Abstract: 963; CROI 2016

Efavirenz Toxicity Manifesting As Cerebellar Ataxia: Case Series From South Africa

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BACKGROUND

Efavirenz (EFV) is widely prescribed in many developing settings – frequently in fixed dose combination (FDC) tablets at a dose of 600mg.

Neurological side effects are frequent; most start days-weeks after EFV initiation and resolve within months. These include dizziness, nightmares and depressed mood.

Guidelines advise that patients 35kg - 40kg should have dose down-adjustment to EFV 400mg daily.

Pharmacokinetics of EFV is affected by the CYP2B6 genotype which determines EFV metabolizer status



METHODS:

Site: Tshepong Hospital: 400 bed adult internal medicine department in Matlosana, North West Province, South Africa (160km SW of Johannesburg) with a large ART treatment cohort of >40,000 people receiving ART in the catchment area

Cases: We report the clinical findings in HIV-infected women receiving FDC ART admitted to hospital with severe ataxia.

Clinical Investigations:

1. Duration of ART and prior contacts with health system, abstracted from clinical records

2. Lumbar puncture

3. Chest x-ray

4. Brain imaging (CT or MRI)

5. CBC, serum vitamin B12, syphilis screen (RPR), TSH

RESULTS

- 10 HIV-infected women, all taking FDC EFV600mg with severe cerebellar ataxia, all had broad-based gait, unable to walk unaided, and 8/10 unable to sit unaided, all had staccato speech.
- Two on rifampin-containing TB treatment
- One on phenytoin – only one with nystagmus
- 4/10 had recent prior admissions: one with psychosis

CHARACTERISTICS	
Women	10/10
Median Age	30.5 (IQR: 25-35) years
Duration of EFV prior to admission	2 (IQR:1-3.5) years
Weight	34.6 (IQR:29.3-40.5) kg
CD4	299 (244.5-510) cells/mm^3
Suppressed viral load	9/10 suppressed on admission

Other investigations

1. **Lumbar punctures:** all normal
2. **Brain Imaging:** 8 atrophy, 2 normal, no mass lesions
3. **Syphilis screen:** 8/8 done - all negative
4. **Vitamin B12**: none with levels <133pl/mL
5. **TSH:** None with elevated levels

EFV concentrations 24-48 hours post admission (therapeutic range 1-4mg/L)
9/10: >20 mg/L,
1/10: 18.6mg/L

Outcomes

2 deceased: 10 and 14 days after discharge, with CD4 70 and 572, respectively.

7 Syndrome resolved: A median time of 8 weeks (IQR 5.5-13) after cessation of EFV.

1 restarted on FDC in clinic → recurrence of symptoms.

Therapeutic Intervention:
6/8 EFV switched to lopinavir/ritonavir
2/8 EFV 400 →one recurrence

CONCLUSIONS

- Although there are two prior reports of EFV ataxia in children, we report cerebellar EFV toxicity (CET) in adults with low body weight
- Late presentation suggests cumulative toxic effect of EFV
- Very high EFV concentrations suggest these patients had either slow or very slow CYP2B6 metaboliser genotypes, although this was not assessed.
- Screening for CYP2B metaboliser status prior to EFV – especially <45kg?
- FDC dosing with EFV600mg does not accommodate low weight individuals and FDC EFV400mg should be made widely available
- Gait ataxia in HIV-infected adults < 45kg on EFV for at least six months should trigger consideration of CET.