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Use of very-high-dose olanzapine in treatment-resistant schizophrenia

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1. Introduction

Schizophrenia is a debilitating illness with an estimated lifetime prevalence of around 0.7% (McGrath et al., 2008). In 2001, the World Health Organization described schizophrenia as one of the ten most disabling diseases in the world (Saraceno et al., 2005). It affects nearly all areas of patients' social, family and professional lives. Its cost for society is high, both directly (hospitalizations, treatment, dysfunctional social skills) and indirectly (loss of productivity) (McGrath et al., 2008). Its course can be marked by resistance to antipsychotic treatment, meaning that therapeutic support is sometimes challenging for the practitioner, with results that are partial and unsatisfactory.

Despite the development of a new generation of molecules, bringing greater efficacy and fewer side effects, some patients still fail to respond to treatment. The rate of treatment-resistant schizophrenia (TRS) is estimated to be between 30 and 60%, depending on which criteria are used (Solanki et al., 2009). If first-line treatments prove ineffective, there are still many options available, not least the gold standard, clozapine. If this fails, then clozapine

augmentation is one possible solution, not to mention the use of alternative antipsychotics, anticonvulsants or nonpharmacological options, including electroconvulsive therapy and transcranial magnetic stimulation for resistant auditory hallucinations (Mcilwain et al., 2011). Another therapeutic option is the prescription of atypical antipsychotics at high doses. Since the late 1990s, high-dose olanzapine has become a worthwhile alternative for clozapine-resistant or intolerant patients. Three out of four randomized, double-blind clinical trials have concluded that high-dose olanzapine (25–45 mg/d) is just as effective as clozapine (100–600 mg/d), and is also well tolerated (Tollefson et al., 2001; Bitter et al., 2004; Meltzer et al., 2008). Only one study, conducted in patients aged 10-18 years and treated with 10-30 mg/d, failed to find any advantage to prescribing high-dose olanzapine versus clozapine (Kumra et al., 2008). A number of case reports have underlined the usefulness of high-dose olanzapine. Many of them describe its use at doses of between 25 mg/d (Martín et al., 1997; Rodríguez-Pérez et al., 2002) and 60 mg/d (Lerner, 2003; Qadri et al., 2006). They all highlight its good neurological tolerance, but report weight gain as a common side effect. In a recently published case report, we reported the case of two patients who were treated with very high doses of olanzapine (80 and 100 mg/d) (Batail et al., 2012). They both had TRS and had reached a therapeutic dead end. One of them had contracted a fever owing to clozapine-related agranulocytosis. The other patient had early-onset TRS, and high-dose olanzapine was tried as an alternative before resorting to clozapine (Batail et al., 2012). They both became responders at doses above 60 mg/d, with good tolerance except for a 10-kg weight gain in one, controlled by dietary measures. In this report, we raised the question of the psychopharmacological mechanism behind the therapeutic response at such high doses. Since then, the question of the efficacy and tolerance of high-dose olanzapine has come to the fore. Why are such high doses needed to elicit a clinical response in these patients? Do patients with TRS have lower plasma concentrations of olanzapine as a result of reduced gastrointestinal absorption or increased hepatic metabolism? In other words, how far do pharmacokinetic properties matter? To our knowledge, there are no published data on the pharmacokinetics of olanzapine at doses above 60 mg/d. According to the literature, the dose-concentration relationship remains linear for olanzapine regimens at doses < 60 mg/d (Callaghan et al., 1999; Mauri et al., 2007). Therefore, patients who are resistant to conventional olanzapine doses may have either linear pharmacokinetic characteristics, implying that pharmacodynamic factors come into play in treatment resistance, or nonlinear pharmacokinetics, which would justify an increasing dose strategy in order to achieve an

effective olanzapine blood concentration. The first option would appear to be the most relevant.

In the present study, we assessed the pharmacokinetics of olanzapine at both conventional and high doses. We hypothesized that there is a linear dose-concentration relationship at very high doses, just as the literature have highlighted it at doses < 60 mg/d.

2. Methods

2.1. Patient population

Participants were recruited at Rennes University Psychiatric Hospital either as inpatients or as outpatients. We included patients who had been diagnosed with schizophrenia or schizoaffective disorder in accordance with DSM-IV criteria and were being treated with olanzapine. Exclusion criteria were other DSM-IV diagnoses (bipolar disorder, autism, etc.) and addictions (alcohol, cannabis, heroin, cocaine, etc.).

The participants were aware of the purpose of the study, and gave their informed consent. The study was approved by the Human Research Ethics Committee of Rennes University Hospital (Brittany, France) and was conducted in accordance with the Declaration of Helsinki and its subsequent revisions.

2.2. Study design

We implemented a prospective, observational, open-study design. In accordance with the literature, patients were included after a steady-state olanzapine regimen lasting at least 8 days (Callaghan et al., 1999). They were assessed once, either in the course of their hospitalization or during an outpatient consultation.

2.2.1. Clinical assessment

The clinical assessment was conducted by an experienced psychiatrist.

We recorded the participants' general characteristics, including age and sex, tobacco, tea and/or coffee consumption, psychiatric, medical and surgical history, olanzapine treatment history, and history of other treatments.

In line with the literature, therapeutic side effects were assessed with two scales: the Extrapiramidal Syndrome Rating Scale (ESRS), which focuses on neurological side effects, and the Udvalg for Kliniske Undersogelser (UKU), a more general scale that measures psychic, neurological, neurovegetative and other side effects. Schizophrenic symptoms were assessed by means of the Positive and Negative Syndrome Scale (PANSS). The Clinical Global Impression scale (CGI) yielded a qualitative assessment.

2.2.2. Biological assessment

2.2.2.1. Methodology

In order to study trough concentrations of olanzapine and N-desmethyl olanzapine blood levels, blood samples were taken at least 21–24 hours after the last dose. For patients who were on high doses taken twice daily (4 patients), blood sampling was done 12 hours after the last dose.

Patients on very high-dose olanzapine (> 60 mg/d) underwent weekly biological assessments (blood count, liver function) and electrocardiograms.

2.2.2.2. Serum sampling

The serum samples were collected as follows: 7-10 ml of venous blood was collected in vacuum tubes containing heparin directly in the ward during routine blood tests.

The analyses were performed on a Thermo™ (San Jose, CA, USA) TSQ Quantum HPLC-coupled tandem mass spectrometer (LC-MS/MS).

Olanzapine and N-desmethyl olanzapine serum concentrations were obtained with a fully validated LC-MS/MS analytical method commercialized by Chromsystems Instruments & Chemicals GmbH (Gräfelfing, Germany) called “MassTox® TDM Series A – Neuroleptics 1”, featuring calibrators, quality controls, solvents and an analytical column.

2.3. Statistical analyses

Statistical analyses were performed on all included and assessed patients (intention-to-treat analysis) with R software (<http://www.R-project.org/>). All results are reported as means \pm *SD* for continuous variables and rate for discrete variables. In line with the literature, the UKU subscale scores are described in terms of side effect occurrences. ESRS subscale scores are reported as means \pm *SD*. The significance threshold for all the tests was set at 5% ($p < 0.05$).

A descriptive analysis of clinical characteristics and the dose-concentration relationship was carried out for the whole group. For the dose-concentration relationship, after calculating Pearson's correlation coefficient, we used a linear model to assess the effects of sex, age, body mass index (BMI) tobacco (number of cigarettes per day), and coffee/tea consumption.

3. Results

A total of 50 patients were included in the study.

3.1. Whole group analysis

Clinical characteristics are summarized in Table 1. Age in the total sample ranged between 19 and 60 years. Illness severity, as assessed by the mean score on the severity scale of the CGI, was moderate.

Co-medications were benzodiazepine (12 patients; 26.09%), anticonvulsants (3; 6.52%), other neuroleptics (cyamemazine or loxapine) (11; 23.91%), antiparkinsonism drugs (3; 6.52%), and antidepressants (5; 10.87%). Pharmacological and biological characteristics are summarized in Table 2.

3.1.1. Dose–concentration relationship

Figure 1 illustrates the relationship between trough olanzapine concentration and the daily oral dose of olanzapine. We found a link between these two variables (Pearson's $r = 0.83$, $p < 0.001$, 95% CI [0.72, 0.90]). Linear regression coordinates were $y = 1.91x + 10.25$.

A linear model used to assess the effects of sex, age, tobacco (number of cigarettes per day), and coffee/tea consumption on the dose-concentration relationship revealed negative effects of tobacco ($p < 0.005$) and coffee/tea consumption ($p < 0.001$), but no significant effect of sex (positive effect of female sex, $p = 0.06$).

3.1.2. Concentration–tolerance relationship

Very few secondary side effects were reported, whatever the olanzapine regimen, and there was a low reported occurrence of neurological signs. Dyskinesia was described in two patients, one at 80 mg/d (Olanzapine Trough Concentration (OTC) = 186.3 ng/ml), the other at 15 mg/d (OTC = 48.1 ng/ml). Dystonia affected one patient at 80 mg/d (OTC = 186.3 ng/ml). Parkinsonism was observed in four patients, one at 80 mg/d (106.1 ng/ml), one at 40 mg/d (OTC = 71.8 ng/ml), and two at 10 mg/d (OTC = 40.1 ng/ml, and OTC = 32.4 ng/ml). In two of them, loxapine or cyamemazine had been co-prescribed. Three patients who were treated with 20 (OTC = 34.1 ng/ml), 30 (OTC = 60 ng/ml) or 40 mg/d (OTC = 71.8 ng/ml) had akathisia. All three of them were also receiving loxapine or cyamemazine. All the neurological side effects were given light or moderate intensity ratings.

4. Discussion

Ours was the first study to explore the pharmacokinetics of olanzapine used at doses above 60 mg/d in patients with schizophrenia.

4.1. Clinical considerations

Our sample comprised a majority of men (60%) and smokers (70%), which is in accordance with the literature (McGrath et al., 2008; Mueser McGurk, 2004; Van Os et Kapur, 2009). Age was homogeneously distributed between the ages of 19 and 60 years, with a majority aged in their thirties. Mean disease duration was therefore approximately 10 years. The response rate was 68%, which corresponds to the upper part of the range that is classically reported (0–76%) (Suzuki et al., 2011). A part of patients, included during consultations, had been stable for a long time, which may have contributed to this result.

4.2. Pharmacological and biological aspects

First, the mean daily oral dose of olanzapine for the whole sample was 31.3 mg/d, that is, higher than the dose currently recommended by the health authorities. Therefore, the

biological characteristics of our sample exhibited the same upward trend as the pharmacological one. The trough olanzapine concentration (70.02 ng/ml) was close to the upper limit of the therapeutic reference range (between 20 and 80 ng/ml (Hiemke et al., 2011)) recommended by the Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie (AGNP). The same is true for the C / D average in our sample was 2.34 ng / ml / mg / day for a recommended range between 0.87 and 2.38 (Hiemke et al., 2011).

4.3. Dose–concentration relationship

We observed a strong linear correlation (Pearson's $r = 0.83$) between the olanzapine daily oral dose and trough olanzapine concentration, which validated our main hypothesis of a linear dose-concentration relationship for olanzapine, even at very high doses. This result is consistent with the literature (Callaghan et al., 1999; Mauri et al., 2007). Tobacco significantly decreased the olanzapine plasma concentration in our sample, in accordance with current knowledge (Callaghan et al., 1999; Carrillo et al., 2003; Mauri et al., 2007; Nosawa et al., 2008; Patel et al., 2011; Weiss et al., 2005): tobacco has been identified as an inducer of cytochrome P450 1A2, with a consequent multiplication of enzymatic activity by a factor of 2-6 (Carrillo et al., 2003). A negative effect of tea/coffee consumption was also found. There are very few data on the inductive effects of caffeine (Perera et al., 2012) on olanzapine metabolism. There is a similar dearth of information about the inductive effect of green tea extract on clozapine metabolism (Jang et al., 2005) and the activity of cytochrome P450 1A2 (Schönthal, 2011). Data for green tea and coffee should be analyzed separately, in order to disentangle their effects on olanzapine metabolism.

4.4. Concentration–tolerance relationship

In our sample, olanzapine treatment was well tolerated, particularly with regard to neurological features. This result is in accordance with the literature (Callaghan et al., 1999; Mauri et al., 2007). The neurological side effects we observed were in patients treated with doses between 10 and 80 mg/d, but the fact that they had co-prescriptions for other antipsychotics raises the issue of how far olanzapine was actually responsible for these effects. However, it must be pointed out that the observational design of our study leave us with a positively selected sample. In fact, patients who do not tolerate olanzapine on any dose may have been discontinued from treatment early on. Therefore, the interpretation of these

results must be restricted to a descriptive analysis of our sample and can not be generalized. Thus, olanzapine through its H1 antihistaminic and 5HT_{2C} antagonistic properties, has been reported in many studies (Qadri et al., 2006; Rodríguez-Pérez et al., 2002; Weiss et al., 2005) to increase appetite and disturb metabolism. Our study was not designed to assess these aspects (single assessment).

5. Conclusion

To conclude, our study yielded one main result: the linearity of the dose concentration relationship, even at very high doses of olanzapine. Our results also highlighted the need to find psychopharmacological explanations for the therapeutic response and tolerance of very high doses of olanzapine for TRS. The linearity of the dose-concentration relationship shows that pharmacokinetics cannot provide the whole explanation. High-dose responding and tolerating patients may have a specific brain dopamine D2 receptor occupancy profile that explains this clinical observation. Accordingly, the pharmacodynamic characteristics of olanzapine in TRS patients who respond to high doses now need to be assessed. It would be worthwhile conducting further research, such as PET studies, to explore those issues. They would doubtless open up new perspectives, such as highlighting regions of interest involved in olanzapine response and tolerance at high doses when resistance is described at low doses (≤ 20 mg/d). This would allow us to explore the neural basis of TRS and identify potential brain targets for innovative treatments such as deep brain stimulation.

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Table

Table 1.

Clinical characteristics of the whole sample.

| Variable | Sample |
|--------------------------------|--------------------|
| Age (years) ($N = 50$) | 35.42 ± 1.48 |
| Sex (male) ($N = 50$) | 30 (60%) |
| Tobacco | |
| Smokers ($n = 46$) | 31 (67%) |
| Cigarettes/day ($n = 46$) | 10.91 ± 1.55 |
| PANSS ($n = 41$) | |
| Positive score | 14.23 ± 0.94 |
| Negative score | 17.28 ± 0.95 |
| Psychopathology score | 30.42 ± 1.65 |
| Total score | 61.93 ± 3.12 |
| ESRS ($n = 42$) | |
| Dyskinesia subscale | 1 (2.38%) |
| Dystonia subscale | 1 (2.38%) |
| Parkinsonism subscale | 5 (11.91%) |
| Akathisia subscale | 4 (9.52%) |
| UKU ($n = 42$) | |
| Psychic subscale | $3.21 \pm 0.31/27$ |
| Neurological subscale | $0.27 \pm 0.10/24$ |
| Neurovegetative subscale | $1.02 \pm 0.22/33$ |
| Others | $1.42 \pm 0.31/57$ |
| CGI | |
| Severity scale ($n = 41$) | 4.14 ± 0.22 |
| Improvement scale ($n = 37$) | 25 (68%) |

Figure

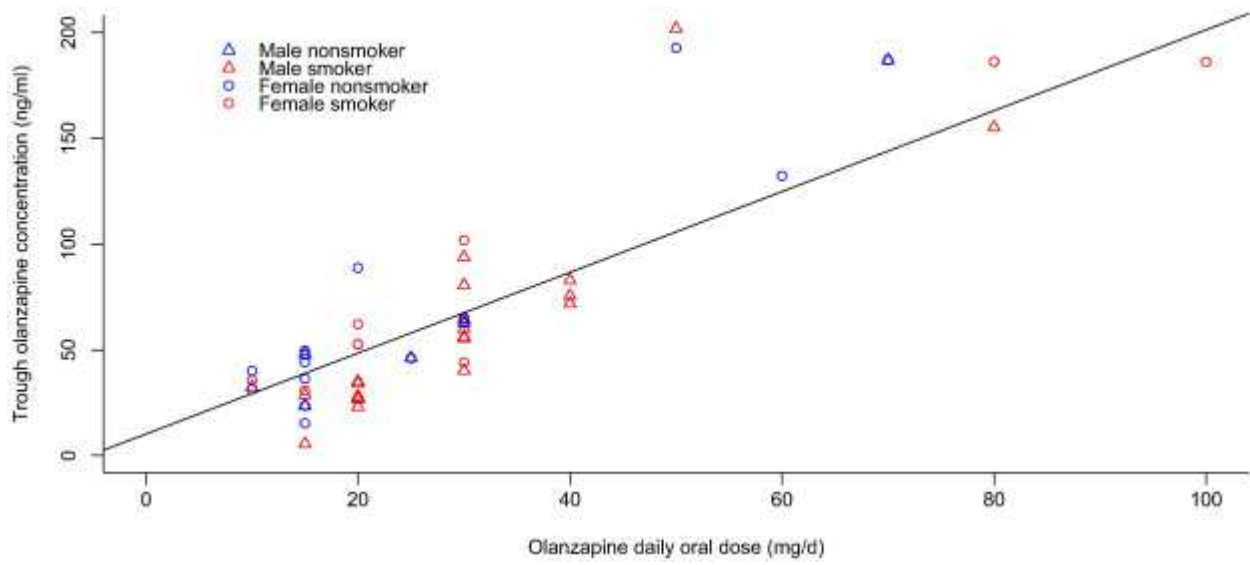


Fig. 1. Relationship between trough olanzapine concentration and daily oral dose of olanzapine.