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Plasma Concentration of Risperidone: Correlation with Clinical Response in Patients with Schizophrenia

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ABSTRACT

Background: Determination of plasma concentration of antipsychotic drug may provide a valuable tool in dose adjustment and therapeutic efficacy but studies in this area are limited and controversial.
Purpose: To assess the relation between plasma concentration of Risperidone and its active metabolite (Paliperidone) and clinical response in Egyptian patients with schizophrenia.
Patients and methods: One hundred inpatients diagnosed with schizophrenia were enrolled in the study. Fifty inpatients (33 males, 17 females, with age between 20- 60) completed the study. Risperidone was given in two fixed dose: 6 mg daily (Group I) and 8 mg daily (Group II) for three months. Positive and Negative Syndrome Scales (PANSS) were used for determination of psychopathological state and High- performance liquid chromatography (HPLC) was used for measurement of plasma concentration. These assessments were performed at 1 and 3 months.
Results: A highly significant decrease was found in PANSS subscales and total score at 1 and 3 months ($P < 0.001$). There is no correlation between plasma concentration of either Paliperidone or Risperidone, or the active moiety and clinical response at 1 or 3 months (P value > 0.05).
Conclusion: Measuring plasma concentration of Risperidone is not useful to enhance efficacy of treatment at 1 or 3 months. More research is required for assessment of other factors affecting the efficacy of Risperidone e.g., receptor occupancy and pharmacogenetics.

Keywords: Risperidone, plasma, schizophrenia, clinical response

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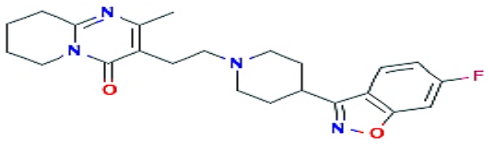
INTRODUCTION

Schizophrenia is ranked among the top ten disabling medical conditions and impacts 1% of the adult population worldwide[1]. Schizophrenia has a major negative effect on quality of life [2]. Moreover, patients with schizophrenia are two - three times much more likely to die early than the overall population[3]. The efficacy of risperidone in treatment of schizophrenia has been investigated in many studies [4, 5, 6, 7]. The chemical structures of Risperidone and its active metabolite; 9- hydroxyrisperidone (Paliperidone) are shown in figure 1.

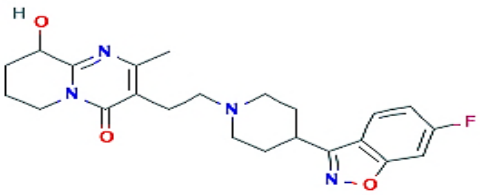
The quantification of drug concentration in blood plasma or serum is known as therapeutic drug monitoring (TDM). It can be a useful tool to modify the dose of antipsychotic drug according to different characteristics of the patient to obtain the highest possible clinical response and tolerability [8, 9]. Several studies examined the relation between plasma concentration of risperidone and efficacy but there is disagreement among these studies. Some showed a positive correlation [5, 10, 11] and others had negative result [12, 13]. Thus, the value of therapeutic drug monitoring of Second Generation Antipsychotics (SGAs) (aside from clozapine) remains an open question [14] and more research is required.

Aim of the study:

Determine the relation between plasma concentration of risperidone and its active metabolite (Paliperidone) and clinical response in Egyptian patients with schizophrenia.



Risperidone
3-[2-[4-(6-fluoro-1,2-benzoxazol-3-yl)piperidin-1-yl]ethyl]-2-methyl-6,7,8,9-tetrahydropyrido[1,2 a]pyrimidin-4-one



Paliperidone
3-[2-[4-(6-fluoro-1,2-benzoxazol-3-yl)piperidin-1-yl]ethyl]-9-hydroxy-2-methyl-6,7,8,9-tetrahydropyrido[1,2-a]pyrimidin-4-one

Figure 1: Chemical structure of Risperidone and Pliperidone.

MATERIAL AND METHODS

1. Patients

One hundred patients were enrolled in this study from the inpatient unit of Minia Psychiatry and Addiction Hospital- Egypt General Secretariat of Mental Health, with an age range of (20 – 60) years. The study included men and women with DSM-5 diagnosis of schizophrenia. Patients had not been receiving antipsychotic medications for the previous month. Patients were excluded if treated with a second antipsychotic in addition to Risperidone or in case of pregnancy or lactation or treated with Electroconvulsive therapy (ECT).

Fifty patients completed the study and fifty patients dropped out due to poor compliance, early improvement and discharge from the hospital before blood sample withdrawal. The fifty patients who completed the study have been classified into two groups according to the dosage of Risperidone. Patients received 6 mg daily (Group I) and patients received 8 mg daily (Group II). Patients were divided into two groups to compare between them in plasma concentration. Assignment to group was based on severity of symptoms. Doses (6 mg and 8 mg) were selected because admitted patients had severe symptoms and doses less than 6 mg (4 mg) is less effective in treating such patients. This study was approved by the Ethics Committee of Minia University. Written informed consent to participate in this study was obtained from the patients or their nearest relatives before the study.

2. Assessments

On the first session, Assessment of pretreatment clinical status using Positive and Negative Syndrome Scale (PANSS) for determination of efficacy was performed for each patient by a M.D. psychiatrist and 2 psychiatrists have master's degree with experience 3 years post degree. Thereafter, 6 mg/day of risperidone was administered in two doses 2 mg at 8 a.m. and 4 mg at 8 p.m. (Group I). For (Group II), 8 mg/day of Risperidone was administered in two equally divided doses at 8 a.m. and 8 p.m. No other drug was given except anti-parkinsonian drug (If indicated) for moderate extra pyramidal side effects.

All patients were seen in the inpatient (for one month ± 2 days) and outpatient (after three months) unit by the same physician and clinical pharmacist. During risperidone treatment, clinical assessment by the PANSS for efficacy was conducted at one and three months in the same manner as performed on the first day of admission. Assessment was done at 1 M as most efficacy occurred after this period and assessment extended to 3 M to examine the correlation between plasma concentration and clinical response after 3 M. Patients' compliance was determined by clinical pharmacist at two weeks interval through communication with relatives either by interview or by phone.

All blood samples (5 ml) for the determination of Risperidone and 9-hydroxy risperidone (paliperidone) concentrations were obtained at the end of 1 and 3 months, between 7:00 and 9:00 a.m., before the antipsychotic morning dose, approximately 12 h after the bedtime dose. Blood samples were collected into heparinized tubes followed by centrifugation at a speed 4000 rpm for 10 min. Resultant clear plasma was separated and frozen instantly at -20^{o}C until assayed.

3. Determination of Risperidone and Paliperidone

Chemicals: Risperidone and Clozapine (as internal standard) were kindly donated by Delta Pharma (Egypt) and APEX Pharma (Egypt), paliperidone was purchased from Baoji Guokang Bio- Technology Co. Ltd (China).

Sample preparation: Extraction procedures were performed using acetonitrile (ACN) for protein precipitation as described by Ansermot *et al*. To 1 ml aliquot of plasma sample, 50 µl of the I.S. working solution (1µg/ml) (the concentration is 50 ng/ ml) and 3 ml of ACN were added (plasma to precipitant ratio of 1:3). The mixture was vortexed for 3 minutes and centrifuged at 15,000 rpm for 20 min at room temperature to remove proteins. The clear supernatant was transferred into a 10 ml glass test tube with a conical bottom and evaporated to dryness in vacuum oven at 40 °C. The residue was reconstituted in 0.5 ml of the mobile phase at initial composition (buffer/ACN, 70:30), Each sample was filtered with 0.45 µm filter. Finally, the clear supernatant was transferred into glass micro vials and 40 µl was injected onto the HPLC system for analysis [15].

High- performance liquid chromatography (HPLC) conditions:

HPLC method was used according to Avenoso *et al*. HPLC analysis was carried out using an Agilent 1260 series. The separation was carried out using C18 column (4.6 mm x 250 mm i.d., 5 µm). The mobile phase consisted of 0.05M KH2PO4 (pH=3.7): acetonitrile (70:30) at a flow rate 1 ml/min. The injection volume was 40 µl for each of the sample solutions [16] and quantification was performed on a photodiode array detector monitored at 277 nm to obtain good resolution between peaks [17]. Standard curves for drugs and spiked plasma were prepared and constructed by linear regression analysis of the analyte / internal standard peak-area ratio versus the respective concentration of the analyte in the calibrators. From the recorded peak area, the ratios of drug to internal standard were obtained and concentrations were calculated.

4. Data analysis and statistics

All analyses were performed using SPSS version 20. P- value less than 0.05 was regarded as statistically significant. Chi square test was used to compare demographic data between groups. Repeated Measures ANOVA (within subjects) was run to compare PANSS score over months of treatment using Bonferroni test. Independent t-test was performed to compare groups in plasma concentration. Pearson test was used for correlation between efficacy and plasma concentration. Linear and Stepwise regression analysis were used for confounding factors.

RESULTS

One hundred patients were enrolled in this study, fifty patients dropped out due to different reasons showed in table 1. There was no statistically significant difference between those patients and patients who completed the study regarding demographic data and PANSS score at baseline (P value > 0.05). After exclusion of patients who dropped out, all statistics were done on the fifty patients who completed the study. These patients were 66 % males and 34 % females, with an age range of (20 – 60) years. The fifty patients were divided into two groups according to the dosage of Risperidone. Group I including 25 patients received 6 mg/ day and Group II including 25 patients received 8 mg/ day. Demographic details are shown in table 2. There is no significant

Table 1: Reasons of patient dropout

	Frequency	Percent
Decision of relatives.	7	14 %
Early improvement	11	22 %
Early discharge before blood sampling	7	14 %
Poor compliance	25	50 %

Table 2: Demographic data of patients

Age	**Group I**		**Group II**		**Total**			
	N	%	N	%	N	%	Chi	P value
20-29	11	44	11	44	22	44	0.154	0.985
30-39	6	24	7	28	13	26		
40-49	7	28	6	24	13	26		
50-60	1	4	1	4	2	4		
Total	25	100	25	100	50	100		
Gender	Group I		Group II		Total			
	N	%	N	%	N	%	Chi	P value
male	16	64	17	68	33	66	0.089	0.765
female	9	36	8	32	17	34		
Total	25	100	25	100	50	100		
Marital state	Group I		Group II		Total			
	N	%	N	%	N	%	Chi	P value
single	14	56	13	52	27	54	1.573	0.455
married	9	36	7	28	16	32		
divorced	2	8	5	20	7	14		
Total	25	100	25	100	50	100		

Group I: patients received 6 mg, Group II: patients received 8 mg.

Table 3: Effect of time on severity of symptoms across 3 months

	Baseline	1 M	3 M	P value
	N=50	N=50	N=50	
Positive subscale	29.7 ± 5.1	15.2 ± 4.6	14.9 ± 4.6	0.001
Negative subscale	20.1 ± 7.2	12.5 ± 4.6	12.6 ± 5.7	0.001
General psychopathology subscale	43 ± 8.6	26.4 ± 6.6	25.7 ± 6.9	0.001
Total score	92.8 ± 16.1	54.1 ± 13.9	53.1 ± 15.3	0.001

1 M, 3 M: one and 3 months after treatment with Risperidone

difference between Group I and Group II in age, gender, marital state (P value > 0.05) (table 2).

1. Efficacy of Risperidone

We hypothesized that Risperidone seems to be effective in symptoms reduction and it is verified. Results of ANOVA show a highly significant reduction of symptom severity across 3 months including positive subscale (P < 0.001), negative subscale (P < 0.001), general psychopathology subscale (P < 0.001) and total score of PANSS (P < 0.001) (table 3).

We hypothesized more decrease in symptom reduction after 3 months compared to baseline than reduction that happened after 1 month, but this is not verified. ANOVA results (Pairwise comparison) show a highly significant difference between baseline and 1 month in positive subscale, negative subscale, general psychopathology subscale and total score (P < 0.001). The same is found between baseline and 3 months (P < 0.001). However, no significant difference is found between 1 and 3 months in all subscales as well as total score of PANSS (P

value > 0.05) (figure 2). Most of improvement took place in the first month and went into plateau after that.

2. Dose and plasma concentration

The chromatogram of un-extracted working solution of Paliperidone, Risperidone and Clozapine (internal standard) is shown in figure 3. The chromatogram of an extracted plasma sample obtained from a patient is shown in figure 4. We hypothesized that higher doses of Risperidone are associated with higher plasma concentration and it is verified to some extent. Independent t- test was carried out. The values of Paliperidone, Risperidone and active moiety (sum of Risperidone and Paliperidone) plasma concentration were shown in table 4. Although Group II had higher values after 1 month, the difference between the groups in all plasma concentrations is non-significant (P > 0.05). The same is found after 3 months (P > 0.05) (table 4).

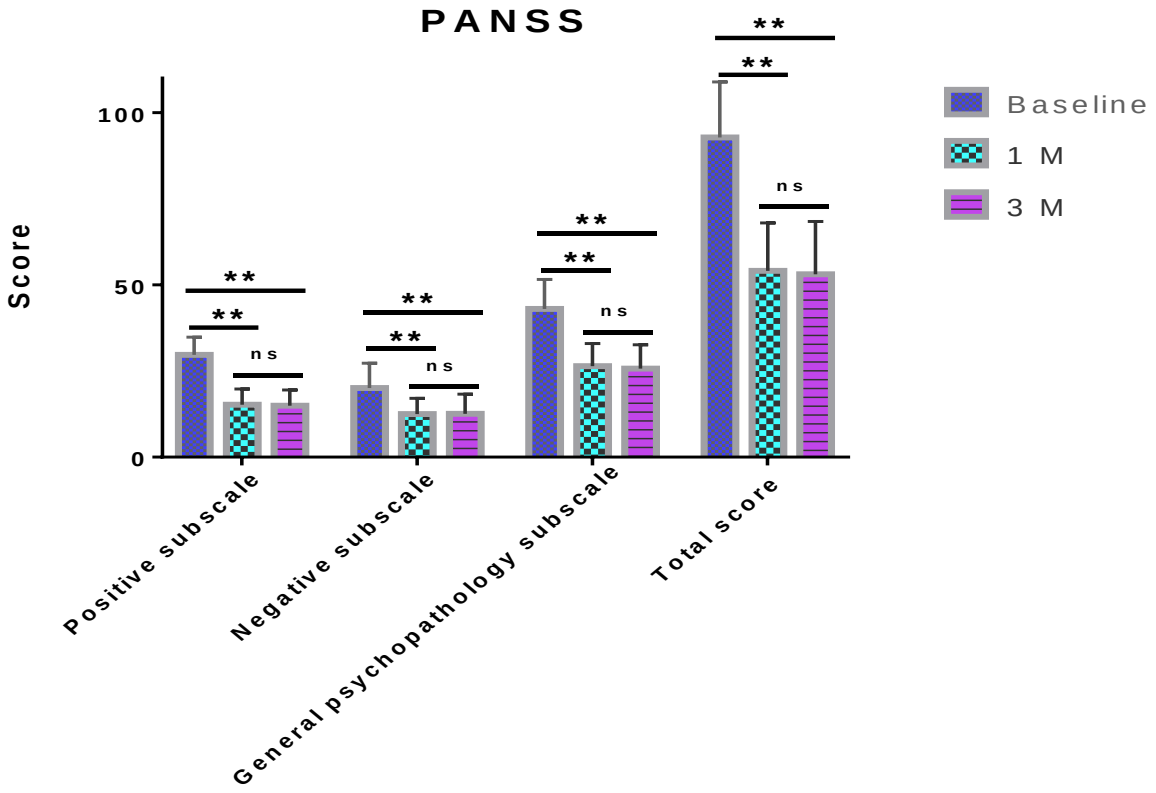


Figure 2: Comparison between PANSS score (N=50) at baseline, 1 M and 3 M

Table 4: Plasma concentration at 1 M, 3 M

Drug	M ± S.D.		T	P value
	Group I (ng/ ml)	Group II (ng/ ml)		
PAL Plasma 1 M	95.1 ± 88.7	113.1 ± 84.1	0.74-	0.47
PAL Plasma 3 M	83.8 ± 69.6	94.8 ± 65.5	0.58-	0.56
RIS. Plasma 1 M	27.2 ± 13.7	27.5 ± 15.4	0.05-	0.96
RIS. Plasma 3 M	17.2 ± 8	19.3 ± 10.7	0.82-	0.42
Active moiety 1 M	122.4 ± 91.9	140.6 ± 88	0.71-	0.48
Active moiety 3 M	100.9 ± 72.1	114.2 ± 70.1	0.66-	0.51

1 M, 3 M: one and 3 months after treatment with Risperidone,
Group I: patients received 6 mg, Group II: patients received 8 mg, PAL: Paliperidone, RIS: Risperidone

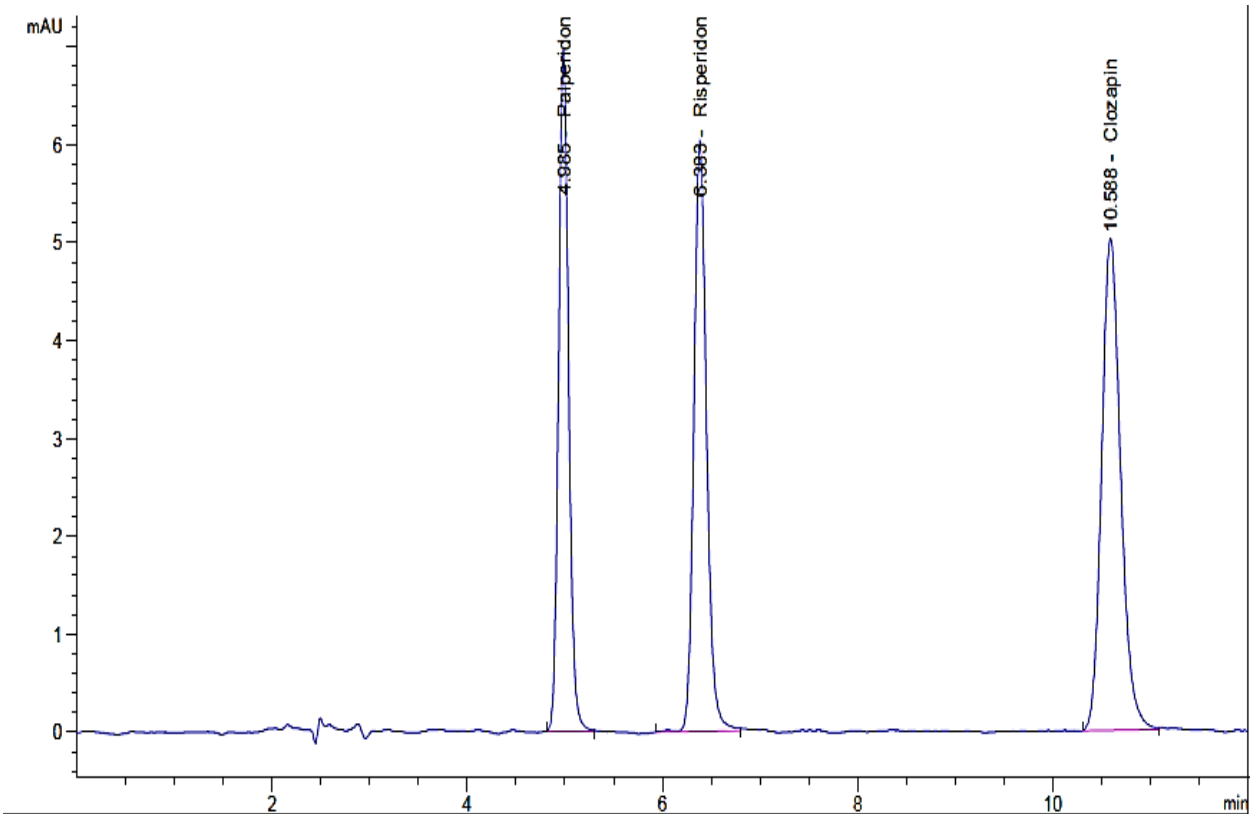


Figure 3: Chromatogram of pure standard drugs (2 µg/ml) Paliperidone, Risperidone and Clozapine.

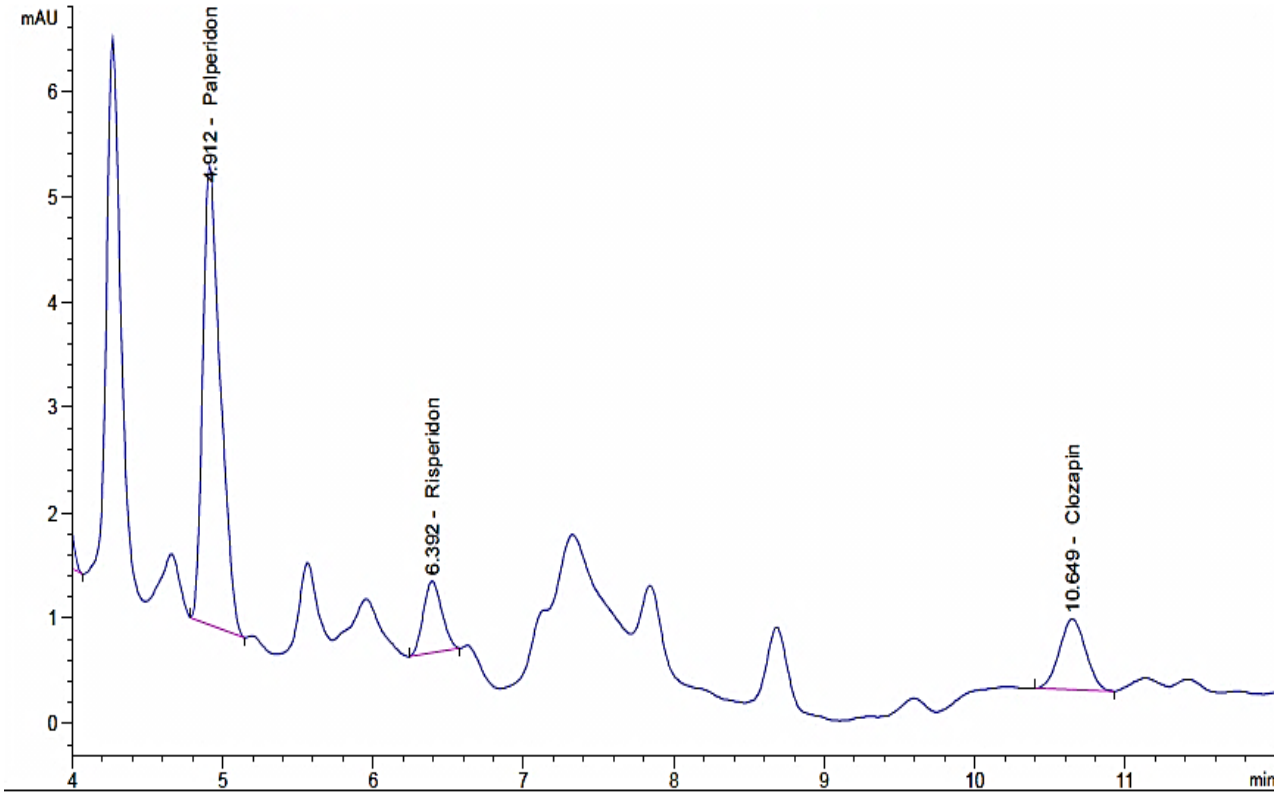


Figure 4: Chromatogram of plasma from patient.

3. Plasma concentration and efficacy

We hypothesized that plasma concentration correlates with efficacy, but this is not verified. Pearson correlation test was performed. There is no correlation between plasma concentrations of either Paliperidone or Risperidone, or active moiety and the improvement in positive subscale, negative subscale, general psychopathology subscale and total score of PANSS after one-month treatment with Risperidone (P value > 0.05) (table 5). The same lack of correlation is found after 3 months treatment with Risperidone (table 6).

Multiple linear regression analysis was conducted to evaluate the effect of various independent variables, including group, age, sex, marital state, cigarettes smoking, residence, plasma concentration (Paliperidone, Risperidone, active moiety), PANSS scores at baseline and total side effects on the improvement in PANSS subscales and the total score (as dependent variable). Multiple linear and stepwise regression analysis revealed that plasma concentration of Risperidone, Paliperidone, and active moiety are not predictors for improvement in PANSS score either after 1 month or after 3 months of treatment with Risperidone (tables 7, 8, 9,10).

Table 5: Correlation between plasma concentrations of Paliperidone, Risperidone, active moiety and improvement in PANSS score after one month.

	PAL. Plasma 1 M			**RIS. Plasma 1 M**			**Active moiety 1 M**		
	r	P value	N	r	P value	N	R	P value	N
Improvement Positive subscale 1 M	.033	.818	50	.182	.205	50	.061	.676	50
Improvement Negative subscale 1 M	.010	.948	50	-.034	.814	50	.004	.980	50
Improvement General psychopathology subscale 1 M	.134	.355	50	.165	.254	50	.155	.283	50
Improvement Total score 1 M	.082	.573	50	.133	.356	50	.100	.491	50

PAL: Paliperidone, RIS: Risperidone, 1 M: one month after treatment with Risperidone

Table 6: Correlation between plasma concentrations of Paliperidone, Risperidone, active moiety and improvement in PANSS score after three months.

	PAL. Plasma 3 M			**RIS. Plasma 3 M**			**Active moiety 3 M**		
	r	P value	N	r	P value	N	R	P value	N
Improvement Positive subscale 3 M	-.166	.248	50	.099	.495	50	-.144	.320	50
Improvement Negative subscale 3 M	-.116	.424	50	-.093	.519	50	-.124	.393	50
Improvement General psychopathology subscale 3 M	-.080	.582	50	.054	.709	50	-.068	.641	50
Improvement Total score 3 M	-.132	.362	50	.024	.871	50	-.122	.400	50

PAL: Paliperidone, RIS: Risperidone, 3 M: three months after treatment with Risperidone

Table 7: Multiple regression analysis to detect the predictors affecting improvement in PANSS subscale at 1 M

Independent variables	Positive	Negative	General psychopathology	Total
	P	P	P	P
Group	.730	.547	.778	.841
age	.006*	.022*	.019*	.007**
sex	.217	.978	.489	.444
Marital state	.181	.035*	.199	.092*
residence	.011*	.002*	.005**	.002**
smoking	.186	.420	.979	.512
PAL. Plasma 1 M	.599	.844	.356	.726
RIS. Plasma 1 M	.844	.198	.299	.190
Positive subscale 0	.001**	.697	.585	.295
Negative subscale 0	.051	.000*	.204	.718
General psychopathology subscale 0	.127	.264	.001**	.002**
Total Side effects 1 M	.480	.615	.680	.905
R	.825[a]	.871[a]	.805[a]	.807[a]
R 2	.680	.758	.648	.651

PAL.: Paliperidone, RIS: Risperidone, 1 M: one month, 0: baseline

Table 8: Stepwise regression analysis to detect the predictors affecting improvement in PANSS subscale at 1 M

Independent variables	β	P	R	R2	sig.
Improvement in positive subscale					
Positive subscale 0	.592	.001**	.764	.584	.001
residence	-7.576	.003**			
smoking	-2.952	.009**			
age	2.319	.001**			
Improvement in negative subscale					
Negative subscale 0	.595	.000**	.859	.738	.001
Marital state	1.930	.008**			
residence	-7.060	.001**			
age	1.371	.027*			
Improvement in general psychopathology subscale					
General psychopathology subscale 0	.622	.001**	.767	.588	.001
age	2.755	.003**			
residence	-9.871	.006**			
Improvement in total score					
General psychopathology subscale 0	1.166	.001**	.750	.563	.001
age	6.200	.001**			
residence	-21.471	.004**			

Table 9: Multiple regression analysis to detect the predictors affecting improvement in PANSS subscale at 3 M

Independent variables	Positive	Negative	General psychopathology	Total
	P	P	P	P
Group	.051	.938	.358	.305
age	.266	.605	.100	.211
sex	.449	.875	.493	.630
Marital state	.040*	.009**	.106	.027*
residence	.220	.323	.096*	.147
smoking	.174	.376	.729	.392
PAL. Plasma 3 M	.740	.295	.058	.186
RIS. Plasma 3 M	.548	.059	.052	.088
Positive subscale 0	.001**	.117	.312	.015*
Negative subscale 0	.135	.001**	.198	.713
General psychopathology subscale 0	.364	.859	.001**	.019*
Total Side effects 3 M	.415	.368	.879	.540
R	.802[a]	.798[a]	.796[a]	.770[a]
R2	.644	.637	.634	.592

PAL.: Paliperidone., RIS: Risperidone, 3 M: three months, 0: baseline

Table 10: Stepwise regression analysis to detect the predictors affecting improvement in PANSS subscale at 3 M.

Independent variables	β	P	R	R2	sig.
Improvement in positive subscale					
Positive subscale 0	.803	.001**	.759	.575	.001
Marital state	2.349	.004**			
Group	-2.852	.019*			
smoking	-2.670	.024*			
Improvement in negative subscale					
Negative subscale 0	.594	.001**	.732	.535	.001
Marital state	2.837	.002**			
Improvement in general psychopathology subscale					
General psychopathologysubscale0	.695	.001**	.684	.468	.001
Improvement in total score					
Total score 0	.681	.001**	.663	.440	.001
Marital state	6.677	.018*			

DISCUSSION

Regarding to efficacy of Risperidone, pairwise comparison of PANSS score by ANOVA test revealed that there is a highly significant reduction of all PANSS symptom scores after one and three months after treatment with Risperidone. However, there is no more symptom reduction between 1M and 3 M. This indicated that improvement doesn't continue to increase for 3 months. This agrees with Riedel *et al*. study whose treatment duration was six weeks [4]. It also agrees with Bondolfi *et al*. who reported that the response to risperidone treatment has appeared in the first and the second week and majority of patients were improved after 8 weeks [5].

The result is in contrast with Mauri *et al*. who reported a significant decrease in the total PANSS score besides general psychopathology subscale score after one

month of treatment while a significant improvement in positive PANSS subscale scores was found later. While negative subscale showed a slower improvement at the third month [6]. The result is also in contrast with Aymard *et al*. who illustrated that Positive symptoms decreased after about the second month and the negative symptoms improved secondly [7]. This may be due to small number of patients in these studies (n= 24, 15 respectively).

About the method of analysis, It is specific and sensitive HPLC method for the simultaneous determination of Risperidone and Paliperidone concentrations [16] and using photodiode array detector has a significant advantage including good resolution between peaks [17]. Regarding to the relation between plasma concentration and dose; comparing plasma concentration between groups revealed that no correlation between the dose and plasma concentration of Paliperidone, Risperidone, active moiety either after 1 month or 3 months of treatment with Risperidone. This is in agreement with several studies which showed no correlation between risperidone dosage and risperidone and Paliperidone plasma levels [18], or active moiety [6] or their ratio [19].

On the other hand, our result is in contrast to some studies that showed positive results; Yoshimura *et al*., concluded that a significant positive correlation between the dose of risperidone and each of risperidone, Paliperidone and the active moiety plasma levels was established [20], [21]. While Riedel *et al*. determined a positive correlation with active moiety [4]. This may be explained that the difference between the two doses isn't enough to produce a significant difference. Aravagiri *et al*. concluded that a good relationship was shown between the daily dose of risperidone and both the plasma concentration of Paliperidone and the total active moiety concentrations, but a weak relationship was found with risperidone concentration [22]. This may be explained by the wide range of doses used in their study (2-16 mg/day).

A literature search revealed no such studies in Egyptian patients with schizophrenia. For the relation between plasma concentration and efficacy, there is no correlation between efficacy and plasma concentrations of either Paliperidone or Risperidone, or active moiety after 1 M and 3 M. These results accord with several studies [5], [10], [11], [18], [4], [23], [24], [19], [25], [26] who reported no correlation between efficacy and plasma concentration of Risperidone, Paliperidone or active moiety. The lack of correlation may be attributed to the large intra- individual and inter- individual variations in the plasma levels of risperidone and its active metabolite that is reported by Aravagiri *et al*. [22] which may be attributed to genetic variation in metabolism. They confirmed these results in additional study [27]. Another possible explanation for this result is that the clinical improvement is associated with the accomplishment of therapeutic concentration of risperidone and its active metabolite Paliperidone and any increase in plasma concentration was not accompanied by increase in efficacy [19] . In addition, it was reported that receptor occupancy; a striatal D2 like receptors achieved by Risperidone dose of 6 mg; is between 75-80 % in most patients with schizophrenia [28] . Moreover, studies have revealed that patients treated with the same doses of Risperidone had considerable variation in levels of D2 like receptor occupancy [29], [30]

This is in contrast to Pascal Odou *et al*. who reported a relationship between efficacy score and serum concentration of the active moiety. A possible explanation for this might be the different tool used in assessment of efficacy; in this study, Clinical Global Impression (CGI) rating scale was used [12]. Our result is against Mauri *et al*. who found a relationship between active moiety and PANSS improvement [6]. This may be attributed to the small number of patients (n=24). Also, he calculated improvement in PANSS as percent; not score as our study. Our result is also against Aymard *et al*. who established a positive linear correlation only between plasma concentration of Paliperidone and efficacy [7]. This rather different result may be due to a different tool of improvement assessment, Global Assessment of Functioning scale (GAF) was used. Another study had an opposite result to our study was Yasui- Furukori that found a significant correlation between plasma levels of risperidone and active moiety and improved total Brief Psychiatric Rating Scale (BPRS) scores [13]. There are several possible explanations for this result as the different scale used in assessment (BPRS tool), short duration of the study (four weeks), as well as different method of plasma determination Liquid chromatography-mass spectrometry- mass spectrometry (LC-MS-MS) method.

CONCLUSION

The present study was designed to determine the efficacy of risperidone in patients with schizophrenia and the relation between efficacy and plasma concentration of Risperidone, Paliperidone and active moiety. One of the more significant findings to emerge from this study is that no correlation was found between efficacy and plasma concentration of Risperidone, Paliperidone or active moiety. The second major finding is that no difference in degree of improvement between 1 and 3 months. The results of the study indicate that duration of this study (1 month) is appropriate for determination of efficacy. This study demonstrates that the estimation of plasma Risperidone concentration is not useful to enhance efficacy of treatment in patients with schizophrenia. This will save effort and money for patients, doctors and government. More research is required for other factors affecting the efficacy of Risperidone e.g., receptor occupancy and pharmacogenetics. However, with a relatively small sample size, caution must be applied, as the findings might not be transferable on a larger scale.

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DISCLOSURE

All authors have no conflict of interest to declare.

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