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Clinical predictors of response to olanzapine or risperidone during acute episode of schizophrenia

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ABSTRACT

The study attempted to identify clinical variables which could predict the response to a second-generation antipsychotic treatment during acute episodes among schizophrenic patients. Socio-demographic, premorbid and clinical variables were studied in a population of 95 diagnosed with schizophrenia, as defined in the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSMIV), during an acute treated phase, in a multicentre prospective study. Patients were assigned to olanzapine or risperidone treatment in an open design. Clinical evaluations were performed at D0, D42 and D180. Good response to treatment was defined as a Positive and Negative Syndrome Scale (PANSS) reduction greater than 20% and a Brief Psychiatric Rating Scale (BPRS) score lower than 35. Univariate analysis revealed earlier age at onset of schizophrenia and earlier age at first prescription of antipsychotic among non-responders compared with good responders at D42. Non-responders also had a clinical profile at the onset of antipsychotic treatment characterised by more severe forms of the acute episode as shown by higher scores at the positive, general and overall PANSS scale and on CGI-S and BPRS scores. With a multivariate logistic regression model, age at onset and overall duration of illness remained the only clinical criteria identified as predictors of response to antipsychotic treatment at D42. Clinical variables do not clearly appear to be good predictors of treatment efficacy.

1. Introduction

Today, second-generation antipsychotic drugs are the first-line treatment for schizophrenic patients. They have helped to reduce an important therapeutic difficulty met with first-generation neuroleptics, that is, the appearance of neurological side effects, which is the cause of frequent spontaneous interruption of psychotropic drug (Leslie and Rosenheck, 2002). Besides this improved tolerance, several studies have revealed that antipsychotics, particularly olanzapine and risperidone, are as efficient as neuroleptics, if not more so, against positive and negative symptoms (Chouinard et al., 1993; Beasley et al., 1996; Tollefson et al., 1997; Beasley et al., 1999; Leucht et al., 1999; Purdon et al., 2000). However, the percentage of non-response or partial response to treatment during acute phases remains high (Freedman, 2005; Gardner et al., 2005; Lieberman et al., 2005). Only 60–70% of patients show a clinically significant decrease in psychotic symptomatology during a first episode of the illness, and barely 50% during relapses (Lieberman et al., 1996), with no possible prediction of non-response risk as a function of the selected treatment. Evolution of schizophrenia is marked by frequency of relapses (Kane, 1996). In clinical practice, the choice of antipsychotic is often made empirically, because of the limited amount of data available on the predictors of a response to antipsychotic treatment.

There have been descriptions of predictive factors of poor response to treatment, mainly among patients treated with conventional neuroleptics: notable among these are positive family history of mental disorder (McGlashan, 1986), gender (females having a better rate of response) (Navarro et al., 1996; Goldstein, 1998), early age at onset of schizophrenia, number of relapses (van Kammen et al., 1996; Lieberman, 1999), duration of untreated psychosis (DUP) (Loebel et al., 1992; McGlashan 1999; Marshall et al., 2005; Perkins et al., 2005) and psychiatric comorbid conditions (Sim et al., 2006). Regarding clinical criteria, severity of symptomatology seems to predict poor

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response to treatment during acute phases (Robinson et al., 1999). Pronounced negative symptomatology (Scottish Schizophrenia Research Group, 1987; Lieberman et al., 1996; Umbricht et al., 2002) and/or cognitive deterioration (Scottish Schizophrenia Research Group, 1987; Robinson et al., 1999) have been associated with lack of response. For positive symptoms, the data are contradictory. In recent studies, positive symptoms in hallucinatory patients were associated with a poorer response to treatment during acute phases (Bartko et al., 1990; Szymanski et al., 1996; van Kammen et al., 1996; Robinson et al., 1999), whereas previous studies associated them with a favourable response (Moeller et al., 1985; Breier et al., 1987). These discrepancies reveal the difficulty of conducting methodologically reliable observational studies under naturalistic condition (Robinson et al., 1996; Kasper and Kufferle, 1998; Hofer et al., 2000).

Concerning predictive factors of response to the second generation of antipsychotics, relevant studies are also available (Lane et al., 2002; Perkins et al., 2004; Haro et al., 2006). Lane et al. (2002) were one of the first teams to search for predictors of response to risperidone in a 6-week prospective study and did not find any significant impact of gender, age, age at illness onset, duration of illness, or number of prior hospitalisations on the response value. As regards clinical criteria, the predictive value of clinical presentation at the time of admission regarding the response to second-generation antipsychotics remains controversial (Hatta et al., 2003; Crespo-Facorro et al., 2007). Authors then attempted to identify what degree of non-response shortly after initiation of antipsychotic drug treatment could predict non-response at 4 weeks and showed that patients with no improvement of symptoms during the first 2 weeks of treatment are unlikely to respond at week 4 and may benefit from a change of treatment (Leucht et al., 2007). Furthermore, the first 2 weeks' improvement in positive symptoms can predict the treatment response to antipsychotics at week 4 (Chang et al., 2006; Lin et al., 2007). Thus, little is known about clinical predictors associated with favourable or unfavourable response to treatment for second-generation antipsychotics and there are no criteria for guiding the choice of prescription, before initiation of treatment, in practical reality. We thus conducted a multi-centre prospective and observational study aiming at improving the identification of socio-demographic, premorbid and clinical variables that could predict response to second-generation antipsychotic treatments (olanzapine or risperidone) during acute phases of schizophrenia.

2. Methods

2.1. Design of the study

During a 2-year period, we systematically included schizophrenic patients hospitalised for an acute episode in one of the three sites of this open, uncontrolled, multicentre prospective study. The study was submitted to and approved by an ethics committee (CCPPRB Auvergne). Each patient, if included, signed an informed consent to participate in the study. Olanzapine or risperidone was assigned non-randomly, and started without any wash-out period, with daily dosages ranging, respectively, between 5 and 20 mg and 2 and 8 mg. The daily dosages could be adjusted by the psychiatrist throughout the study and could exceed the recommended starting dose range. Monotherapies were favoured, and co-prescriptions were as limited as possible. The study lasted over the first 6 months of treatment. Our study was part of a pharmacogenetic study published elsewhere (Meary et al., 2008).

2.2. Population

Patients were Caucasian in origin, aged 18 years and above, diagnosed with schizophrenia under Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) criteria (American Psychiatric Association, 1994), with a total Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962) score above 45 and a PANSS (Positive and Negative Syndrome Scale, Kay et al., 1987) score over 70 during the intake visit. They were not treated with olanzapine or risperidone, and showed a clinical condition that justified the prescription of either of these treatments. The patients started the study as inpatients and stayed in hospital until D42 as inpatients or in psychiatric day hospital care. Treatment dispensation was performed by nurses to control adherence. Patients showing known resistance to neuroleptic treatments, under the criteria defined by Kane et al. (2001), were not included.

2.3. Assessments

2.3.1. Assessment of illness: diagnosis and history

Clinical assessments were carried out during the intake visit (D0), at D42 and at D180. Patients were interviewed during the second week of the treatment, using the French version of the Diagnostic Interview for Genetic Studies (DIGS) (Preisig et al., 1999), to confirm the diagnosis of schizophrenia and to specify age at onset, family history, as well as possible co-morbidities, notably the ingestion of toxic substances in the month prior to the intake. During this interview, duration of untreated psychosis, defined as the time between the first appearance of psychotic symptoms and the implementation of an adequate specific treatment (Marshall et al., 2005), was measured as precisely as possible, based on the interview and on data in the medical record.

2.3.2. Assessment of response to treatment

The initial clinical assessment on D0 and the assessment of the treatment's clinical efficiency 42 days after introduction of the treatment were based on the Positive and Negative Syndrome Scale (PANSS) and Clinical Global Impressions Scale Improvement and severity (CGI) (Guy, 1976) scales. The definition of response to treatment was based on a relative improvement criterion (reduction on the PANSS scale greater than 20%) and on a threshold improvement score (BPRS < 35). To discuss the stability of predictive criteria as a function of the definition of response, we chose to study the predictability of the response to treatment with a different definition of response (CGI response). This new definition was based on a reduction of CGI-S (a two-point reduction from baseline to D42 for initial scores between 4 and 6 and a one-point reduction from baseline to D42 for initial scores between 1 and 3 (Haro et al., 2003; Haro et al., 2005)).

The five-factor PANSS analysis was used as a potential response predictor. It gathers the information obtained with this scale into five factors each of which consists of associations of relevant items resulting from a factorial analysis (Lançon et al., 1999; Lançon et al., 2000). The five factors considered in this study were the *Negative Factor* (N1, N2, N3, N4, N6, G7, G13, G15, G16), the *Positive Factor* (P1, P3, P5, P6, G1, G9, G12), the *Excitation Factor* (P4, P7, N7, G4, G8, G14), the *Cognitive Factor* (P2, N5, G10, G11, G5), and the *Anxiety/Depression Factor* (G2, G3, G6) (Lançon et al., 1999). Each observer (AM, GB, CL) had previously been trained in the use of the PANSS with standardised video tools and achieved an inter-rater reliability of 0.82.

2.3.3. Assessment of side effects of treatment

Side effects were evaluated through the Simpson and Angus Extrapyramidal Symptom Scale (Simpson and Angus, 1970), Barnes' Akathisia Scale (Barnes, 2003) and the Abnormal Involuntary Movement Scale (Guy, 1976), and the record of body mass index (BMI) at D0 and D42. The associated therapies introduced over the term of the study were the subject of a compilation.

2.4. Statistical analyses

Numerical data were expressed as frequency and percentage (%). Measured data were expressed as mean (SD). The association of the selected variables with treatment was assessed by comparing responders and non-responders with regard to the baseline values of the selected variables using unpaired *t*-test for continuous and χ^2 for categorical data, respectively. To protect against chance findings based on multiple comparisons, we applied the Bonferroni correction on *t* tests. Statistical correlation analysis was conducted by means of parametric methods (Pearson). Logistic regression was used to examine a multivariate prediction model that included all potentially useful variables for discriminating the two groups. All hypotheses were tested by using a two-sided significance level of 0.05. Statistics and data processing were carried out with the SAS statistical software package.

3. Results

3.1. Sample description

A total of 95 Caucasian patients, meeting DSM-IV criteria for schizophrenia were included. The mean age of our population was 33.59 years, SD = 11.45; the mean age at onset of the illness was 22.99 years, SD = 6.20; the mean duration of untreated psychosis was 2.56 years, SD = 4.82; the mean number of hospitalisation was 3.27, SD = 2.31; 69 patients were men (73%); 56 were treated with olanzapine (mean daily dosage at D42 = 19.41 mg, SD = 9.31), 39 with risperidone (mean daily dosage at D42 = 6.42 mg, SD = 4.82). Thirty-six patients were treated for a first episode. No patient dropped out at D42 (Table 1). Thirty-eight patients received co-treatment. Thirty patients received benzodiazepines (clonazepam and alprazolam), 21 received an antidepressant therapy (venlafaxine, escitalopram) and seven received a mood stabiliser (valproate). There was no