Clinical Cancer Investigation Journal-ISSN: 2278-0513

Comparison of side effects of risperidone fabricated by Bakhtar Biochemistry Factory with Risperdal produced by Janssen-Cilag Company, Belgium

Abstract

This study aimed to compare the side effects of risperidone produced by Bakhtar Biochemistry Factory with Risperdal fabricated by Janssen-Cilag Co., Belgium. Twenty-two patients diagnosed with schizophrenia based on DSM-IV-TR criteria and defined inclusion criteria were studied in private clinics of some psychiatrists in Isfahan city. The patients were randomly and double-blindly examined in two groups of the Iranian and imported drugs (2 and 1, respectively) at a dose of 6 mg daily every 2 weeks for 3 months. Motor and non-motor side effects were assessed using the AIMS scale. The most common non-motor effects, weight, vital signs, and blood factors were evaluated by specially prepared forms during the study. Data was analyzed statistically using SPSS software by paired t-test, Mann-Whitney, Chi-square, covariance, Fisher's exact, and Pearson's tests.

The changes in AIMS scores during the study averaged 0 ± 0 and 0.88 ± 0.5 in groups 1 and 2, respectively ($p = 0.133$). The mean weight changes during the study were 7.10 ± 5.1 and 5.02 ± 4.1 kg in groups 1 and 2 ($p = 0.719$), respectively. The two groups were not significantly different in the study's three parameters of vital signs, blood factors, and common non-motor complications. The two drugs were not statistically different regarding clinical side effects and were similar.

Keywords: *Schizophrenia, Risperidone, Side effects, Bakhtar Biochemistry Factory.*

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Introduction

Schizophrenia is a severe and chronic mental health disorder with a variable clinical syndrome, but it essentially causes disorders in thought, perception, emotion, movement (action), and behavior. The disease comes with positive and negative symptoms. The former appears with additional reflexes or distortion of normal behavior, whereas the latter emerges with the reduction or loss of normal actions. These symptoms appear variably in individuals each time (1-2). Anxiety and excitement may be transient, occurring within a few days or months during schizophrenia. Thus, the presence of emotion alone or even the symptoms of conversion does not rule out a diagnosis of schizophrenia. Anxiety and depression, as well as the symptoms of obsession, manifested as obsessive-compulsive disorder, are common during the acute or subacute stages of schizophrenia (1). Schizophrenia is a good diagnosis if it is detected simultaneously with the major symptoms of schizophrenia, mania syndrome, or depression (2, 1).

Effective drug treatment for schizophrenia was generally absent prior to 1952. This situation changed with the introduction of chlorpromazine (Thorazine) in France in 1952. Chlorpromazine was effective in treating hallucinations, delusions, and excitement, but it had side effects similar to Parkinson's. In 1958, the first atypical antipsychotic, clozapine, was discovered with no extrapyramidal side effects, but the risk of agranulocytosis was determined in 1% of people a few years later in 1976. Risperidone, olanzapine, quetiapine, ziprasidone, and other compounds were discovered afterward, which were associated with reduced EPS side effects and no risk of agranulocytosis (1).

Drugs in this group have more effects on negative symptoms, and their effects on positive symptoms are at least equal to those of old antipsychotics relative to traditional drugs (3-4); they have fewer extrapyramidal side effects (5-3, 4). There is less need for using accompanying anti-Parkinson drugs (6, 7). They cause the faster beginning of therapeutic effects (8, 9), more patient satisfaction and safety (9-10), and reduced re-affection and hospitalization (9, 11).

Comparing new generation drugs indicates only a slight weight gain with risperidone, not ziprasidone. Compared to the rest (12, 13), prolactin levels increase only by olanzapine and not by the rest (14,15). Risperidone results in lower hyperlipidemia (16) and, along with olanzapine, is effective in treating schizophrenia (17). Hyperglycemia was observed with olanzapine and clozapine (18), and the latter is not used as a first-line treatment for schizophrenia due to its agranulocytosis (19). Either risperidone or olanzapine is acceptably the first choice in schizophrenic patients (20).

Risperidone entered the market in 1994 and is the second atypical antipsychotic approved in the United States (3). This drug has a low-to-moderate affinity for 5-HT1C, 5-HT1A, and D1 receptors, a slight affinity for cholinergic (and adrenergic) muscarinic receptors, and a moderate affinity for adrenergic receptors, M1, and peptidergic receptor sites (3, 21-23).

Risperidone is abundantly and rapidly absorbed following oral administration, and the oral bioavailability is approx. 70%. The

peak oral plasma concentrations of risperidone and the 9-hydroxy risperidone metabolite are 1 and 3 h, respectively. Food has no impact on the rate or amount of risperidone absorption (22, 23). According to the above, the present study aimed to compare the motor side effects of risperidone produced by Bakhtar Biochemistry Factory with Risperdal made by Janssen-Cilag Co., Belgium.

Methods

The study was performed as a triple-blind randomized controlled clinical trial among patients referred to psychiatric wards and clinics affiliated with the Isfahan University of Medical Sciences. The washout period and the study duration were 14 days and 12 weeks, respectively. Patients were randomly divided into two groups, one of which received risperidone produced by Bakhtar Biochemistry Factory, and the other group was prescribed risperidone from the Janssen-Cilag Co., Belgium. Clinical interviews and AIMS questionnaires recorded the recovery and motor side effects during the study (9).

In this study, imported risperidone tablets (Risperdal® 4 mg from Janssen-Cilag Co.) in 200 plastic bags were obtained from the representative office of Daru Pakhsh Co. in Tehran. Risperidone (4 mg tablets, Bakhtar Biochemistry Factory, Kermanshah, Iran) packed inside three large plastic bags as the first batch series of the factory was sampled from different places of each plastic bag so that about 1000 tablets from each bag were prepared with a total of 3,000 tablets (4 mg).

The risperidone made by Bakhtar Biochemistry Factory (dark green, thinner, and shorter tablets) differs from that of Janssen-Citag Co. (light green, thicker, and longer tablets) in terms of shape and size. Therefore, the tablets were inserted into capsules to create blinding conditions in the study. Lactose powder was used to fill the void space around the tablet inside the capsule. Blue and red capsules were used to differentiate between 2 and 4 mg tablets.

Full or half tablets were inserted in red or blue capsules, and some lactose was added to prevent moving the tablets inside the capsules, which were placed separately in plastic bags labeled A-4 mg, A-2 mg, B-4 mg, and B-2 mg and prepared for the coding step.

The patient received the tablets in person every week, but they were provided with the tablets for 2 weeks in case of their long distance from the study site. In the first week of the study, the patient received seven blue capsules (2 mg) in a small plastic bag for 1 week. In the second week, they returned the tablet bags of the former week and were given seven red capsules (4 mg) for a further week. In the third week, they also received seven red and seven blue capsules (6 mg in total) by returning the tablet bags of the previous week. This procedure continued in the same way until the end of the study.

At the end of 3 months, a trough blood sample of 10 ccs was taken from the patient, centrifuged, and kept frozen at 60 °C. This sample was taken to examine the blood concentrations of the two drugs in another analysis to determine if the two groups were different in terms of clinical consequences and motor side effects. Patients were evaluated based on medical history, psychophysical examination, and laboratory profiles prepared in special forms.

To evaluate the blood factors and the effect of drugs on patients, they were prescribed a laboratory test before starting treatment. At the study completion after week 12, another test consisting of the same items was also prescribed to patients (9). The disease duration between the two groups was compared using the independent t-test. The gender, marital status, and occupation status in the two groups were compared by the Chi-square test. Mann-Whitney test was used to compare the educational level in the two groups, and the type of diagnosis in the two groups was compared with Pearson's Chi-square test. Fisher's exact test was used to compare the two groups' smoking habits, recovery ratio, and the rate of non-motor/motor side effects. The study's beginning and end in each group paired were compared using the t-test. Covariance analysis was used to compare the mean changes of the two groups.

Results

In this study, 12 (9 and 3 patients from groups 1 and 2, respectively) out of 34 included patients were excluded from the study. Demographic characteristics of the remaining 22 patients (9 and 13 patients from groups 1 and 2, respectively) indicated that the numbers of men vs. women, single subjects vs. married, unemployed than employed patients, and non-smokers vs. smokers were higher in both groups. Both groups' patients were literate, mostly holding a high school diploma. The most common types of diagnosis in both groups were paranoid, indistinguishable, and residual.

As shown in Table (1), the mean changes in AIMS scores were zero and 0.5 in groups 1 and 2, respectively, and the two groups were not statistically different (P = 0.133). The differences between AIMS scores in weeks zero and week 12 were zero and 0.5 in groups 1 and 2, respectively, which were not statistically significant.

Table 1. Mean changes of AIMS scores in the two groups.

Tools	Group		Baseline[3]		End of the study[2]		Variations[1]		P-Value	
		N	Mean	S.D.	Mean	S.D.	Mean	S. D.	Within-group	Between-group
AIMS	1	9	0	0	0	0	0	0	*	0.133

	2	13	0	0	0.5	0.88	0.5+	0.88	0.082	

*Because the standard deviation is zero, the test is not performed on these values.

2 and 1 indicate the 1st and 12th assessment sessions, respectively, and 3 denotes variations from the beginning to the end of the study.

Table 2 indicates drowsiness, confusion, rhinitis, nausea, constipation, menstrual disorders, and galactorrhea in both groups, and the two groups are not statistically different. In both groups, drowsiness and rhinitis/galactorrhea were of the utmost and the least prevalence, and erectile dysfunction and orgasmic disorder were not observed in the subjects.

Table 2. Prevalence of the most important immobile side effects

Side effects	Group 1 (n = 9)		Group 2 (n = 13)		
	N	%	N	%	P-value
Drowsiness	9	100	13	100	
Confusion	8	88.9	11	84.6	0.642
Rhinitis	1	11.1	1	7.7	0.662
Nausea	6	66.7	7	53.8	0.439
Constipation	6	66.7	9	69.2	0.628
Erectile dysfunction	0	0	0	0	*
Orgasmic disorder	0	0	0	0	*
Menstrual disorders	3	100	1	50	0.400
Galactorrhea	1	11.1	1	7.7	0.662
	*The test is not done as the standard deviation is zero.				

Although the severity of these complications was measured during the study, the results were not presented due to the absence of a specific statistical test.

Table (3) shows that the average changes in the pulse were significantly different between the two groups. However, the two groups are not statistically different regarding systolic blood pressure (SBP), diastolic blood pressure (DBP), and weight. In weeks zero and 12, the pulse difference increased in group 1 and decreased in group 2, but it was not statistically significant (P = 0.200). The difference between SBP increased in group 1 and decreased in group 2 in weeks zero and 12, but these differences were not statistically significant (P = 0.495). In weeks zero and 12, DBP increased in group 1 and decreased in group 2, but this difference was not statistically significant (P = 0.136). The weight was different in group 1 (5.1 kg) and group 2 (4.1 kg) in weeks zero and 12, and weight gain in group 2 showed a significant difference between weeks zero and 12 (P = 0.013). However, the difference between the two groups was not statistically significant, particularly in weight gain.

Table 3. Changes in vital signs and weight

Variables	Group		Baseline		End of the study		Variations[4]		P-Value	
		N	Mean	S.D.	Mean	S.D.	Mean	S. D.	Within-group	Between-group
Pulse (beat/min)	1	9	84.2	9.08	87.6	6.32	+3.3	10.5	0.369	0.044
	2	13	84.3	6.97	79.7	9.25	-4.6	12.39	0.200	
SBP (mm Hg)	1	9	105	7.50	110	6.61	+5	11.99	0.246	0.495
DBP (mm Hg)	2	13	112.3	8.81	107.9	8.99	-4.4	10.39	0.150	
	1	9	70.6	7.26	76.7	7.07	+6.1	10.54	0.120	0.136
Weight (kg)	2	13	73.1	10.90	72.8	6.65	-0.2	8.93	0.927	
SBP (mm Hg)	1	9	64.8	16.02	69.8	19.8	+5.1	7.1	0.065	0.719
DBP (mm Hg)	2	13	64.5	9.36	68.5	9.91	+4.1	5.024	0.013	

6: Changes from the beginning to the end of the study

Table (4) shows that the average changes of HCT, Hb, RBC, BUN, prolactin, FBS, and Neut increased in each group. However, more increases were observed in the mean changes of FBS BUN and prolactin in group 1 and the average changes of HCT, Hb, RBC, and Neut in group 2. However, the two groups did not differ significantly in these changes.

The average changes in platelet, MCV, and basophils decreased in both groups, but further reductions were found in the mean changes of MCV and platelet in group 1 and basophils in group 2; the two groups were not statistically

significant in these changes. The mean changes of Lym, P, SGOT, SGPT, and MCHC increased in group 1 and decreased in group 2. The two groups differed significantly only in MCHC levels (P = 0.05), and there were no significant differences between the two groups in the other parameters.

The mean changes of WBC, MCH, Eos, and Ca decreased in group 1 and increased in group 2, there was a statistically significant difference between the two groups only in Eos levels (P = 0.038), and no significant differences were observed in the other parameters.

The sodium and creatinine changes averaged zero in group 1, but the amount of sodium increased, and the creatinine level decreased in group 2. These parameters were not statistically different between the two groups.

Concerning intragroup variations, the difference between prolactin, SGPT, SGOT, FBS, P, K, Lym, Neut, MCHC, HCT, Hb, RBC, and BUN increased in group 1. However, platelet, Baso, Eos, WBC, MCH, MCV, and Ca decreased while Na and creatinine did not differ from the beginning and end of the study. The differences in these parameters were not statistically significant.

In group 2, the parameters of RBC, K, WBC, HCT, Hb, and Ca increased at the end compared to the beginning of the study with P-values of 0.015, 0.044, 0.022, and 0.035, 0.034, and 0.036, respectively, showing statistically significant differences. The parameters of prolactin, FBS, Na, Eos, Neut, MCH, and BUN increased slightly in the same group. The decreased levels were recorded in SGOT, P, platelets, Bas, Lym, MCHC, MCV, and creatinine, which were not statistically significant.

Table 4. Changes in laboratory parameters

Laboratory parameters	Group		Baseline		End of the study		Variations[5]		P-Value	
		N	Mean	S.D.	Mean	S.D.	Mean	S. D.	Within-group	Between-group
RBC (1/mm^3)	1	9	5098000	401584.36	5414000	378259.17	+316000	446407.89	0.189	0.758
	2	13	4690000	346734.77	5083333	467814.06	+393333	380952.75	0.015	
Hb(g/dI)	1	9	14.62	1.11	15.40	1.11	0.78+	0.96	0.144	0.774
	2	13	13.6	1.8	14.47	1.69	0.867+	1.086	0.044	
HCT (%)	1	9	44.06	3.76	45.7	3.75	1.64+	3.76	0.385	0.876
	2	13	41.23	5.5	44.04	4.76	2.81+	2.98	0.022	
MCV(μ_3)	1	9	86.5	4.89	84.46	4.91	2.04-	2.09	0.095	0.424
	2	13	86.05	5.07	85.81	4.47	0.244-	4.46	0.87	
MCH(pg)	1	9	28.7	1.19	28.5	1.67	0.2-	1.26	0.741	0.867
	2	13	28.32	1.84	28.48	1.67	0.156+	1.94	0.81	
MCHC (g/dl)	1	9	33.22	1.36	33.74	0.60	0.52+	1.89	0.573	0.05
	2	13	32.98	0.80	32.83	0.80	0.144-	1.02	0.682	
WBC (1/cm^3)	1	9	7680	1903.15	6780	1025.67	-900	1415.98	0.228	0.27
	2	13	5588.89	1499.27	6844	1276.82	1255.55+	1488.45	0.035	
Neut (%)	1	9	59.68	12.47	60	9.54	0.32+	11.56	0.954	0.367
	2	13	60.61	9.64	64.2	9.083	3.59+	5.08	0.067	
Lym (%)	1	9	33.4	9.56	37	9.49	3.68+	9.6	0.44	0.199
	2	13	33.49	10.45	32.13	7.74	1.35-	6.68	0.559	
Eos (%)	1	9	2	0.707	1.2	0.274	0.8-	0.76	0.078	0.038
	2	13	1.51	1.2	1.69	1.31	0.178+	0.6	0.401	
Bas (%)	1	9	1.8	1.3	1.62	0.383	0.18-	1.65	0.82	0.275
	2	13	1.31	1.01	1.30	0.714	1.11-	1.32	0.98	
Platelet (1/mm^3)	1	9	258200	73339.6	239200	53166.7	-19000	31432.47	0.248	0.589
	2	13	268555	51046.819	252222	22813.25	16333.3-	52031.2	0.374	
Sodium (meq/1)	1	9	140.2	3.56	140.2	1.79	0	4.64	1	0.698
	2	13	139.55	1.51	141.0	3.53	1.4+	3.78	0.285	
Potassium (meq/1)	1	9	4.42	0.42	4.58	0.41	0.16+	0.397	0.419	0.655
	2	13	4.25	0.2007	4.55	0.43	0.3+	0.35	0.034	
Ca (mg/dl)	1	9	9.44	0.69	9.2	0.57	0.24-	0.945	0.600	0.158

	2	13	9.2	0.51	9.6	0.495	0.400+	0.477	0.036	
P (mg/dl)	1	9	4.42	0.580	4.9	1.025	0.48+	0.48	0.090	0.609
	2	13	4.07	0.790	4.47	0.618	0.4-	0.689	0.12	
FBS (mg/dl)	1	9	80	3.16	86.6	9.83	6.6+	8.7	0.165	0.776
	2	13	86.78	9.83	87.33	7.38	0.55+	10.064	0.873	
SGOT (IU/L)	1	9	26.4	7.8	27.6	9.8	1.2+	2.59	0.385	0.428
	2	13	34.78	37.2	25.33	11.8	9.44-	30.78	0.384	
SGPT (IU/L)	1	9	22	13.4	31.6	23.33	9.6+	10.14	0.102	0.329
	2	13	32.44	52.2	20.33	19.164	12.11-	53.95	0.52	
Prolactin (mIU/L)	1	9	1057.4	1151.4	1862	1537.37	804.6+	975.94	0.139	0.271
	2	13	1203.11	1228.94	1285.3	822.65	82.22+	1221	0.845	
BHCG (+/-)	1	9	-	-	-	-	-	-	*	*
	2	13	0	0	0	0	0	0	*	
BUN (mg/dl)	1	9	19.4	6.8	23.4	4.28	+4	7.65	0.307	0.854
	2	13	21.8	8.7	23.6	5.32	1.8+	6.9	0.453	
Creatinine (mg/dl)	1	9	0.64	5.48	5.48	0	1	1	1	0.751
	2	13	0.80	0.239	0.1453	0.113+	0.242	0.198	0.198	

8: Changes from the beginning to the end of the study. These values are not tested as the SD is zero.

According to Table 5, the average disintegration time and the standard deviation of imported healthy tablets are less than those of Iranian ones. The disintegration time and the standard deviation of Iranian capsulated tablets (healthy and half ones) were greater than those without capsules (healthy and half tablets).

Table 5. Disintegration times (seconds) of tablets

Healthy imported tablets without capsules	Half Iranian tablets with capsules	Half Iranian tablets without capsules	Healthy Iranian tablets with capsules	Healthy Iranian tablets without capsules
215	510	235	600	248
216	529	236	601	256
217	536	237	642	300
226	544	243	743	310
228	718	258	744	313
227	730	300	745	320
221 ± 1.1	594.5 ± 101.01	251.5 ± 25.26	679.16 ± 72.62	291.16 ± 31.11

The values in the last row belong to $\bar{X} \pm SD$ (mean ± standard deviation).

Discussion

In the present study, the motor side effects of the two drugs were measured using the AIMS scale. Slight complications of EPS were observed in group 2 but without statistically significant differences. It seems that motor disorders were largely prevented by gradually increasing the dose to 6 mg over 2 weeks and dividing the daily dose into two daily doses. According to a previous study, risperidone at doses > 6 mg/day usually presents EPS side effects (24). The slight motor side effects observed by the Iranian drug cannot be discussed in detail due to the sample size at this stage. However, this phenomenon calls for more accurate attention in the continuation of the project.

There were no differences between the two groups in non-motor side effects such as drowsiness, confusion, rhinitis, nausea, constipation, erectile dysfunction, orgasmic disorder, menstrual disorders, and galactorrhea. Drowsiness was the most common complication in both groups in which all patients suffered from drowsiness, as widely reported in other studies (9).

Although the results of vital signs showed significant changes in the pulse, these changes are not clinically and statistically valuable. However, comparing the two groups revealed a statistically significant difference due to pulse changes in two directions. The slight difference in the number of heartbeats might result from human measurement errors or patient fluctuations during the day. However, it is impossible to discuss this observation specifically due to no specific clinical differences in both groups. No significant changes were seen in the other parameters of vital signs. The differences in SBP

and DBP observed at baseline and week 12 are due to measurement fluctuations and, therefore, are insignificant.

Weight gains of 5.1 kg and 4.1 kg were recorded in group 1 (imported risperidone) and group 2 (Iranian risperidone), and weight changes were not statistically significant in group 2 (Iranian risperidone) at the beginning and the end of the study. More weight gain was detected in group 1 (imported risperidone), but no statistically significant difference was found in weight changes in group 1 (imported risperidone) due to the smaller sample size. Altogether, both drugs cause weight gain and are not different in this regard. Weight gain was reported in other studies. Nasr-o-Allah reported that the weight gain resulting from risperidone treatment was lower than other atypical drugs and was often dose-independent. Gureje and Conly (9) measured average weight gains of 4.5 kg and 2.1 kg, respectively, resulting from risperidone administration, which was not very different from our results.

According to our laboratory findings, some parameters increased, and the rest decreased in both groups. Although statistically significant differences were observed between the two groups in the numbers of EOS and MCHC, this difference was insignificant and insufficiently perceptible clinically.

Prolactin increased in both groups, but this increase was not statistically significant between the study's beginning and end. An increase in prolactin levels induced by risperidone treatment was reported elsewhere (26). Changes in the other parameters do not appear significant due to their non-significance and the absence of reports on such changes in similar studies. In this study, a disintegration test was performed on the tablets inside the capsules with those without capsules to ensure the blinding method. The presence of capsule shells and lactose powder increased the disintegration time of the tablets, but these changes are limited and will not have a significant clinical effect.

Ultimately, the definite result is that both drugs are similar in terms of side effects and are not clinically and statistically different with this sample size.

Conclusion

The two drugs are not significantly different clinically and statistically, and both are similar in terms of side effects.

Acknowledgments

None.

Conflict of interest

None.

Financial Support

None.

Ethics Statement

All Permissions to conducting this research has been approved.

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