A 6 week prospective randomized comparative study of metabolic adverse effects of Risperidone and Iloperidone in patients with schizophrenia

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Abstract

Introduction: The antipsychotics Risperidone and Iloperidone are the two different benzisoxazole derivatives that are structurally different and metabolized differently. Risperidone has moderate effects on metabolic parameters. Iloperidone is comparable to placebo in this regard according to western literature. We wish to study this on Indian population.

Methods: it is a prospective randomized study having three visits, on day 1, 21 and 42. Forty patients with schizophrenia, 20 each on Risperidone and Iloperidone were compared for weight, BMI, FBS, PPBS and fasting lipid profile using repeated measures ANOVA and t test.

Results: Ten percent of subjects on Risperidone and 15% on Iloperidone had significant weight gain. The mean weight gain was 2.5 kg and 2.75 kg with Risperidone and Iloperidone respectively. Both weight and BMI were comparable. Within the group, Risperidone caused significant rise in lipids; where as Iloperidone caused significant increase in both lipids and sugar. Across the groups there was no significant difference.

Conclusions: The study reveals that Iloperidone is associated with weight gain, change in BMI as well as alteration in blood sugar and lipids that is comparable with Risperidone, even at a lower chlorpromazine equivalent dose, in contrast to the western literature where, its impact on metabolic parameters are said to be at placebo level.

Keywords: BMI, Cholesterol, FBS, Ilopridone, PPBS, Risperidone, Triglycerides, Weight gain.

Introduction

Risperidone and Iloperidone are the second generation antipsychotics (SGA). Risperidone is a benzisoxazole derivative and an approved antipsychotic agent for the treatment of schizophrenia and the acute manic phase of bipolar disorder. It has a strong binding affinity for serotonin ($5\text{-}HT_{2A}$ and $5\text{-}HT_7$) and dopamine D_2 receptors. It has a lower acute incidence of overall adverse effects than Haloperidol at therapeutic dosages of 4-6 mg/day[(1,2)]. Extrapyramidal syndromes and sequelae of prolactin elevation have been the common and consistent adverse effects of Risperidone. Though there is an active weight gain, it tends to plateau within a few months[(3,4)]. The CATIE trial reported an average weight gain of 0.8 lb with Risperidone. About 14% subjects gained more than 7% of their body weight[(5)]. The risk of developing type 2 DM with risperidone comes after that of clozapine and olanzapine[(6)]. Studies have consistently found that Risperidone causes hyperlipidemia less frequently than clozapine and olanzapine. Possible underlying causes of lipid dysregulation include weight gain, dietary changes, and glucose intolerance[(7,8)].

Iloperidone was approved in 2009 by the US Food and Drug Administration for the acute treatment of schizophrenia[(9)]. It belongs to the class of piperidinyl-benzisoxazole derivatives. Though structurally similar to Risperidone, it does not have a tricyclic structure like other SGAs. Further, it is metabolized differently because it lacks the piperidinyl ring found in Risperidone. Thus it is neither a metabolite of Risperidone nor does its metabolites produce any metabolites in common with other agents. It shows high affinity for dopamine D_3 receptors, $5HT_{2A}$ receptors, norepinephrine α_1/α_{2c} receptors apart from D_2. Low affinity to histamine H_1 receptors would theoretically predict a low propensity for causing sedation or weight gain[(10)]. Twelve percent of patients experienced clinically significant weight gain, largely during initiation phase of treatment[(11)]. Another study revealed that Iloperidone, Paliperidone, Quetiapine, and Risperidone have a medium risk of glucose dysregulation and weight gain, as compared to Olanzapine and Clozapine which have highest risk[(12)]. In the long term studies of Iloperidone and Haloperidol, increase in the levels of total cholesterol and triglycerides were numerically larger in patients receiving haloperidol[(13)].

Thus studies have shown that both Risperidone and Iloperidone have some metabolic adversities, though not as severe as Olanzapine. Iloperidone being a newer second generation antipsychotic drug, has been shown to have a safe metabolic profile. Our objective is to test this and compare the two drugs on Indian population.

Methods

The study was approved by the institutional ethics committee. This is a prospective randomized comparative study wherein we assessed the metabolic parameters of patients with schizophrenia, who were administered a monotherapy with Risperidone or Iloperidone. The study was conducted in the department

of psychiatry of a tertiary care teaching hospital at Mysuru. The informed consent process was done by the authors. The subjects were explained in their language about the purpose of study and its benefits to them as well as possible adverse effects. Then, written consent was taken on the consent form before recruiting them. The patient enrollment was done for eight months, from Jan 2015 to Aug 2015. The last visit of the last patient was completed on 8th Oct 2015. Patients having met the criteria for schizophrenia according to ICD 10 and consenting to participate in the study were recruited. Both male and female patients in the age range of 18-60 yrs were included. Those with a known history of poor compliance to treatment and those with severe medical or psychiatric co-morbid disorders were excluded. The drugs were administered as per the allocation by computerized randomization. The dose range as per the protocol was 4 to 8 mg for Risperidone and 4 to 16 mg for Iloperidone. No concomitant medication like benzodiazepines and trihexiphenidyl were allowed. However those who were already taking medication for comorbid stable medical disorders were asked to continue same treatment.

The study involved three visits. After the initial visit of enrollment into the project, second visit was after three weeks and final visit was after 6 weeks; with a range of ± 2 days for each visit. The sample size was calculated considering prevalence of schizophrenia in our country which is 8.7 million, i.e. 3.1%. The level of significance kept at 5% and effect size 8%. It was calculated using the formula $n=4pq/d^2$.

Where p is the prevalence
q is 1-p
d is 0.8
Accordingly n is 43.33. Thus we had to enroll 22 subjects for each group. Among the 61 subjects screened and interviewed, a total of 44 were enrolled into the study. They were divided into two groups based on the medication they received.

Group 1. Received Risperidone in the dose range of 4-8 mg/day (n=22).

Group 2. Received Iloperidone in the dose range of 4-16 mg/day (n=22).

Forty subjects completed all the three study visits. Two subjects on Iloperidone were lost to follow up and two on risperidone were discontinued as they developed severe EPS. The symptomatic improvement during visits was assessed based on unstructured clinical interview. Then the metabolic parameters were assessed. The weight and BMI was measured in every visit. The biochemical tests were done during first and third visits. FBS, PPBS and Fasting lipid profile that included LDL, HDL, Cholesterol and Triglycerides, were the biochemical tests done. All the blood samples were analyzed in the central laboratory of the hospital. After the informed consent process, each patient was asked to come on appointment nil orally overnight for study related assessments. Those who were admitted in the hospital were assessed the next day. All assessments of a particular patient were completed on a single day and the allotted medication started the same day. Clinical improvement in psychopathology was assessed during all visits with unstructured interview. The statistical analysis was done using descriptive statistics for socio-demographic variables and t test as well as repeated measure ANOVA for comparative statistics.

Results

This is a prospective randomized comparative study involving 3 visits. We compared the socio demographic and metabolic parameters of study population who were administered Risperidone or Iloperidone.

The table 1 shows that the socio-demographic characteristics of the two groups are comparable. There was no significant difference across the two groups for age and sex. The mean age for Risperidone group was 35.05±9.71 and for Iloperidone group it was 29.75±8.14. In the Risperidone group there were 10 males and 10 females. The Iloperidone group had 11 males and 9 females. Apart from one patient on Risperidone who was a Muslim, all others were Hindus. They were also evenly matched for income.

The table 2 gives a comparison of the weight gain and BMI across the two groups over the six weeks of the study. The approximate weight gain with Risperidone was about 2.5 kg and with Iloperidone it was 2.75 kg. Within the groups, both drugs showed statistically significant weight gain (p=0.000 in both cases). Two from Risperidone group (10%) and three from Iloperidone group (15%) had significant weight gain, defined as ≥7% of base line weight. However when both drugs were compared for mean weight gain, they were not statistically significant. Same finding has been observed with respect to BMI too.

Risperidone is seen to be friendlier as far as carbohydrate levels are concerned in our study. Within the group both fasting and postprandial sugar levels were unchanged after 6 weeks. However in case of Iloperidone, both FBS (p=0.001) and PPBS (p=0.038) had increased significantly. Further PPBS after 6 weeks showed a rising trend with Iloperidone compared to Risperidone (p=0.064).

Lipid levels, especially that of LDL, cholesterol and triglycerides had risen with both study drugs. Within groups, LDL had increased significantly with both Risperidone (p=0.000) and Iloperidone (p=0.006) after 6 weeks. It was also true with cholesterol (Risperidone- p=0.018; Iloperidone- p=0.013) levels. HDL levels were more or less unchanged in both groups. Serum triglyceride level was significantly more in Risperidone group (p=0.000). In the Iloperidone group though blood levels of triglyceride had increased at the end of the study, it was not statistically significant. The table 3 has compared the two study

drugs for rise in sugar and lipids. It is evident that Iloperidone is associated with a rise in fasting and postprandial blood sugar, which is not the case with Risperidone in our study population. The rise in lipid levels with both drugs is comparable. The mean drug dose of both drugs across all visits is shown in table 4. It shows that our study subjects have received both drugs in the therapeutic dosage range.

Table 1: Socio demographic variables

Socio-demographic variables		Risperidone n (%)	Iloperidone n (%)	p
Education	Illiterate	10 (50)	7 (35)	0.196
	School	9 (45)	8 (40)	
	College	1 (5)	5 (25)	
Occupation	Labour	13 (65)	10 (50)	0.476
	Home maker	5 (25)	6(30)	
	Business	2 (10)	2 (10)	
	Unemployed	0 (0)	2 (10)	
Family type	Nuclear	14 (70)	15 (75)	0.723
	Extended	6 (30)	5 (25	
Marital status	Single	5 (25)	7 (35)	0.490
	Married	15 (75)	13 (65)	
Domicile	Rural	14 (70)	15 (75)	0.832
	Sub urban	4 (20)	4 (20)	
	Urban	2 (10)	1 (5)	
Religion	Religion	19 (95)	20 (100)	0.311
	Muslim	1 (5)	0 (0)	

Table 2: Comparison of weight gain and BMI changes across two groups

Metabolic parameters	Risperidone (n=20)		Iloperidone (n=20)		P
	Visit 1	Visit 3	Visit 1	Visit 3	
Weight	56.20 ± 9.07	58.75 ± 9.74	53.40 ± 11.16	56.28 ± 11.10	0.737
BMI	23.59 ± 3.22	24.64 ± 3.39	21.78 ± 3.44	23.01 ± 3.31	0.624

Table 3: Comparison of blood sugar and lipid levels across the study groups (in mg/dL)

Biochemical parameters	Risperidone (n=20)		Iloperidone (n=20)		p
	Visit 1	Visit 3	Visit 1	Visit 3	
FBS	85.75 ± 17.55	85.35 ± 15.19	87.20±14.73	97.70±12.83	0.113
PPBS	120.65 ± 25.06	121.55 ± 21.54	119.60±20.14	32.80±27.61	0.064
Fasting LDL	88.40 ± 25.66	107.35±25.54	90.00±29.24	102.20±30.78	0.836
Fasting HDL	39.20±3.70	40.25±2.97	40.95±9.51	42.50±7.93	0.300
Fasting cholesterol	137.10±33.94	153.30±29.73	130.45±32.37	51.95±36.15	0.666
Fasting triglycerides	119.45±35.41	141.35±38.53	118.45±29.01	28.60±34.82	0.494

Table 4: Mean dose of the study drugs in 'mg' across all the visits

Study drugs	Visit 1	Visit 2	Visit 3
	Mean ± SD	Mean ± SD	Mean ± SD
Risperidone	5.30 ± 1.75	5.00 ± 1.65	4.60 ± 1.39
Iloperidone	9.00 ± 2.79	7.80 ± 2.14	7.40 ± 2.01

Discussion

This is a prospective randomized comparative study wherein we compared Risperidone and Iloperidone for metabolic adverse effects. The initial experience with an antipsychotic matters a lot for long term compliance. The metabolic syndrome is seen as the major drawback with atypical antipsychotics. Though it can be a serious complication in the long term, changes can be noticed as early as 4 weeks. Iloperidone has been reported to be safer and comparable to placebo as far as metabolic adverse effects are concerned[13]. Our objective is to look into the early metabolic derangements with Iloperidone and to compare it with the gold standard atypical antipsychotic Risperidone.

Several clinical trials have shown that Risperidone consistently causes a weight gain of up to 3 kg and it reaches a plateau after about 10 weeks[14,15]. Even in our study Risperidone caused similar weight gain. With Iloperidone, in a pooled analysis of nine phase II and III double blind or open label trials, there were no clinically relevant changes in metabolic parameters including body weight, blood glucose, total cholesterol and triglycerides[16]. Studies have shown that about 13% of subjects taking Iloperidone gain weight. The mean change in weight from baseline to endpoint in the short term studies with Iloperidone was 2 kg. During the long term studies where Iloperidone and Haloperidol were compared, about two-thirds of the total weight gain with Iloperidone at end point occurred during the first 6 weeks[13]. Also, weight gain with Iloperidone is dose dependent. It was higher with a dose of 18-24 mg/day compared to 12-16 mg/day[17]. In our study, a similar raise in mean weight of 2.75 kg occurred in 6 weeks, though the mean dose in our study was as low as 8 mg/day. This could be due to the racial differences, Indians responding well to a lower dose of Iloperidone. Significant weight gain was seen in 10% of subjects in Risperidone group and 15% in Iloperidone group, which is comparable to the earlier studies[5,11]. Mean weight gain, when compared for the two study drugs did not differ significantly.

It is established that atypical antipsychotics alter insulin and glucose metabolism though Risperidone is found to have insignificant impact here[15]. In our study Risperidone did not alter FBS and PPBS levels after 6 weeks. Iloperidone on the other hand showed a comparatively higher FBS level, though not significant ($p=0.113$) and showed a raising trend in case of PPBS ($p=0.064$). Pooled analysis of short term studies with Iloperidone has shown that there is no clinically relevant change in metabolic parameters including blood glucose[13]. However in the long term studies of Iloperidone and Haloperidol, mean glucose levels increased from baseline by 5.90 mg/dL with Iloperidone whereas it decreased by 0.49 mg/dL with Haloperidol[18]. In another comparison of Iloperidone with Ziprasidone and placebo, fasting blood sugar levels increased by 7.9, 4.7 and 3.2 mg/dL in 4 weeks in that order, indicating higher but insignificant levels of increase for Iloperidone[19]. In our study FBS had increased by 11 mg/dL and PPBS by 13mg/dL after 6 weeks which is a slightly higher rise of blood glucose levels than the previous studies.

Risperidone causes some elevation in serum triglycerides, though much less than Olanzapine and Clozapine[15]. Most reviews mention that Iloperidone causes a negligible elevation in the blood levels of cholesterol and triglycerides though reports for LDL and HDL were not available to authors despite extensive literature search[13,16,20,21]. In a comparison with Ziprasidone and placebo, mean changes in total cholesterol were 8.1, 4.1 and -0.5 mg/dL and changes in triglycerides were 0.8, 4.6 and 19.5 mg/dL for Iloperidone, Ziprasidone and placebo respectively after 4 weeks[19]. In our study, both Risperidone and Iloperidone elevated all the components of lipid profile i.e. LDL, HDL, cholesterol and triglycerides. The mean increases were 19 mg/dL for LDL, 1 mg/dL for HDL, 16mg/dL for cholesterol and 22 mg/dL for triglycerides in the Risperidone group. In the Iloperidone group, the mean values elevated by 12 mg/dL for LDL, 1.5 mg/dL for HDL, 21 mg/dL for cholesterol and 10 mg/dL for triglycerides. All elevations were comparable and no drug was superior to the other with respect to the increases in lipid levels. However both drugs caused a moderate elevation of lipids parameters in contrast to earlier studies that Iloperidone causes least interference with lipids.

The doses of drugs influence the results. In our study, there was a mild reduction of dosage by the end of the study owing to clinical improvement. The dose of Risperidone was in the range of 4 to 6 mg across the visits and Iloperidone dose varied from 7.5 to 9 mg, both being in the range of therapeutic doses. The doses equivalent to 100 mg/day of chlorpromazine is 2mg/day for Risperidone and 6mg/day for Iloperidone[22,23]. Thus the chlorpromazine equivalent dose of Risperidone was slightly higher compared to Iloperidone in this study. Iloperidone at a higher dose than this might have probably caused more metabolic derangements.

This is a randomized prospective study, a design most suited for such comparative studies. Though attrition rate is sometimes a major drawback in such designs, it was only 11% in this study with 40 out of 44 subjects completing the study having three visits, on day 1, 21 and 42. However, though ours is a randomized study, we did not randomize the doses. Further, it was not a placebo controlled study, owing to the ethical issues of the institutional ethics committee. Our sample size is not large enough for generalization of our findings.

Conclusion

Our study shows that both Risperidone and Iloperidone causes comparable rise of blood sugar and

lipid levels over six weeks. The maximum impact of Iloperidone in comparison with Risperidone in our study was on blood sugar, especially postprandial sugar. Also within the groups, Iloperidone caused significant increase in both lipid and sugar levels, though Risperidone increased only the lipid levels. Thus Iloperidone has a similar metabolic risk as that of Risperidone, though its metabolic adverse effects were comparable to placebo in the western studies. Long term studies with a larger sample size and matched chlorpromazine equivalent doses are needed to generalize our result. All in all, Iloperidone also needs to be used cautiously with respect to metabolic safety, especially in long term use.

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