Schizophrenia Research 166 (2015) 207–211

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Colonic transit diagnostic test shows significant gastrointestinal hypomotility in clozapine-treated patients in comparison with subjects treated with other antipsychotics

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ARTICLE INFO

Article history:
Received 28 March 2015
Received in revised form 11 May 2015
Accepted 13 May 2015
Available online 29 May 2015

Keywords:
Atypical antipsychotics
Constipation
Clozapine
Rome criteria

ABSTRACT

Background: Constipation occurs in 25–60% of the subjects during administration of the antipsychotic drug (AP) clozapine (CLZ).
Methods: We used a colonic transit diagnostic test that quantifies in a single abdominal X-ray the number of silver O-ring markers out of 25 units ingested five days before. The quantity of markers is directly proportional to the degree of gastrointestinal hypomotility, and elimination of over 80% of the markers is considered normal. The test was applied to three groups of AP-treated subjects for at least three consecutive months: CLZ alone ($n = 45$), CLZ + Other APs ($n = 28$), and Other APs ($n = 64$).
Results: The number of remaining markers at day 5 (mean ± S.D.) was significantly higher in the CLZ alone (10.8 ± 10.6) and in the CLZ + Other APs (9.7 ± 9.7) groups than in the Other AP group (4.5 ± 6.7), Kruskal–Wallis test: $p = 0.004$. No significant associations were found between the number of markers, age, AP dose and treatment duration. All subjects who passed <80% of markers – which approximately corresponds to the 60th percentile of marker elimination – showed a scattered marker distribution along the colon, thus suggesting colon inertia. In subjects with hypomotility, 38.5% of the CLZ group, 25% of the CLZ + Other APs group, and 25% of the Other APs group were negative for the Rome III clinical criteria of constipation, thus showing objective, not subjective, hypomotility.
Conclusions: This study objectively confirms significant gastrointestinal hypomotility associated with CLZ administration.

1. Introduction

Clozapine (CLZ) is a first-line antipsychotic agent (AP) used in treatment-resistant schizophrenia (Remington et al., 2013). It is also used as an off-label indication in severe bipolar disorder (Li et al., 2014) and conduct disorders in dementia and mental retardation (De Leon J, personal communication). However, CLZ is currently under-prescribed mainly because of its hematological, metabolic, cardiovascular and gastrointestinal side effects, mandatory monitoring, lack of pharmaceutical promotion, complexity of use, and availability of Other APs (Agid et al., 2010; Nielsen et al., 2012). Constipation has been reported in 25–60% of CLZ-treated patients (Centorrino et al., 1994; Lieberman et al., 1994; Hayes and Gibler, 1995; Meltzer et al., 2003; De Hert et al., 2011a,b). In a review of side effects in short-term trials of several APs, constipation was reported by 21.3% of 61 patients (De Hert et al., 2011b). Only zotepin-treated subjects reported a higher frequency of constipation than CLZ-treated ones (39.6% out of 163 subjects).

Constipation belongs to the general syndrome of gastrointestinal hypomotility. When complicated, it may lead to ileus and bowel ischemia with fatalities related to sepsis and colon perforation. A historical prospective database study of 26,720 patients with schizophrenia conducted between 1996 and 2007 detected 123 cases of ileus. Treatment with CLZ was found to significantly increase the risk of ileus (OR = 1.99 CI: 1.21–3.29) and fatal outcome (OR: 6.73 CI: 1.55–29.17)

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http://dx.doi.org/10.1016/j.schres.2015.05.025
0920-9964/

(Nielsen and Meyer, 2012). Collectively, case report data analysis has shown that mortality is higher with CLZ than with Other APs, reaching as much as 27.5% in the cases of complicated constipation (Peyrière et al., 2009; De Hert et al., 2011a, 2011b; Cohen et al., 2012; Nielsen and Meyer, 2012).

In a literature search conducted until March 31st, 2015, the authors found that the radiological evaluation of gastrointestinal motility in CLZ-treated patients has mainly been conducted in subjects with complicated gastrointestinal side effects and has been published as case reports or case series. We confirm here that otherwise healthy CLZ-treated patients, when assessed with a simplified colonic transit diagnostic test, show more gastrointestinal hypomotility than patients treated with Other APs.

2. Methods

2.1. Subjects

This study was conducted between March 2014 and March 2015 at two Venezuelan psychiatric institutions: the Center for Attention of Patients with Schizophrenia and their Families (CATESFAM, Maracaibo, Zulia) and the Psychiatry and Psychology Unit, Merida Clinic, Mérida. All the CLZ-treated subjects were invited to participate and all agreed to do so. The Other AP-treated group consisted of patients attending their regular visit at these two centers. The CATESFAM and the University of The Andes (Mérida) ethics' committees approved the protocol. Patients or the responsible caretaker signed an informed consent of voluntary participation.

The inclusion criteria were: 1) voluntary participation in the study and 2) having received AP treatment for at least three consecutive months. Subjects with vomits, fever, gastrointestinal infections, acute or chronic abdominal pain or recent changes in evacuation habits were excluded from the study. Two patients were excluded for these clinical reasons.

2.2. Procedure

2.2.1. Colonic transit test

Twenty five radio-opaque markers consisting of O-shaped silver rings (weight average: 0.12 g, diameter average: 5 mm, density: 1.5 g/L) were packed in two gelatin type capsules and were ingested after breakfast during the first visit. Subjects were instructed to keep their regular diet and avoid the use of laxatives during the study period. An abdominal X-ray in horizontal position was obtained in fasting conditions at day 5 after the capsule ingestion. The number of markers was registered by one of us (T.B.) and by a radiologist who was blind to the subjects' treatment. In the few cases of disagreement, the image was discussed by both observers, and a consensus was reached.

When there were more than 15 markers at day 5, another X-ray was obtained one week later. In all the cases, all the markers had been already passed.

Besides the quantification of markers at day 5, an international consensus establishes that, in a negative test, at least 80% of markers must have passed (Wasserman et al., 2008). The higher the number of markers detected in the abdominal X-ray, the stronger the degree of hypomotility. Commercially available markers in the United States (Konsyl Products) consist of 24 marker capsules. Because this product requires a USA medical license to be purchased, we used a locally developed set of markers. Since 80% of 24 markers is not a round number (19.2), we instead used 25 markers. This provides a cut-off value of 20 expulsed markers (or 5 or less remaining markers) to define a normal test.

The procedure was tested in ten healthy volunteers with normal gastrointestinal transit: 4 females (age: 41.0 ± 15.7 years) and 6 males (age: 34.8 ± 16.3 years). The number of markers at day five was 1.6 ± 1.4. The Spearmen correlation between number of markers and age was non-significant: $r = 0.18$, $p = 0.6$. No abdominal discomfort was reported, and white cell counts, erythrocyte sedimentation rate, and liver enzymes were normal at day 10.

2.2.2. Clinical and laboratory evaluation

The clinical chart was reviewed in order to obtain the psychiatric diagnosis according to the DSM-IV-RT version, current and past pharmacological treatments. The current AP treatment was expressed in olanzapine and chlorpromazine equivalents (Gardner et al., 2010). The patient was asked about constipation symptoms and was diagnosed according to the Rome III criteria for functional constipation (Table 1). Smoking habits were not evaluated.

The following variables were assessed at baseline: weight, height, body mass index (kg/m^2) and blood pressure. A fasting cubital blood sample was obtained to quantify glucose, lipids, thyroid stimulating hormone, tri-iodothyronine and thyroxine.

2.2.3. Statistical analysis

We used the S.P.S.S. 17.0 version (SPSS Inc. Chicago, Illinois, USA). Continuous variables were analyzed with the ANOVA test when normally distributed, and with the Kruskall–Wallis chi-squared and the median tests when displaying a non-normal distribution. Covariance analysis was conducted with the univariate linear model.

Categorical variables were analyzed with the chi-squared and the binary logistic regression analysis. Spearman's bivariate correlation analysis and linear multiple regression analysis were conducted between the number of markers, and clinical, demographic and biochemical variables. Results were considered significant when $p < 0.05$.

3. Results

3.1. Demographic and clinical data

The study was conducted in 137 outpatients divided into 3 treatment groups CLZ alone (n = 45), CLZ + Other APs (n = 28), and Other APs (n = 64). The Other AP group included more females than each one of the 2 CLZ groups, but the patients' average age was similar (Table 2).

The CLZ dose (in mgs) was: CLZ alone group: 155 ± 86 (range: 12.5–350), and CLZ + Other AP group: 165 ± 125 (range: 12.5–500). The AP dose (in olanzapine and chlorpromazine equivalents) was significantly higher in the CLZ + Other AP group than in the other 2 groups. The AP treatment duration was significantly lower in the Other AP group than in both CLZ groups (Table 2). The Other APs were (number and percentage in [brackets]): CLZ + Other AP group: risperidone: 14 (50%), quetiapine: 7 (25%), others and combinations: 7 (25%); Other AP group: quetiapine: 21 (32.8%), risperidone: 16 (25%). olanzapine 12 (18.8%), others and combinations: 15 (23.4%). In most subjects of

Table 1
Rome III diagnostic criteria for functional constipation:*.

1. Must include two or more of the following:

a. Straining during at least 25% of defecations
b. Lumpy or hard stools in at least 25% of defecations.
c. Sensation of incomplete evacuation for at least 25% of defecations.
d. Sensation of anorectal obstruction/blockage for at least 25% of defecations.
e. Manual maneuvers to facilitate at least 25% of defecations (e.g., digital evacuation, support of the pelvic floor).
f. Fewer than three defecations per week.

2. Loose stools are rarely present without the use of laxatives.
3. Insufficient criteria for irritable bowel syndrome.
*Criteria fulfilled for the last months with symptom onset at least 6 months prior to diagnosis.

From Wasserman et al., (2008).