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APREPITANT HAS LITTLE INDUCTIVE EFFECT ON CYP3A4 ACTIVITY WHEN COADMINISTERED WITH DEXAMETHASONE. S. A. Stoch, M. Fedgchin, A. Majumdar, C. Gargano, E. Pequignot, K. Gottesdiener, K. J. Petty, D. Panebianco, H. Greenberg, Merck Research Laboratories, Thomas Jefferson University, Blue Bell, PA.

BACKGROUND: Aprepitant (APR) is a neurokinin-1 receptor antagonist approved, in combination with a corticosteroid and a 5-hydroxytryptamine3 receptor antagonist, for the prevention of chemotherapy-induced nausea and vomiting. Corticosteroids and APR both induce CYP3A4 activity and thus this study was conducted to determine if coadministration of APR and a corticosteroid results in significant CYP3A4 induction in vivo.

METHODS: This double-blind, 2-period, crossover study was conducted in 12 healthy subjects to assess the potential inductive effect of a triple-therapy antiemetic regimen versus a dual antiemetic regimen on CYP3A4 activity.

Regimen	APR	Ondansetron (OND)	Dexamethasone (DEX)
Triple[1]	D1: 125 mg PO D2–3: 80 mg PO	D1: 32 mg IV	D1: 12 mg PO D2–4: 8 mg PO
Dual		D1: 32 mg IV	D1: 20 mg PO D2–4: 16 mg PO

[1] Doses of DEX were reduced to achieve comparable exposure to dual regimen.

Single doses of oral (2 mg) and IV (1 mg) stable isotope ($^{13}C_5{}^{15}N_1$) labeled midazolam (MDZ) were simultaneously administered on Days -1 (baseline), 6, 8, 15, and 22 as probes to independently assess the effects on systemic vs systemic + first pass CYP3A4 activity.

RESULTS: The fold-changes from baseline in oral and intravenous MDZ $AUC_{0-\infty}$ were used as the primary assessments of CYP3A4 activity and are summarized in the table below. The difference between the dual vs triple regimen on days 8, 15, and 22 was primarily due to slight CYP3A4 inhibition by the dual regimen. The mean fold-changes from baseline following the triple antiemetic regimen were all close to 1.0.

CONCLUSION: APR, when used in combination with DEX as part of a triple antiemetic regimen, is unlikely to have significant inductive effects on CYP3A4 activity.

		MDZ AUC0–∞ Geometric Mean Fold Change†† from Baseline†		Ratio of Geometric Mean Fold Change†† (Triple/Double) with 90% CI†	
	Day	Triple Regimen	Dual Regimen		P-value††
Oral MDZ	6	0.84	0.84	1.00 (0.80, 1.25)	>0.250
	8	0.91	1.45	0.63 (0.49, 0.78)	<0.010
	15	0.93	1.40	0.66 (0.53, 0.83)	<0.010
	22	0.83	1.18	0.70 (0.56, 0.88)	<0.010
IV MDZ	6	0.90	1.02	0.88 (0.74, 1.03)	0.184
	8	0.93	1.25	0.74 (0.63, 0.87)	<0.010
	15	0.90	1.14	0.79 (0.67, 0.93)	0.017
	22	0.94	1.07	0.88 (0.75, 1.04)	0.198

CI = Confidence interval.

†Geometric means, CIs, ratios, and fold changes back-transformed from least-squares means from ANOVA, performed on natural log-transformed values.

††Tests null hypothesis of no between-treatment difference versus two-sided alternative.

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EFFECT OF AGE AND GENDER ON THE PHARMACOKINETICS OF SOLIFENACIN. R. Smulders, MD, M. Taekema, DVM PhD, W. Krauwinkel, MSc, M. Raghoebar, PhD, Yamanouchi Europe b.v., Leiderdorp, The Netherlands.

BACKGROUND: Overactive bladder (OAB) is a syndrome consisting of urinary frequency and urgency, with or without urge incontinence. Solifenacin is a new muscarinic receptor antagonist for the treatment of OAB. This trial was designed to study the effect of age and gender on the steady state pharmacokinetics (PK) of solifenacin at two dose levels.

METHODS: 47 healthy subjects [24 young (aged 35 (20–55)); 23 elderly (68 (64–78)); 12 males in each age group] were enrolled in an open-label, crossover trial. Solifenacin 5 or 10 mg was administered, once daily, during two 14-day study periods separated by a washout period. PK variables were C_{max}, AUC_{0-24h}, $t_{½}$, and t_{max}.

RESULTS: A dose-proportional increase was observed for C_{max} and AUC_{0-24h} in young and elderly subjects. In elderly subjects C_{max} and AUC_{0-24h} were 16% (90% CI 0.973–1.373) and 20% (1.003–1.435) higher, resp., compared to young subjects. Mean t_{max} and $t_{½}$ were slightly higher in elderly subjects versus young subjects. Values for C_{max} and AUC_{0-24h} were equivalent between males and females [0.947 (0.796–1.127) and 0.977 (0.815–1.172) resp.]. Mean t_{max} was comparable in men and women; there was a tendency towards a shorter $t_{1/2}$ in women. Mean t_{max} and $t_{1/2}$ remained unaffected when increasing the dose from 5 to 10 mg.

CONCLUSIONS: Slight differences in PK of solifenacin were observed between young and elderly, and male and female subjects. However, these were considered not clinically relevant and no dose adjustment based on age or gender is recommended.

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UGT1A1 AND UGT1A9 VARIANTS AFFECT THYROXINE GLUCURONIDATION IN HUMAN LIVERS. A. Yoder Graber, BA, F. Innocenti, MD, PhD, J. Ramirez, MS, P. X. Chen, MD, S. Das, PhD, M. J. Ratain, MD, University of Chicago, Chicago, IL.

BACKGROUND/AIMS: Thyroxine (T_4) is prescribed in patients with hypothyroidism, and is known to undergo glucuronidation. Previous studies propose 1A1 and 1A9 as the main isoforms for T_4G formation, but a complete 1A screening has not been performed. This study aimed to investigate the relevance of genetic polymorphisms in *1A1* and *1A9* and screen all the functional 1A isoforms for T_4G formation.

METHODS: Thirty human liver microsomes were genotyped for the *1A1* $(TA)_n$ and the *1A9* $-118T_{9>10}$ promoter polymorphisms. cDNA transfected 1A1, 1A3, 1A4, 1A6, 1A7, 1A8, 1A9 and 1A10 were screened for T_4 glucuronidation activity and normalized by relative protein expression. T_4G formation was measured by HPLC.

RESULTS: There was a significant correlation between both *1A1* $(TA)_{6>7}$ and *1A9* $-118T_{9>10}$ genotypes and T_4 glucuronidation ($P<0.01$). The highest T_4G formation was observed with 1A3 followed by 1A8, 1A1, 1A10, 1A9, and 1A7 and was undetectable with 1A4 and 1A6.

CONCLUSIONS: *1A1* $(TA)_n$ and the *1A9* $-118(T)_{9>10}$ promoter polymorphisms affect T_4 glucuronidation rates. Moreover, our data propose 1A3 as another 1A isoform potentially involved in T_4G formation. Future studies should further characterize the enzyme efficiencies of these UGTs and determine the clinical relevance of these findings.