# How nephrotoxic is the therapy with Entecavir and Adefovir for patients with HVB chronic hepatitis?

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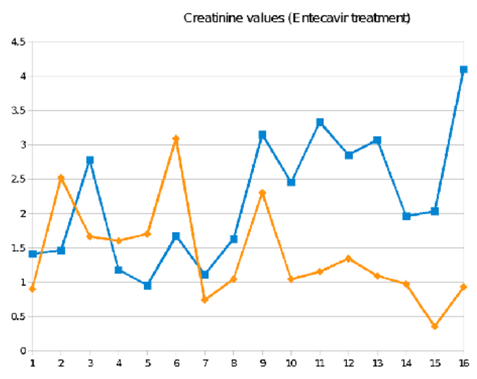
## Introduction

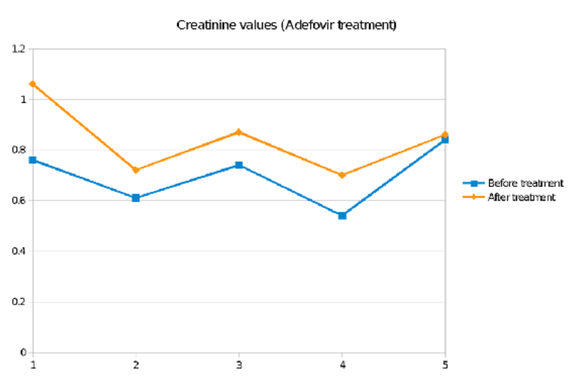
HBV chronic hepatitis has a high worldwide prevalence (estimated at 350 million carriers). One of the complications of the disease is represented by secondary renal impairment. In addition, these patients receive antiviral drugs with potential nephrotoxicity. Drug therapy with nucleosidic/nucleotidic analogues needs to be adjusted to the GFR. Adefovir is a known nephrotoxic drug and it is contraindicated in patients with a GFR < 10 ml/min/1.73 $m^2$ and in hemodyalised patients. The aim of our study was to assess the nephrotoxicity of Entecavir and Adefovir in patients with chronic hepatitis B by measuring serum creatinine, N-acetyl-β-D-glucosaminidase (NAG), as well as the eGFR before and at 6 months of therapy

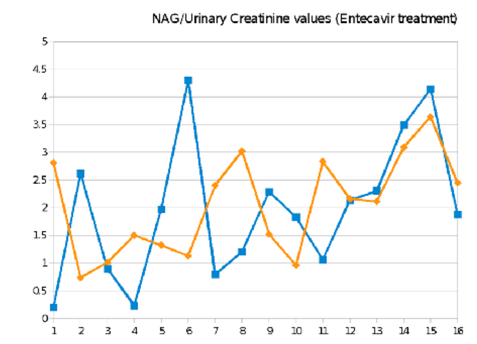
| Drug | CrCl > 50 (ml/min) | 30 < CrCl < 50 (ml/min) | 10 < CrCl < 30 (ml/min) | CrCl < 10 (ml/min) |
|---|---|---|---|---|
| Adefovir | 10 mg p.o. q.d. | 10 mg p.o. every 48h | 10 mg p.o. every 72h | No dosing recommended |
| Entecavir | 0.5 mg p.o. q.d. | 0.25 mg p.o. q.d. | 0.15 mg p.o. q.d. | 0.05 mg p.o. q.d. |

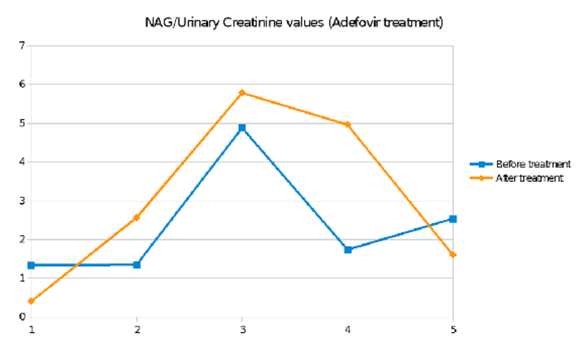
## Methods

21 patients (5 female, 16 male, mean age of 41.18±11.188) with chronic hepatitis B were enrolled in the study. 13 patients received 0.5 mg of Entecavir; 3 patients had previously been treated and gained resistance to Lamivudine and received 1 mg of Entecavir in the course of our study and 5 patients received 10 mg of Adefovir, all of these previously treated with Pegylated Interferon. NAG (colorimetrical method), urinary creatinine and serum creatinine were measured before and at 6 months of therapy. Statistical analysis (Wilcoxon signed-rank test, independent samples t-test) was performed using SPSS version 21




## Results

After 6 months of therapy 18 out of the total 21 patients presented with an increase in serum creatinine (Z= -2.816, p=0.005) and the NAG/urinary creatinine ratio did not suffer a statistically significant change (Z= -0.643, p= 0.520); 17 patients presented with a decrease in the eGFR (Z= -2.798, p= 0.005) and no significant difference was found between the group treated with Entecavir and the group treated with Adefovir concerning the variables in question

**Wilcoxon Signed Ranks Test**

| | Ranks | N |
|---|---|---|
| Creatinine2 – Creatinine1 | Negative Ranks | 3[ah] |
| | Positive Ranks | 18[ai] |
| | Ties | 0[aj] |
| | Total | 21 |
| NAG/UC2 – NAG/UC1 | Negative Ranks | 10[aw] |
| | Positive Ranks | 11[ax] |
| | Ties | 0[ay] |
| | Total | 21 |
| GFR2 - GFR1 | Negative Ranks | 17[az] |
| | Positive Ranks | 4[ba] |
| | Ties | 0[bb] |
| | Total | 21 |

ah. Creatinine2 < Creatinine1
ai. Creatinine2 > Creatinine1
aj. Creatinine2 = Creatinine1
aw. NAG/UC2 < NAG/UC1
ax. NAG/UC2> NAG/UC1
ay. NAG/UC2 = NAG/UC1
az. GFR2 < GFR1
ba. GFR2 > GFR1
bb. GFR2 = GFR1

**Wilcoxon Signed Ranks Test Statistics**

| | Creatinine2 – Creatinine1 | NAG/UC2 – NAG/UC1 | GFR2 - GFR1 |
|---|---|---|---|
| Z | -2.816[b] | -0.643[b] | -2.798[d] |
| Asymp. Sig. (2-tailed) | .005 | .520 | .005 |

a. Wilcoxon Signed Ranks Test
b. Based on negative ranks.
c. The sum of negative ranks equals the sum of positive ranks.
d. Based on positive ranks.

**T-test Group Statistics**

| Antiviral Therapy | | N | Mean | Std. Deviation | Std. Error Mean |
|---|---|---|---|---|---|
| Δ Creatinine | Entecavir | 16 | .0306 | .18746 | .04686 |
| | Adefovir | 5 | .1440 | .10164 | .04545 |
| Δ NAG/UC | Entecavir | 16 | .0850 | 1.49413 | .37353 |
| | Adefovir | 5 | .6980 | 1.73386 | .77541 |
| Δ GFR | Entecavir | 16 | -9.8711 | 29.94595 | 7.48649 |
| | Adefovir | 5 | -27.6284 | 15.78522 | 7.05937 |

**t-test for Equality of Means**

| | | t | df | Sig. (2-tailed) | Mean Difference | Std. Error Difference | 95% Confidence Interval of the Difference | |
|---|---|---|---|---|---|---|---|---|
| Δ Creatinine | Equal variances assumed | -1.279 | 19 | .216 | -.11338 | .08862 | -.29885 | .07210 |
| Δ NAG/UC | Equal variances assumed | -.773 | 19 | .449 | -.61300 | .79295 | -2.27267 | 1.04667 |
| Δ GFR | Equal variances assumed | 1.257 | 19 | .224 | 17.75728 | 14.12841 | -11.81382 | 47.32837 |

## Conclusions

Drug therapy with Entecavir and Adefovir lead to a slight decrease in renal function (increase in serum creatinine, decrease in the eGFR), but did not present with an increase in the tested tubular leasion biomarkers. The decrease in renal function was not accompanied by a change in the CKD stage according to the KDIGO classification

## References

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