LB-3

POSITRON EMISSION TOMOGRAPHY TO QUANTIFY BRAIN NICOTINE ABSTINENCE. E. F. Domino, MD, H. Tsukada, PhD, University of Michigan, Hamamatsu Photonics K.K., Japan, Ann Arbor, MI.

BACKGROUND: The hypothesis for this research was that brain dopamine (DA) utilization would decrease during abstinence from repeated nicotine administration.

METHODS: Six young Macaca mulatta monkeys were given 0.9% NaCl or nicotine in doses of 32 or 100 μg/kg i.m. bid for 9 days. On the 10th day, PET measurements were repeated before and after nicotine. The PET studies were done in habituated, trained, and fully conscious animals.

RESULTS: Compared to the control condition, the binding potential (k3/k4) of [11C]raclopride in dorsal or ventral striatum did not change with either dose following acute repeated nicotine, or in the nicotine abstinent state. Compared to control, acute nicotine in either dose did not affect the DA utilization rate constant (k3) in dorsal or ventral striatum as measured by [Beta-11C]L-DOPA. However, in monkeys given nicotine repeatedly, after overnight nicotine abstinence, DA utilization was reduced significantly. A subsequent nicotine dose increased DA utilization to slightly above control levels. The ventral striatum showed greater changes than the dorsal striatum.

CONCLUSIONS: The reduced rate of DA synthesis as assayed with [Beta-11C]L-DOPA during nicotine abstinence and its reversal by nicotine provides an important PET measure of brain nicotine dependence and withdrawal.

LB-4

REDUCTION OF HALOPERIDOL-INDUCED SIDE EFFECTS BY ACP-103 IN HEALTHY VOLUNTEERS. A. E. Grahnen, PhD, K. E. Vanover, PhD, D. M. Weiner, PhD, L. Nilsson, MD, B. Tolf, PhD, U. Hacksell, PhD, M. R. Davis, PhD, Quintiles Nordic Region, ACADIA Pharmaceuticals, Uppsala, Sweden.

BACKGROUND/AIMS: A novel serotonin 2_A (5-$HT2_A$) receptor inverse agonist, ACP-103, was tested to determine the potential of ACP-103 to inhibit central nervous system side effects produced by haloperidol.

METHODS: Healthy male volunteers participated in a randomized, double blind, placebo-controlled, single dose crossover study. All subjects received a single dose of haloperidol (7.5 mg) in combination with either a single dose of placebo or a single dose of ACP-103 (100 mg). The washout period between treatment combinations was two weeks.

RESULTS: Haloperidol caused measurable akathisia in 13 of 18 subjects and induced approximately a 3-fold increase in prolactin secretion. ACP-103 treatment caused a measurable and temporally consistent decrease in haloperidol-induced akathisia compared to placebo treated subjects as measured by the Barnes Akathisia Scale. ACP-103 significantly reduced haloperidol-induced hyperprolactinemia.The pharmacokinetics of haloperidol and ACP-103 were not affected by their co-administration. No serious adverse events were reported.

CONCLUSIONS: Data suggest that ACP-103, when co-administered with existing antipsychotic drugs, may reduce their side effects and expand their range of efficacy. ACP-103 is being developed as an adjunctive therapy for schizophrenia and as a therapy for treatment-induced dysfunction in Parkinson's disease.

LB-5

AN OPEN-LABEL CLINICAL EVALUATION OF TIGECYCLINE (TGC) CONCENTRATIONS IN SELECTED TISSUES AND FLUIDS. M. H. Gotfried, MD, K. A. Rodvold, PharmD, M. Cwik, PhD, S. M. Troy, MS, G. Dukart, MD, E. J. Ellis-Grosse, PhD, Pulmonary Associates, P. A.; College of Medicine, University of Arizona, College of Pharmacy and Medicine, University of Illinois at Chicago, IIT Research Institute, Life Sciences Operation, Wyeth Research, Phoenix, AZ.

BACKGROUND/AIMS: TGC, an expanded spectrum glycylcycline in development for the treatment of skin and skin structure infections and intraabdominal infections, has a large volume of distribution (Vss≈600 L). TGC concentrations were measured in serum, lung, colon, gallbladder, bone, bile, and synovial fluid.

METHODS: Serum TGC was determined (by LC/MS/MS) predose, at end of 30-minute infusion of the single 100-mg TGC dose, and at tissue collection (during scheduled elective surgery).

RESULTS: At the time of this analysis, data from 54 subjects (of 120 planned) were available. Serum samples from 52 and tissue/fluid samples from 49 subjects were analyzed. Median TGC serum concentrations were 1425 ng/mL, 198 ng/mL, and 60 ng/mL at end of infusion, 4 hours, and 24 hours, respectively. Gallbladder, lung, and colon had the highest TGC concentrations; synovial fluid and bone had the lowest. One (1) death, the only serious adverse event (AE), occurred after the study; it was not related to TGC. Treatment-related AEs of nausea (23, 43%) and vomiting (7, 13%) were most frequently reported. No subject withdrew because of AEs.

CONCLUSIONS: Based on this analysis, a 100-mg TGC dose distributes into gallbladder, lung, and colon at or above MICs shown by *in vitro* data to be efficacious, and into bone tissue and synovial fluid. In animal studies, labeled TGC achieved high concentrations in bone. Tight TGC-bone binding, with poor extraction for assay, may have occurred in this study, rather than low bone uptake. The study is ongoing.

	Concentration	**Mean±SD tissue/serum ratios**			
	Range (ng/g)	4 hrs	8 hrs	12 hrs	24 hrs
Gallbladder (n=17)	238-20,700	39±40	15±19	85±79	38±42
Lung (n=2)	653-1890	8.6[a]	NA	NA	14.6[a]
Colon (n=11)	87-995	2.1±1.9	1.7±2.3	2.1±2.5	NA
Bone (n=19)	BQL-269	0.35±0.16	NA	1.10±1.25	NA
Synovial fluid (n=15)	26-181	0.58±0.24	NA	0.89±0.49	0.71±0.15

a: 1 subject at each time point; NA=data not available; BQL=below quantitation limit.