Antiviral HIV treatment - a new cause of transient neonatal adrenal insufficiency

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Background HIV drugs Lopinavir and Ritonavir have been previously reported to cause transient adrenal insufficiency in three preterm newborns. To our knowledge, the effect of other HIV antviral drugs on steroidogenesis has not been described yet.

Aim To study the possible effect of HIV drug treatment perinatally on adrenal function in a neonate; a) clinical follow up was assessed and b) drugs (Efavirenz, Tenofovir, Emtriticabine and Zidovudine) were tested in vitro.

In vivo studies We report on a preterm girl who was identified to have high levels of serum 17-hydroxyprogesterone (17OHP) in newborn screening, but no clinical signs of congenital adrenal hyperplasia (CAH). She was treated after birth with HIV antiviral drug Zidovudine for prevention of vertical transmission. The HIV positive mother was on treatment with Atripla (Efavirenz, Tenofovir, Emtricitabine) during pregnancy and thereafter.

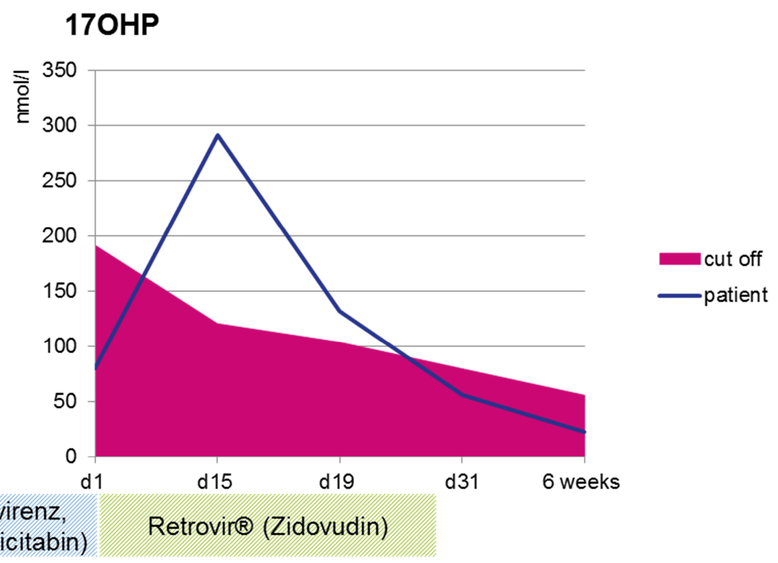
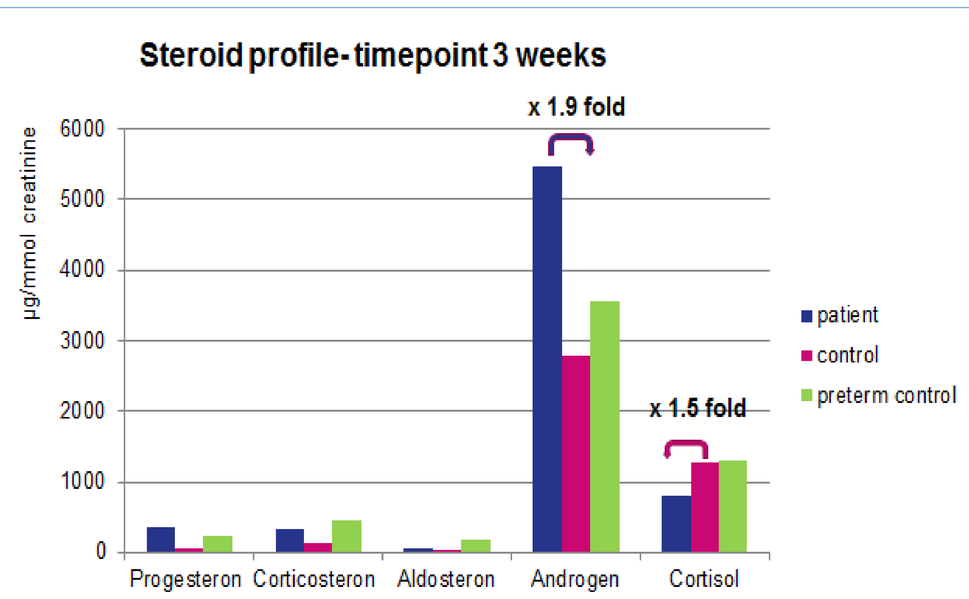


Fig.1 17OHP was in the normal range for gestational age on d1, but it increased rapidly thereafter. Then 17OHP normalized within 4 weeks and after termination of antiviral therapy.



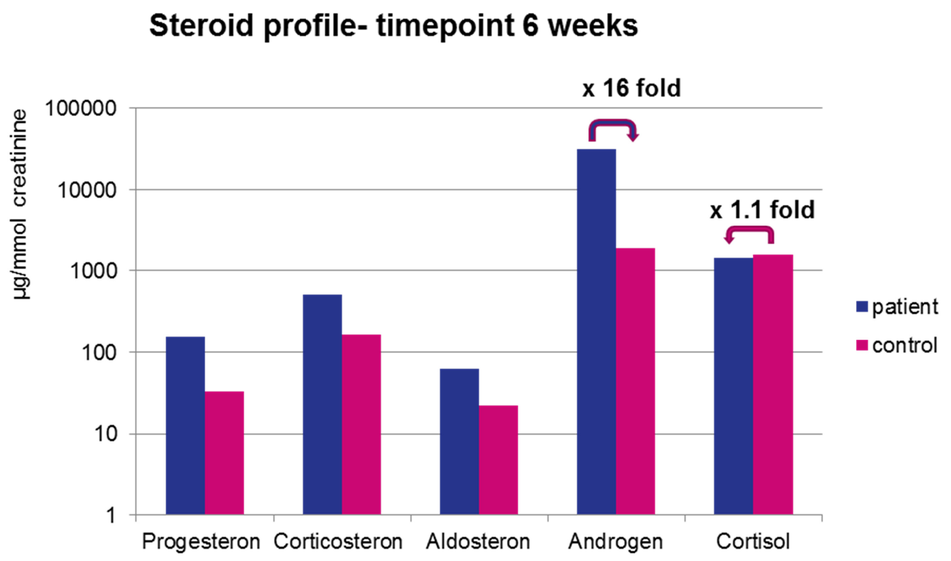
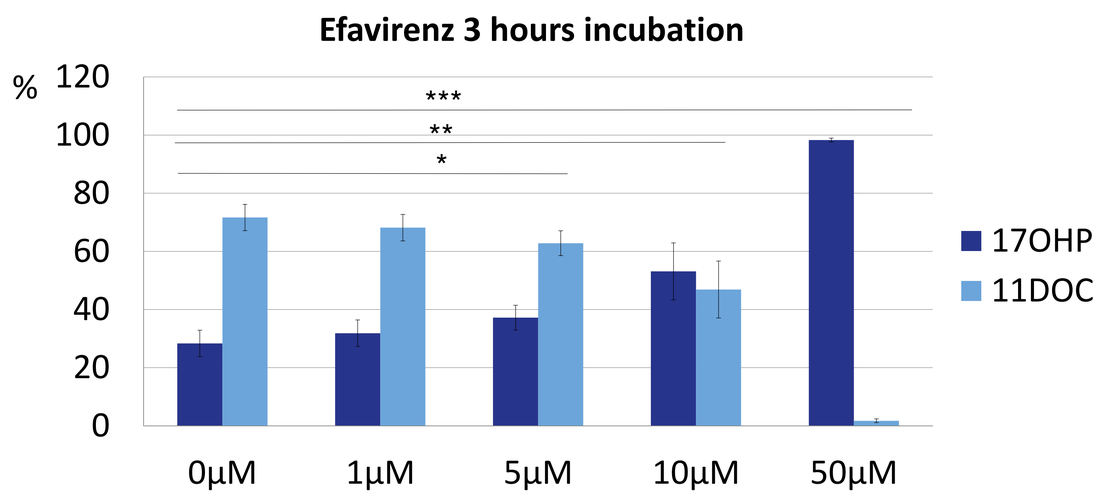


Fig.2 The urinary steroid profile showed elevated progesterone and androgen metabolites with low-normal cortisol metabolites suggesting diminished 21-hydroxylase activity.

Fig.3 The urinary steroid profile showed a normal cortisol, but unfortunately still elevated androgens at 6 weeks of age. Genetic testing of the CYP21A2 gene excluded the mutations in P30L, I2G-Splice, Del 8 bp E3, I172N, Cluster E6, V281L, L307 frameshift, Q318X, R356W, P453S, R483P. Sequencing of the whole gene is pending.

In vitro studies/methods Effect of Efavirenz, Tenofovir, Emtricitabine and Zidovudine was tested on adrenal steroidogenesis in adrenal H295R cells. Cells were treated with substances at physiologic and supraphysiologic concentrations for 3 and 24 hours. The 21-hydroxylase activity was assessed by looking at the conversion of labelled [3H] 17-hydroxyprogesterone (17OHP) to 11-deoxycortisol (11DOC) using thin layer chromatography (TLC) as readout.

Results We observed significantly decreased 21-hydroxalyse activity in cells treated with Efavirenz at 5µM and 10µM concentrations incubated for 3 hours. Cytotoxic effect of supraphysiologic concentration (50µM) of Efavirenz caused a dramatic reduction of 21-hydroxylase activity. Other tested drugs (Zidovudine, Emtricitabine and Tenofovir) did not affect 21-hydroxylase activity.



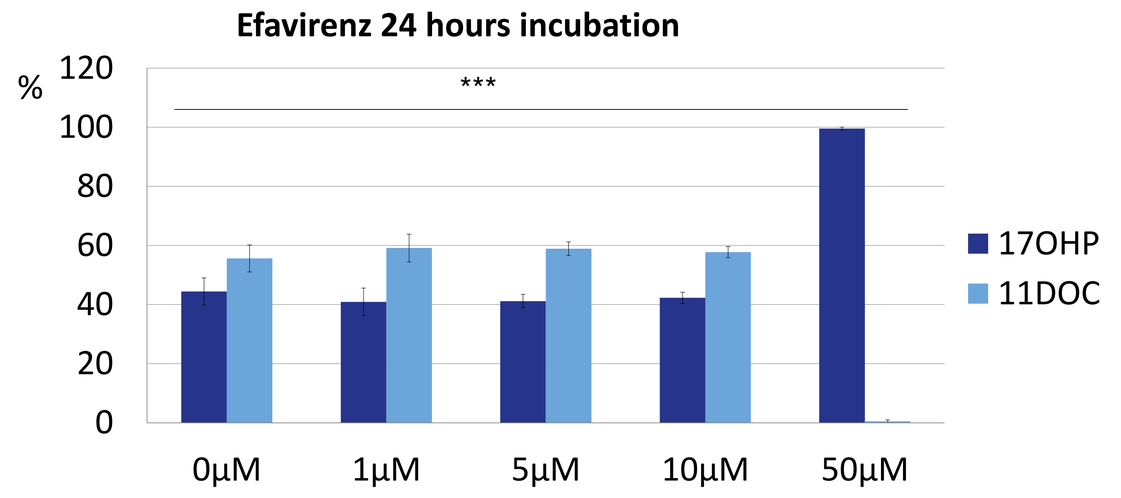


Fig.4 A + B The quantification of four independent experiments (mean±SD) is given. *p < 0.05, **p < 0.01, *** p <0.001.

Conclusion Treatment with Efavirenz affects steroidogenesis in our cell experiments at concentrations in clinical use. Our index case with laboratory investigations shows that the HIV drug Efavirenz may cause transient adrenal insufficiency resulting in pathologic neonatal screening for CAH. Therefore children on HIV drugs may require special attention for possible adrenal crisis in emergency situations and emergency supplementation of glucocorticoids may be warranted.

References

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55ESPE 20--P1

Adrenal

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DOI: 10.3252/pso.eu.55ESPE.2016

Poster presented at: ESPE 2016 PARIS

PosterSessionOnline.com