



**Attachment 1**  
**Massachusetts General Hospital Study Report Synopsis**

## MASSACHUSETTS GENERAL HOSPITAL CLINICAL STUDY REPORT SYNOPSIS

A PET STUDY EXAMINING PHARMACOKINETICS, DETECTION AND LIKABILITY, AND DOPAMINE TRANSPORTER RECEPTOR OCCUPANCY OF SHORT- AND LONG-ACTING ORALLY ADMINISTERED MPH FORMULATIONS IN ADULTS

Thomas J. Spencer, MD<sup>1,2</sup>; Jerrold F. Rosenbaum, MD<sup>1,2</sup>; Alan J. Fishman, MD, PHD<sup>1,2</sup>;  
Joseph Biederman, MD<sup>1,2</sup>; Patrick E. Ciccone, MD<sup>3</sup>; Darin Dougherty, MD<sup>1,2</sup>

<sup>1</sup>Harvard Medical School, Boston, MA

<sup>2</sup>Massachusetts General Hospital, Boston, MA

<sup>3</sup>McNeil Consumer & Specialty Pharmaceuticals, Fort Washington, PA

**Introduction:** Both the abuse potential and the likability of stimulant medications are associated with the rapid onset of presynaptic dopamine transporter (DAT) blockage in the brain. Previous studies of this association have compared intravenous and oral administration of stimulant medications. To this end, we conducted a study using PET and C-11 altropine to compare the pharmacokinetics of CNS DAT receptor occupancy of OROS MPH and immediate release MPH (MPH-IR). The main objective of this study was to better understand the mechanism of action of long-acting stimulant formulations and an estimation of the relative abuse potential of the two formulations. Specifically, we wanted to compare the pharmacokinetics of central DAT receptor occupancy of 90 mg OROS MPH and 40 mg of immediate release MPH-IR using PET scanning with C-11 altropine as the ligand using therapeutic doses of these compounds. The doses of medication (90 mg OROS MPH and 40 MPH-IR) were chosen on the basis of an expected similar plasma maximum plasma concentration (C<sub>max</sub>). We hypothesized that 1) CNS DAT receptor occupancy would be greater for MPH-IR than OROS MPH in the early period after oral administration and greater for OROS MPH later, 2) the time to maximal DAT receptor occupancy of MPH-IR would be shorter than that of OROS MPH, and 3) that subjective feelings would be greater on MPH IR than OROS MPH due to CNS kinetics, despite less than 1/2 the total dose and a similar plasma C<sub>max</sub>.

**Methods:** Twelve healthy human subjects were recruited sequentially. Six subjects were studied with MPH IR and six subjects with OROS MPH. Subjects were between 18 and 55 years of age, right handed and in good health. All subjects had a complete medical history and physical examination before imaging. In females, inquiry about the subject's current reproductive status was made. In addition, the following laboratory tests were performed: ECG, full blood count, blood chemistries, urinalysis (including drug screen and, in females, a pregnancy test).

Subjects underwent PET imaging before and after administration of oral doses of MPH IR or OROS MPH. The doses of MPH (40 mg IR and 90 mg OROS) were chosen to match expected plasma C<sub>max</sub> values. Over three days of scanning, subjects were scanned at baseline and 1, 3, 5 and 7 hours after medication. On the two days of scanning after MPH administration, venous blood was drawn hourly for quantification of plasma concentration of d and l- MPH hourly over 10 hours.

PET imaging: Images were acquired using a HR+ (CTI, Knoxville, TN) PET camera. The primary imaging parameters of the HR+ camera are in-plane and axial resolution of 4.5 mm FWHM, 63 contiguous slices of 2.5 mm separation. Images were acquired in 3D mode and reconstructed using an iterative algorithm to an in-plane resolution of 4.5 mm FWHM. Photon attenuation measurements were made with rotating pin sources containing 68 Ge.

For each scan, approximately 5 mCi of C-11 Altropane was injected intravenously over 30 seconds and serial PET images acquired. Dynamic image collection started at the same time as the infusion and images were acquired in 15 second frames for the first 2.0 min. and in 1 minute frames for the remaining 88 min. On the second and third days of scanning, after initial scans there was a period of 2 hours for decay of residual radioactivity, and then radiopharmaceutical injection and imaging procedures were repeated.

The binding potential for C-11 Altropane (B'<sub>max</sub> / K<sub>D</sub>) were calculated using a kinetic model comparing data from the striatum and cerebellum. Dopamine transporter occupancies were calculated as (B'<sub>max</sub> / K<sub>D</sub> baseline- B'<sub>max</sub> / K<sub>D</sub> MPH / B'<sub>max</sub>/K<sub>D</sub> baseline) x 100.

To obtain the estimated plasma MPH level required to occupy 50% of DAT (ED<sub>50</sub>), the percent DAT occupancy (P) was linearized by plotting the logarithm of P divided by (100- P) versus the logarithm of the plasma level concentrations (ng/ml). The linear regression permitted the determination of the ED<sub>50</sub> which corresponds to the 0 value on the y-axis.

**Results:**

Plasma d-MPH concentrations: Plasma d-MPH levels were measured hourly after receiving 90 mg of OROS MPH or 40 mg of MPH IR (Table 1). Plasma d-MPH levels were greater after MPH IR than OROS MPH at hours 1 to 3, relatively similar at hour 4 and less after MPH IR than OROS MPH at hours 5 to 10.

**Table 1. Plasma d-Methylphenidate Levels**

Hour	MPH IR (Mean±SD)		CONCERTA (Mean±SD)	
0	0	0	0	0
1	11.1 <sup>b</sup>	4.9	5.8	3.8
2	13.5 <sup>c</sup>	4.0	7.8	2.8
3	12.2 <sup>a</sup>	3.2	9.2	2.7
4	9.9	2.2	10.9	2.7
5	7.9 <sup>c</sup>	2.0	13.3	3.5
6	6.3 <sup>c</sup>	1.7	15.8	5.1
7	4.8 <sup>c</sup>	1.4	16.1	5.6
8	3.9 <sup>c</sup>	1.4	16.3	4.5
9	3.0 <sup>c</sup>	1.0	16.3	3.2
10	2.4 <sup>c</sup>	0.8	15.0	2.9

<sup>a</sup> p < 0.05 MPH IR vs. CONCERTA

<sup>b</sup> p < 0.01 MPH IR vs. CONCERTA

Average maximum plasma d-MPH levels were greater (trend) on OROS (14.1 ± 3.7 versus 17.7 ± 4.7, F=4.2, p=0.05, MPH-IR versus OROS MPH respectively). Moreover, the average time to maximum plasma d-MPH levels was approximately 3 1/2 times as long on OROS MPH (2.2 ± 0.8 versus 7.5 ± 1.2, F=170, p<0.0001, MPH-IR versus OROS MPH respectively).

DAT occupancies: DAT occupancies have been measured at 1, 3, 5 and 7 hours after receiving 90 mg of OROS MPH or 40 mg of MPH IR. DAT occupancies were greater after MPH IR than OROS MPH at hour one (p<0.05, total and right), relatively similar at hours 3 and 5 and smaller after MPH IR than OROS MPH at hour 7 (p<0.001). Average maximum DAT occupancies of total (left + right), left and right striatum on both medication formulations are presented in Table 2. Average maximum DAT occupancies were similar on MPH IR to those of OROS MPH. The average times to maximum occupancy were approximately three times as long on OROS MPH than MPH IR (p<0.05).

**Table 2. Maximum DAT Occupancies and Time to Maximum DAT Occupancy After Medication Formulations**

	MPH IR Mean ± SD		CONCERTA Mean ± SD	
Max Occupancy (Total)	71.5	7.7	67.6	5.5
Max Occupancy (left)	71.8	8.4	66.8	5.5
Max Occupancy (right)	71.3	7.1	68.8	5.6
Time to Max Occupancy (Total)	1.7 <sup>a</sup>	1.0	5.0	2.5
Time to Max Occupancy (left)	1.7 <sup>b</sup>	1.0	5.3	2.3
Time to Max Occupancy (right)	1.3 <sup>b</sup>	0.8	5	2.5

<sup>a</sup> p < 0.05 MPH IR vs. CONCERTA

<sup>b</sup> p < 0.01 MPH IR vs. CONCERTA

DAT Occupancy and Plasma Levels: Dopamine transporter occupancies were significantly correlated with the plasma concentration of d-threo MPH ( $t=6.6$ ,  $df=45$ ,  $p<0.00$ ). The plasma concentration associated with 50% blockade of the DAT was estimated to be 5.66 ng/ml. The relationship of plasma d-MPH concentration to DAT occupancy differs significantly for the two formulations. The plasma MPH concentration by drug formulation interaction was significant ( $t=20.4$ ,  $df=43$ ,  $p<0.0001$ ). The increase in DAT occupancy with increasing plasma MPH concentration was greater for the IR group than the OROS group.

Drug Rating Questionnaire (DQRS) Visual Analog Scale (VAS): Scores on the VAS of the DQRS represent graded responses from a score of 1 to a possible 29. Subjects on MPH IR reported a greater subjective response on all three scales than those on OROS MPH. Responses were greater at hour three (question 1  $p<0.05$ , question 2,3 trend) and hour four (question 1, 2, 3  $p<0.05$ ).

**Conclusion:** Despite more than twice the total dose, our findings indicate that OROS MPH has a slower velocity of association as well as disassociation on target brain receptors. A slower CNS uptake of OROS was expected since it parallels serum concentrations of MPH in the two formulations. However, there was evidence of altered CNS kinetics beyond that predicted by individual plasma concentrations. The increase in DAT occupancy with increasing plasma MPH concentration was greater for the IR group than the OROS group. In addition, despite similar maximum DAT occupancies, there was a greater subjective response to MPH IR than OROS MPH. These results support the hypothesis that subjective response is associated with the kinetics of the MPH formulation. These results have important implications on the clinical characteristics of the two formulations of MPH including magnitude and duration of effect, tolerance and substance abuse potential.

These results support the hypothesis that subjective liking is associated with the kinetics of each MPH formulation. These results have important implications for the clinical characteristics of the two formulations of MPH, including the substance abuse potential.