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A RANDOMISED, DOUBLE BLIND, PLACEBO CONTROLLED SINGLE ASCENDING DOSE STUDY OF PYM50018, WITH AN OPEN LABEL CROSS-OVER STAGE TO ASSESS FOOD EFFECT. D. H. Wessels, MBChB, MBA, R. Grover, FRCA, A. Frend, PhD, S. Levene, FRCPCH, L. Potgieter, PhD, PAREXEL CPRU, Phytopharm PLC, BioDynamics Research Limited, FARMOVS-PAREXEL, London, United Kingdom.

BACKGROUND AND AIMS: PYM50018 has neuroprotective properties and an emerging safety profile that make it a promising candidate for the treatment of neurodegenerative disorders, such as amyotrophic lateral sclerosis. This study evaluated the pharmacokinetics, safety and tolerability of the compound, together with the effect of food on its bioavailability.

METHODS: Forty healthy males 18 to 45 years who met the entry criteria were included. Four groups of ten subjects were randomly allocated to receive placebo (n=2) or PYM50018 (n=8; 80 mg, 240 mg, 480 mg or 960 mg). One group also received PYM50018 (240 mg) on two further occasions either after breakfast or fasted.

RESULTS: Exposure to PYM50018 increased proportionately with dose. At higher exposures a second, slower elimination phase became apparent. Exposure to PYM50018 was increased after a high fat breakfast, as compared with the fasted state. There were no clinically significant changes in the safety parameters or adverse events.

CONCLUSIONS: PYM50018 is well tolerated by healthy male subjects as a single oral dose of up to 960 mg. Systemic exposure to oral PYM50018 is dose proportional. Food has a significant effect on the absorption kinetics of PYM50018.

PII-62

ACUTE EFFECTS OF CIGARETTE SMOKING ON GLOBAL CEREBRAL BLOOD FLOW (GCBF) IN OVERNIGHT ABSTINENT TOBACCO SMOKERS. T. Shinohara, K. Nagata, E. Yokoyama, MD, M. Sato, MD, S. Matsuoka, I. Kanno, J. Hatazawa, E. F. Domino, MD, Research Institute for Brain and Blood Vessels, Showa Hospital, University of Michigan, Ann Arbor, MI.

BACKGROUND/AIMS: The acute effects of tobacco smoking on gCBF were studied.

METHODS: Positron emission tomography (PET) with H215O was used to measure quantitatively CBF in 10 right handed male volunteer tobacco smokers. After 12 hr abstinence, gCBF measurements (baseline, 5% CO2/95% O2, and cigarette smoking) were made. gCBF was adjusted based on the vascular reactivity to CO2 and PaCO2 during smoking.

RESULTS: Mean gCBF during smoking compared with baseline did not change. However, an increase in nicotine arterial plasma correlated inversely with gCBF; gCBF increased in seven, decreased in seven, and was unchanged in five sessions. gCBF increased during smoking when baseline gCBF was low, whereas gCBF decreased when baseline gCBF was high.

CONCLUSIONS: Individual differences suggest important bimodal effects of smoking on the brains of different tobacco smokers.

PII-63

DISPOSITION OF NICOTINE AND COTININE IN RAT BLOOD AND BRAIN TISSUE, AND THEIR EFFECTS ON STRIATAL CONCENTRATIONS OF DOPAMINE AND SEROTONIN. Y. L. Chang, PhD, P. L. Tsai, PhD, L. C. Hung, BS, Y. C. Chou, PhD, J. H. Tien, MS, T. H. Tsai, PhD, Department of Pharmacy, Taipei Veterans General Hospital, Institute of Traditional Medicine, National Yang-Ming University, National Research Institute of Chinese Medicine, Taipei, Taiwan.

BACKGROUND: Concentrations of nicotine and cotinine following peripheral administration of nicotine to rats were determined to assess nicotine disposition in both brain and blood. The feasibility of microdialysis coupled with liquid chromatography system for direct analysis of neurotransmitters in the rat striatum was investigated. The purposes of the present study were to elucidate the pharmacokinetics of nicotine and evaluate their effects on brain dopaminergic and serotonergic neurotransmission in rat brain.

METHODS: We coupled a microdialysis sampling with on-line automatic analysis chromatographic system to characterize the pharmacokinetics of both nicotine and cotinine. The electrochemical detection system was employed to determine the striatal dialysates which included dopamine, serotonin and their respective metabolites after i.v. administration of nicotine.

RESULTS AND CONCLUSIONS: The results showed nicotine is easy to distribute into the central nervous system. Both drug levels and AUC of nicotine in brain were significantly higher than those in blood. On the other hand, levels of dopamine and serotonin had no significant change compared to baseline after nicotine administration. DOPAC are elevated than baseline in about 100 min interval. Concentrations of both HVA and 5-HIAA were consistently higher than baseline levels. The results showed nicotine have significant impacts on both dopaminergic and serotonergic neurotransmission in rat brain.

PII-64

PATIENT SATISFACTION WITH TRANSDERMAL OXYBUTYNIN: INTERIM RESULTS FROM THE MATRIX STUDY. R. Goldberg, MD, MPH, P. Sand, MD, N. Dahl, T. Lackner, PharmD, Northwestern University, Watson Pharma, Inc., University of Minnesota, Evanston, IL.

BACKGROUND/AIMS: Transdermal oxybutynin (OXY-TDS) has been proven safe and effective in treating overactive bladder (OAB), with a low incidence of anticholinergic AEs. The anticholinergic AE profiles of oral agents may compromise persistence. We have initiated a study to evaluate QoL, safety, pt satisfaction, and persistence in OAB pts on OXY-TDS.

METHODS: The Multicenter Assessment of Transdermal Therapy in Overactive Bladder with OXY-TDS (MATRIX study), an open-label, randomized, long-term, multicenter, prospective study, is to enroll 2500 community-dwelling adults. Pt-centered outcomes include persistence, tolerability, QoL, personal well-being, mood, social functioning, and activities of daily living. Validated questionnaires administered at baseline, 3 and 6 mos. Pt satisfaction data captured monthly via outbound calls.

RESULTS: Currently 676 pts are enrolled. Mean age is 62.4 y (21% $\geq$ 75 y); 86% female, 85% Caucasian. Of pts enrolled, 186 had been on therapy for 1 mo. Of these, 80% found the patch to be convenient; 78% were satisfied with ease of application; 36% felt the patch offers benefits over previous OAB pharmacotherapy, including effectiveness (33%), tolerability (34%), and ease of application (37%).

CONCLUSIONS: Preliminary results provide positive pt feedback on OXY-TDS. Pts are satisfied with treatment and feel it offers benefits over previous OAB treatments.