval adjustment for hemodialysis is a once-weekly dose [1]. Our patient, however, was not a chronic hemodialysis patient. He received two sessions of hemodialysis with an ultrafiltration only session (2 hours) in between. As expected, the clearance of tenofovir was slower on IHD and absent during UF. The HBV load further decreased to 3.38 IU log. (Fig. 1B)

Discussion

Since we were able to do PK sampling during three different RRT modalities in the same patient we were in the optimal situation to compare the differences in tenofovir clearance for CVVH, IHD as well as ultrafiltration. This observational study is to our knowledge the first to examine the frequency of adjusted renal dosing of TDF in CVVH.

The tenofovir concentration stayed well above the lower limit of the therapeutic range [4]. There was never a subtherapeutic level (defined as lower than 0.05 mg/L = the population C\text{trough} in the normal patient population) during this type of RRT, indicating an adequate dosing interval.

As shown in Fig. 1B the HBV load in our patient decreased from 4.96 log IU to 4.51 log IU six weeks later. No obvious safety events were recorded during this dosing schedule.

Conclusion:

Tenofovir disoproxil fumarate 300 mg every four days in subjects on CVVH targets an adequate tenofovir exposure. Our data demonstrate the adequacy of a once-weekly dose during IHD sessions
and the absence of clearance during ultrafiltration. Both observations are helpful in guiding patients on first-line antiviral drug treatment for chronic HBV infection.

Keywords: hepatitis B virus, tenofovir disoproxil fumarate, renal insufficiency, continuous venovenous hemofiltration, renal replacement therapy, pharmacokinetics.
Acknowledgements

WJ Kwanten for helpful editorial assistance with figure preparation.
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