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Drug Interaction Study Of Apixaban With Cyclosporine Or Tacrolimus: Results From A Phase 1, Randomized, Open-Label, Crossover Study In Healthy Volunteers

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Background

- Apixaban is a direct factor Xa inhibitor approved for treatment of venous thromboembolism (VTE).
- It is metabolized by the CYP3A4, and is a substrate to the permeability glycoprotein (P-gp) and breast cancer resistance protein (BCRP) transporters.
- The combined use of apixaban with a strong dual inhibitor of P-gp and CYP3A4 such as ketoconazole results in a 2-fold increase in apixaban exposure necessitating dose adjustment.
- Cyclosporine and tacrolimus are indicated for prophylaxis of organ rejection in patients receiving allogeneic renal, cardiac, or hepatic transplants.
- Cyclosporine is a weak inhibitor of CYP3A4 and potent inhibitor of both P-gp, BCRP.
- Tacrolimus is believed to share overlapping inhibitor activity on these pathways but is considered a weaker inhibitor than cyclosporine.
- Thus, concentrations of apixaban may potentially increase in transplant patients medicated with calcineurin inhibitors.

Aims

- To determine the effect of 100 mcg cyclosporine coadministered daily for 3 days on the pharmacokinetic parameters of apixaban following coadministration of a single oral dose of 10 mg to healthy volunteers.
- To determine the effect of 2 mg tacrolimus coadministered daily for 3 days on the pharmacokinetic parameters of apixaban following coadministration of a single oral dose of 10 mg to healthy volunteers.
- Pharmacokinetic (PK) parameters included AUC_{0-24}, AUC_{0-∞}, C_{max}, T_{max}, apparent terminal t_{1/2}.

Subjects and Methods

- 12 healthy adult males received three treatments in a crossover design (Figure 1).
- Apixaban plasma concentration was determined using a validated LC-MS/MS assay.

Results

Subject Demographics

| Number of Subjects (N=12), n (%) | Male | 12 (100.0) |
| Age (yr) | Range | 25-54 |
| BMI (Kg/m²), range | 24-33 |
| Race | Black or African American | 9 (75) |
| White | 3 (25) |

Apixaban Pharmacokinetic Interaction with Cyclosporine and Tacrolimus

- The concentration-time profile of 10 mg apixaban alone was compared to the concentration-time profile of 10 mg apixaban when cyclosporine (Figure 2A) or tacrolimus (Figure 2B) was coadministered.
- The apixaban plasma concentration reached its peak (T_{max}) at 2.5 hours postdose.
- All subjects had quantifiable predose concentrations of apixaban on day 1 of each treatment period. All subjects had quantifiable plasma apixaban concentrations up to 24 hours postdose.
- Summary statistical comparison of PK parameters from subjects administered 10 mg apixaban alone compared to apixaban with cyclosporine and tacrolimus coadministration is presented in Table 2.

Discussion

- The confidence interval for only C_{max} but not AUC_{0-24} or AUC_{0-∞} lay completely above 1, indicating that overall apixaban exposure is unaffected when coadministered with cyclosporine.
- The observed change in apixaban exposure with cyclosporine reflects the effect of combined inhibition of P-gp and BCRP transporter-mediated efflux as well as CYP3A4 metabolism.
- The CI for both AUC_{0-24} and AUC_{0-∞} but not C_{max} lay completely below 1, suggesting a small decrease in apixaban exposure when coadministered with tacrolimus.
- The observed decrease in apixaban exposure with tacrolimus was unexpected. The inhibitory potency of tacrolimus on P-gp, BCRP transporters is not well characterized.
- In the absence of potent inhibitory activity at the transporters, the coadministration of apixaban and tacrolimus, could potentially result in a competitive inhibition of transporter-mediated efflux, contributing to increased efflux and elimination of apixaban.
- The change in apixaban exposure with cyclosporine or tacrolimus is not expected to meaningfully alter the safety and efficacy of apixaban based on the magnitude of other drug interactions listed in the product label.

Conclusion

- Multiple-dose administration of 100 mg cyclosporine or 5 mg tacrolimus daily with a single dose of 10 mg apixaban was generally well tolerated by the healthy subjects in the study.
- Coadministration of cyclosporine or tacrolimus and apixaban had no clinically meaningful effect on the PK of apixaban.
- Apixaban and cyclosporine or tacrolimus may be coadministered without dose adjustment.

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