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BIOAVAILABILITY OF ADALIMUMAB FOLLOWING SUBCUTANEOUS INJECTIONS IN RHEUMATOID ARTHRITIS PATIENTS. R. Velagapudi, PhD, P. Noertershauser, PhD, W. Awni, PhD, R. Granneman, PhD, H. Kupper, MD, Abbott Laboratories, Parsippany, NJ.

AIM: To assess bioavailability (BA) of adalimumab following subcutaneous (sc) injections in rheumatoid arthritis (RA) patients using a sparse sampling approach.

METHODS: Blood samples were collected at selected visits up to 2.5 years from a Phase I, multi-center, randomized study in 54 adult RA patients on stable doses of MTX. Patients (18 per group) received either: a) 1 mg/kg sc adalimumab, b) 1 mg/kg iv adalimumab, or c) placebo. The same treatment was repeated in ~ 4 weeks, and 4 weeks later, all groups received 1 mg/kg sc open-label dosing every other week for 2.5 years. Serum adalimumab concentrations were measured using an immunoassay. Population pharmacokinetic (PK) analyses were performed using NONMEM software.

RESULTS: A two-compartment population PK model was used. The population estimate of absolute BA of adalimumab following the sc route was 58%. The mean (CV%) of individual post-hoc CL and Vss were 11.2 mL/h (54.6%) and 6.0L (16.2%), respectively.

CONCLUSIONS: The absolute BA of adalimumab following sc administration in patients on stable methotrexate therapy was approximately 58%. Adalimumab kinetics appeared to be linear and time invariant over 2.5 years.

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EFFECT OF GRAPEFRUIT JUICE ON CABERGOLINE PHARMACOKINETICS IN PATIENTS WITH PARKINSON'S DISEASE. M. Nagai, MD, PhD, A. Nakatsuka, H. Yabe, MD, T. Moritoyo, MD, PhD, M. Nomoto, MD, PhD, Clinical Pharmacology and Therapeutics, Ehime University School of Medicine, Touon, Ehime, Japan.

BACKGROUND: Cabergoline is one of the synthetic ergoline dopamine agonists, which is widely used for the treatment of Parkinson's disease (PD). Cytochrome P-450 (CYP) 3A4 contributes to metabolize Cabergoline. It has been well known that grapefruit juice inhibits CYP3A4 enzyme located in the gut wall. To investigate whether grapefruit juice influences the pharmacokinetics of cabergoline, plasma level of cabergoline in patients of PD was evaluated.

METHODS: Five patients with PD treated with cabergoline were enrolled. Plasma concentrations of cabergoline before and after coadministration of grapefruit juice were evaluated. The plasma concentration of cabergoline was determined using a LC/MS/MS.

RESULTS: The plasma concentration of cabergoline increased approximately 1.7 times, when grapefruit juice was taken together with cabergoline. Adverse events were not observed during this trial.

CONCLUSIONS: Coadministration of grapefruit juice with cabergoline increases bioavailability of cabergoline. A relatively large therapeutic window of cabergoline may allow the concomitant treatment with grapefruit juice, and this combination treatment may augment the antiparkisonian effect of cabergoline.

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CLINICAL AND IN-VITRO INVESTIGATIONS TO ASSESS TRANSPORTER BASED DRUG INTERACTION POTENTIAL OF A PARTIAL ALPHA AGONIST R450. S. E. Bellibas, MD, D. Schwab, PhD, B. Liu, MD, E. Gaudeul-Ehrhart, MD, P. Weigl, BS, A. Dorr, Hoffmann-La Roche Inc., XIQ Inc., Nutley, NJ.

Since R450 is a compound actively secreted by kidneys with a renal clearance (CL_R) exceeding normal GFR; it was decided to be investigated further for exact mechanism of excretion and assess DDI potential based on any possible active transporters.

First, a clinical study was performed on 12 healthy female subjects aged 40–65 years using cimetidine and probenecid as probe drugs for cationic and anionic transport mechanisms at renal tubular level. While probenecid had no effect, cimetidine caused a statistically significant change in exposure by reducing CL_R from 11.8 L/hr to 8.7 L/hr.

Furthermore, in cell-line study, the bi-directional transport of R450 in wild-type LLC-PK1 cells was inhibited by verapamil, while no inhibition was observed by a P-gp specific inhibitor although caused partly inhibition in P-gp transfected cells (human MDR1, mouse mdr1a). A complete inhibition was observed in P-gp transfected LLC-PK1 cells using verapamil as an inhibitor suggesting R450 is a weak substrate for P-gp and also mediated by multiple transporters.

Based on these observations it was concluded that R450 was a substrate for mainly organic cationic transporters in addition to possible other multiple transporters including P-gp with a lesser degree.

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AN ASCENDING MULTIPLE-DOSE STUDY OF THE SAFETY AND PHARMACOKINETICS OF A SUSTAINED-RELEASE FORMULATION OF DESVENLAFAXINE SUCCINATE IN HEALTHY SUBJECTS. L. S. Richards, MA, J. A. Behrle, MS, A. I. Nichols, PhD, R. J. Fruncillo, MD, PhD, J. Paul, PhD, Wyeth Research, Collegeville, PA.

BACKGROUND/AIMS: To assess the safety, tolerability, and pharmacokinetics (PK) of ascending multiple oral doses of a sustained-release formulation of desvenlafaxine succinate (DVS-SR) in healthy subjects.

METHODS: A randomized, placebo-controlled, ascending multiple-dose study was conducted with 36 healthy male subjects. In cohorts of 12 subjects (9 DVS-SR and 3 placebo), 3 dose levels (300, 450, and 600 mg) were given q24h for 14 days after a medium-fat breakfast. Routine laboratory tests, vital signs, and electrocardiograms (ECG) were measured throughout the study. The plasma concentrations of desvenlafaxine (DV) were analyzed by model-independent methods.

RESULTS: DVS-SR was generally well tolerated at doses up to 450 mg, defined as the maximum tolerated multiple dose. Nausea was a common adverse event in all three dose cohorts. Orthostatic hypotension was observed in 6 of 9 subjects in the 600 mg DVS-SR dose group. There were no clinically relevant changes in ECG intervals and routine laboratory tests. DV was slowly absorbed with a mean t_{max} occurring 5 to 8 hours after dose administration. C_{max} and AUC increased proportionally over the ranges of 300 to 600 mg and 300 to 450 mg for single and multiple doses, respectively. The single-dose $AUC_{0-\infty}$ and steady-state AUC_{0-24h} were similar at each dose level.

CONCLUSION: DVS-SR was safe and well tolerated at multiple doses of up to 450 mg. Single-dose PK can be used to predict multiple-dose PK.