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Case Report

Antenatal tenofovir induced acute kidney injury in a neonate born to seropositive mother- A case report

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ABSTRACT

Acute kidney injury (AKI) is an independent risk factor for morbidity and mortality in neonates. The causes of neonatal AKI are varied and multifactorial . Broadly ,these can be divided into prerenal, renal, and postrenal pathologies and have long standing consequences .Neonates admitted to NICU have frequent nephrotoxic drug exposure postnatally, however antenatal /transplacental exposure has not been adequately studied and reported. Here we present a case of a newborn with AKI secondary to antenatal tenofovir exposure .Mother was diagnosed with HIV four years prior to conception and was on TLD(tenofovir disoproxil,lamivudine,dolutegravir) regimen . Drugs were continued throughout pregnancy with good compliance. Baby was delivered at term vaginally and was with mother for the first 48 hours. At 50 hours, mother complained that baby has not passed urine, for which renal functions were done and found to be deranged (Creatinine-2.3 BUN-29) .Baby was investigated for all probable causes of acute kidney injury (AKI) .However, all were ruled out based on history, examination and investigations . Urine routine showed eosinophiluria and crystalluria pointing towards drug induced AKI. Baby was hemodynamically stable and breastfeeding well throughout however the renal functions continued to deteriorate (Peak creatinine-4,BUN-40 on DOL7).Baby was managed conservatively with complete resolution by DOL-10. Tenofovir is a nephrotoxic agent and has been reported to cause various foetal side effects. Antenatal exposure to tenofovir warrants close observation and evaluation in neonates.

BACKGROUND:-

Acute kidney injury (AKI) is an independent risk factor for severe cute and chronic morbidities and mortality in neonates. The causes of neonatal AKI are varied and multifactorial and can be broadly classified as prerenal, renal, and postrenal .Neonates admitted to neonatal intensive care unit (NICU) have frequent nephrotoxic drug exposure postnatally, however antenatal /transplacental exposure has not been adequately studied and reported. Routine use of combination antiretroviral drug regimens in pregnancy has resulted in a decline in the rate of maternal to child transmission of HIV from over 20% to less than 1%[1]. Current U.S. guidelines recommend that HIV-infected pregnant women receive a three-drug regimen of two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) and either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI)[3] Current World Health Organization (WHO) guidelines are similar, recommending a three drug regimen of two NRTIs and an NNRTI(4). The preferred NRTIs in pregnancy are zidovudine and lamivudine. Use of tenofovir disoproxil fumarate (TDF), a nucleotide reverse transcriptase inhibitor and preferred drug in non-pregnant adults, has been increasing in pregnancy despite its recommendation as an alternative drug in pregnancy due to concerns about potential adverse effects on the infant. Here we are reporting a case of term neonate presented with AKI caused by antenatal exposure to tenofovir.

CASE PRESENTATION:-

A 38 weeks male term baby, 2760gm, born by lscs to HIV positive primi mother was referred to NICU at 72 hours of life with decreased urine output (only once since birth as per mother) and two episodes of vomiting. The mother was diagnosed with HIV 4 years back for which she was on TLD regimen with good

compliance. Baby was admitted to NICU for urine output monitoring. Renal function tests (RFT)were sent were found deranged creatinine-2.3 urea-29 . Baby was catheterized for strict urine output monitoring .Baby had oliguria with urine output of 0.37ml/kg/hr on Day 4.Initially considering vomiting prerenal causes of AKI were considered and baby was subjected to fluid challenge. However there was no improvement. Although the antenatal scans were normal, to rule out any structural renal anomaly, ultrasound Abdomen KUB and renal doppler was done which was found to be normal. Urine routine and culture reports were also normal. Maternal and neonatal records were reviewed for any nephrotoxic drug exposure. Urinary sodium was 54meq/l ,osmolality was<400,urine to plasma creatinine ratio 9.8 ,suggesting Renal cause of AKI(normal urine sodium<20meq/l,urine osmolality >800)and eosinophiluria suggesting drug induced AKI. Serial renal functions showed further deterioration.Nephrologist opinion was taken and baby was started on restricted potassium free fluid regimen as per insensible losses and monitored . Renal parameters showed gradual improvement with improvement in urine output on Day 8 and biochemical resolution of AKI on Day 10 of life.

Dol(Day of Life)	3	4	5	6	7	8	9	10
Creatinine	2.3	2.9	3.2	3.5	4	3.1	2	0.9
BUN	29	34	36	38	40	28	25	10
Urine output(ml/kg/hr)	0.3	0.37	0.2	0.15	0.2	0.7	1.2	2.4

DISCUSSION:-

Thus we present a case of acute kidney injury manifested on day 3 of life secondary to antenatal exposure to tenofovir in seropositive mother. The baby was evaluated for all other causes and managed conservatively. Not many cases of AKI secondary to antenatal antiretroviral drug exposure have been reported in literature. Antenatal maternal drug exposure should be considered while evaluating a newborn with AKI in first week of life[2]. Mother-to-child transmission (MTCT) of HIV has been reduced significantly by using antiretroviral therapy during pregnancy, labor and delivery, and breastfeeding.[3] Tenofovir disoproxil fumarate (TDF) is a efficacious nucleotide analogue reverse transcriptase inhibitor (NRTI) that has become a first-line agent in ART due to its once-daily dosing and excellent tolerability and compliance.[5] Given the increasing use of TDF in treatment as well as prophylaxis, the incidence of pregnant women being exposed to TDF at the time of conception or during pregnancy is rising [16]. The US Food and Drug Administration has classified TDF as a Pregnancy Category B drug, meaning there is no adequate evidence of risk in humans, and has been insufficiently evaluated. For HIV1–infected pregnant women, TDF is only recommended as an alternative NRTI [17]. Therefore, obtaining and reporting safety information on TDF during pregnancy and its implications on foetus has important public health implications[6]. Most published data on tenofovir and its effect on foetus is derived from retrospective data analysis. Chi et al in their retrospective analysis of 397 sero positive women and their babies reported 0.8% babies (20/198) in the TDF-exposed group adverse events; most common causes of morbidity were septicemia (22) and pneumonia (8) . Sabbatini et al in their report of 33 mother infant dyads from Italy reported 2 of 7 babies with in utero TDF exposure reported congenital pyelectasis . Other isolated reports of teratogenicity, abnormalities of foetal growth, bone and cartilage abnormalities, mitochondrial toxicity and renal injury have been reported, but data is inconclusive regarding the direct role of TDF in these abnormalities. Therefore, more

rigorous research on the safety of TDF in pregnancy is essential. Prospectively collected data, randomized study designs, and serial renal function monitoring of exposed babies and renal biopsy in suspected cases would be particularly resourceful. Given the increase in TDF use among pregnant women and the rapidly changing antiretroviral drug use guidelines, the need for and significance of such literature is compelling.

CONCLUSION

Tenofovir is a nephrotoxic agent and has been reported to cause various foetal side effects. Antenatal exposure to tenofovir warrants close observation and evaluation in neonates.

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