Brain and Plasma Pharmacokinetics of Aripiprazole in Patients With Schizophrenia: An $^{18}$F-Fallypride PET Study

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Objective: Aripiprazole at clinically effective doses occupies some 90% of striatal dopamine 2 and 3 (D$_2$/D$_3$) receptors. In order to further characterize its extrastriatal and time-dependent binding characteristics, the authors conducted positron emission tomography (PET) studies with the D$_2$/D$_3$ antagonist $^{18}$F-Fallypride at varying time points after the last aripiprazole administration in patients with schizophrenia.

Method: Sixteen inpatients with a DSM-IV diagnosis of schizophrenia or schizoaffective disorder receiving treatment with aripiprazole underwent an $^{18}$F-Fallypride PET scan. Receptor occupancy was calculated as the percentage reduction in binding potential relative to unblocked values measured in eight age-matched, medication-free patients with schizophrenia. In addition, aripiprazole serum concentrations were determined as part of a routine therapeutic drug monitoring program in a large group of patients (N=128) treated with aripiprazole.

Results: Mean dopamine D$_2$/D$_3$ receptor occupancy was high in all brain regions investigated, with no binding difference across brain regions. Nonlinear regression analysis revealed maximum attainable receptor occupancy (E$_{max}$) values close to saturation. The values for serum concentration predicted to provide 50% of E$_{max}$ (EC$_{50}$) were in the range of 5–10 ng/ml in all brain regions. The D$_2$/D$_3$ receptors were completely saturated when serum aripiprazole concentration exceeded 100–150 ng/ml. The mean concentration in the large clinical patient sample was 228 ng/ml (SD=142).

Conclusions: Because of its high affinity for D$_2$/D$_3$ receptors and its long elimination half-life, aripiprazole at clinical doses occupies a high fraction of its target receptor everywhere in the brain. Its dissociation from those receptors is very slow, such that the authors calculate from the results that in patients with serum aripiprazole concentrations in the range typical for clinical practice, D$_2$/D$_3$ receptors must remain nearly saturated for as long as 1 week after the last dose.

It is now widely accepted that the antipsychotic effects of dopamine receptor antagonists occur within a “therapeutic window” between 60% and 80% of striatal dopamine 2 and 3 (D$_2$/D$_3$) receptor occupancy. The incidence of extrapyramidal side effects increases when occupancy exceeds the 80% threshold (1). This rule seems to apply also for most of the second-generation antipsychotics (2). However, in a $^{11}$C-Raclopride positron emission tomography (PET) study in normal volunteers to determine the optimal dose of aripiprazole for clinical trials in schizophrenia, it was shown that aripiprazole occupies more than 90% of striatal D$_2$/D$_3$ receptors at clinically effective doses (3). This finding was recently confirmed in patients with schizophrenia (4). On the basis of these findings, we concluded that the original conception of a “therapeutic window” of antipsychotic drug action applies to antagonists only (5). However, all the above-mentioned observations were made with reference to receptor occupancy in striatal structures only. With the advent of high-affinity radiotracers belonging to the class of substituted benzamides, it became possible to quantify extrastriatal dopamine receptors. While earlier PET studies with the moderate-affinity D$_2$/D$_3$ antagonist $^{11}$C-Raclopride demonstrated that the second-generation antipsychotics clozapine and quetiapine occupy striatal D$_2$/D$_3$ receptors to a significantly lesser extent than do other antipsychotics (2, 6, 7), it was later consistently shown in studies with high-affinity ligands that these two compounds nonetheless occupy a significantly higher proportion of temporolimbic than striatal D$_2$/D$_3$ receptors (8, 9). We demonstrated that the clinical antipsychotic efficacy of clozapine is likely more related to its binding in the temporal cortex than to its striatal binding (8). This “preferential” extrastriatal binding of...
second-generation antipsychotics, which was initially observed by Pilowsky et al. (10), has since been shown for several other second-generation antipsychotics, at least to a modest extent (11, 12). On the other hand, a recent PET study by Agid et al. found that striatal D2 blockade predicted antipsychotic response better than frontal, temporal, and thalamic receptor occupancy (13). The potential reasons for some controversial aspects of this phenomenon (14) have been discussed previously (8, 15).

One of the most widely used radiotracers for the quantification of extrastriatal D2/D3 receptors is \[^{18}F\]fallypride (16, 17). This ligand displays similarly high affinities for D2 and D3 receptors and negligible affinity for any other common neurotransmitter (18). Its fluorine-18 label offers the advantage of a longer physical half-life compared with, for example, the carbon-11 label of \[^{11}C\]raclopride. \[^{18}F\]Fallypride is an ideal tracer for the study of both striatal and extrastriatal receptors in a single PET scan. Human studies have consistently demonstrated that a 180-minute dynamic scan allows for establishment of a transient equilibrium both in extrastriatal regions of low receptor abundance and in the striatum (16, 17).

To further characterize aripiprazole’s extrastriatal binding and temporal changes in its binding in relation to its serum concentration, we conducted PET studies with \[^{18}F\]fallypride in patients with schizophrenia at varying time points after the last drug administration. Furthermore, to determine the clinical relevance of the serum concentration/occupancy relationship, we measured the serum concentration of aripiprazole in a large sample of patients with schizophrenia who were treated with this drug under clinical conditions.

**Method**

The study was approved by the ethics committee of the Medical Faculty of the RWTH Aachen University, Aachen, Germany, and the German radiation safety authorities. Twenty-four patients with schizophrenia were enrolled in the study after giving written informed consent. Sixteen patients underwent scanning while being treated with aripiprazole, and eight patients who were drug-free on admission to the hospital served as a comparison group. All PET investigations were performed in the Department of Nuclear Medicine of the RWTH Aachen University. In addition, aripiprazole serum concentrations were determined as part of a routine therapeutic drug monitoring program in a large sample of patients (N=128) who were treated with aripiprazole. These patients were treated in the Department of Psychiatry of the University of Mainz, Mainz, Germany.

**Participants**

The comparison group consisted of eight patients 18 to 58 years of age (mean=31 years, SD=14) suffering from schizophrenia as defined by DSM-IV criteria. They had been free of any psychotropic medication for at least 6 months, with the exception of small doses of lorazepam in some instances. All comparison subjects received a physical examination, a mental state examination, blood and urine analysis, electroencephalography, electrocardiography, and cerebral MRI.

The patient group consisted of 16 medicated patients (15 of them male; mean age=30 years, SD=10, range=19–50) who were diagnosed with either schizophrenia or schizoaffective disorder according to DSM-IV criteria. The mean age of the medicated patients did not significantly differ from that of the unmedicated participants. All patients had received an ongoing stable daily dose of aripiprazole (5–30 mg/day) according to clinical needs for at least 4 weeks prior to scanning. Seven patients received concomitant antidepressant medication, three patients were treated with zopiclone for insomnia, and five patients received lorazepam.

**Clinical Sample**

The large clinical patient sample consisted of 128 patients (34% women; mean age=33.8 years, SD=10.7), from whom a total of 293 serum samples were collected. The mean dose of aripiprazole was 20 mg/day (SD=9, median=15, range=10–60). Blood samples were taken at trough levels at 8 a.m. before administration of aripiprazole.

**Radiochemistry**

The \[^{18}F\]fallypride was synthesized at the Institute for Nuclear Chemistry of the University of Mainz as described in detail elsewhere for its congener \[^{18}F\]desmethoxyfallypride (19). The tosylated precursor, (((S)-N-[(1-allyl)-2-pyrrolidinyl]-methyl)-5-(3-toluenesulfonyloxypropyl)-2,3-dimethoxybenzamide (5 mg, 10 \(\mu\)mol), was dissolved in 1 ml acetonitrile, treated for 5 minutes at 85°C with potassium carbonate (5 mg, 36 \(\mu\)mol), and subsequently reacted with \[^{18}F\]fluoride for 20 minutes at 85°C. \[^{18}F\]Fallypride was isolated using high-performance liquid chromatography and adsorbed on a C18 cartridge, and the product was eluted with 1 ml ethanol. The final fraction was diluted with 9 ml of an isotonic sodium chloride solution and sterilized by ultrafiltration.

**Data Acquisition and Analysis**

Images were acquired on a Siemens ECAT EXACT whole-body PET scanner. Data acquisition comprised a series of 39 time frames (3×20 seconds, 3×1 minute, 3×2 minutes, 3×3 minutes, 21×5 minutes, 2×8 minutes, and 4×10 minutes) for a total scan duration of 180 minutes. After a 15-minute transmission scan, a mean of 207 MBq (SD=48) of \[^{18}F\]fallypride was injected as a bolus intravenously. The specific activity at the time of injection was 194 GBq/\(\mu\)mol (SD=484), corresponding to an injected mass of 2.3 \(\mu\)g (SD=2.6). Neither specific activities (unmedicated patients: 101 GBq/\(\mu\)mol [SD=103]; medicated patients: 235 GBq/\(\mu\)mol [SD=577]) nor injected mass (unmedicated patients: 2.1 \(\mu\)g [SD=1.7]; medicated patients: 2.7 \(\mu\)g [SD=3.0]) differed significantly between unmedicated patients and patients treated with aripiprazole. The injected mass did not correlate with the measured binding potentials (BP) in any region in the unmedicated subjects. Thus, it is unlikely that the radiotracer occupied a significant proportion (>5%) of receptors even in brain regions with low receptor density.

The magnitude of BP was calculated on a voxelwise basis using the Lammertsma simplified reference tissue model, which is based on a two-tissue compartment model (19, 20). The cerebellum was chosen as a reference region because it is generally considered to be nearly devoid of dopamine receptors. We cannot exclude the possibility that the occupancy values in our study were slightly underestimated because of a small degree of specific binding in the cerebellum (21). However, Kessler et al. (22) compared regional binding potentials obtained with Logan plots with metabolite-corrected plasma input function with those obtained with the reference region method and found a correlation coefficient greater than 0.99 with a slope of 1.0 (22). Furthermore, these authors did not detect any differences between cerebellar and white matter binding in the ratio of unblocked versus blocked
states. Thus, underestimation should be less than 5 percent at the
occupancies obtained in our study (23). For determination of D2 /
D3 receptor occupancy, the averaged BPs of eight unmedicated
patients were used as the common baseline value. Images were
reconstructed with filtered backprojection using a Ramp filter
and a Hamming filter (filter width=4 mm). After attenuation and
motion corrections, the whole dynamic emission recording was
quantified with filtered backprojection using a Ramp filter
coordinates using a predefined ligand-specific D2/D3 template.
To this end, a polynomial warping algorithm implemented in the
MEDx software, version 3.43 (Medical Numerics, Germantown,
M d.), was used.

Calculation of D2/D3 Receptor Occupancy

The individual participant’s receptor occupancy was defined as
percentage reduction of BP relative to the baseline BP according
to the following equation:

\[
\text{Occupancy} (\%) = \left(1 - \frac{\text{BP}_{\text{Medicated}}}{\text{BP}_{\text{Unmedicated}}} \right) \times 100
\]

Predefined templates of polygonal volumes of interest were
used to calculate time activity curves for the cerebellum (2.38
\text{cm}^3), the caudate nucleus (0.52 \text{cm}^3), the putamen (1.14 \text{cm}^3), the
thalamus (2.50 \text{cm}^3), the amygdala (0.31 \text{cm}^3), and the inferior
temporal cortex (3.61 \text{cm}^3). The inferior temporal cortex (anterior
and medial parts) was used as representative of cortical binding
because the D2/D3 receptor density in this region is highest com-
pared with all other cortical regions. A mean BPUnmedicated value
for each volume of interest was then calculated by averaging BP
values from eight unmedicated patients. BPMedicated was calcu-
lated in an identical manner for the 16 patient studies.

Aripiprazole Pharmacokinetic Data

Aripiprazole was administered in single doses in the morning
in all cases. Dosing details for individual patients in relation to
tracer injection are provided in Table 1. Blood samples were col-
clected at 8 a.m. (immediately before ingestion of aripiprazole)
and again immediately before [18F]fallypride bolus injection. The
PET scans were started between 1 p.m. and 6 p.m. Aripiprazole se-
rum concentrations were determined according to a previously
published method (24) with high-performance liquid chromatog-
raphy including column switching with online sample cleanup
and online ultraviolet detection of aripiprazole and its main me-
tabolite, dehydroaripiprazole (24). The within-run and between-
run imprecision of the assay was below 15%, and the limits of
quantification were below 50 ng/ml for both analytes.

Statistical Analyses

Statistical analyses were carried out with SPSS, version 14.0
(SPSS, Inc., Chicago). Means and standard deviations were calcu-
lated for serum concentrations and occupancy values. Unpaired t
tests were used to compare D2/D3 BP values for the groups of un-
medicated and aripiprazole-treated patients. A general linear
model for repeated measures with within-subjects factor at five
levels was applied to compare D 2/D3 receptor occupancy in the
five regions evaluated: putamen, caudate nucleus, thalamus,
amygdala, and inferior temporal cortex. Spearman rank correla-
tions were calculated for relationships between aripiprazole
doses and serum concentrations and brain D 2/D3 receptor occu-
pancy values. Serum concentrations (trough serum levels in the
morning and levels at the time of injection) and D2/D3 receptor
occupancy values were fitted to a one-site ligand binding model
by nonlinear regression analysis using Sigma Plot, version 9.0
(Systat, San Jose, Calif.), using the following equation:

\[
\text{Occupancy} (\%) = \frac{E_{\text{max}} \times C_A}{E_{\text{max}} + \frac{[C_A]}{E_{\text{50}}}} + [C_A]
\]

where \(E_{\text{max}}\) is the maximum attainable receptor occupancy,
\(E_{\text{50}}\) is the serum concentration predicted to provide 50% of the
maximum attainable receptor occupancy, and \([C_A]\) is the serum
concentration of aripiprazole. In all analyses, the two-tailed level
of statistical significance was set at \(\alpha = 0.05\).

Results

The entire group of aripiprazole-treated patients had
statistically significantly lower mean D2/D3 receptor BP
values than did the unmedicated patients in the putamen
(mean=4.1 [SD=2.7] compared with mean=24.1 [SD=3.6],
respectively; t=15.2, df=22, p<0.001), the caudate nucleus
(mean=3.4 [SD=2.3] compared with mean=21.8 [SD=3.2];
t=16.3, df=22, p<0.001), the thalamus (mean=0.36 [SD=
When aripiprazole serum concentrations and occupancy values were related to each other according to the law of mass action (see Statistical Analyses in the Method section), serum concentrations were significantly positively correlated with D2/D3 receptor occupancy values for all regions evaluated. Positive correlations were found between aripiprazole serum concentrations and occupancy values in the putamen (r=0.62, df=14, p<0.0001; Figure 1), the caudate nucleus (r=0.61, df=14, p<0.0001), the thalamus (r=0.62, df=14, p<0.0001), the amygdala (r=0.51, df=14, p<0.0001), and the inferior temporal cortex (r=0.57, df=14, p<0.0001; Figure 1). Figure 1 shows the relationship between aripiprazole serum concentration and receptor occupancy in the putamen and the inferior temporal cortex. D2/D3 dopamine receptors were almost completely occupied homogeneously throughout the brain at aripiprazole serum concentrations above approximately 100–150 ng/ml. There were only marginal differences in EC50 values between the analyzed brain regions (range=4–10 ng/ml; Table 2).

Correlations between receptor occupancies and serum concentrations were slightly better in four of the five brain regions when values for aripiprazole and the active main metabolite dehydroaripiprazole were added (putamen: r=0.67, df=14, Emax=95%, EC50=20 ng/ml, p<0.0001; caudate nucleus: r=0.67, df=14, Emax=95%, EC50=18 ng/ml, p<0.0001; thalamus: r=0.70, df=14, Emax=92%, EC50=12 ng/ml, p<0.0001; amygdala: r=0.50, df=14, Emax=89%, EC50=7 ng/ml, p<0.0001; inferior temporal cortex: r=0.60, df=14, Emax=92%, EC50=15 ng/ml, p<0.0001).

The PET scans were performed at a range of time points after the last drug administration (range=4–78 hours; Table 1). Aripiprazole occupancy of D2/D3 dopamine receptors persisted for several days after the last dosing (Table 1). Figure 3 shows parametric BP images of a patient who was treated with a daily aripiprazole dose of 30 mg. He was withdrawn from medication and underwent scanning approximately 78 hours after the last dose. Even after 3 days off medication, the D2/D3 dopamine receptor occupancy in this patient’s brain was close to 80% (putamen, 81%; caudate nucleus, 83%; thalamus, 75%; amygdala, 75%; inferior temporal cortex, 64%). Regardless of the time of the PET scan relative to the last drug administration, serum concentrations and occupancy values could be described by one single concentration/occupancy curve (Figure 1).

**Discussion**

In this study, we demonstrated that aripiprazole almost completely saturates both striatal and extrastriatal D2/D3 receptors over a wide range of serum levels typical of those obtained in clinical practice. With regard to aripiprazole’s striatal binding, our results are entirely concordant with our earlier observations in a PET study with [11C]raclopride in normal volunteers (3, 5), a finding that was recently confirmed in patients with schizophrenia (4). In ad-
dition, we could not detect any preferential extrastriatal binding of aripiprazole. This feature of aripiprazole stands in contrast to the preferential extrastriatal binding of other second-generation antipsychotics. Furthermore, this study showed that the rate of aripiprazole’s dissociation from D2/D3 receptors is very low. Taking into account aripiprazole’s long serum elimination half-life of about 72 hours, our observation of almost complete D2/D3 receptor occupancy above a serum concentration of approximately 100–150 ng/ml suggests that in patients treated with aripiprazole under clinical conditions, D2/D3 receptors remain almost saturated for as long as 1 week after the last drug administration. Our findings have important theoretical and clinical implications, as discussed below.

Aripiprazole is metabolized via the hepatic cytochrome P450 enzyme system, specifically the isoenzymes CYP2D6 and CYP3A4. Inhibition or induction of these enzymes—for example, through comedication—leads to predictable changes in aripiprazole serum concentrations (25). Mutation in the gene encoding for the CYP2D6 isoenzyme can lead to markedly increased aripiprazole serum concentrations (27, 28). Conversely, CYP2D6 ultrarapid metabolizers would be expected to present with unusually low serum concentrations of aripiprazole. Thus, in many clinical situations, individual assessment of the aripiprazole serum concentration may guide further treatment decisions.

Another finding of this study is that aripiprazole produces prolonged occupancy of cerebral D2/D3 dopamine receptors.

### Table 2. D2/D3 Receptor Occupancy, E_max, and E_C50 Values in Selected Brain Regions in 16 Patients With Schizophrenia or Schizoaffective Disorder Receiving Therapeutic Doses of Aripiprazole

<table>
<thead>
<tr>
<th>Region</th>
<th>D2/D3 Receptor Occupancy (%)</th>
<th>E_max (%)a</th>
<th>E_C50 (ng/ml)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Putamen</td>
<td>83</td>
<td>92</td>
<td>10</td>
</tr>
<tr>
<td>Caudate nucleus</td>
<td>84</td>
<td>92</td>
<td>9</td>
</tr>
<tr>
<td>Thalamus</td>
<td>85</td>
<td>90</td>
<td>6</td>
</tr>
<tr>
<td>Amygdala</td>
<td>85</td>
<td>88</td>
<td>4</td>
</tr>
<tr>
<td>Inferior temporal cortex</td>
<td>83</td>
<td>89</td>
<td>3</td>
</tr>
</tbody>
</table>

a E_max=maximum attainable receptor occupancy.

b E_C50=serum concentration predicted to provide 50% of the maximum attainable receptor occupancy.
receptors (Table 1, Figure 3). This observation was expected, given aripiprazole’s high affinity for dopamine receptors and its long plasma elimination half-life (approximately 60–70 hours) (29). We calculate that if aripiprazole were withdrawn in patients with serum levels above 600 ng/ml, the drug would still almost completely occupy D2/D3 receptors for almost 1 week after the last dose. Regardless of the time of the PET scan relative to the last drug administration, the estimated data could be almost perfectly described by a single nonlinear fit according to the law of mass action (Figure 1). These findings seem to contrast somewhat with a recent report that aripiprazole dissociates very rapidly from the D2 receptor (30). However, PET cannot provide information about the temporal dynamics of a pharmaceutical on a microenvironmental synaptic level. Therefore, it is theoretically possible that aripiprazole is slowly released from the D2/D3 receptor from a macroscopic view but still dissociates rapidly if the association rate is comparably high. Nevertheless, our PET studies indicate that “atypicality” in its original sense (absence of extrapyramidal side effects) can be achieved by several mechanisms, such as D2 partial agonism or low D2 affinity (8). We show that transient occupancy of D2/D3 receptors, as seen with some low-affinity second-generation antipsychotics, is not a prerequisite for low liability to extrapyramidal side effects (31). Aripiprazole’s properties as a 5-HT1A agonist and a 5-HT2 antagonist might also contribute to its “atypical” clinical characteristics, although these receptors are occupied to a relatively small extent at clinically used dosages (4).

It has been demonstrated, by us and others (8, 9), that especially low-affinity antipsychotics, such as clozapine and quetiapine, occupy brain D2/D3 receptors to a lesser extent in striatal than in extrastriatal, especially cortical, brain regions. In the present case of aripiprazole, we could not detect regional differences in occupancy. Striatal and cortical binding could be described by virtually identical serum concentration/occupancy curves (Figure 1). A lack of regionally heterogeneous binding and a slow dissociation from D2 receptors have also been described for haloperidol (32, 33). Aripiprazole and haloperidol have in common their high affinity for D2-like dopamine receptors and their long plasma elimination half-life. Therefore, we suggest that the lack of differential regional binding at D2 receptors is not a characteristic that separates first-generation from second-generation antipsychotics. Rather, regional differences in occupancy may occur as a function of affinity of the specific antipsychotic. Compounds with a short half-life and/or a low affinity, such as clozapine, typically present a flat plasma concentration/occupancy curve (8), whereas compounds with a long plasma half-life and/or a high affinity, such as haloperidol, are described by a steep curve. The most likely explanation for differential regional binding of low-affinity compounds is the regionally different competition of these compounds from endogenous dopamine (34). Interstitial
dopamine concentrations in animal striatum are significantly higher compared with cortical concentrations when measured with microdialysis (35, 36). Furthermore, there are markedly different kinetics of dopamine release and reuptake across brain regions (37). For compounds that are characterized by a much higher affinity for D₂ receptors than dopamine itself, this competition might be irrelevant.

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