Drug – Drug Interactions Between Newer Anti-Retroviral Drugs And Anti Epileptics - A Review

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ABSTRACT

Drug – Drug Interactions (DDIs) are the leading cause of drug toxicity and emergence of drug resistance, ultimately leading to increased burden in People Living with Human Immunodeficiency Virus (PLHIV). On an average 55% of people on Anti Retroviral Therapy (ARVs) are co-administered with Anti Epileptic Drugs (AEDs). The introduction of newer anti-retroviral drugs such as dolutegravir, bictegravir, emtricitabine, doravirine are proven to have less side effects, high tolerability and effective decrease in the viral load, but the risk of DDIs still stands to be high. This review briefly describes about the pharmacokinetic properties of dolutegravir, bictegravir, emtricitabine, doravirine, mechanism of interaction between the above mentioned ARVs and AEDs, effect of DDIs on ARVs, effect of DDIs on interacting AEDs, outcome of DDIs and possible management of DDIs. The majority of DDIs were found affecting the metabolism and the absorption of the drugs. UGT1A1, CYP 3A are the two important classes of metabolic enzymes involved in the DDIs and P-glycoprotein (P-gp) is the transporter involved in the DDIs affecting the absorption. Significant interactions have been found in between the above mentioned newer ARV’s with carbamazepine, oxcarbazepine, phenytoin and phenobarbitol.

INTRODUCTION

Drug – Drug Interactions (DDIs) are the leading cause for drug toxicity and emergence of drug resistance, ultimately leading to increased burden in people living with HIV (PLHIV) (Stader et al., 2018). The incidence of seizure disorder in PLHIV is as high as 11%. In addition to it, there are increased incidence of provoked seizures in the case of Central Nervous System (CNS) opportunistic infections. On an average 55% people on anti retroviral therapy (ARVs) are co-administered with Anti Epileptic Drugs (AEDs) (Birbeck et al., 2012).

The introduction of newer anti-retroviral drugs such as dolutegravir, bictegravir, emtricitabine, doravirine are proven to have less side effects, high tolerability and effective decrease in the viral load, but the risk of DDIs still stands to be high and it is significantly increased in the presence of multiple co-morbidities and polypharmacy (Stader et al., 2018). Interaction between AEDs and ARVs are common and can result in altered concentration of both the classes of drugs and in worst case scenarios it may lead to drug toxicity (Deeks, 2018). This
Table 1: substrates of ARV drugs and AEDs

| ARV drugs              | Substrate       | AEDs            | Substrate               | Inducer   | Inhibitor |
|------------------------|-----------------|-----------------|-------------------------|-----------|-----------|
| Dolutegravir (Song et al., 2016) | UGT1A1, CYP3A4, P-gp | Carbamazepine (Anderson, 1998; Zhang et al., 2012) | CYP1A2, CYP3A4, CYP2C9, CYP2C19, P-gp | CYP2C9, CYP3A4, CYP1A2, UGT. |
| Bictegravir (Deeks, 2018) | UGT1A1, CYP3A, P-gp | Oxcarbazepine (Zhang et al., 2012; Johan-nessen and Landmark, 2010) | Alylketoreductases, CYP3A4, P-gp, UGT | CYP2C19 |
| Tenofovir alafenamide fumarate (Hill et al., 2018) | UGT1A1, CYP3A, P-gp | Phenytoin (Anderson, 1998) | CYP2C9, CYP2C19 | CYP2C9, CYP3A Families, CYP1A2, UGT |
| Doravirine (Khalilieh et al., 2016) | UGT1A1, CYP3A | Phenobarbital (Anderson, 1998) | CYP2C9, CYP2C19 | CYP2C9, CYP3A4, CYP1A2 |

The article reviews the DDIs between the newer antiretrovirals such as dolutegravir, bictegravir, tenofovir alafenamide, doravirine and their approved combinations with AEDs.

**Newer anti-retroviral drugs and their pharmacokinetics**

**Dolutegravir (DTG)**

It is an integrase inhibitor, currently being used in combination with other ART drugs (Song et al., 2016). The drug binds to the active site of integrase enzyme and chelates the magnesium ions which inhibit the strand transfer step mediated by the integrase, ultimately abstaining the formation of proviral deoxyribonucleic acid (DNA) (Yadav et al., 2018). Currently dolutegravir; 50 mg, once daily (OD) is the dose used in adults and adolescents, it can be given orally without food, but increased absorption is noted when administered along with the food (Healthcare, 2013).

DTG is extensively bound to alpha-1-acid glycoprotein and albumin, with a volume of distribution of 171 and 90 % of the drug is metabolised through uridine diphosphate glucuronyl transferase (UGT1A1) and 10 % of drug metabolises through cytochrome-3A (CYP-3A). 30% of the metabolites are excreted in the urine and 60 % of the unchanged drug is excreted through faeces (Healthcare, 2013).

**Bictegravir (BIC)**

It is available as fixed drug combination (FDC) with emtricitabine (FTC) and tenofovir alafenamide (TAF). The usual dose of BIC is 50 mg with TAF - 25 mg and FTC - 200 mg, OD, BIC is a second generation integrase inhibitor and the mechanism of action is similar to that of dolutegravir (Hill et al., 2018). Use of BIC is contraindicated with other anti-retroviral drugs except the specified FDC, as it may lead to chelation of bictegravir (Deeks, 2018).

BIC has shown increased absorption when taken along with fatty meal, extensively plasma bound, with plasma half life period of 17.3 hours and metabolised through UGT1A1 and CYP3A4. It is primarily eliminated in the unchanged form through faeces (65%) and as a metabolite through urine (35%) (Sciences, 2018). The FDC can be used in mild to moderate hepatic impairment but it is contraindicated if the creatinine clearance (crcl) is less than 30 ml/min (Deeks, 2018).

**Tenofovir alafenamide fumarate**

TAF belongs to nucleotide analogue reverse transcriptase inhibitor (NtRTIs) class. It is available as a single drug as well in combination with FTC and BIC, the usual dose is 25 mg, OD. TAF is more efficient in achieving higher concentration of tenofovir diphosphate (TFV dp) (metabolite of TAF) in plasma and increased penetration into HIV when compared to tenofovir disoproxil fumarate (TDF) (Ray et al., 2016). The TAF metabolises into TFV dp, which competitively inhibits the reverse transcriptase enzyme and gets incorporated into DNA finally terminating the viral DNA (for Biotechnology Information, 2019).
Table 2: Drug drug interactions between ARV drugs and AEDs

| Drug-Drug interactions | Effect on antiretroviral | Effect on anti-epileptics | Outcome of DDIs | Management |
|------------------------|--------------------------|---------------------------|-----------------|------------|
| 1. Dolutegravir- Carbamazepine (Song et al., 2016). | Reduced concentration of dolutegravir | Usually unchanged | Decrease or loss of therapeutic effect of dolutegravir | If possible avoid combination or Increase dolutegravir dose to 50 mg, BID |
| 2. Dolutegravir- Oxcarbazepine (Kandil et al., 2018). | | | |
| 3. Dolutegravir- Phenytoin (Cattaneo et al., 2019). | | | |
| 4. Dolutegravir- Phenobarbitol (Cattaneo et al., 2019). | | | |
| 1. Bictegravir- Carbamazepine (Healthcare, 2013) | Reduced concentration of bictegravir | Usually unchanged | Decrease or loss of therapeutic effect of bictegravir | Contraindicated use alternative anti convulsants |
| 2. Bictegravir- Oxcarbazepine (Yadav et al., 2018) | | | |
| 3. Bictegravir- Phenytoin (Yadav et al., 2018) | | | |
| 4. Bictegravir- Phenobarbitol (Deeks, 2018). | | | |
| 1. Tenofovir alafenamide- Carbamazepine (Yadav et al., 2018) | Reduced concentration of tenofovir alafenamide | Usually unchanged | Decrease or loss of therapeutic effect of tenofovir alafenamide | Use is not recommended and alteration with other AEDs is suggested |
| 2. Tenofovir alafenamide – Oxcarbazepine (Yadav et al., 2018) | | | |
| 3. Tenofovir alafenamide – Phenytoin (Yadav et al., 2018; Deeks, 2018) | | | |
| 4. Tenofovir alafenamide – Phenobarbitol (Deeks, 2018). | | | |
| 1. Doravirine- Carbamazepine (Khalilieh et al., 2016) | Reduced concentration of doravirine | Usually unchanged | Decrease or loss of therapeutic effect of doravirine | Use is not recommended and alteration with other AEDs is suggested |
| 2. Doravirine – Oxcarbazepine (Khalilieh et al., 2016) | | | |
| 3. Doravirine – Phenytoin Khalilieh et al. (2016) | | | |
It shows increased absorption when taken along with a fatty meal, 80% bound to plasma proteins and metabolised by cathepsin A and carboxyl esterase 1. Only 1% of TAF is eliminated through urine and 35% is eliminated through faeces. TAF use is not recommended in end stage renal disease (ESRD) patients with crcl less than 15 ml/ min, who are not a candidate for dialysis or on chronic hemodialysis, but can be used in mild hepatic impairment (Deeks, 2018; Hill et al., 2018).

**Doravirine**

Doravirine is available in the form of single dose, 100 mg tablet and also as an FDC with lamivudine, 300 mg and tenofovir disoproxil fumarate, 300 mg. It is a novel non-nucleoside reverse transcriptase inhibitor(NNRTI), acts by binding to the hydrophobic pocket near to the active site rendering the inhibitor inactive for viral DNA polymerization (Anderson et al., 2014).

The absorption of doravirine is not affected by presence of food and is rapidly absorbed by oral administration, 75 % of the drug is distributed through protein binding and is metabolised by CYP3A4 and CYP3A5. Excretion of doravirine is mainly through oxidative metabolism and only a minor proportion of the drug is excreted through urine and faeces (Khalilieh et al., 2016).

**Potential mechanism of drug to drug interactions related to co-administration of ARVs and AEDs**

The pharmacokinetic type of DDIs is observed between the ARVs and AEDs. The majority of DDIs are found affecting the metabolism and the absorption of the drugs. UGT1A1, CYP 3A are the two important classes of metabolic enzymes involved in the DDIs and p-glycoprotein (P-gp) is the transporter involved in the DDIs affecting the absorption, the individual substrates, there inducers and inhibitors of the drugs involved in DDIs are mentioned in Table 1 (Palleria et al., 2013).

Carbamazepine (CBZ), oxcarbazepine (OCZ), phenytoin and DTG are substrates of UGT1A1 and CYP 3A, where the former three drugs are potent inducers of the above mentioned enzymes. Co-administration of CBZ or OCZ or phenytoin with DTG, will result in increased metabolism of DTG, the ultimate effect of the DTG and mentioned AEDs are explained in Table 2. So, it is indicated to increase the dosage of DTG to 50 mg/ BID when administered with phenytoin or CBZ or OCZ (Song et al., 2016; Kandil et al., 2018).

Phenobarbital is also a potent inducer of UGT1A1 and CYP 3A and the mechanism is similar to that of CBZ and OCZ, but the reaction is dose dependent. If a low dose of phenobarbital is administered with DTG via monitoring of plasma DTG concentration, there is no requirement for dosage adjustment but in case of high dose, it is advised to increase the dosage of dolutegravir to 50 mg, BID (Hikasa et al., 2018). DTG is currently recommended in combination with lamivudine, 300 mg, where lamivudine doesn’t have any significant interactions with AEDs (Cattaneo et al., 2019).

Plasma level concentration of BIC when co-administered with carbamazepine, oxcarbazepine, phenobarbital and phenytoin which are strong inducers of UGT1A1 and CYP 3A4 is very low and was not acquiring the therapeutic levels (even after administering double strength) in the plasma, so the use is not recommended and alteration with other AEDs is suggested (Deeks, 2018; Hill et al., 2018).

Tenofovir alafenamide fumarate is a substrate for p-glycoprotein (P gp), UGT1A1 and CYP 3A. It is known that strong inducers of P-gp such as carbamazepine and oxcarbazepine can alter the absorption pattern and decrease the concentration of drug in the plasma, so the use is contraindicated. Use of phenobarbital, phenytoin and oxcarbazepine is not recommended as they are strong inducers of CYP 3A and UGT1A1 and resulting low plasma concentration (Hill et al., 2018).

Use of carbamazepine, phenytoin, oxcarbazepine is not recommended with doravirine as the mentioned AEDs will induce the metabolism of doravirine through up regulation of UGT1A1 and CYP 3A, so it is suggested to use alternative AEDs (Boyle et al., 2019).

**CONCLUSIONS**

The newer ARVs are not potential enzyme inducers or inhibitors, the DDIs profile of the newer ARVs are very limited. But they still possess to have some significant interactions with AEDs which can ultimately lead to loss of the therapeutic efficacy of the interacting ARV drugs, it is seen that the AEDs are unaffected due to the DDIs. So monitoring of the patients who are co-administered with ARVs and AEDs are suggested, particularly when the patient is receiving AEDs such as carbamazepine, phenytoin, oxcarbazepine and phenobarbital.

**Conflict of Interest**

None.

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