Abstract Rationale: Previous work suggests clozapine preferentially targets limbic cortical dopamine systems, which could help account for its lack of extrapyramidal side effects (EPS) and superior therapeutic efficacy. Objectives: To test the hypothesis that olanzapine, a novel atypical antipsychotic drug, occupies temporal cortical D2/D3 receptors to a greater extent than striatal D2/D3 receptors in vivo. Methods: Nine schizophrenic patients taking either olanzapine \((n=5; \text{mean (SD) age: } 32.5 (6.5) \text{ years; daily dose: } 18.3 (2.6) \text{ mg})\) or sertindole \((n=4; \text{mean (SD) age: } 30.3 (7.4) \text{ years; daily dose: } 16 (5.6) \text{ mg})\) were studied with \([123\text{I}]\)epidepride \((S)-(1-ethyl-2-pyrrolidinyl)methyl]-5-iodo-2,3-dimethoxy-benzamide\) and single photon emission tomography (SPET). An estimate of \([123\text{I}]\)epidepride ‘specific binding’ to D2/D3 receptors was obtained in patients and age-matched healthy volunteers. A summary measure was generated representing striatal and temporal cortical relative %D2/D3 receptor occupancy by antipsychotic drugs. Occupancy data were compared with previously studied groups of patients receiving typical antipsychotic drugs \((n=12)\) and clozapine \((n=10)\). Results: Mean striatal and temporal cortical %D2/D3 receptor occupancy in olanzapine-treated patients was 41.3% (SD 17.9) and 82.8% (SD 4.2), respectively. Unexpectedly low levels of striatal relative %D2/D3 receptor occupancy were seen in two patients with typical antipsychotic-drug-induced movement disorder prior to switching to olanzapine. In the temporal cortex, mean D2/D3 dopamine receptor occupancy levels above 80% were seen for all antipsychotic drugs studied. Conclusions: The atypical antipsychotic drugs olanzapine and sertindole, in common with clozapine, demonstrate higher occupancy of temporal cortical than striatal D2/D3 dopamine receptors in vivo at clinically useful doses. This could help mediate their atypical clinical profile of therapeutic efficacy with few extrapyramidal side effects. Limbic selective blockade of D2/D3 dopamine receptors could be a common action of atypical antipsychotic drugs.

Key words Olanzapine · Antipsychotic drug · Dopamine D2/D3 receptor · Epidepride · Single photon emission tomography · Schizophrenia

Introduction

The novel antipsychotic drug olanzapine \((2\text{-methyl-4(4-methyl-1-piperazinyl)-1,1-hydroxy-thieno[2,3-b][1,5]benzodiazepine})\) is useful for the first-line treatment of psychosis (Lieberman 1996). It is a thienobenzodiazepine derivative with a wide range of receptor affinities for 5HT\(_{3a}\) \((K_i=4\pm0.4 \text{ nM})\), D1 \((K_i=31\pm0.7 \text{ nM})\), D2 \((K_i=11\pm2 \text{ nM})\), H1 \((K_i=7\pm0.3 \text{ nM})\), and \(\alpha_1\)-adrenergic receptors \((K_i=19\pm1 \text{ nM})\) (Moore et al. 1993; Bymaster et al. 1996). Olanzapine does not require intensive blood monitoring for haematological side effects. Its therapeutic profile meets the criteria for an atypical antipsychotic drug (defined recently as an antipsychotic drug producing few or no extrapyramidal side effects at clinically useful doses (Kerwin 1994; Pickar 1995; Beasley et al. 1997; Tran et
Dopamine D2 receptor subtypes (including D2short and D2long isoforms, D3 and D4 receptors) have been characterised (Sokoloff et al. 1990; Van Tol et al. 1991) and are present in limbic cortical regions (including temporal poles, amygdala and hippocampus) (Kessler et al. 1993; Hall et al. 1996). Limbic cortical dopamine D2/D3 receptor populations could be important therapeutic targets for antipsychotic drugs. It is now possible to evaluate this in vivo with the high-specificity and -affinity D2/D3 ligand [123 I]epidepride (Kessler et al. 1993; Hall et al. 1996; Pirker et al. 1997).

Recent data suggest clozapine treatment results in preferential occupancy of D2/D3 dopamine receptors in temporal cortex, in excess of striatal D2/D3 blockade (Pilowsky et al. 1997; Xiberas et al. 1999). Clozapine could mediate its effects, at least in part, by selective blockade of extrastriatal D2/D3 dopamine receptors. Electrophysiological studies show olanzapine selectively affects dopamine neuronal firing of A10 (ventral tegmental area neurons projecting to limbic cortical regions), but not A9 (substantia nigra neurons projecting to striatum) (Bymaster et al. 1996). There are no full studies reporting occupancy of limbic cortical D2/D3 receptors by olanzapine or sertindole in living human subjects; however, recent PET data suggest olanzapine treatment results in 80–90% occupancy of temporal cortical D2/D3 receptors in vivo (Xiberas et al. 1999; Meltzer et al. 1999).

We used [123 I]epidepride single photon emission tomography (SPECT) to test the hypothesis that olanzapine-treated patients (n=5) show preferential blockade of temporal cortical D2/D3 receptors. Patients in this study were compared with sertindole (n=4)-treated patients, and a previously collected database of clozapine-treated patients [n=10, mean (SD) age: 30.9 (10.4) years; mean (SD) dose: 445 (193.6) mg] and typical antipsychotic-treated patients (n=12, mean (SD) age: 39.6 (10.7) years; mean (SD) dose 669 (516.8) mg chlorpromazine milligram equivalents].

Materials and methods

An open-label parallel study was undertaken comparing striatal and limbic cortical D2/D3 receptor occupancy (estimated by [123 I]epidepride SPET), clinical efficacy and tolerability in patients randomised to an 8-week trial of either olanzapine or sertindole treatment (see below for protocol design and detailed method).

Subjects

Ethical permission was obtained from the Bethlem and Maudsley NHS Trust Ethics committee and the UK Administration of Radioactive Substances Advisory Committee (ARSAC). Patients were recruited from clinical services at the Bethlem and Maudsley NHS Trust, London, UK. After a complete description of the study to the subjects, written informed consent was obtained.

1. Inclusion criteria for patient entry into the study were: male or female patients 18–45 years of age; diagnosis of schizophrenia, schizoaffective, or schizophreniform disorder as defined in DSM-IV. Patients were mild to moderately ill as defined by an initial score on the PANSS total of greater or equal than 60. Female patients of childbearing potential were using a medically accepted means of contraception. Each patient had to have a level of understanding sufficient to communicate intelligently with the investigator, nurse or study coordinator.

Protocol design

After inclusion in the trial, patients were assigned by random allocation to one of two treatment groups: olanzapine (10, 15, or 20 mg/day) or sertindole (12, 16, 20, or 24 mg/day). Randomisation was performed remote from the study centre, and treatment arms were enclosed in a sealed envelope opened by the investigator on the day of inclusion. Dosing was freely titrated for optimal control of symptoms by a trained psychiatrist (V.B.). Concomitant treatment with benzodiazepines was permitted to treat agitation or insomnia. Patients were seen and assessed weekly for 8 weeks. At the first visit patients had to sign informed consent, provide blood for screening tests and start a flexible washout period lasting from 2 to 9 days depending on clinical need. At the second visit (after the washout period) medication was begun, and after 6 weeks of treatment a [123 I]epidepride SPET scan was performed. Dose levels of medication were determined by clinical need, according to the patient’s symptom severity by the psychiatrist (V.B.) assessing them. Six olanzapine-treated patients were included in the trial. One case (OLZ4) was excluded from the final analysis due to failure to tolerate the SPET scan (see details in “Results”). Two patients (OLZ3 and OLZ6) had received previous treatment with depot neuroleptic drugs. Four sertindole-treated patients were studied.

Symptom ratings

Symptoms and side effects were rated at baseline (visit one) and at weekly intervals during the subsequent 7 weeks. Clinical ratings were as follows: current psychopathology was assessed by the SCI-PANSS, a structured interview for the positive and negative symptoms scale (Kay et al. 1987); and the CGI, the clinical global impression scale (Guy 1976); and the depressive symptoms were assessed with the MADRS (Montgomery and Asberg 1979). Motor side effects were rated using the Simpson & Angus scale (SA) (Simpson and Angus 1970) for parkinsonian effects, the Abnormal Involuntary Movements Scale (AIMS 1974) for symptoms of tardive dyskinesia and the subjective and objective Rating Scale for Drug-Induced Akathisia (AK) (Barnes 1989).