Available online at www.sciencedirect.com
ScienceDirect
Psychiatry Research: Neuroimaging 148 (2006) 175–183
PSYCHIATRY RESEARCH NEUROIMAGING
www.elsevier.com/locate/psychresns

Dopamine D_2 receptor occupancy by risperidone: Implications for the timing and magnitude of clinical response

Ana M. Catafau[a,b], Iluminada Corripio[a,*], Victor Pérez[a], Juan Carlos Martin[c], Alain Schotte[d], Ignasi Carrió[a], Enric Alvarez[a]

[a]*Departments of Nuclear Medicine and Psychiatry, St Pau Hospital, U.A.B. (Autónoma University from Barcelona), Barcelona, Spain*
[b]*GSK Centre for Imaging in Psychiatry, Clinical Pharmacology Discovery Medicine, Psychiatry, Centre of Excellence for Drug Discovery, Barcelona, Spain*
[c]*Department of Nuclear Medicine, Parc Taulí Hospital, Sabadell, Barcelona, Spain*
[d]*Janssen Research Foundation, Beerse, Belgium*

Received 6 March 2005; accepted 2 February 2006

Abstract

The objective of the study is to investigate whether dopamine D2 receptor occupancy by risperidone and plasma levels over time can account for therapeutic efficacy and the latency period to response. Thirty-eight examinations with ^{123}I-IBZM single photon emission computed tomography were performed on 22 patients with schizophrenia, at diagnosis, 48 h after starting risperidone treatment and at a stable dose. Risperidone plasma levels were determined and psychopathologic evaluations (Brief Psychiatric Rating Scale, Positive and Negative Syndrome Scale) were carried out. No differences in the striatal/occipital (*S*/*O*) ratio or plasma levels were found between examinations at the 48-h time point and when a stable dose level had been established, so these parameters could not account for the latency period required for clinical response. D2 receptor occupancy at 48 h correlated positively with clinical improvement after 2 weeks of treatment. Therefore, if these results are confirmed, D2 receptor occupancy at the beginning of treatment with risperidone may be a predictor of subsequent clinical response.

Keywords: Antipsychotics; Dopamine receptors; Latency period; Schizophrenia; SPECT

1. Introduction

Since the introduction of antipsychotic medication as a treatment for patients with schizophrenia, extensive research has been carried out to identify factors that may predict clinical response. Functional and molecular neuroimaging have been used for this purpose. Cerebral dysfunction patterns in perfusion single photon emission computed tomography (SPECT) (Fitzgerald et al., 2000) and excessive dopaminergic D2 receptor (D2R) stimulation during amphetamine challenge in schizophrenic

Abbreviations: Brief Psychiatric Rating Scale; BPRS; Dopaminergic D2 receptors; D2R; Extrapyramidal Side Effects; EPS; ^{123}I-Iodobenzamide; IBZM; Positive and Negative Syndrome Scale; PANSS; Positron Emission Tomography; PET; Region of Interest for Striatum; ROIs; Single Photon Emission Computed Tomography; SPECT; Striatum/Occipital uptake ratio; S/O ratio.

*Corresponding author. Department of Psychiatry, Sta. Creu and St. Pau Hospital, C/ Sant Antoni Maria Claret 167, 08025 Barcelona, Spain.
E-mail address: icorripio@hsp.santpau.es (I. Corripio).

0925-4927/$ - see front matter © 2006 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.pscychresns.2006.02.001

Table 1
Demographic features, clinical and paraclinical findings

	N	Age (years)	Gender (M/F)[1]	Dose (mg)	Plasma levels (ng/ml)	*S*/*O* ratio[2]	SAS[3]
Pre-treatment	9	22.80 (18–28)	4/5			1.84 (1.64–2.02)	
48 hours	11	24.55 (18–33)	4/7	4.50 (1.00–9.00)	5.38 (2.00–15.00)	1.34 (1.18–1.62)	0.72 (0.00–8.00)
Stable dose	20	26.00 (18–45)	8/10	4.00 (1.00–7.50)	4.69 (1.75–13.60)	1.32 (1.09–2.02)	3.00 (0.00–9.00)

Values are given as mean (range).
[1](M/F): male/female. [2]*S*/*O* ratio: striatal/occipital ratio. [3]SAS: Simpson–Angus Scale scores.

patients visible on neuro-receptor SPECT, have been suggested as predictors of response (Abi-Dargham et al., 2000). Nevertheless, a biological factor easily identifiable soon after the beginning of antipsychotic treatment has yet to be found.

Antipsychotics are neurochemically active, as D2R antagonists, from the first doses of treatment (Brücke et al., 1992). However, although clinical response to antipsychotic therapy is variable, in most cases, it is not immediate, and up to 6 weeks of treatment may be required before clinical improvement occurs. Based on the dopaminergic hypothesis of schizophrenia, this latency period from the beginning of antipsychotic treatment to the improvement of clinical symptoms could be attributed to a slow D2R occupancy rate, with the degree of D2R occupancy at the beginning of treatment being insufficient to induce a clinical effect. Therefore, it could be assumed that the time required to manifest clinical improvement is the time required to achieve a sufficient level of D2R occupancy. However, in humans, this hypothesis has yet to be demonstrated in vivo.

Pharmacodynamics and pharmacokinetics provide some insight into the mechanism of action of antipsychotic compounds. Classically, antipsychotic plasma levels have been used as an indirect measure of cerebral D2R occupancy. Positron emission tomography (PET) and SPECT have been shown to be useful tools for measuring D2R occupancy in vivo (Farde et al., 1989, Tauscher et al., 1999; Bernardo et al., 2001), although the relationship between in vitro (i.e. plasma levels) and in vivo (functional neuro-imaging) measurements remains unclear.

Sequential studies of both in vivo D2R occupancy and clinical efficacy could contribute to the understanding of the antipsychotic mechanism of action and the latency period required for clinical response. However, most PET and SPECT studies have measured D2R occupancy at a single time point, usually once the dose of antipsychotic medication has been stabilized. Since the publication of PET studies showing differences in atypical D2R occupancies, overtime, there has been growing interest in the study of the interaction between antipsychotic drugs and dopamine receptors soon after the beginning of treatment (Gefvert et al., 1998; Kapur et al., 2000).

In the present study, the temporal sequence of D2R occupancy, plasma levels, and clinical efficacy was investigated in psychotic patients treated with the atypical antipsychotic risperidone. The aim of the study was to investigate if pharmacokinetic (plasma levels) and pharmacodynamic (D2R occupancy) factors over time could account for the efficacy and latency period of antipsychotic action.

2. Methods

2.1. Patients

Participants comprised 22 patients with schizophrenia (12 females and 10 males, mean age = 24 years, range = 18–55 years). Table 1 summarizes their demographic and clinical characteristics. At inclusion, 18 patients were neuroleptic-naïve and four were neuroleptic-free, with more than 6 months of washout. None of the patients had received any depot antipsychotics in the year before the study. Permissible concomitant medication was restricted to anticholinergic agents and benzodiazepines. Diagnoses, in accordance with DSM-IV criteria, were schizophreniform disorder ($n = 12$), and schizophrenia ($n = 10$). Patients with a history of substance abuse (with the exception of nicotine), past or present neurological disease, or any other organic disturbance that might have interfered with the aim of the study were excluded from participation. Pregnancy in female patients was ruled out before scanning by a negative β-HCG test. All 22 patients included in the study were treated with risperidone, which was started at trial onset. Risperidone doses were adjusted by the treating psychiatrist to each patient's clinical needs. Doses of risperidone were considered to be stabilized after 2 weeks of treatment. Only one patient required a 9-mg dose; all the others were on low doses (Table 1). The mean risperidone doses at 48 h and after 2 weeks were not statistically different (4.5 ± 2 vs. 3.9 ± 2 mg/day). Risperidone was administered once a day, 12 h before the