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THE EFFECT OF TOPIRAMATE (TPM) ON DURAL BLOOD FLOW (DBF) IN MIGRAINEURS DURING AND AFTER AN INFUSION OF NITROGLYCERIN (GTN). A. Amer, D. Wack, A. Supala, L. A. Hershey, E. M. Bednarczyk, University at Buffalo, Buffalo, NY.

BACKGROUND: Administration of nitric oxide (NO) donors provides a reliable model of migraine induction. NO was reported to cause a reproducible dilation of meningeal vessels and delayed inflammation in rat meninges. This may contribute to the pathogenesis of migraine headaches. TPM, an anti-seizure drug, has shown efficacy in migraine prophylaxis, however, the mechanism of this effect is unclear. We studied the effect of GTN infusion on DBF in migraineurs before and after an 8-week course of TPM.

METHODS: Migraineurs with and without aura (IHS criteria) underwent measurement of DBF using ^{15}O-water ($H_2{}^{15}O$) and positron emission tomography (PET). Measurements were made at baseline and following stepwise infusion of GTN at 0.125, 0.25 and 0.5 mcg/kg/min (~15 min at each dose step), and were repeated following 8 w of treatment with a maximal dose of 100mg BID of TPM. Quantitative measurement of blood flow was done in a series of regions of interest (ROI) including an ROI inclusive of the dura mater.

RESULTS: The following table shows DBF (mL/min/g) measurements obtained from 8 migraineurs; mean (SD). ANOVA demonstrated no statistically significant interaction between TPM and GTN ($p>0.05$).

	Baseline	0.125*	0.25*	0.5*	30 min post*	60 min post*
Pre TPM	0.44 (0.1)	0.47 (0.1)	0.48 (0.2)	0.44 (0.1)	0.47 (0.1)	0.44 (0.1)
Post TPM	0.77 (0.6)	0.60 (0.2)	0.51 (0.1)	0.52 (0.2)	0.52 (0.2)	0.47 (0.1)

* GTN (mcg/kg/min).

CONCLUSIONS: Migraineurs, on or off TPM, did not show a significant change in their DBF during and shortly after GTN infusion. Delayed measurements of regional cerebral blood flow at different ROIs including the dura mater may reveal a possible involvement of human meninges in migraine pathogenesis.

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TOBACCO SMOKING MODULATES BRAIN MU OPIOID RELEASE. E. F. Domino, MD, D. J. Scott, BA, M. M. Heitzeg, PhD, R. A. Koeppe, PhD, L. Ni, MS, S. K. Guthrie, PhD, J. Zubieta, MD, PhD, University of Michigan, Ann Arbor, MI.

BACKGROUND/AIMS: The aim of this research was to prove that tobacco smoking releases endogenous brain mu-opioids using [11C]carfentanil, a selective mu-opioid agonist.

METHODS: Six healthy male tobacco smokers were abstinent overnight for at least 10 hours before the scans, after which they smoked denicotinized and average nicotine cigarettes (nicotine 0.08 and tar 9.1 mg and nicotine 1.01 mg and tar 9.5 mg, respectively). Whole brain PET data were acquired, non-linear warped and coregistered into ICBM space, and analyzed using SPM99.

RESULTS: Significant differences were found in [11C]carfentanil displacement between the denicotinized and average nicotine tobacco conditions. The initial hypothesis that smoking an average nicotine cigarette in contrast to smoking a denicotinized cigarette would release brain mu-opioids was confirmed. [11C]Carfentanil binding was reduced in the right rostral and dorsal cingulate gyrus ($p<0.03$ and 0.001). Unexpectedly, decreased mu-opioid release also was found with increased [11C]carfentanil binding in the left amygdala and ventral striatum and right thalamus ($p<0.0001$).

CONCLUSIONS: These findings indicate a more complex role for the endogenous brain mu-opioid system in human tobacco smoking and indicate the need for further research.

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LONG-TERM EFFECTS OF RAMELTEON ON ENDOCRINE FUNCTION IN PATIENTS WITH CHRONIC INSOMNIA IN A DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE III STUDY. G. S. Richardson, MD, S. Wang-Weigand, MD, S. Sainati, MD, PhD, S. Demissie, MSc, DrPH, Henry Ford Hospital Sleep Disorders and Research Center, Takeda Global Research & Development Center, Detroit, MI.

BACKGROUND: Ramelteon, an MT_1/MT_2 receptor agonist developed for insomnia treatment, was evaluated for long-term effects on endocrine function.

METHODS: In a double-blind multicenter trial, 122 patients (aged 18-45 yr) with chronic insomnia received placebo or ramelteon 16 mg nightly for 6 months. Multiple endocrine variables were analyzed at baseline and monthly.

RESULTS: There were no consistent statistically significant differences between treatments on measures of thyroid function (total T4, free T4, TSH and total T3), adrenal function (AM cortisol and ACTH), or on most reproductive endocrine measures (LH, FSH, estradiol [women], total and free testosterone [men]). There were small, but statistically significant, differences in prolactin levels between groups: overall mean change from baseline of 2.9 μg/L (22.8% change) with ramelteon and −0.6 μg/L (4.4% change) with placebo. The effect on prolactin appeared to be transient and was only seen in women. No clinical signs of elevated prolactin were reported; average menstrual cycle length, duration of menses, and ovulation probability did not differ between groups. AE incidence was similar between groups; most AEs were mild or moderate (3 patients had SAEs unrelated to study drug).

CONCLUSION: Long-term treatment of chronic insomnia with ramelteon had no appreciable effect on multiple measures of endocrine function compared to placebo. A mild, transient increase in prolactin was observed in women, but it had no significant clinical effect.

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SAFETY, TOLERABILITY AND PHARMACOKINETICS (PK) OF MULTIPLE DOSES OF LECOZOTAN, A NOVEL $5HT_{1A}$ ANTAGONIST, IN HEALTHY ELDERLY SUBJECTS. V. Parks, Bsc, S. V. Raje, PhD, A. A. Patat, MD, A. Plotka, MS, B. Astruc, MD, D. Chassard, MD, Wyeth Pharmaceuticals France, Division Wyeth Research, Wyeth Research, Wyeth, Biotrial, Aster-Cephac, Paris - La Défense Cedex, France.

BACKGROUND/AIMS: Lecozotan is a potent and silent $5\text{-}HT_{1A}$ antagonist being developed for the treatment of cognitive deficits associated with Alzheimer's disease. The objective of this study was to assess the safety, tolerability, and PK of multiple oral doses of Lecozotan in elderly subjects (> 65 yrs old), a population similar to the target patient population.

METHODS: This was a randomized, double-blind, placebo-controlled study in 16 subjects who received 5 mg q12h of Lecozotan or placebo (12 active, 4 placebo) for 14 days. Safety evaluations included adverse events (AE), vital signs, ECG, and lab tests up to 48 hours after the last dose. A complete PK profile was obtained on days 1 and 14.

RESULTS: Lecozotan was safe and well tolerated after multiple dosing. Few mild to moderate AEs were recorded in 4 out of 16 subjects. There were no clinically significant changes in vital signs, ECGs, and routine laboratory tests. Lecozotan t_{max} was < 1 hour and $t_{1/2}$ was 9 - 11 hours. Steady-state Cl/F was ~33 mL/h/kg. Steady-state was achieved by day 3 of q12h administration and accumulation ratio was 1.8. Mean steady-state $AUC_{0\text{-}12h}$ was within 13% of the mean single-dose $AUC_{0\text{-}\infty}$ suggesting reliable multiple-dose predictability from single-dose PK. Cl/F in elderly was ~ 25% lower in comparison to young subjects.

CONCLUSIONS: Lecozotan was safe in elderly subjects up to multiple daily doses of 10 mg and the elderly PK profile was characterized by a mild decrease in clearance, which does not justify any dosage adjustment.