

EFFICIENCY OF QUETIAPINE IN SCHIZOPHRENIA: CLINICAL TRIAL

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Abstract:

During the last years the atypical antipsychotics also known as second generation antipsychotics together with first generation antipsychotics have occupied a special position in the treatment of psychotic disorders.

Purpose: Assessment of the severity and evolution of symptoms in schizophrenia based on BPRS scale (Brief Psychiatry Rating Scale) and CGI scale (Clinical Global Impression during Seroquel treatment in common clinical practice.

Objective: Assess the severity of the patient's schizophrenia at the time when they entered the study and after the administration of treatment, using the scores obtained after the CGI scale application.

Material and method: Non-interventional observational study conducted at „Socola” Hospital of Iași. 138 patients were involved (male and female), with ages > 18 years, newly diagnosed or with a recorded diagnosis of schizophrenia, irrespective of the clinical form, according to the criteria of DSM VI. The patients involved in the study have received doses ranging between 400 and 750 mg/day of Seroquel for 24 weeks, with a previous period of titration, being assessed throughout 6 patient rounds according to common clinical practice.

Results and conclusions: The administration of Seroquel determined a clear improvement of the clinical condition, shown by the decrease of BPRS and CGI scales at the 6 rounds. At the end of the 24 weeks of treatment with Seroquel, the average BPRS score was of 16,96 compared to 45,02 at the beginning of the program. Throughout the study, the severity of the illness assessed according to CGI scale was diminished for most patients. At the beginning of the study 93 % of patients without previous antipsychotic medication and respectively 96 % of patients with previous antipsychotic medication had a moderate to very severe illness (CGI-S score > 4). At the end of the study 76.2 % of patients without previous antipsychotic medication and respectively 77.8 % of patients with previous antipsychotic medication had only a mild degree of illness, at the borderline of pathology or were normal from a clinical perspective (CGI score < 3). The reduction of the illness' severity was similar for the two groups of patients with or without previous medication. The score of the clinical global impression improvement (CGI-I) had a positive evolution for more than 96 % of the rated patients. The data were processed and statistically studied, finding a significant statistical difference in the decreasing evolution of BPRS scores from one round to another. The comparative study of BPRS scores between the two groups with or without previous medication, showed that patients without previous had significantly lower scores after 5 months ($p = 0.013$) and respectively 6 months ($p = 0.002$) of therapy with Seroquel. This pointed out that although their initial symptoms were more severe in comparison with the patients receiving medication (BPRS score considerably higher, $p = 0.002$) the therapeutic benefit was a lot more significant after 5 months of treatment.

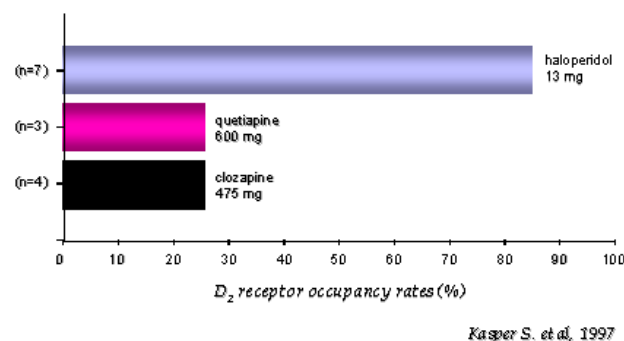
This study demonstrates the efficiency of Seroquel for patients with schizophrenia-related disorders. At the same time, it is a secure and well-tolerated antipsychotic medication. All these facts represent factors of favorable prognosis, forecasting a positive evolution of the illness preventing the appearance of subsequent relapse.

Key words: quetiapine, schizophrenia, well-tolerated antipsychotic medication, increased compliance

Introduction

The appearance of atypical antipsychotics was required by the need to achieve a much more efficient therapeutic control of schizophrenia. A common feature of this group of substances is the safety of administration, tolerability and an obviously lower development of side-effects compared to first generation antipsychotics.

Seroquel (quetiapine fumarate) is an atypical antipsychotic drug belonging to the class of multireceptor antipsychotics and characterized by high affinity to α_1 -HT_{2A}, α_1 -HT_{1A}, α_1 -HT₆, α_1 -H₁, α_1 and a low affinity to α_1 -D₂, α_1 -D₄ and α_1 -M₁ (Richelson E. and collaborators, 2000). The studies of functional neuro-imaging revealed further data about the level of D₂ receptor occupation by quetiapine, thus explaining antipsychotic efficiency as well as the special side-effect profile (low level of extrapyramidal symptoms, absence of hyperprolactinemia, in opposition with classical neuroleptics). Conventional antipsychotics block up to 80 % of DA₂ receptors. Clozapine and quetiapine occupy almost 30 %, therefore explaining the weak possibility of causing extrapyramidal symptoms. (Kasper *et al*, 1997)



Seroquel is rapidly absorbed after oral administration and is connected to serotonin and dopamine receptors' clinically efficient levels for at least 12 hours (Gefvert *et al* 1998).

Clinical data show that a daily dose ranging between 300 – 450 mg is suitable for the majority of schizophrenia patients, although it may be adjusted between 150 – 175 mg/d based on clinical response and tolerability. In schizophrenia, patients Seroquel proved to be efficient in treating positive symptoms (Small *et al* 1997), negative symptoms (Arvanitis *et al* 1997, Borison *et al* 1996, Small *et al* 1997), cognitive symptoms (Purdon *et al* 1999, Velligan *et al* 1999) and affective symptoms (Hellewell *et al* 1998). Clinical practice and subsequent studies showed that a dose of 600 mg/d helps control symptoms in the majority of adults (Kopala *et al* 2004). It was also shown that Seroquel is at least as efficient as typical antipsychotics (Copolov *et al* 2000, Kasper and Muller-Spahn 2000) although Seroquel is more efficient than haloperidol in the improvement of negative symptoms and prompted a higher response rate compared with chlorpromazine (Peuskens and Link 1997). Moreover, Seroquel is at least as efficient as risperidone (Mullen *et al* 1999) and shows a clinical profile that suggests an antipsychotic efficiency at least similar to olanzapine.

In addition, Seroquel is well tolerated. In clinical trials, the share of patients who discontinued treatment due to side effects amounted to 5.4 %, significantly lower than with haloperidol (11.3 %), chlorpromazine (11.2 %) and risperidone (11.5 %). The appearance of EPS associated to Seroquel treatment is not higher than with placebo administration and is significantly lower than with haloperidol and chlorpromazine treatment (*Copolov et al 2000*). Moreover, unlike risperidone and olanzapine, an increased dose of Seroquel does not trigger an increased rate of EPS, a characteristic only featured by clozapine. At the same time, an increased dose of Seroquel is not accompanied by high levels of prolactin, instead, there were decreases of initially high plasma prolactin levels due to previous treatment with other antipsychotics (*Copolov et al 2000*). The potential risk of weight gain after the Seroquel treatment (*Jones et al 2000, Westhead et al 2000*) is significantly cut down as compared to olanzapine or clozapine treatment. The minimal cardiovascular effects caused by Seroquel prompted the conclusion that blood monitoring, blood pressure measurements and routine ECG are unnecessary.

Design and Method

This non-interventional study was conducted in „Socola“ Hospital of Iași, the subjects involved were patients with a recorded diagnosis of schizophrenia for which the specialist decided either initiation of Seroquel treatment (in newly diagnosed patients) or switching from previous treatment to Seroquel administration.

All the rounds in this observational, non-interventional study were performed according to standard practice. During the first round, the patients were recorded in the study after signing the informed consent providing access to their personal information; psychiatric examination and a brief physical examination were performed, when vitals, height and weight, previous antipsychotic medication, concomitant drug administration (anticholinergic included), adverse reactions to treatment and BPRS/CGI scores (severity) were recorded. Subsequent rounds tracked the evolution of symptoms; BPRS/CGI scores (severity/improvement), weight and concomitant medication were recorded. The practitioners recorded the adverse reactions spontaneously reported during the treatment. For newly diagnosed patients who initiated the Seroquel administration, it underwent titration according to the approved prospectus, while for patients previously treated with antipsychotics and switched to the new therapy, Seroquel titration was performed simultaneously with the withdrawal of the previously administered antipsychotic. This titration procedure was carried out for 7 days, followed by 5 weeks of Seroquel flexible dosing based on the individual clinical response. Subsequently, the specialist was able to perform additional adjustments observing the approved maximum dose of 750 mg/d divided in 2 intakes.

Eligible patients were men and women over 18 years of age, with an established diagnosis of schizophrenia for whom the specialist practitioner had decided to initiate Seroquel treatment irrespective of this program. The patients who had previously signed the informed consent providing access to their information were included.

Anamnesis and a physical examination were performed upon inclusion in the study. Previous antipsychotic medication and adverse reactions to treatment were particularly taken into account. The physical examination included also recording of height, weight, blood pressure and pulse. Psychiatric evaluation included psychiatric interview and recording BPRS and CGI scores. On the other rounds, the BPRS and CGI scores were recorded based on psychiatric examination.

The efficiency indicators of the drug used in the study were the improvement of the clinical global impression – illness severity (CGI-S) and of the BPRS score as compared to baseline, as well as the favorable changes of the clinical global impression – improvement (CGI-I).

Adverse reactions reported spontaneously during treatment were recorded according to the usual clinical practice.

A descriptive statistical test was performed (ANOVA test, Student – T – Test).

Results

The study involved 138 patients, with an average age of 39 years and an overall average of 38 years. In the studied group, the distribution of the patients according to sex and age was uniform. These patients were diagnosed with different types of schizophrenia or schizophrenia-related disorders.

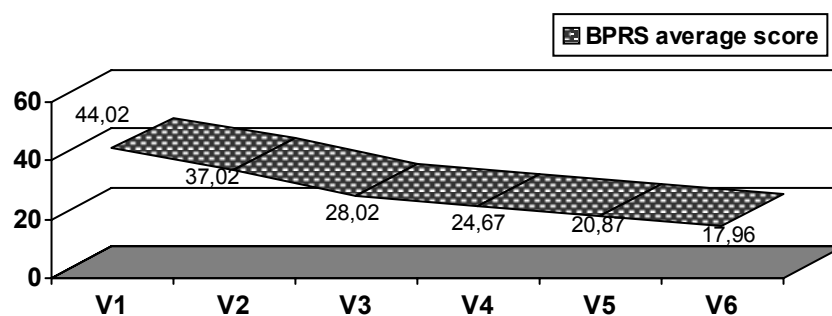
When the study began 33 patients were discovered with medical records, 14 males (42.7 %) and 19 females (57.3 %). Regarding the psychiatric records like the medical records, a slight predominance of females was noticed. For 51 patients found with psychiatric records, 28 were females (55.0 %) and 23 males (45.0 %). The average weight of patients involved in the study was 72.3 kg.

The average doses of Seroquel administered during the study, on the 6 patient rounds, were: first dose – 517,38 mg, second dose – 593,02 mg, third dose – 621,76 mg, fourth dose – 628,43 mg, fifth dose – 630,12 and sixth dose – 626,81 mg, so an average increase of 100 mg of Seroquel was necessary between the first and the last round (V6).

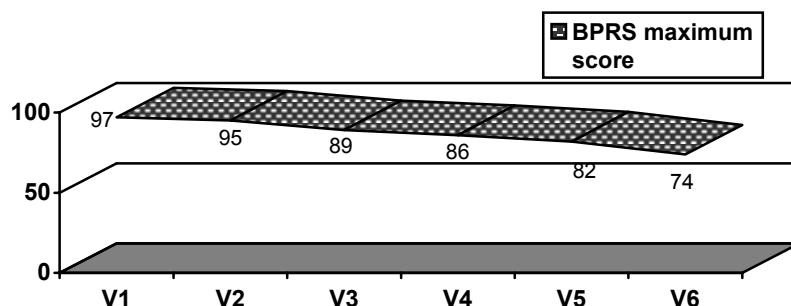
During the study, the disease severity, estimated according to the CGI-S scale was considerably reduced for the majority of the examined patients. At the beginning of the study, 92.4 % of the patients without a previous antipsychotic medication and 95.7 % of the patients with a previous antipsychotic medication respectively had a moderate to a severe disease (score CGI-S > 4). At the end of the study 76.3 % of the patients without a previous antipsychotic medication and 78.4 % of the patients with a previous antipsychotic medication respectively showed only slight symptoms, at the limit of pathology or were clinically normal (Score CGI < 3). The reduction of the disease severity for the two groups of patients with and without a previous medication was similar.

The Score of the Clinical Global Impressions – Improvement (CGI-I) had a favourable evolution for more than 95 % of the examined patients. After a month since the study started 84.3 % of the patients without medication and 78.9 % of the patients without medication showed a minimum to a great improvement of the symptoms (score CGI-I < 3) percentage which increased from 96.2 % and 96.4 % respectively after 24 weeks of therapy with Seroquel.

The BPRS evolution in time, as an instrument for the assessment of the therapy efficiency, showed a clear improvement proved by the decrease of the score on the 6 rounds. At V1 the average score was 45,02, at V2 – 36,02, at V3 – 29,02, at V4 – 23,67, at V5 – 19,87 and at V6 – 16,96 (fig. 1).

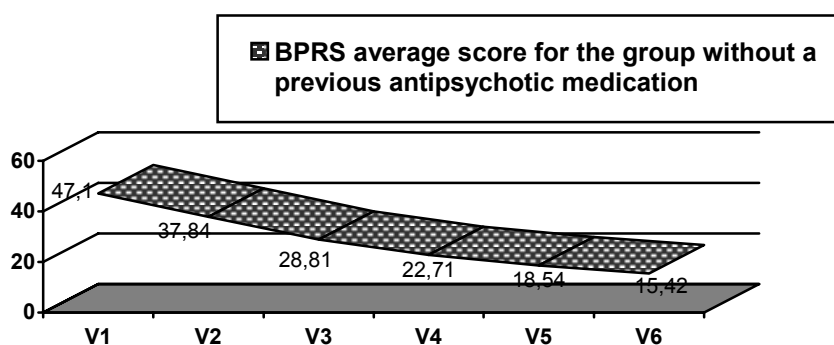


The efficiency is supported also by the evolution of the maximum scores on the BPRS scale recorded at each patient round. At V1 the maximum score was 97 points, then at V2 – 95, at V3 – 89, at V4 – 86, at V5 – 81 and at V6 – 74 points.

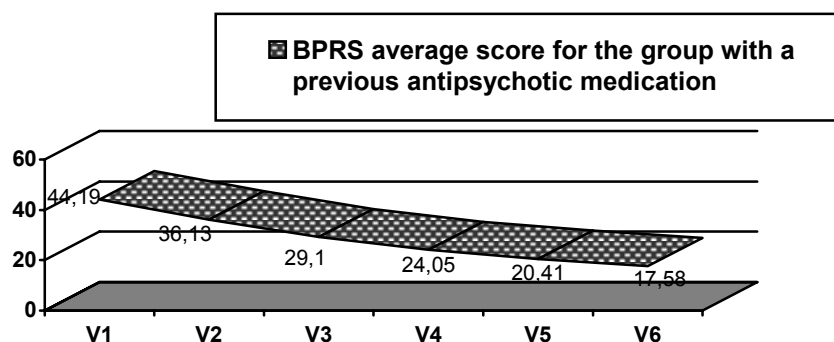


A parallel analysis of the scores obtained by the patients was carried out, the patients being divided into two groups based on whether they were previously treated with antipsychotic medication. A favorable evolution was recorded both for the patients who weren't previously treated with antipsychotic medication and for the patients who were previously treated.

Therefore, at V1 the BPRS average score recorded for the patients without a previous antipsychotic medication was 47,1, at V2 37,84, at V3 28,81, at V4 22,71, at V5 18,54, and at V6 15,42.



In patients treated with antipsychotic medication prior to the therapy with Seroquel the evolution of the scores ranged as follows: at V1 the BPRS average score was 44,19, at V2 36,13, at V3 29,1, at V4 24,05, at V5 20,41, at V6 17,58.



After the statistical analysis of the data, a relevant difference in the decreasing of the BPRS scores from one round to another was noticed, both for the group of patients without a previous medication and for the group of patients who were previously treated with another antipsychotic medication. (Student – test $p = 0.001$). The comparative analysis of the BPRS scores between the two groups showed that the patients who were not previously treated had a lower scores after 5 months ($p = 0.013$ ANOVA test) and 6 months respectively ($p = 0.002$ ANOVA test) of therapy

with Seroquel. This shows that although initially the symptoms were more severe than to the patients who received medication (significantly higher BPRS score, $p = 0.002$ ANOVA test) the therapeutic benefit was significantly more important after 5 months of treatment.

The arguments in the favor of Seroquel's efficiency brought by the analysis of BPRS score are also supported by the evolution of the rates on the CGI-S and CGI-I scales.

A clinical, gradual improvement, with relevant differences between the consecutive rounds was noticed, which is a positive landmark and proof of Seroquel efficiency in the treatment of schizophrenia-related psychiatric disorders.

Safety and Tolerability

No adverse events to impact upon the compliance or safety of patients were recorded during the study. No patient left the study due to adverse events.

Discussions

This study proves that Seroquel, administered in daily dosage of 400 – 750 mg, twice / day is efficient in the treatment of schizophrenia-related psychotic disorders. A gradual decrease in the BPRS score was noticed as objective indicator of the clinical severity. In other words, the intensity of symptoms of the involved subjects decreased or even remitted. This positive evolution was recorded in all patients whether treated with antipsychotic medication before enrolment or not. The results obtained on the assessment of the clinical impression are in accordance with the evolution trend of BPRS scores, while a big difference was noticed between the severity of the disorder at baseline in comparison with the end of the study (V6) and a constant favorable evolution of the improvement in the clinical global impression (CGI-I) maintained during the entire period of research.

There were no adverse events or other incidents to determine early leaving from the study, aspects which support good safety and tolerability, predictors of patient compliance.

The data recorded are in agreement and support the specialty literature, which states and proves both the efficiency and a good safety and tolerability of Seroquel in these patients.

Conclusions:

This study shows Seroquel's efficiency in patients with schizophrenia-related disorders. At the same time, it is a safety, well-tolerated antipsychotic medication. These factors predict a favourable prognosis, anticipating a good evolution of the disorder along with the prevention of occurrence of subsequent relapses.

REFERENCES:

1. Kasper S. (1997) Dopamine D2 receptor binding in typical and atypical neuroleptics. *Biol Psychiatry*; 41 (75): 67S Abs 227.
2. Richelson E. (1999). Receptor pharmacology of neuroleptics: relation to clinical effects. *J. Clin. Psychiatry* 60 (suppl 10): 5-14
3. Arvanitis L.A., Miller B.G. and the Seroquel Trial 13 Study Group. Multiple fixed doses of Seroquel (quetiapine) in patients with acute exacerbation of schizophrenia: a comparison with haloperidol and placebo. *Biol Psychiatry* 1997;42:233-246
4. Borison R.L., Arvanitis L.A., Miller B.G. ICI 204, 636, an atypical antipsychotic: efficacy and safety in a multicenter, placebo-controlled trial in patients with schizophrenia. US Seroquel Study Group. *J Clin Psychopharmacol* 1996;16:158-169
5. Copolov D.L., Link C.G.G., Kowalczyk B. A multicentre, double-blind, randomized comparison of quetiapine (ICI 204,636, Seroquel) and haloperidol in schizophrenia. *Psychol Med* 2000; 30:95-106
6. Emsley R.A., Raniwalla J., Bailey P.J. et al. A comparison of the effects of quetiapine (Seroquel) and haloperidol in schizophrenic patients with a history and a demonstrated partial response to conventional antipsychotic therapy. *Int Clin Psychopharmacol* 2000;15(3):121-131
7. Gefvert O., Bergström M., Långström B., et al. Time course of central nervous dopamine-D₂ and 5-HT₂ receptor blockade and plasma drug concentrations after discontinuation of quetiapine (Seroquel) in patients with schizophrenia. *Psychopharmacology* 1998;135:119-126

8. Hellewell J.S.E., Kalali A.H., Langham S.G. et al. Patient satisfaction and acceptability of long-term treatment with quetiapine. In J Psych Clin Pract 1999;3:105-113
9. Hellewell J., McKellar M., Raniwalla J. Seroquel: efficacy in aggression, hostility and low mood of schizophrenia. Abstract presented at the CINP Congress 1998, Glasgow, UK.
10. Jones A.M., Rak I.W., Raniwalla J. et al. Weight changes in patients treated with Seroquel (quetiapine). Schizophrenia Res 2000;41:206 and poster presented at Winter Workshop 2000, Davos, Switzerland
11. Kasper S., Muller-Spahn F. Review of quetiapine and its clinical applications in schizophrenia. Exp Opin Pharmacotherapy 2000;1:783-801
12. Mullen J., Reinstein M., Bari M. et al. Quetiapine and risperidone in outpatients with psychotic disorders: results of the QUEST trial. Presented at the 12th ECNP Congress 1999, London, UK
13. Peuskens J., Link CGG. A comparison of quetiapine and chlorpromazine in the treatment of schizophrenia. Acta Psychiatr Scand 1997;96:265-273
14. Purdon S., Malla A., Labelle A. et al. Long-term treatment with quetiapine improves cognitive function in schizophrenia: a double-blind study. Presented at the ACNP Annual Meeting 1999, Acapulco, Mexico
15. Small J.G., Hirsch S.R., Arvanitis L.A. et al. Quetiapine in patients with schizophrenia. A high- and low-dose double-blind comparison with placebo. Seroquel Study Group. Arch Gen Psychiatry 1997;54:549-557
16. Velligan D.I., Newcomer J., Pultz J. et al. Changes in cognitive functioning with quetiapine fumarate versus haloperidol. Poster presented at the ACNP Annual Meeting 1999, Acapulco, Mexico
17. Westhead E.K. et al. Long term effect of quetiapine on weight in patients with schizophrenia receiving no concomitant antipsychotic medication. Int J Neuropsychopharmacol 2000;3(1):S147 and poster presentation P.01.206

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