IJPSR (2020), Volume 11, Issue 6 (Research Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 12 July 2019; received in revised form, 25 November 2019; accepted, 10 February 2020; published 01 June 2020

# PHARMACOKINETIC DRUG INTERACTIONS BETWEEN HMG-COA REDUCTASE INHIBITORS PITAVASTATIN WITH CONCOMITANTLY USED TICAGRELOR

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**Keywords:**

Pitavastatin, Ticagrelor, HMG-COA reductase inhibitors, Pharmacokinetic parameters

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**ABSTRACT:** In the present research, the pharmacokinetic Drug-drug interactions between HMG-COA reductase inhibitors Pitavastatin with concomitantly used Ticagrelor have been studied. Pitavastatin is a member of the blood cholesterol lowering medication class of statins while Ticagrelor is a platelet aggregation inhibitor. Combination therapy with statins and other cardiovascular medications is recommended for patients at high atherosclerotic cardiovascular patient's risk. The effect of Pitavastatin on the pharmacokinetics of Ticagrelor was studied on male Wistar rats divided into four different groups, I group is control group, II group of healthy rats administrated with Pitavastatin only in single-dose per day. III group of healthy rats administrated with Ticagrelor in a single dose per day and IV Group of healthy rats administrated with Pitavastatin and Ticagrelor in a single dose per day. The result evaluated by student's paired T-Test and the results indicate no significant increase in peak plasma concentration of Pitavastatin (7.12 ± 2.12 ng/ml) and Ticagrelor (80.02 ± 3.03 ng/ml) when administrated alone or in combination (7.32 ± 1.12 ng/ml and 82.83 ± 4.13 ng/ml) on first day (day 1). Similarly, no significant increase in peak plasma concentration of Pitavastatin (8.12 ± 1.12 ng/ml) and Ticagrelor (89.02 ± 4.13 ng/ml) when administrated alone or in combination (8.32 ± 1.62 ng/ml and 90.93 ± 3.25 ng/ml) observed on the eighth (day 8). The study results also indicate no statistically significant difference in $t_{max}$, AUC and $T_{1/2}$ for both the drug administrated alone and combination treatment.

**INTRODUCTION:** The usual effects of a drug are enhanced or diminished by another drug being taken by the patient results in drug interaction. Polypharmacy and drug interactions are common particularly among seniors. A survey of elderly individuals living in the community reported that 29% were taking five or more prescription drugs regularly [1].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.11(6).2801-06

The article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.11(6).2801-06

The investigators estimated that roughly 1 in 25 individuals were at risk [2]. Many patients who were admitted to the hospital with a variety of drug-related adverse events had experienced a drug interaction. The drug interactions do not have pharmaco-dynamics or pharmacokinetic basis. The pharmacodynamics can be easily anticipated and avoided [3].

Compounds that are highly extracted by the liver or intestine exhibit poor oral bioavailability. In addition, clearance is high, and half-life tends to be short. Plasma concentrations for a given dose vary widely between patients and multiple daily doses are required to maintain concentrations at therapeutic levels [4].

Many of these drugs are substrates for CYP3A4, the most abundant form of cytochrome P450 in the liver, and the predominant P450 enzyme in the enterocyte. Inhibitors of drug metabolism can improve bioavailability, lower clearance, reduce variability in plasma concentrations and prolong half-life. All of these factors make it easier to achieve and maintain therapeutic concentrations. In addition, the total daily dose can be reduced which results in cost reduction for both patients and the insurance companies. This may be particularly valuable in making medications more accessible in developing countries with limited budgets for high-priced pharmaceuticals [5].

Statins reduce mortality in atherosclerotic cardiovascular patients (ASCVD) and in many primary prevention patients [6, 7]. High-intensity statin therapy was recommended for patients with ASCVD age ≤75 years and moderate-to high-intensity treatment recommended for in people with ASCVD and age >75 years, diabetes mellitus in patients with 10-year ASCVD risk ≥7.5% [8]. Combination therapy with statins and other cardiovascular medications is higher for patients at high ASCVD risk. Therefore, the objective of the present research is to investigate the pharmacokinetic drug interactions between HMG-COA reductase inhibitors Pitavastatin with concomitantly used Ticagrelor.

## MATERIALS AND METHODS:

**Materials:** Pitavastatin and Ticagrelor obtained as a gift sample from MSN Laboratories, Hyderabad, India. The solvents methanol and water used were of HPLC grade procured from Finar chemicals Ltd., Ahmadabad.

**Animal Study Procedure:** Twenty four healthy Male Wistar rats (weighing 200-220 g) obtained from the animal house of CMRCP, Hyderabad which was segregated into four different groups of six animals. The animals maintained at 50% RH, animals fed with *ad libitum* and water. The protocol of the animal study was approved by the institutional animal ethical committee with No. IAEC/1657/CMRCP/T2/Ph D-16/78.

**Study Design:** The rats were segregated into four groups. Each group consists of six animals. The open-labeled parallel study design was followed [9].

**Group I:** Control Group.

**Group II:** Pitavastatin alone in a single dose per day in healthy animals.

**Group III:** Ticagrelor single dose per day.

**Group IV:** Pitavastatin and Ticagrelor concomitant as a single dose per day concomitant administration as single animals.

**Blood Sample Collection:** After the administration of the drug, 0.5 ml of blood samples drawn from each anesthetized (Isoflurane) rat at different time intervals. The samples collected and stored in 10% of K2EDTA anticoagulants (20 µl). Samples collected at 0 (predose), 0.5, 1, 2, 4, 6, 8, 10, 12, 16 and 24 h (post-dose). The blood samples centrifuged at 2500-3000 rpm for 5-6 min. The plasma samples stored in pre-labeled microcentrifuge tubes -30 °C for bioanalysis. The procedure repeated on the Eighth day (day 8). Pharmacokinetic parameters calculated with Win Nonlin® 5.1 software and data compiled [10, 11].

**Plasma Samples Preparation for HPLC Analysis:** The rat plasma (0.5 ml) samples mixed with 2.5 ml cold absolute ethanol followed by centrifugation for precipitating proteins. The precipitate mixed with 1 ml ACN and vortexed for about 1-2 min. Plasma centrifuged at 5000 rpm for 10-12 min, Acetonitrile added to the organic layer and dried over nitrogen at room temperature. Samples reconstituted in 200 µL of 70% of Acetonitrile and 30% water prior to analysis [12].

**Pharmacokinetic Analysis:** The AUC0-t (0-24 h) and $AUC_0$-α(0-∞) determined using the linear trapezoidal rule. The $AUC_{0-t}$ calculated by the formula AUC0-t + [Clast/K] where C last is the last measured plasma concentration in µg/ml. The K value indicates the limitation rate constant. The parameters like AUC, mean residence time, Volume of distribution (V/f), elimination half-life [t½] and total clearance (Cl/f) calculated using pharmacokinetic program RAMKIN.

**Peak Plasma Concentration ($C_{max}$):** The point of maximum drug concentration in plasma is called as the peak and the concentration of drug at the peak is known as peak plasma concentration.

**Time of Peak Plasma Concentration ($t_{max}$):** The time for the drug to reach peak concentration in the plasma is called as the time of peak concentration.

The above two parameters are obtained from the observed concentration versus time data in each animal group mean.

**Half-Life [t½]:** Half-life of the drug is the time required to reduce the concentration of drugs by 50%. It can be calculated from the elimination rate constant, assuming the elimination to be a first-order process.

$$t_{½} = 0.693/K$$

Where K - elimination rate constant

**Area under the Curve [AUC]:** The AUC time curve extended to infinite time represents the bioavailability of a drug. It is determined via the linear trapezoidal rule from zero hours to the last sampling time, t. It is the area under zero moment curves.

For the remaining area (Wagner's approximation)

$$\therefore \text{The total } AUC_{0-\alpha} = AUC0\text{-}t + AUC_{t-\alpha}$$

$$= AUE0\text{-}t + C(t) / K$$

When C(t) - concentration at the last time point.

**Statistical Analysis:** Statistical comparisons of the pharmacokinetic study among, Pitavastatin, Ticagrelor carried out by students paired T-Test. The $P<0.05$ considered t statistically significant. The mean ± S.E.M calculated.

## RESULTS AND DISCUSSION:

**Study of Plasma Level Concentrations:** The plasma level, Mean ± S.E.M of Pitavastatin (ng/ml) alone and in combination with Ticagrelor on first day (day 1) was recorded. The concentrations at different time intervals like 0. 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12, 16 and 24 h of Pitavastatin alone plasma on first day (day 1) are 0 ± 0, 0.77 ± 0.39, 1.88 ± 0.24, 2.13 ± 0.21, 3.34 ± 1.14, 4.12 ± 1.32, 5.22 ± 1.44, 6.24 ± 1.23, 7.12 ± 2.12, 4.22 ± 1.37, 3.62 ± 1.95, 2.25 ± 1.23, 1.82 ± 1.34, 0.12 ± 1.43, 0 ± 0 respectively and Pitavastatin combined with Ticagrelor are 0 ± 0, 1.07 ± 0.39, 2.28 ± 1.24, 3.22 ± 1.21, 4.64 ± 1.14, 5.12 ± 1.34, 5.34 ± 1.54, 6.54 ± 1.45, 7.32 ± 1.12, 5.22 ± 1.37, 4.62 ± 1.95, 2.75 ± 1.23, 1.62 ± 1.34, 0.52 ± 1.43, 0 ± 0 respectively.

Mean ± S.E.M, plasma levels (ng/ml) of Pitavastatin alone and in Combination with Ticagrelor on eighth day (day 8) was found at time intervals of 0. 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12, 16 and 24 h. The plasma concentrations of Pitavastatin alone are 0.77 ± 0.39, 2.37 ± 1.39, 3.88 ± 1.24, 4.12 ± 1.66, 5.34 ± 1.14, 5.54 ± 1.87, 6.23 ± 1.13, 6.98 ± 1.45, 8.12 ± 1.12, 5.22 ± 1.37, 4.62 ± 1.95, 3.25 ± 1.23, 2.82 ± 1.34, 1.12 ± 0.53, 0.11 ± 0.01 respectively and Pitavastatin combined with Ticagrelor 0.97 ± 0.39, 1.77 ± 0.39, 3.28 ± 0.24, 4.22 ± 0.22, 4.64 ± 0.14, 5.43 ± 0.34, 6.26 ± 0.45, 6.78 ± 0.43, 7.62 ± 0.62, 5.22 ± 0.37, 4.62 ± 0.95, 2.75 ± 0.23, 1.62 ± 0.34, 0.52 ± 0.43, 0.32 ± 0.02 respectively.

Mean ± S.E.M, plasma levels (ng/ml) of Ticagrelor alone and in Combination with Pitavastatin on first day (day 1) was found the concentrations are different time intervals like 0. 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12, 16 and 24hrs and the plasma concentrations of Ticagrelor alone on first day (day1) are 0 ± 0, 11.71 ± 1.11, 32.18 ± 1.12, 44.27 ± 2.13, 57.76 ± 2.43, 67.23 ± 3.41, 80.02 ± 3.03, 72.11 ± 3.22, 68.26 ± 2.54, 58.32 ± 2.13, 44.21 ± 2.56, 31.42 ± 1.83, 22.54 ± 1.72, 11.12 ± 1.11, 0 ± 0 respectively, Ticagrelor in combination with Pitavastatin on first day (day 1) 0 ± 0, 11.99 ± 1.22, 31.38 ± 1.32, 42.81 ± 2.45, 57.81 ± 3.43, 61.13 ± 3.44, 82.83 ± 4.13, 72.22 ± 4.21, 68.16 ± 3.55, 58.12 ± 2.42, 46.11 ± 1234, 32.32 ± 2.54, 24.24 ± 1.93, 9.32 ± 1.57, 0 ± 0 respectively.

Mean ± S.E.M, plasma levels (ng/ml) of Ticagrelor alone and in Combination with Pitavastatin on Eighth day (day 8) was found the concentrations are different time intervals like 0. 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12, 16 and 24 h and the plasma concentrations of Ticagrelor alone on Eighth day (day 8) are 7.12 ± 1.31, 15.31 ± 1.11, 32.51 ± 2.42, 45.17 ± 2.52, 59.46 ± 2.43, 68.33 ± 2.21, 89.02 ± 4.13, 78.32 ± 3.42, 67.31 ± 224, 62.42 ± 3.63, 49.31 ± 2.64, 32.52 ± 2.83, 27.44 ± 3.22, 11.22 ± 1.11, 6.21 ± 1.21 respectively, Ticagrelor in combination with Pitavastatin on Eighth day (day 8) are 7.32 ± 1.56, 15.29 ± 1.47, 33.48 ± 1.28, 46.84 ± 2.75, 58.62 ± 3.67, 73.33 ± 3.34, 90.93 ± 3.25, 78.22 ± 3.88, 69.21 ± 2.46, 58.12 ± 3.35,

46.11 ± 2.27, 32.32 ± 1.87, 24.74 ± 2.45, 13.13 ± 1.347, 7.22 ± 1.32 respectively.

The Mean ± Standard Error Mean (S.E.M) of plasma concentration of Pitavastatin alone on the first day (day 1) at different time points compared with a combination treatment of Ticagrelor and Ticagrelor on first day (day 1) is shown in **Fig. 1**. Similarly eighth day (day 8) plasma concentrations were shown in **Fig. 2**. The Mean ± Standard Error Mean (S.E.M) of plasma concentration of Ticagrelor alone on the first day (day 1) at different time points compared with the combination treatment of Ticagrelor and Pitavastatin on the first day (day 1) is shown in **Fig. 3**. Similarly, eighth day (day 8) plasma concentrations were shown in **Fig. 4**. From the results of plasma concentrations there are no significant changes for comparing of alone Pitavastatin plasma concentrations and in combination with Ticagrelor and also there was no significant difference for comparing of alone Ticagrelor plasma concentrations and in combination with Pitavastatin.

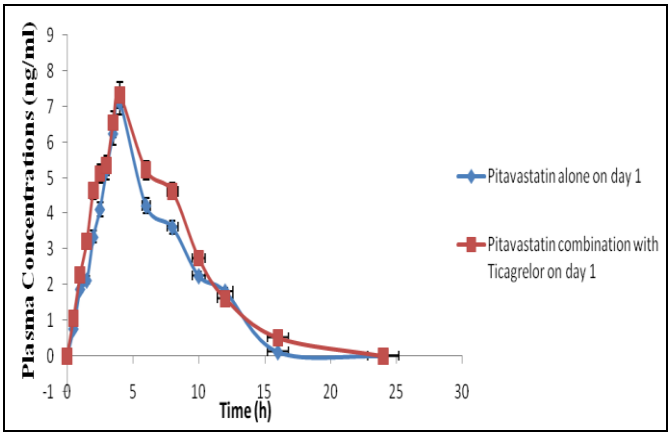


**FIG. 1: PLASMA LEVELS OF PITAVASTATIN (ng/ml) AND ITS COMBINATION WITH TICAGRELOR ON FIRST DAY (DAY1)**

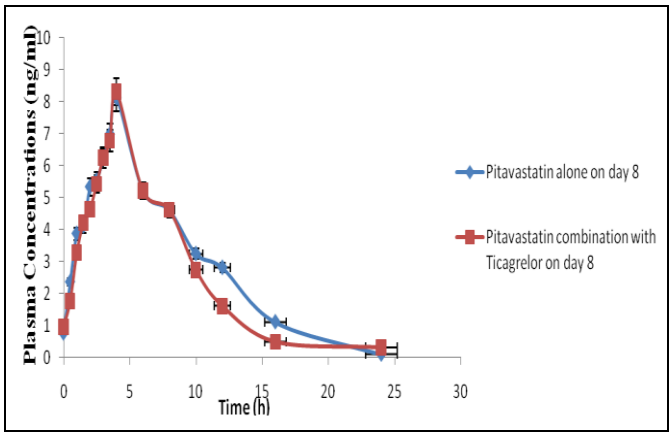


**FIG. 2: PLASMA LEVELS OF PITAVASTATIN (ng/ml) AND ITS COMBINATION WITH TICAGRELOR ON EIGHTH DAY (DAY 8)**

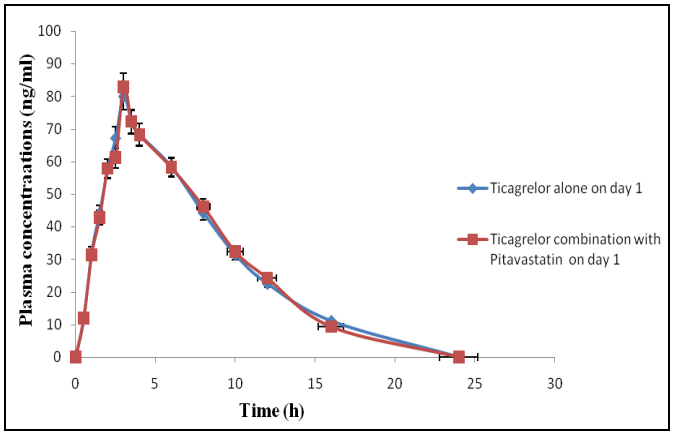


**FIG. 3: PLASMA LEVELS (ng/ml) OF TICAGRELOR ALONE AND IN COMBINATION WITH PITAVASTATIN ON FIRST DAY (DAY 1)**

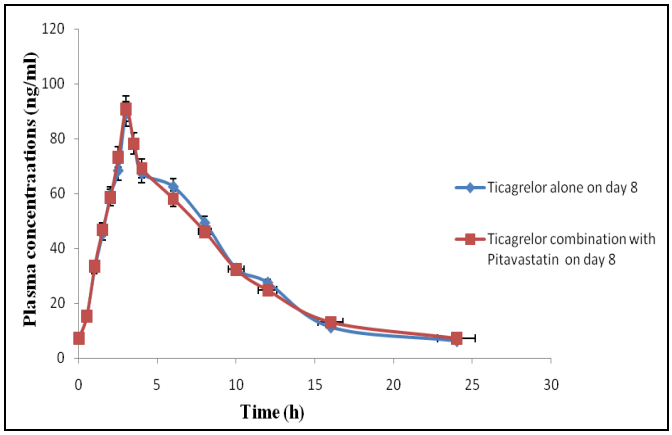


**FIG. 4: PLASMA LEVELS (ng/ml) OF TICAGRELOR ALONE AND IN COMBINATION WITH PITAVASTATIN ON EIGHTH DAY (DAY 8)**

**Study of Pharmacokinetic Parameters:** Different Pharmacokinetic parameters of Pitavastatin, Ticagrelor alone and combined treated parameters were studied in this study. Pharmacokinetic parameters like $C_{max}$, $t_{max}$, AUCo-t, AUCo-inf, $T_{1/2}$ was studied

Pharmacokinetic parameters of Pitavastatin alone and in Combination with Ticagrelor on first day (day 1), Pitavastatin alone parameters are $C_{max}$ 7.12 ± 2.12 ng/ml, $t_{max}$ 4 ± 0 h, AUCo-t, 82.41 ± 5.34 ng/ml/h, AUCo-inf, 98.12 ± 5.56 ng/ml/h, T1/2 7.17 ± 0.28. Pitavastatin in combination with Ticagrelor the parameters are $C_{max}$ 7.32 ± 1.12 ng/ml, $t_{max}$ 4 ± 0 h, AUCo-t, 89.47 ± 6.12 ng/ml/h, AUCo-inf, 102.15 ± 5.85 ng/ml/h, $T_{1/2}$ 7.23 ± 0.09 h. The results were shown in **Table 1**.

**TABLE 1: PHARMACOKINETIC PARAMETERS OF PITAVASTATIN ALONE AND COMBINATION WITH TICAGRELOR ON FIRST DAY (DAY1) (N=6) IN DIABETIC RATS**

| Parameters | Pitavastatin alone | Pitavastatin combination with Ticagrelor |
|---|---|---|
| $C_{max}$(ng/ml) | 7.12 ± 2.12 | 7.32 ± 1.12 |
| $t_{max}$(h) | 4 ± 0 | 4 ± 0 |
| $AUC_{o-t}$ (ng/ml/h) | 82.41 ± 5.34 | 89.47 ± 6.12 |
| $AUC_{o-inf}$ (ng/ml/h) | 98.12 ± 5.56 | 102.15 ± 5.85 |
| $T_{1/2}$ (h) | 7.17 ± 0.28 | 7.23 ± 0.09 |

Pharmacokinetic parameters of Pitavastatin alone and in combination with Ticagrelor on 8th day (day 8), Pitavastatin alone parameters are $C_{max}$ 8.12 ± 1.12 ng/ml, $t_{max}$ 4 ± 0 h, AUCo-t 92.56 ± 3.58 ng/ml/h, AUCo-inf, 107.3 6 ± 5.63 ng/ml/h, $T_{1/2}$ 7.46 ± 0.024 h. Pitavastatin in combination with Ticagrelor the parameters are $C_{max}$ 8.32 ± 1.62 ng/ml, $t_{max}$ 4 ± 0 h, AUCo-t, 97.38 ± 4.49 ng/ml/h, AUCo-inf 118.49 ± 6.44 ng/ml/h, 7.48 ± 0.0188 h. The results were showed in **Table 2**.

**TABLE 2: PHARMACOKINETIC PARAMETERS OF PITAVASTATIN ALONE AND COMBINATION WITH TICAGRELOR ON EIGHTH DAY (DAY 8) (N=6)**

| Parameters | Pitavastatin alone | Pitavastatin combination with Ticagrelor |
|---|---|---|
| $C_{max}$(ng/ml) | 8.12 ± 1.12 | 8.32 ± 1.62 |
| $t_{max}$(h) | 4 ± 0 | 4 ± 0 |
| $AUC_{o-t}$ (ng/ml/h) | 92.56 ± 3.58 | 97.38 ± 4.49 |
| $AUC_{o-inf}$ (ng/ml/h) | 107.36 ± 5.63 | 118.49 ± 6.44 |
| $T_{1/2}$ (h) | 7.46 ± 0.024 | 7.48 ± 0.018 |

**TABLE 3: PHARMACOKINETIC PARAMETERS OF TICAGRELORALONE AND COMBINATION WITH PITAVASTATINON FIRST DAY (DAY 1) (N=6) IN DIABETIC RATS**

| Parameters | Ticagrelor alone | Ticagrelor in combination with Pitavastatin |
|---|---|---|
| $C_{max}$(ng/ml) | 80.02 ± 3.03 | 82.83 ± 4.13 |
| $T_{max}$ (h) | 3 ± 0 | 3 ± 0 |
| $AUC_{o-t}$ (ng/ml/h) | 791.37 ± 4.60 | 794.91 ± 5.41 |
| $AUC_{o-inf}$(ng/ml/h) | 926.34 ± 4.36 | 937.79 ± 6.88 |
| $T_{1/2}$ (h) | 6.5 ± 0 | 6.5 ± 0 |

Pharmacokinetic parameters of Ticagrelor alone and in combination with Pitavastatin on first day (day 1), Ticagrelor alone parameters are $C_{max}$ 80.02 ± 3.03 ng/ml, $t_{max}$ 3 ± 0 h, AUCo-t 791.37 ± 4.60 ng/ml/h, AUC0-inf, 926.34 ± 4.36 ng/ml/h, $T_{1/2}$ 6.5 ± 0 h. Ticagrelor in combination with Pitavastatin the parameters are $C_{max}$ 82.83 ± 4.13 ng/ml, $t_{max}$ 3 ± 0 h, AUCo-t 794.91 ± 5.41 ng/ml/h, AUCo-inf, 937.79 ± 6.88 ng/ml/h, T1/2 6.5 ± 0 h. The results were showed in **Table 3**.

Pharmacokinetic parameters of Ticagreloralone and in Combination with Pitavastatin on Eighth day (day 8), Ticagrelor alone parameters are $C_{max}$ 89.02 ± 4.13 ng/ml, $t_{max}$ 3 ± 0 h, AUCo-t 887.79 ± 5.21 ng/ml/h, AUCo-inf, 1025.27 ± 5.36 ng/ml/h, T1/2 6.50 ± 0 h. Ticagrelorin Combination with Pitavastatin the parameters are $C_{max}$ 90.93 ± 3.25 ng/ml, $t_{max}$ 3 ± 0 h, AUCo-t 897.96 ± 6.23 ng/ml/h, AUCo-inf, 1037.47 ± 6.78 ng/ml/h, $T_{1/2}$ 6.50 ± 0 h. The results were showed in **Table 4**.

**TABLE 4: PHARMACOKINETIC PARAMETERS OF TICAGRELORALONE AND COMBINATION WITH PITAVASTATIN ON EIGHTH DAY (DAY 8) (N = 6)**

| Parameters | Ticagrelor alone | Ticagrelor in combination with Pitavastatin |
|---|---|---|
| $C_{max}$(ng/ml) | 89.02 ± 4.13 | 90.93 ± 3.25 |
| $T_{max}$ (h) | 3 ± 0 | 3 ± 0 |
| $AUC_{o-t}$ (ng/ml/h) | 887.79 ± 5.21 | 897.96 ± 6.23 |
| $AUC_{o-inf}$(ng/ml/h) | 1025.27 ± 5.36 | 1037.47 ± 6.78 |
| $T_{1/2}$ (h) | 6.5 ± 0 | 6.5 ± 0 |

The Pitavastatin is completely absorbed after oral administration with a peak plasma concentration of 7.12 ± 2.12 ng/ml after 4 h of dosing on the first day (day1). In combination with Pitavastatin with Ticagrelor on the first day (day 1), the peak plasma concentration of Pitavastatin $C_{max}$ 7.32 ± 1.12 ng/ml occurred 4 h after dosing. There was no significant increase in peak plasma concentration levels. Similarly, Ticagrelor is completely absorbed after oral administration with peak plasma concentration 80.02 ± 3.03 ng/ml occurred 3 h after dosing on the first day (day 1), in combination with Pitavastatin with Ticagrelor on the first day (day 1). The peak plasma concentration of Ticagrelor 82.83 ± 4.13 ng/ml occurred 3 h after dosing.

There were no significant changes in the peak plasma concentration levels, on the eighth day (day 8) of Ticagrelor alone and combination with Pitavastatin on the eighth day (day 8). Peak plasma concentrations are 89.02 ± 4.13 ng/ml and 90.93 ± 3.23 ng/ml, respectively (results were showed in **Table 1**, **2**, **3**, **4**.

**CONCLUSION:** In this study, the pharmacokinetic drug-drug interaction between Pitavastatin and Ticagrelor was statistically analyzed. From the current data, Pitavastatin seems to be a safer statin for comedication with Ticagrelor. The study conducted on male Wister rats for eight days (day 1 to day 8) indicated no statistically significant ($P > 0.05$) variation in peak plasma concentration and other pharmacokinetic parameters of both drugs when administrated alone or in combination.

These results demonstrate that Pitavastatin and Ticagrelor can be co-prescribed safely for cardiovascular medications for patients at high atherosclerotic cardiovascular patients, with no clinically meaningful pharmacokinetic interactions. Further study is needed to analyze various pharmacokinetic interactions of Pitavastatin and Ticagrelor in humans by systematic investigations.

**ACKNOWLEDGEMENT:** Nil

**CONFLICTS OF INTEREST:** Nil

## REFERENCES:

1. Qato DM, Alexander GC, Conti RM, Johnson M and Schumm P: Use of prescription and over-the-counter medications and dietary supplements among older adults in the United States. The Journal of the American Medical Association 2008; 300: 2867-78.
2. Juurlink DN, Mamdani M, Kopp A, Laupacis A and Redelmeier DA: Drugdrug interactions among elderly patients hospitalized for drug toxicity. The Journal of the American Medical Association 2003; 289: 1652-58.
3. Ament PW, Bertolino JG and Liszewski JL: Clinically significant drug interactions. American Family Physician 2000; 61: 1745-54.
4. Anastasio GD, Cornell KO and Menscer D: Drug interactions keeping it straight. American Family Physician 1997; 56: 883-94.
5. Gerntholtz T, Pascoe MD, Botha JF, Halkett J and Kahn D: The use of a cyclosporine-ketoconazole combination making renal transplantation affordable in developing countries. The European Journal of Clinical Pharmacology 2004; l60: 143-48.
6. Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, Brown L, Warnica JW, Arnold JM, Wun CC, Davis BR and Braunwald E: The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels: cholesterol and recurrent events trial investigators. The New England Journal of Medicine 1996; 335: 1001-09.
7. Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, Beere PA, Langendorfer A, Stein EA, Kruyer W and Gotto AM: Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS: air force/texas coronary atherosclerosis prevention study. The Journal of the American Medical Association 1998; 279: 1615-22.
8. Sever PS, Dahlöf B, Poulter NR, Wedel H, Beevers G, Caulfield M, Collins R, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O'Brien E and Ostergren J: ASCOT Investigators. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm (ASCOT-LLA): a multi centre randomised controlled trial. Lancet 2003; 361: 1149-58.
9. Nagy CF: Concurrent administration of donepezil HCl and sertraline HCl in healthy volunteers: assessment of pharmacokinetic changes and safety following single and multiple oral doses. British Journal of Clinical Pharmacology 2004; 58: 25-33.
10. Davit BM: Comparing generic and innovator drugs: a review of 12 years of bioequivalence data from the United States Food and Drug Administration. Annals of Pharmacotherapy 2009; 43: 1583-97.
11. Meredith P: Bioequivalence and other unresolved issues in generic drug substitution. Clinical therapeutics 2003; 25: 2875-90.
12. Black AE: Metabolism and excretion of atorvastatin in rats and dogs. Drug Metab and Disposition 1999; 27: 916-23.

**How to cite this article:**
Siddiqui HMA and Roshan S: Pharmacokinetic drug interactions between HMG-COA reductase inhibitors pitavastatin with concomitantly used ticagrelor. Int J Pharm Sci & Res 2020; 11(6): 2801-06. doi: 10.13040/IJPSR.0975-8232.11(6).2801-06.