

THE TEMPORAL AND EXTRASTRIATAL D2/D3 RECEPTOR BINDING PROFILE OF ARIPIPRAZOLE IN PATIENTS WITH SCHIZOPHRENIA

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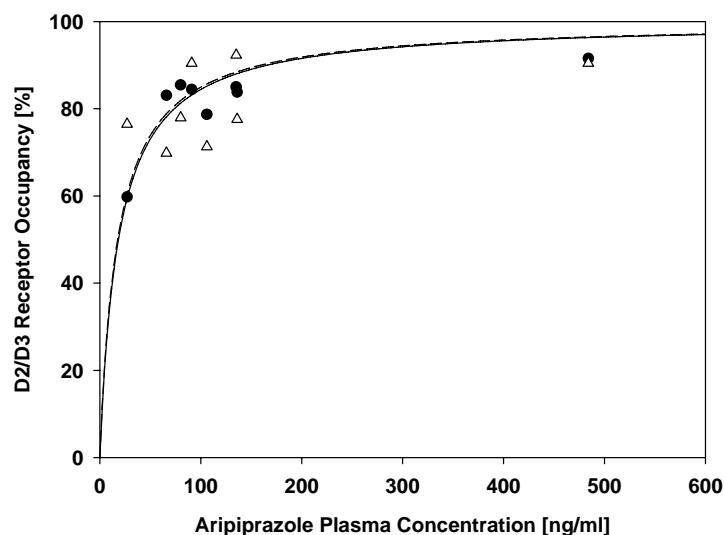
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Introduction: It is now widely accepted that the antipsychotic effects of dopamine receptor antagonists occur within a “therapeutic window” between 60 and 80% D2 receptor occupancy. The incidence of extrapyramidal side effects increases above the 80% threshold (Farde et al., Arch Gen Psychiatry 1992, 49: 538-544). Although clozapine and quetiapine seem to be exceptions, this rule does also apply for most of the “atypical” antipsychotics. However, our [¹¹C]raclopride PET study in normal volunteers to determine the optimal dose of aripiprazole for clinical trials in schizophrenia demonstrated that these rules apply to antagonists only. Here we showed that aripiprazole occupies more than 90% of striatal D2 receptors at clinically effective doses without extrapyramidal side-effects (Yokoi et al., Neuropsychopharmacology 2002, 27: 248-259; Gründer et al., Arch Gen Psychiatry 2003, 60: 974-977). In order to further characterize aripiprazole’s extrastriatal and temporal binding characteristics, we performed PET studies with [¹⁸F]fallypride ([¹⁸F]FP) in patients with schizophrenia at varying time points after the last drug administration.

Methods: D2-like dopamine receptors were quantified with positron emission tomography and [¹⁸F]FP in 12 patients suffering from schizophrenia (DSM-IV). The PET scans were performed at varying time points after the last drug administration (range 5-78 h). Time activity curves were generated after normalization using a template for cerebellum, caudate nucleus, putamen, temporal and frontal cortices, thalamus, amygdala, pituitary, colliculi, and substantia nigra. Binding potentials were calculated by means of the simplified reference tissue model. Receptor occupancy was calculated as percent reduction in binding potential, with unblocked values taken from a sample of 12 age-matched normal volunteers. Aripiprazole plasma concentrations were determined immediately before injection of the radiotracer. Plasma concentrations and percent binding data were fit to a simple one-site ligand binding model by nonlinear regression.

Results: Analysis of the data of six of the patients revealed very high mean D2/D3 receptor occupancies in

all brain regions (mean ± standard deviation, putamen 80 ± 11%, range 60-92%; caudate 83 ± 9%, range 66-93%; thalamus 80 ± 9%, range 68-90%; superior temporal cortex 79 ± 9%, range 70-90%), with slightly higher values in extrastriatal regions at very low plasma concentrations only. D2/D3 receptor occupancy was still in the range between 71 and 83% in a patient who had received his last dose 78 h prior to the PET scan. Aripiprazole plasma concentrations ranged from 27 ng/ml to 484 ng/ml. Nonlinear regression analysis revealed E_{max} (maximum attainable receptor occupancy) values close to saturation in all brain regions. EC₅₀ (plasma concentration predicted to provide 50% of the maximum attainable occupancy) values ranged from 4 ng/ml in the superior temporal cortex to 14 ng/ml in the putamen.



Relationship between aripiprazole plasma concentration and D₂/D₃ dopamine receptor occupancy in the putamen (black circles) and in the inferior temporal cortex (white triangles) in eight patients with schizophrenia (daily doses 5 - 30 mg)

Discussion: Our preliminary analyses suggest that aripiprazole due to its high affinity to D2/D3 receptors and its very long elimination half-life of about 72 hours at clinically used doses occupies very high amounts of its target receptor homogeneously throughout the brain and that dissociation from those receptors is very slow. It can be calculated from our results that in patients with plasma concentrations above approximately 400 ng/ml D2/D3 receptors are still almost saturated for nearly one week after the last dose.