The Pharma Innovation Journal 2020; 9(3): 67-69

www.ThePharmaJournal.com

The Pharma Innovation

ISSN (E): 2277- 7695
ISSN (P): 2349-8242
NAAS Rating: 5.03
TPI 2020; 9(3): 67-69

www.thepharmajournal.com
Received: 26-01-2020
Accepted: 28-02-2020

M Prashanthi Evangelin
Department of Chemistry, Southern Institute of Medical Sciences, Andhra Pradesh, India

Dr. P Prem Kumar
Southern Institute of Medical Sciences, Andhra Pradesh, India

B Gopi Krishna
Doctor of Pharmacy, Southern Institute of Medical Sciences, Andhra Pradesh, India

S Yashita Raga
Doctor of Pharmacy, Southern Institute of Medical Sciences, Andhra Pradesh, India

S Yashita Raga
Doctor of Pharmacy, Sothern Institute of Medical Sciences, Andhra Pradesh, India

SVS Gopi Raju
Doctor of Pharmacy, Sothern Institute of Medical Sciences, Andhra Pradesh, India

Corresponding Author:
M Prashanthi Evangelin
Department of Chemistry, Southern Institute of Medical Sciences, Andhra Pradesh, India

Doravirine: A review

M Prashanthi Evangelin, Dr. P Prem Kumar, B Gopi Krishna, S Yashita Raga and SVS Gopi Raju

Abstract
HIV-1 patients with failure regimen due to resistant mutant's leads to the development of third new antiviral agent called Doravirine to treat infection in 2018 which was metabolized through CYP3A pathway. It is a highly specific and unique NNRTI (non-nucleoside reverse transcriptase inhibitor) with high *in vitro* activity against wild type virus and mutant viruses containing NNRTI resistance mutations (K103N, Y181C, G190A, E138K, and K103N/Y181c). Doravirine shows excellence aqueous solubility when compared with second generation NNRTIs so, it has more chances for further development and this promising novel drug had preferred for the treatment of AIDS, which is currently in its phase III clinical development. It shows strong *in vivo* antiviral activity with good tolerability and it shows adverse effects like nausea, dizziness, vomiting, abdominal pain and abnormal dreams to the some extent. The present literature reviews about the different analytical methods of Doravirine.

Keywords: Doravirine, NNRTI, antiviral, analytical method

Introduction
Human immunodeficiency virus (HIV) is one of the most prevalent disease where HIV-1 reverse transcriptase (HIV-1 RT) is successful target in anti-retro viral therapy. Due to their potency, low toxicity and high specificity Non-nucleoside reverse transcriptase (NNRT) inhibitors occupy a valuable place among HIV-1 RT inhibitors. Almost six drugs were finalised for HIV-1 therapy in which one of the main drug was doravirine [1].
However in *in vitro*, doravirine is active against NNRT inhibitors resistant strains with a single dose daily [2]. Food doesn't affect the bioavailability of doravirine alone or other in fixed dose combinations [3]. This drug is metabolised through CYP450 3A and can be co-administrated with many of drugs like statins, oral contraceptives [2], aluminium/magnesium-containing antacid or proton pump inhibitors [4], elbasvir+grazoprevir or ledipasvir-sofosbuvir [5], atorvastatin [6] etc. Strong CYP3A inducers such as rifampicin shouldn't be co-administered with doravirine. However in the place of rifampicin low CYP3A inducer like rifabutin can be co-administered if doravirine dosing is raised from100mg once to twice daily [7, 8]. Diabetes associated with HIV patients can concomitantly use metformin 100mg and doravirine 100mg without any dose adjustment [9]. This drug is well tolerated in patients with severe renal impairment [10] and hepatic impairment [11]. Doravirine is well tolerated than efavirenz in case of neuropsychiatric and cutaneous adverse events [12]. For previously untreated patients combination of doravirine with two nucleoside reverse transcriptase inhibitors will be predominant therapy option [13]. However in elderly and adult women dose adjustment is not required [14].

Source of Literature
Ming Yao, Laishun Chen and Nuggehally R Srinivas *et al.* [15] developed a liquid chromatographic-mass spectrometric (LC-MS) assay for the determination of Doravirine in rat heparinized plasma using reversed-phase HPLC combined with positive atmospheric pressure ionization (API) mass spectrometry. After protein precipitation of plasma samples (0.1ml) with acetonitrile a 50µl aliquot of the supernatant was mixed with 100µl of 10mM ammonium formate (pH 4.0). An aliquot of 25µl of the mixture was injected onto a BDS Hypersil C_{18} column (50×2mm; 3µm) at a flow-rate of 0.3 ml/min. The mobile phase comprising of 10mM ammonium formate (pH 4) and acetonitrile (60:40, v/v) was used in an isocratic condition, and Doravirine was detected in single ion monitoring (SIM) mode. Standard curves were linear ($r^2 \geq 0.994$) over the concentration range of 4-1000ng/ml. The mean predicted concentrations of the quality control (QC) samples deviated by less than 10%

from the corresponding nominal values; the intra-assay and inter-assay precision of the assay were within 8% relative standard deviation.

M.V. Kumudhavalli *et al*. [16] In order to estimate the doravirine in tablet dosage form reverse phase high performance liquid chromatographic method was developed. An inertsil C-18, 5µm column having dimensions 250x4.6mm as internal diameter in isocratic mode with mobile phase of Tetrabutyl ammonium hydrogen sulphate buffer solution and Acetonitrile in the ratio of 40:60v/v. The flow rate was 1.5ml/min and effluents were monitored at 225nm. The retention time for Itraconazole was 5.617min.

Sanchez RL et al., [17] This investigation is mainly concerned with absorption, distribution, metabolism and elimination of doravirine (MK-1439). Later on two clinical trials were conducted in healthy individuals: an oral single dose [^{14}C] doravirine (350 mg, ~200 µCi) trial (n = 6) and an intravenous (IV) single-dose doravirine (100 µg) trial (n = 12). *In vitro* metabolism, protein binding, apparent permeability and P-glycoprotein (P-gp) transport studies were conducted. On oral administration of doravirine, the absorbed drug gets converted into oxidative metabolite (M9) which is generated by CYP3A4 via metabolism. On IV administration of doravirine, clearance and volume of distribution were found to be 3.73 L/h (95% confidence intervals (CI) 3.09, 4.49) and 60.5 L (95% CI 53.7, 68.4), respectively. Studies found that *in vitro*, doravirine has low protein binding capacity (unbound fraction 0.24) but has good passive permeability. Though doravirine was a P-gp substrate, P-gp efflux is not involved in either absorption or elimination of drug. Finally, doravirine is a drug with low clearance which is 8primarily eliminated by CYP3A-mediated metabolism.

Li-khang Zang, Ross Yang [18], Doravirine is used in therapy of HIV-1 as a non-nucleoside reverse transcriptase inhibitors (NNRTI). Purity of pharmaceutical is essential for drug regulation authorities to show either pharmacological or toxicological effects. Along with these drug impurity profiles is also essential to maintain safety and potency of drug. Impurities in the pharmaceuticals can be identified by latest achievements in mass spectrometry instrumentation using minute amount of sample. Structural determination of the major impurities of Doravirine can be identified by Ultra Performance Liquid Chromatography-high-resolution-Tandem Mass Spectrometry (UHPLC-HRMS/MS) technique which results in five trace-level impurities of Doravirine.

Ka Lai Yee, Rosa I. Sanchez, Patrice Auger, Rachael Liu, Li Fan, Ilias Triantafyllou, Ming-Tain Lai, Mike Di Spirito, Marian Iwamoto, Sauzanne G. Khalilieh [19], In order to treat the patients with human immunodeficiency virus type 1 (HIV-1) Doravirine, a well-tolerated, highly potent and non-nucleoside reverse transcriptase inhibitor (NNRTI) which acts as a obstacle to resistance is highly essential for therapy. Doravirine is metabolized through CYP3A4 substrate while efavirenz is CYP3A4 inducer so, it is essential to estimate the pharmacokinetic profile of two drugs. By conducting an experiment on healthy adults doravirine pharmacokinetic was evaluated when switched from efavirenz to doravirine. Firstly, doravirine 100mg was given for 5 days once daily (OD). After 7 days wash out period administration of efavirenz 600mg OD for 14 days was done, simultaneously doravirine 100mg OD for 14 days was administered. Collection of blood samples was done to evaluate pharmacokinetic profile of drug. Twenty healthy adults were listed, and 17 completed the study. Cessation of efavirenz after one day, the doravirine area under the concentration-time curve from predosing to 24 h post dosing ($AUC_{0–24}$), maximum observed plasma concentration (C_{max}), and observed plasma concentration at 24 h post dosing (C_{24}) were reduced by 62%, 35%, and 85%, respectively, compared with the values with no efavirenz pretreatment. By the day 14 of efavirenz cessation this decreases recovered to 32%, 14%, and 50% for $AUC_{0–24}$, C_{max}, and C_{24}, respectively. On the second day of efavirenz cessation, doravirine C_{24} touched the projected therapeutic trough concentrations, based on *in vitro* efficacy. On the day 1 and day 15 the geometric mean concentrations of efavirenz were 3,180 ng/ml and 95.7 ng/ml respectively and the therapeutic concentration of efavirenz was >1,000 ng/ml until day 4. In a virologically suppressed population there is no need of dose adjustment in order to maintain therapeutic concentrations.

References

1. Namasivayam V, Vanngamudi M, Kramer VG, Kurup S, Zhan P, Liu X *et al*. The journey of HIV-1 non-nucleoside reverse transcriptase inhibitors (NNRTIs) from lab to clinic. J Med Chem. 2019; 10:4581-4883.
2. Johnson M, Kumar P *et al*. Switching to Doravirine/Lamivudine/Tenofovir Disoproxil Fumarate (DOR/3TC/TDF) Maintains HIV-1 Virologic Suppression through 48 weeks: Results of the Drive-Shift Trial. J Acquir immune Defic Syndr, 2019; 81(4):463-472.
3. Behm MO, Yee KL *et al*. The effect of food on Doravirine bioavailability: Results from two pharmacokinetic studies in healthy subjects. Clin Drug Investig. 2017; 37(6):571-579.
4. Khalilieh SG, Yee KL *et al*. A study to evaluate Doravirine pharmacokinetics when coadministered with Acid-Reducing Agents. J Clin Pharmacol. 2019; 59(8):1093-1098.
5. Ankrom W, Sanchez RI *et al*. Investigation of Pharmacokinetic interactions between Doravirine and Elbasvir-Grazoprevir and Ledipasvir-Sofosbuvir. Antimicrob Agents Chemother. 2019; 63(5):e02491-18.
6. Khalilieh SG, Yee KL *et al*. Results of a Doravirine-Atorvastatin Drug-Drug interaction study. Antimicrob agent's chemother. 2017; 61(2):01364-16.
7. Khalilieh SG, Yee KL *et al*. Doravirine and the potential for CYP3A-mediated drug-drug interactions. Antimicrob Agents Chemother. 2019; 63(5):e02016-18.
8. Khalilieh SG, Yee KL *et al*. Multiple doses of rifabutin reduce exposure of doravirine in healthy subjects. J Clin Pharmacol, 2018.
9. Sanchez RI, Yee KL *et al*. Evaluation of the pharmacokinetics of metformin following administration with Doravirine in healthy Volunteers. Clin. Pharmacol Drug Dev, 2019.
10. Ankrom W, Yee KL *et al*. Severe Renal impairment has minimal impact on Doravirine Pharmacokinetics. Antimicrob Agents Chemother. 2018; 62(8):e00326-18.
11. Khalilieh S, Yee KL *et al*. Moderate hepatic impairment does not affect doravirine pharmacokinetics. J Clinphar, acol. 2017; 57(6):777-783.
12. Colombier MA, Molina JM. Doravirine: a review. Curr Opin HIV AIDS. 2018; 13(4):308-314.
13. Molina JM, Squires K *et al*. Doravirine versus ritonavir-boosted darunavir in antiretroviral-naive adults with HIV-1 (DRIVE-FORWARD): 48-week results of a randomised, double-blind, phase 3, non-inferiority trial. Lancet HIV.

2018; 5(5):e211-e220.
14. Behm MO, Yee KL, Fan L, Fackler P. Effect of gender and age on the relative bioavailability of doravirine: results of a phase 1 trial in healthy subjects. Antivir Ther. 2017; 22(4):337-344.
15. Yao M, Chen L, Srinivas NR. Quantitation of itraconazole in rat heparinized plasma by liquid chromatography-mass spectrometry. Journal of Chromatography B: Biomedical Sciences and Applications. 2001; 752(1):9-16.
16. Kumudhavalli MV. Isocratic RP-HPLC, UV Method Development and Validation of Itraconazole in Capsule Dosage Form. International Journal of Pharmaceutical Sciences and Research. 2011; 2(12):32-69.
17. Sanchez RL, Fillgrove KL *et al*. Characterization of the absorption, distribution, metabolism, excretion and mass balance of doravirine, a non-nucleoside reverse transcriptase inhibitor in humans. Xenobiotica. 2018; 28:1-11.
18. Li-Khang Zang, Ross Yang. Characterisation of impurities of HIV NNRTI doravirine by UHPLC- High resolution MS and tandem MS analysis: Characterisation of impurities of doravirine. Journal of mass spectrometry. 2016; 51(10).
19. Ka Lai Yee, Rosa I Sanchez *et al*. Evaluation of doravirine pharmacokinetics when switching from efavirenz to doravirine in healthy subjects. Antimicrobial agents and chemotherapy. 2017; 61(2):e01757-16.