Progress in Neuro-Psychopharmacology & Biological Psychiatry 54 (2014) 315–320

Contents lists available at ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

Use of candidate gene markers to guide antipsychotic dosage adjustment

Nuwan C. Hettige, Clement Zai, Monica Hazra, Carol Borlido, James L. Kennedy, John Strauss, Bernard Le Foll, Albert Wong, Gary Remington, Vincenzo De Luca *

Centre for Addiction and Mental Health, Department of Psychiatry, University of Toronto, 250 College St, Toronto, ON, M5T 1R8, Canada

ARTICLE INFO

Article history:
Received 23 May 2014
Received in revised form 1 July 2014
Accepted 2 July 2014
Available online 9 July 2014

Keywords:
Antipsychotics
CPZe
Defined daily dose
Genetics
Schizophrenia

ABSTRACT

Objective: To improve antipsychotic treatment in schizophrenia patients, many studies have investigated genetic polymorphisms associated with antipsychotic metabolizing enzymes and receptors. While these studies have typically focused on drug response, few have investigated genetic influences on antipsychotic dosage. This study set out to analyze the association between 134 SNPs in 38 candidate genes and antipsychotic dosage in schizophrenia patients.
Methods: For our analysis, 300 patients with a diagnosis of either schizophrenia or schizoaffective disorder were recruited between the ages of 18 and 75. A cross-sectional assessment was used, in which data were collected from each participant through an interview and self-report questionnaire. Antipsychotic dose was standardized according to the chlorpromazine equivalents, defined daily dose and relative to the maximum dose specified in the product monograph. Participants were genotyped using a Customized Illumina Chip comprising 134 SNPs, and all markers were screened for nominal significance.
Results: The analysis showed a nominally significant association with the GFRA1 gene.
Conclusion: The common variants investigated in this study had no major influence on the antipsychotic dosage prescribed in study participants. It remains, though, that this strategy may prove valuable clinically and warrants further investigation.

1. Introduction

Among the world's population, approximately 1% suffers from schizophrenia and its debilitating symptoms (van Os and Kapur, 2009). Though they vary among individuals, these symptoms typically include delusions, sensory hallucinations, flat or blunted emotions, and disorganized thoughts and speech (Fletcher and Frith, 2009; Hovington and Lepage, 2012; Phan and Kreys, 2011). Schizophrenia is thought to arise due to a combination of environmental and genetic factors with an average age of onset around late adolescence and early adulthood leading to chronic impairment throughout the patient's life (Xu et al., 2013). As a major cause of disability, schizophrenia can have severe economic, health, and personal consequences on patients and those around them, especially without adequate treatment.

The primary mode of treatment for schizophrenia is through the administration of antipsychotic (AP) medications (van Os and Kapur, 2009). A major concern for physicians aiming to treat patients is attempting to improve treatment outcome and reduce side effects associated with the AP medication. Therefore, choosing the appropriate AP drug(s) is based on a combination of benefits, costs, and potential risks. The majority of AP drugs can be classified as either typical or atypical APs. Generally, atypical APs are the preferred class of drugs as they demonstrate improvements on a variety of symptoms with fewer side effects than typical APs (Vieta, 2010). However, AP medication, regardless of class, may have undesirable side effects or ineffective responses. AP side effects typically include weight gain, involuntary tremors, tardive dyskinesia, and agranulocytosis (Arranz and de Leon, 2007; Meltzer, 2012; Zhang and Malhotra, 2011). Unfortunately, there is a great deal of variability in patients' response to the range of AP medications available (Zandi and Judy, 2010).

The current practice for physicians is to prescribe medication through 'trial and error', administering a variety of drugs believed to alleviate the patient's symptoms (Xu et al., 2013). Using the same dose and drugs, some patients may eventually go into remission while others show no significant change or potentially a worsening of symptoms. As there is limited empirical evidence to be able to predict the appropriate drug and dose for each individual, medication is adjusted after the patient has undergone the debilitating side effects (Hermes and Rosenheck, 2012; Lipkovich et al., 2005; Suarez et al., 2009). As a result,

Abbreviations: AP, Antipsychotics; CPZe, Chlorpromazine equivalents; DDD, Defined Daily Dose; PM%, Percentage of maximum dosage according to product monograph; GFRA1, *GDNF* family receptor alpha 1; GDNF, glial cell derived neurotrophic factor; CARTPT, Cocaine- and Amphetamine-Regulated Transcript Protein.

* Corresponding author. Tel.: +1 416 535 8501x34421; fax: +1 416 979 4666.
E-mail address: vincenzo_deluca@camh.net (V. De Luca).

http://dx.doi.org/10.1016/j.pnpbp.2014.07.001
0278-5846/

medication may be switched or a higher dosage may be recommended. This approach can have major implications on the health outcomes of patients, often leading to severe adverse reactions, treatment non-compliance, and significant delays in treatment. Rather than continuing to put patients through an arduous process of selecting the best medication, recent research has suggested that pharmacogenetic testing may be a superior alternative to determine suitable drugs and dosage for effective treatment.

It is known that a combination of clinical, demographic, environmental and genetic factors have a profound impact on the treatment outcome (Arranz et al., 2011). Pharmacogenetic studies have previously been successful in attributing individual variability in AP response to genetic differences. Although limited to a small number of case reports, studies on monozygotic twins and same sex family members have supported the hypothesis of a genetic influence on AP response variability (Arranz and de Leon, 2007). Identical twins were also shown to have equivalent responses to treatment with APs such as clozapine and olanzapine (Mata et al., 2001; Vojvoda et al., 1996). In addition, identical twins also demonstrate similar adverse effects (Muller et al., 2001; Wehmeier et al., 2005).

Genetic factors contribute to the individual variability in AP response and dosage through the modulation of drug pharmacokinetics and/or pharmacodynamics (Poolsup et al., 2000). Pharmacokinetic (PK) factors demonstrate a clear relationship with genetic variability for treatment response. There are a number of monogenetic traits controlling pharmacokinetic processes (i.e. drug metabolization), and environmental interactions with PK factors are easily recognized compared to pharmacodynamic factors (Arranz and Kapur, 2008). Therefore, pharmacogenetic studies targeting drug transporters, drug-metabolizing enzymes, and drug receptors show promise in predicting optimal AP drug dosage and eventually individualized treatment (Gervasini et al., 2010). Given the unique nature in which APs exert their effects on different individuals, dose adjustments would compensate for the genetic differences that influence blood concentrations of APs.

According to previous findings, genotyping may provide an important key to maximizing the benefits of AP medication and minimizing unnecessary drug exposure (Nnadi and Malhotra, 2007). However, it is important to note that there are several factors that determine the dosage of typical and atypical APs in the treatment of schizophrenia (Lehman et al., 2004). Many studies have investigated the genetic polymorphisms of AP drug metabolizing enzymes (Urichuk et al., 2008), focusing mostly on drug response while few have investigated a genetic influence on AP dosage. For this study, we selected a panel of candidate genes, focusing on AP receptors and genes implicated in the neurobiology of schizophrenia. Due to limitations in including a large number of SNPs in the customized panel, we did not include genes involved in pharmacokinetic processes. Instead, the first group of genes in the panel involved in neurotransmission was selected because neurotransmission regulated by AP administration. The second group included genes that have been postulated to be involved in different neurobiological hypotheses of schizophrenia pathophysiology (Table 1). The goal of the present study is to test the association between standardized AP dosage and our selected candidate genes, proposed to be involved in AP response and the neurobiology of schizophrenia.

2. Materials and methods

2.1. Subjects and assessments

We recruited 300 patients from the Centre for Addiction and Mental Health (CAMH) between the ages of 18 and 75. All participants met the criteria for either schizophrenia or schizoaffective disorder based on the structured clinical interview for DSM-IV (SCID-I/P) (First et al., 2002). Participants were excluded based on evidence of intellectual disability and/or the presence of neurodegenerative disorders. In addition, those who have experienced brain injury trauma with a loss of consciousness and a history of major substance abuse prior to the onset of illness were excluded to ensure that the onset of the participant's symptoms was not directly attributed to physical trauma or the intake of drugs. Written informed consent was obtained for participation in the study as well as for release of participants' medical history in order to verify oral accounts and/or obtain missing information.

Assessments were conducted cross-sectionally using a structured interview and self-report questionnaires. The interview incorporated the Structured Clinical Interviews for DSM-IV (SCID-IV) in order to diagnose participants, as well as to assess for additional psychiatric symptoms and comorbid diagnoses. In situations where a diagnosis could not be reliably defined, the individual was excluded from the analysis. The Family Interview for Genetic Studies (FIGS) (Maxwell, 1992) was also administered to determine the prevalence of schizophrenia and other psychiatric disorders among first-degree relatives.

Information regarding the participants' ethnicity was also collected, with individuals classified as either European Caucasian or non-European Caucasian.

Suicide attempt lifetime was assessed by the means of the Beck Suicide Ideation Scale (Beck and Steer, 1991) and subjects with at least one suicide attempt lifetime were classified as attempters. Suicide attempters and non attempters were compared to test for significant differences regarding AP dosage.

Participants' current AP and dose at the time of the interview were collected through self-report and review of clinical charts to increase accuracy. Cases in which there was ambiguity or discrepancy regarding current treatment were excluded.

2.2. Clinical analysis

Analyses of clinical data were performed using SPSS (v.15.0). AP dosage was standardized using three approaches: CPZe conversion according to Gardner et al. (2010), the Defined Daily Dose (DDD), (WHO, 2010) and percentage of maximum dosage according to product monograph (PM%) (CPS, 2012).

Suicide attempters and non-attempters were compared to test for significant differences regarding CPZe, DDD, and PM%.

Chi-square tests were employed to compare categorical variables and comparisons of continuous variables were assessed with *t*-tests for independent samples. Tests of significance were done with a confidence interval of 95% with an alpha level of 0.05.

2.3. Genetic analysis

We selected 134 SNP markers from 38 candidate genes involved in the neurobiology and pharmacological treatment of schizophrenia. The full list of 134 SNP markers and genes is included in Table 1. The 134 SNP panel was genotyped using a customized Illumina Bead Chip.

All analyses were run using the equivalent AP dosage as a continuous variable, and the principal component analysis (PCA) was used to correct for ethnic stratification. All genotype tests were run using the additive model using the Correlation/Trend test. We corrected for multiple testing using the FDR method; furthermore, we tested the correlation of all clinical outcomes with age at the time of assessment, which was incorporated as a covariate in the genetic test only when significantly associated with the outcome. All genetic association tests were performed using SVS 7.4.0 (www.goldenhelix.com/kb).

3. Results

Our sample consisted of 256 individuals with a diagnosis of schizophrenia and 44 with schizoaffective disorder; the number of White European Caucasian individuals was 259 (Table 2). There were 207 males and 93 females and we found no significant