Relation between plasma concentration of Risperidone and its efficacy in patients with schizophrenia: A review article

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Received: November 21, 2020; revised: December 15, 2020; accepted: December 28, 2020

Abstract

Aim of the work: To determine the relation between Risperidone plasma concentration and its efficacy in patients with schizophrenia to assess the value of therapeutic drug monitoring in clinical practice.

Method: In February 2020, a search was conducted in the period from 2000 to 2020 using Google scholar, Pubmed and Science Direct as search engine. The key words used in this search were Risperidone, plasma concentration, schizophrenia. Articles were selected for inclusion in this search if they involved a test for the correlation between plasma concentration and efficacy.

Results: Limited number of studies was found. Among 14 studies, 10 yielded no correlation between Risperidone plasma levels and its efficacy while 4 studies showed positive results. To investigate the relation between Risperidone plasma concentration and clinical response, the most common tools used are HPLC for determination of plasma concentration and PANSS for assessment of clinical response.

Conclusion: The majority of studies showed no correlation and therapeutic drug monitoring of Risperidone is still unclear. Further research is needed in this area.

Key words

Risperidone, plasma, schizophrenia, efficacy

1. Introduction

Atypical antipsychotic were effective in treatment of schizophrenia and safer than classical neuroleptics because these drugs cause extrapyramidal side effects [EPSs], tardive dyskinesia or hyperprolactinemia less than classical antipsychotics [1]. Risperidone was among the first of these atypical antipsychotic agents [2], [3]. The therapeutic efficacy of risperidone in schizophrenia is attributed to the combination of dopamine [D2] and serotonin [5HT2] receptor antagonism [4]. It has proven efficacy in the treatment of schizophrenia positive and negative symptoms [5] as well as cognitive impairment [6]. The measurement of drug plasma concentration may play an important role in modifying the dose to obtain the highest clinical response [7], [8]. The utility of therapeutic drug monitoring of second generation antipsychotics [except clozapine] is still debated, though limited evidence from some studies is promising [9].

Risperidone mainly undergoes 9-hydroxylation in the liver producing the active metabolite 9-Hydroxy- Risperidone, which is marketed as Paliperidone [10]. What we know about plasma concentration of Risperidone and its active metabolite [Paliperidone] [Figure 1] is largely based upon empirical studies conducted in this field. A large and growing body of this literature has investigated the relationship between Risperidone plasma concentration and its efficacy. It has been investigated by various studies, leading to contrasting results. Summary of these studies is revealed in table 1. Only 14 studies were included in the review due to limited studies in this area relating Risperidone plasma concentration to efficacy in patients with schizophrenia. Among 14 studies, 10 yielded negative results and 4 were positive. The following studies showed no correlation between plasma concentration and efficacy.

Key words: Risperidone, plasma, schizophrenia, efficacy
Table 1: studies involving relation between Risperidone plasma levels and efficacy.

<table>
<thead>
<tr>
<th>Study</th>
<th>Method of analysis</th>
<th>Drug</th>
<th>Tool of efficacy assessment</th>
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<tbody>
<tr>
<td>No correlation</td>
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<tr>
<td>Bondolfi et al. [1998]</td>
<td>radioimmunoassay</td>
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<td>Lee et al. [1999]</td>
<td>HPLC</td>
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<td>Spina et al. [2001]</td>
<td>HPLC</td>
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<td>Chen et al. [2004]</td>
<td>LC-MS</td>
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<td>Riedel et al. [2005]</td>
<td>HPLC</td>
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<td>Kakihara et al. [2005]</td>
<td>HPLC</td>
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<td>Wang et al. [2007]</td>
<td>HPLC</td>
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<td>Lostia et al. [2009]</td>
<td>LC-MS</td>
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<td>Du et al. [2010]</td>
<td>HPLC</td>
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<tr>
<td>Paulzen et al. [2017]</td>
<td>HPLC/UV</td>
<td>CGI</td>
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<td>Positive correlation</td>
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<tr>
<td>Odou et al. [2000]</td>
<td>HPLC</td>
<td>CGI</td>
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<td>Mauri et al. [2001]</td>
<td>HPLC</td>
<td>BPRS and PANSS</td>
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<td>Aymard et al. [2002]</td>
<td>HPLC</td>
<td>PANSS, CGI, GAF, QLS</td>
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<tr>
<td>Yasui-Furukori et al. [2010]</td>
<td>LC-MS-MS</td>
<td>BPRS</td>
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</table>

In an important multicenter study, its design is controlled double blind, 43 in-patients diagnosed as chronic schizophrenic were enrolled to be given Risperidone [in range 3-10 mg per day] for eight weeks. Treatment efficacy was assessed using two famous tools; the Clinical Global Impression [CGI] and Positive And Negative Syndrome Scales [PANSS] scale. Plasma concentrations of Risperidone and Paliperidone were determined by a radioimmunoassay method. Bondolfi et al found that clinical response was not correlated to neither plasma concentrations of the active moiety [the total of Risperidone and Paliperidone] or Risperidone nor Paliperidone [11].

Lee et al carried out a study involving 20 schizophrenic patients in Singapore treated with oral Risperidone. Dosage of Risperidone was titrated in week 1 according to clinical observations from 1 mg to 5 mg per day. This dosage was kept until the end of week 2. Additional dosage adjustments were permitted until week 6. PANSS was evaluated at baseline, after 2 weeks and 8 weeks. Concentrations of Risperidone and its active metabolite were investigated using high performance liquid chromatography [HPLC] technique. It was found that there was no correlation between reduction of total PANSS as percentage and plasma concentration of the active moiety in the enrolled patients. The response rate ≥ 20% reduction of total PANSS was 85% [12].

In another study, 42 schizophrenic patients who experienced an acute exacerbation of the disorder were given Risperidone at dosages ranging from 4 to 9 mg/day for six weeks. The study design was open and Risperidone dose was adjusted separately according to clinical response of each patient. Plasma concentrations of Risperidone and Paliperidone were determined using HPLC method. Psychopathological state was evaluated by using PANSS, and patients were considered responders if they showed a twenty % or greater decrease in total PANSS score at final assessment compared with baseline. Spina et al indicated that no relationship was found between percent change in total PANSS score and plasma levels of Risperidone, Paliperidone and active moiety. Likewise, no correlation was found between active moiety levels and percent change in PANSS positive, negative and general subscales score. In addition, no significant difference between patients who respond to the drug and non-responders was found in mean plasma concentration of Risperidone, Paliperidone and active moiety [13].

In a small-scale study, ten patients were given Risperidone for one year in a study conducted by Chen et al. The dosage of RIS was 4.50 ± 1.43 mg. The Brief Psychiatric Rating Scale [BPRS] and Global Assessment of Functioning scale [GAF] were used for evaluation of clinical response. In this study, plasma concentrations of risperidone and Paliperidone were examined using advanced analytical technique: liquid chromatography-tandem mass spectrometry assay [LC-MS]. Chen et al concluded that there was no significant correlation between plasma concentrations of Risperidone, Paliperidone, active moiety or BPRS total scores or GAF scores [14].

A study was accomplished by Riedel el al in which Risperidone was given to eighty-two patients diagnosed with schizophrenia in an open dose clinical trial. The mean oral dose of Risperidone was 4.3±0.9 mg. The duration of the study was six weeks. Assessment of clinical state was performed using two tools; including CGI and PANSS. Plasma levels of Risperidone and Paliperidone were investigated using HPLC. Riedel et al showed an unanticipated result that non-responders to the treatment with the antipsychotic [Risperidone] showed significantly higher plasma levels of the active moiety than responders [15].

In a study conducted by Kakihara et al, the relationships between plasma concentrations of Risperidone and clinical responses, was examined. This study included one hundred thirty six patients whose diagnoses were schizophrenia, schizoaffective disorder, delusional disorder and brief psychotic disorder. Those patients were being treated with Risperidone alone at a Mean ± SD [range] dose of 3.8±1.4 [1–8] mg/day for two weeks. The clinical state was evaluated using PANSS tool to assess the clinical improvement. The analytical method that used for determination of both the drug and its metabolite in plasma was HPLC method. It has conclusively been shown that no correlation between plasma level of the active moiety [Risperidone and Paliperidone] and PANSS was found [16].

A major study was conducted in which one hundred eight Chinese schizophrenic patients were given Risperidone at dosages ranging from 2-8mg/day for 8 weeks. BPRS tool was used for clinical efficacy assessment. Plasma concentrations of both [Risperidone and Paliperidone] were tested at the end of the study using a specific technique [HPLC method]. The results obtained by Wang et al showed that there was no significant correlation between the concentration of active moiety and clinical response [17].

Lostia et al. inspected the relation between plasma concentration and efficacy in a study in which fifteen patients were admitted to a psychiatric care unit and were given oral Risperidone with dose range [4–6] mg/day. At week 1 and week 3 of hospital stay, serum levels were measured and clinical scales were assessed. Risperidone and its active metabolite were examined using a specific analytical method; liquid chromatography tandem mass spectrometry. Clinical state of patients enrolled in
the study was evaluated by PANSS, CGIs and BPRS. The authors stated that no correlation between plasma concentrations either sum or ratio of [Risperidone and its metabolite], and clinical improvement was found. Nevertheless, the authors concluded that clinical improvement is associated to the accomplishment of steady state concentration of Risperidone and its active metabolite Paliperidone and are retained, but not continued, with continued RIS treatment [18]. Du et al. investigated plasma concentrations of Risperidone and its metabolite. One hundred thirty schizophrenic patients were enrolled in the study. They were given oral Risperidone for two months. Risperidone dose was initiated at 2 mg/day and gradually increased to 6 mg/ day. Plasma Risperidone and Paliperidone were analyzed using [HPLC]. PANSS was used for evaluation of clinical efficacy. The authors didn’t find any significant correlation between plasma levels of active moiety and improvements in PANSS of the subjects included in the study [19]. In a major study conducted by Paulzen et al. plasma concentrations of Risperidone, Paliperidone and the active moiety in patients treated with Risperidone were compared between 64 patients [responders to the drug] and 526 patients [non-responders]. Data regarding clinical response were assessed with [CGI] Scale. It is illustrious that Risperidone daily dose did not be different between responders and non-responders. The concentrations of both the drug and its active metabolite were investigated by a specific technique; [HPLC] associated with ultraviolet detection [HPLC/UV]. Paulzen et al study resulted in non-significance difference in plasma levels of active moiety between the two groups [responders and non-responders]. Moreover, non-responders showed higher plasma concentrations of Risperidone and the active moiety in addition to higher metabolic ratios than responders did. After monitoring for demographic and clinical characteristics of patients, difference between responders and non-responders continued only for plasma concentrations of the active moiety in the groups with lower dose. The authors concluded that understanding the mechanisms included and factors related to the clinical response in patients treated with antipsychotic agent is of pronounced importance [20]. In contrast, the following studies reach different conclusions, finding a relation between plasma concentration and efficacy: This is a retrospective study in northern France including clinical and drug-monitoring data collected from fifty patients that were given Risperidone. It was administered daily in average dose [6.2 ± 3 mg]. In this study, CGI rating scale was used for the clinical evaluation and a specific method; HPLC was used for determination of the concentration of the active moiety in serum. Odou et al. demonstrated that there is a relationship between efficacy score and serum concentration of the active moiety. The authors concluded that statistical analysis revealed a significant increase in efficacy when the serum concentration of active drug was between 25 and 150 μg/L compared with when it was out of this range [21]. Mauri et al conducted a clinical trial including twenty-four chronic schizophrenic outpatients. They were treated with Risperidone at the dosage of 2-9 mg/day for a year. Two tools were used for clinical assessment, BPRS and PANSS. Plasma concentration of Risperidone and its metabolite were investigated after 12 months by the HPLC method. A curvilinear relationship between active moiety and percent of improvement in PANSS was observed by Mauri et al showing the patients with the higher PANSS improvement, active moiety plasma levels ranging from 15 to 30 ng/ml [22]. In an open setting, a study has been performed including fifteen patients. They were given daily doses of 4.5 ± 2.3 mg [range 2-8] and followed up from 3 to 12 months. The authors used more than one tool for clinical evaluation: PANSS, CGI, GAF in addition to the Quality of Life Scale [QLS]. Plasma levels were measured by HPLC. The authors reported that positive linear correlation was established only between plasma concentration of 9-hydroxyresperidone and the score of the GAF but not score of PANSS [23]. In a study performed by Yasui-Furukori et al, fifty-one schizophrenic patients with acutely exacerbation were treated with 6 mg Risperidone per day for four weeks. BPRS tool was used for clinical assessment that accomplished at baseline and each week. Liquid chromatography- mass spectrometry- mass spectrometry [LC-MS-MS] method was used in measurement of plasma concentrations. In this study, a significant correlation was established between plasma levels of Risperidone and improved positive and cognitive symptoms as well as total BPRS scores. In addition, the author reported that plasma concentrations of the active moiety were significantly correlated with improved total BPRS scores besides improved score and percent of improvement in anxiety- depression subscale [24].

Conclusion

In the previous studies, the dose of Risperidone was in range between 1-10 mg per day; except one study [24] in which a fixed dose was used. The duration of most studies was short; between two weeks and two months; except two studies extended to one year [22], [14]. The number of patients was small; it ranged between10-82; except three studies in which more than one hundred patients were involved [16], [17], [19]. Most studies used HPLC method in the determination of plasma concentration except three studies used LC-MS-MS method [24], [18], [14] and only one study used radioimmunoassay [11]. Regarding to efficacy, most studies used PANSS tool except two studies used CGI [21], [20] and three other studies used BPRS [24], [17], [14]. In conclusion, to investigate the relation between Risperidone plasma concentration and clinical response, the most common tools used are HPLC for determination of plasma concentration and PANSS for assessment of clinical response. The majority of studies showed no correlation but further studies are required in this area.

Declarations of interest: none.

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