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Sociodemographic and treatment related variables are poor predictors of haloperidol induced motor side effects

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ABSTRACT

Age, haloperidol plasma levels and sex are associated with haloperidol induced motor side effects according to some lines of evidence, even though some conflicting findings mandate further research. We here report that age and sex were associated with dystonia during the early phases of treatment ($p = 0.0006$ and $p = 0.008$ respectively), but are overall poor predictors of the Extrapyramidal Symptom Rating Scale scores' variation over time (first month of treatment) in a sample of 60 acutely ill haloperidol treated psychotic patients. We conclude that age, sex and haloperidol plasma levels are not robust predictors of haloperidol induced motor side effects. Nonetheless, some limits of the study including the small sample size and the imputation of missing data could have diminished the power of detecting minor impacts of the investigated clinical predictors of the haloperidol induced motor side effects.

1. Introduction

Haloperidol is a first generation antipsychotic (Joy et al., 2006; Waraich et al., 2002) still in use for the treatment of schizophrenia. Haloperidol may cause acute and chronic motor side effects at a variable rate among patients. Knowing in advance who will experience some haloperidol induced motor side effect would be relevant to the clinical practice. It has been reported that age, gender and haloperidol plasma levels may predict the haloperidol induced motor side effects (Addonizio and Alexopoulos, 1988; Aguilar et al., 1994; Goff et al., 1991; Moleman et al., 1982; Swett, 1975) but findings are not consistent: motor side effects may be worse in elderly patients (Masand, 2000), and some Authors reported lack of association between gender and motor side effects (Jeste et al., 1996). The object of the present paper is to further investigate this debated issue. In particular, we explored different aspects of side effects through the detailed investigation of the subscales of the Extrapyramidal Symptom Rating Scale which includes dyskinesia, dystonia and parkinsonism.

2. Methods

2.1. Study population

60 Caucasian acutely ill psychotic in patients were recruited at the Department of Psychiatry, Ludwig-Maximilians-University of Munich, Germany. Inclusion criteria were: age in a range from 18 to 60 and a diagnosis of schizophrenia. Exclusion criteria were: a known contraindication for treatment with haloperidol, tardive dyskinesia, severe neurological or medical disorders, organic brain diseases, pregnancy, acute suicidality and co-medication (β-blockers, antidepressants, biperiden or benzodiazepines). This sample was previously investigated by our group with regards response to treatment (Giegling et al., 2009).

2.2. Drug administration

Perorally administered haloperidol was the starting treatment. Patients were switched to a second generation antipsychotic either if they developed severe motor side effects or after control of positive symptoms. In those cases, patients were no more included in the investigation and their last observations carried forward were analyzed. The study was approved by the local ethics committee

Abbreviations: SCID, Structured Clinical Interview for DSM Disorders; ESRS, Extrapyramidal Symptom Rating Scale.

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and carried out in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and later revisions.

2.3. Study design

All patients were treated naturalistically according to the international guidelines.

2.4. Haloperidol plasma sampling and measurement

Blood sampling for the detection of haloperidol plasma levels was scheduled three hours later the first administration of the day. Haloperidol plasma levels were measured at days 1, 3, 7, 14, 21 and 28 by high-performance chromatopgraphy with solid-phase extraction using benperidol as internal standard. The limit of detection was 0.5 ng/ml.

2.5. Assessment instruments

Structured interviews (SCID) were administered at baseline. Extrapyramidal Symptom Rating Scale (ESRS) (Chouinard and Margolese, 2005) was administered at days 1, 3, 7, 14, 21 and 28. All tests were administered by two psychiatrists with reliable inter-rater evaluation results ($k>0.80$). Haloperidol plasma levels were measured at days 1, 3, 7, 14, 21 and 28 by high-performance liquid chromatography. Common laboratory procedures were applied to decrease the interference of possible drug metabolites or comedications.

2.6. Primary outcome and hypothesis under investigation

Primary outcome was the ESRS scores' variation over time, including overall and subscales scores. Age, gender and haloperidol plasma levels were the predictors of the primary outcome. The following set of variables was included in the model as containing possible confounders: age at onset, familiar status, education, psychiatric disease in family, diagnosis, course of disease, number of episodes, number of hospitalizations prior to the index episode, duration of the last hospitalization prior to the index episode, any psychiatric medication prior to the study, reason of discontinuation of the haloperidol pharmacotherapy.

2.7. Data analysis

Repeated measure ANOVA/ANCOVA was the test of choice for evaluating the impact of predictors considered in combination towards the primary outcome. The same methodology served for the identification of the impact of the possible confounding factors towards the primary outcome. Any possible confounding factor found to be significantly correlated with the primary outcome entered the analysis as a covariate. In case of significant findings after ANOVA/ANCOVA analysis, a Post Hoc analysis was applied. In case of significant association and in any case when appropriate, a correlation test was applied in order to detect the magnitude and the direction of correlation of association between outcome and predictors.

2.8. Correction for multiple testing and analysis of power

Three variables were tested as predictors: age, haloperidol plasma levels and gender. Thus, significance level was set at $p=0.05/3=0.016$ (Bonferroni correction) in order to correct for multiple testing. Under this assumption, we had sufficient power (1-beta = 0.80) to detect a difference of $f=0.25$ between two groups assessed six times, given an observed mean correlation of the primary output of 0.2. This corresponded to an explained variance varying in a range from 3% to 9.5% according to a within groups variance varying from 0.5 to 1.5 respectively. GPower served for the analysis of power (http://www.psycho.uni-duesseldorf.de/aap/projects/gpower/). The other analyses were conducted in R, software release 2.10.1 (http://cran.r-project.org/).

3. Results

3.1. Sample characteristics are reported in Table 1a

ESRS scores distribution (total scores and subscales) are reported in Table 1b.

From all possible confounders (please refer to methods, section 'Primary outcome and hypothesis under investigation'), only age at onset significantly correlated with dystonia subscale scores and entered the analysis as a covariate (Table 2).

With regard to predictors: age, gender and haloperidol plasma levels did not predict ESRS scores distribution over time ($p>0.016$) (Table 3). When subscales were analyzed, some significant association

Table 1a
Sample characteristics.

Variable	Result
Gender	Males = 34 (56%) Females = 26 (44%) Total = 60 (100%)
Age	34.03 ± 10.38 years
Age at onset	29.05 ± 8.68 years
Familiar status	Single = 26 (43%) First time married = 17 (28%) Divorced = 8 (13%) In a partnership = 4 (6.5%) Married for a second time = 1 (1.5%) Separated = 2 (3%) Widowed = 2 (3%) Total = 60 (100%)
Anamnestic findings	No familiarity for psychiatric disorders = 25 (41%) Positive familiarity for psychiatric disorders = 31 (51%) Uncertain familiarity for psychiatric disorders = 4 (6%) Total = 60 (100%)
Course of disease	Residual or negative symptoms = 15 (25%) Chronic symptoms = 15 (25%) Residual symptoms = 11 (18%) Absence of residual symptoms = 10 (16%) Single episode = 9 (15%) Total = 60 (100%)
Diagnosis	Paranoid schizophrenia = 32 (53%) Undifferentiated schizophrenia = 2 (3%) Schizoaffective disorder = 13 (21%) Catatonic schizophrenia = 3 (5%) Schizophreniform disorder = 3 (5%) Brief psychotic disorder = 6 (10%) Delusional disorder = 1 (1.5%) Total = 60 (100%)
Mean number of previous episodes	3.24 ± 3.52
Mean number of previous hospitalizations	3.11 ± 3.21
Mean duration of previous hospitalizations	4.57 ± 11.54 weeks
Mean haloperidol doses	Day 1 = 2.10 ± 4.53 ng/ml Day 3 = 4.40 ± 7.72 ng/ml Day 7 = 4.75 ± 10.85 ng/ml Day 14 = 5.40 ± 10.91 ng/ml Day 21 = 5.25 ± 10.94 ng/ml Day 28 = 5.55 ± 10.89 ng/ml
Cause of treatment discontinuation	Good recovery, discharged = 6 (10%) Good recovery, presence of side effects = 19 (31%) Good recovery, switch to other medication = 6 (10%) Intolerable side effects = 17 (28%) No recovery = 8 (13%) Not discontinued = 4 (6%) Total = 60 (100%)