PI-79

AGE-GENDER STUDY OF SRA-333, A NOVEL 5-HT_{1A} ANTAGONIST. A. Patat, V. Parks, S. Raje, A. Plotka, B. Dietrich, Wyeth Research, 3 Clinical Research, Paris, France.

BACKGROUND: SRA-333 is a new potent, silent 5-HT_{1A} antagonist proposed for the treatment of cognitive deficits associated with Alzheimer's disease.

METHODS: This was a single-dose, randomized, double-blind, placebo-controlled, 2-period cross-over study in 48 healthy subjects (8 men and 8 women in each of the following age groups: 18–45, 65–74, and equal or above 75 years) with 5 mg SRA-333. Evaluations consisted of safety and tolerability, pharmacokinetics (PK), and pharmacodynamics using the Cognitive Drug Research Battery (Reading, UK).

RESULTS: SRA-333 was safe and well tolerated in both young and elderly subjects. The incidence of treatment-emergent adverse events in elderly subjects was 50% less than that in young subjects. There were no clinically relevant changes in vital signs, ECG interval or laboratory tests. The t_{max} for SRA-333 was <1h. Mean $t_{1/2}$ increased from 9.5 h to 14.4 hr in elderly subjects because of a decrease in oral clearance (17% in men, 25% in women). C_{max} and AUC were not significantly different between young and elderly subjects, but C_{max} values were 17% higher in women compared with men, which may be explained by weight differences (mean = 69 vs. 81 kg respectively). SRA-333 had no deleterious effect on attention, vigilance, sensorimotor task or working and episodic memory.

CONCLUSIONS: SRA-333 was well tolerated in all age groups. The PK profile of the elderly subjects was characterized by a mild decrease in clearance that did not justify any dosage adjustment.

PI-80

DISPOSITION OF ROFLUMILAST IN PEDIATRICS. G. Kearns, S. Szefler, S. Abdel Rahman, G. Lahu, K. Zech, T. Bethke, Children's Mercy Hospital, National Jewish Medical Center, ALTANA Pharma AG, Kansas City, MO.

Roflumilast (ROF) is an oral PDE4 inhibitor in development for COPD and asthma. To date, the pharmacokinetics (PK) of ROF and its active N-oxide metabolite (RNO) have been characterized only in adults.

METHODS: 13 children (C; 6–10y) and 12 adolescents (A; 11–16y) with mild asthma enrolled in an open, 2-period parallel study stratified by age. Subjects received sequential single doses of 100 and 250μg. Blood samples (14) were taken up to 72h. ROF & RNO were quantified by HPLC/MS-MS and PK analyzed with standard methods. Within- & between-group comparisons were made using 2-tailed, paired and unpaired t-tests.

	ROF 100μg		ROF, 250μg	
RESULTS (±SD)	**A**	**C**	**A**	**C**
λz, 1/h	0.10 ± 0.004	0.13 ± 0.14	0.07 ± 0.05	0.10 ± 0.06
Tmax, h	0.79 ± 0.50	0.69 ± 0.32	0.75 ± 0.34	0.58 ± 0.19
Cmax, μg/L per μg/kg	1.13 ± 0.31	0.84 ± 0.20	1.05 ± 0.21	0.88 ± 0.25
AUC_∞, μg/L*h per μg/kg	3.53 ± 0.69	3.74 ± 2.67	4.44 ± 2.02	3.91 ± 2.76
Vd/F, L/kg	3.06 ± 0.75	4.27 ± 2.05	4.73 ± 2.25	4.70 ± 2.66
Cl/F, L/h/kg	0.29 ± 0.006	0.38 ± 0.20	0.26 ± 0.10	0.37 ± 0.19

Except for Cmax (100μg; p=0.01), PK parameters were not significantly different between A and C. Dose (μg/kg) and AUC_∞ were linear (r^2=0.34, p<0.01) for all subjects. A and C were not significantly different for mean elimination t½ of ROF (11.7 vs. 13.7h) and RNO (31.1 vs. 27.5h) or RNO formation ratio.

CONCLUSIONS: In patients 6–16y, PK of ROF appears not to vary as a function of age or dose over a 100 to 250μg range. Previous data showed similar disposition of ROF in older adolescents and adults.

PI-81

BREASTFEEDING WOMEN WITH DEPRESSION: MATERNAL AND INFANT WELL-BEING. A. Lee, MSc, W. Ungar, PhD, B. Wang, BSc, M. Romach, MD, S. Ito, MD, Hospital for Sick Children, University of Toronto, Toronto, ON, Canada.

BACKGROUND: To examine the well-being of depressed, breastfeeding women treated with antidepressants (G1), and their infants, for the first year postpartum, compared to those who forgo pharmacotherapy (G2), and to healthy, breastfeeding women (G3).

METHODS: Women-infant pairs were followed-up at 4, 13, 26, 39, and 52 weeks postpartum. The Edinburgh Postnatal Depression Scale (EPDS), Short Form 36 (SF-36), and the Functional Status II Revised (FS-IIR) were used to measure maternal depression, well-being, and infant well-being.

RESULTS: Fifty-six, 32, and 59 women in G1, G2, and G3, respectively completed all follow-ups. The only adverse event associated with antidepressant exposure through breast milk was 1 infant with increased bowel movements following maternal nefazodone dose increases. Although EPDS scores improved over time in all groups, 9 and 31% of women in G1 and G2 respectively were still scoring above 12 at 52 weeks. G2 women had statistically lower SF-36 mental component scores compared to G3 (G1 47.6, G2 42.4, G3 54.6, p<0.01). There were no differences in SF-36 physical component scores. G1 infants scored statistically lower in FS-IIR total and health scores compared to G3.

CONCLUSIONS: Although FS-IIR scores were lower, only 1 infant had minor adverse effects associated with maternal antidepressants. Many women on antidepressants were not adequately treated. Women requiring antidepressants postpartum should continue to breastfeed and be adequately dosed to control their depression.

PI-82

THE REPRODUCTIVE EFFECTS OF BETA INTERFERON THERAPY FOR MULTIPLE SCLEROSIS. R. Boskovic, MD, R. Wade, BSc., G. Koren, MD, The Hospital for Sick Children, Toronto, ON, Canada.

BACKGROUND: Beta interferons, are produced by fibroblasts and are used in the treatment of relapsing-remitting multiple sclerosis (MS). Animal studies and human case reports have suggested that interferons are unlikely to be teratogenic.

OBJECTIVE: of this study is to determine whether interferon therapy during human pregnancy increases reproductive risks in women with MS.

METHODS: This prospective, observational, cohort study consists of three groups of women: an exposed group, a disease matched unexposed group, and a healthy comparative group. Subjects were selected by contacting the Motherisk Program regarding maternal beta interferon or Copaxone® exposure during pregnancy, from 1997 and 2004. After delivery all of the women were re-contacted for a follow-up interview regarding maternal health, pregnancy outcome, and neonatal health.

RESULTS: The study group(n=16, pregnancy outcome 23) were exposed to interferon beta at doses ranging from 25–132 mcg/week There was a decrease in mean birth weight in the exposed group (3.2 ± 0.42 kg) as compare to controls (3.5 ± 0.5 , 3.8 ±0.4, P=0.003). There were 9 spontaneous abortions and one fetal death in exposed group, yielding significantly higher rate of pregnancy loss (P=0.03). There were 2 major malformations (abnormality in the X chromosome, Down's Syndrome) among exposed fetuses.

CONCLUSIONS: Beta interferon therapy in first trimester of pregnancy appears to be associated with an increase risk for miscarriages.