Blood levels and dopamine transporter (DAT) occupancy of orally administered methylphenidate (MPH) in juvenile rhesus monkeys measured by high resolution PET.

Aims: The pharmacokinetics and pharmacodynamics of MPH, in both blood and brain, are of increasing interest to many researchers, including those in the fields of drug abuse and attention deficit disorder (ADD). Previous studies have shown that oral MPH is less bioavailable in adult macaques than in humans, but little is known about the availability of MPH in juvenile macaques. The aim of the present study was to determine the relationship between blood levels and striatal DAT occupancy after oral dosing of MPH in juvenile macaques to help determine drug administration in subsequent studies.

Methods: DAT occupancy for oral MPH (0.80-32 mg/kg) in two male rhesus monkeys (2.5-3.0 yrs old) by displacement of [11C]MPH from the striatum using a high resolution research tomography (HRRT) PET scanner (2.2 mm resolution). Doses of MPH included those producing blood levels within the therapeutic range reported in children with ADD (i.e., 15-25 ng/ml). Levels of MPH in plasma were determined using isocratic HPLC.

Results: The EC50 for DAT occupancy was 21.5 mg/kg with a 95% CI of 13.00 to 35.64. There was a positive relationship between plasma MPH concentration and DAT occupancy, with the EC50 for DAT occupancy occurring in the range considered therapeutic for ADD. Interestingly, blood plasma concentrations in the juvenile monkeys did not reach the therapeutic range until 17 and 32 mg/kg MPH were administered, doses approximately 5 to 10-fold higher than that reported for adult macaques, and 15 to 30-fold higher than reported in children.

Conclusions: This is the first PET occupancy vs. oral MPH study reported in macaques. MPH is less bioavailable in juvenile macaques than adults. Once sufficient
MPH enters the blood, MPH occupancy of striatal DATs occurs at similar blood levels between humans and macaques.

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