Integrative Biomedical Sciences

Research Article

Assessment of Extrapyramidal Symptoms and Hyperprolactinemia with Risperidone in Schizophrenic patients and Evaluation of their Management

Asha K Patel¹, Jayant B Dave^{2*} and Dharmesh Patel³

¹Department of Clinical Pharmacy, Shri Sarvajanik Pharmacy College, Mehsana, Gujarat, India

²P.G. Department, Shri Sarvajanik Pharmacy College, Mehsana, Gujarat, India

³Astha clinic, Ahmedabad and Satellite Hospital (GIPS hospital), Ahmedabad, Gujarat, India

Received: April 14, 2015; Accepted: April 26, 2015; Published: April 28, 2015

Abstract

To check the occurrence of Extrapyramidal Symptoms (EPS) and Hyperprolactinemia (HP) in Schizophrenic patients receiving Risperidone drug and to check the efficacy of the drugs used for the management of these side effects. The study assumes significance in light of reported data that anticholinergic drugs are not very effective in relieving side effects and that they may impair efficacy of antipsychotic drugs to relieve positive symptoms. Thirty one Schizophrenic patients receiving Risperidone drug were assessed for EPS & HP using Simpson Angus Rating Scale (SAS), Barnes Akathisia Rating Scale (BARS), Abnormal Involuntary Movement Scale (AIMS) & estimating prolactin level in blood. The EPS and HP side effects were treated with Trihexiphenidyl, propranolol or diazepam and cabergoline respectively and efficacy was studied for resolving the symptoms. The study revealed that 54.83% of patients on Risperidone showed EPS; majority of these patients (48.38%) developed Parkinsonism and rest (6.45%) developed Akathisia. Besides, 6.45% of the patients developed HP manifested as amenorrhea and menstrual irregularities. Trihexiphenidyl brought about resolution of most (88%) patients with Parkinsonism and partial resolution in remaining patients where tremors & rigidity persisted. propranolol and diazepam brought about the resolution of Akathisia. Cabergoline brought about satisfactory resolution of HP & associated symptoms in all the cases. About 65% of the patients receiving risperidone drug exhibited perceptible side effects. EPS, particularly Parkinsonism was found to be the major adverse effect. All the side effects were adequately resolved by the conventional drugs even at lower levels of the recommended dose improving the compliance of the treatment.

Keywords: Schizophrenia; Extrapyramidal symptoms; Hyperprolactinemia; Risperidone; Trihexiphenidyl; Cabergoline

Introduction

Schizophrenia is a psychiatric disorder characterized by two distinct groups of positive and negative symptoms [1]. Antipsychotics are the drugs used to

treat schizophrenia. They are classified as typical and atypical. The typical Antipsychotic agents are haloperidol, chlorpromazine, fluphenazine, thioridazine, flupenthixol and loxapine, and the atypical group comprises clozapine, quetiapine, Risperidone, olanzapine, sulpiride and sertindole [1,2]. As a mechanism of action they block dopaminergic receptors in the entire CNS; consequently, the nigrostriatal pathway that projects from the substantia nigra to the basal ganglia, that controls

***Correspondence:** Jayant B Dave, P.G. Department, Shri Sarvajanik Pharmacy College, Mehsana, Gujarat, India, Tel: +91 9825035232; E-mail: drjbdave@yahoo.co.in

EPS and tuberoinfundibular pathway that controls the prolactin secretion are blocked, resulting in Extrapyramidal side effects (EPS) and hormonal side effects respectively [3].

The EPS may be treated by reducing the Antipsychotic dose or with antiparkinsonian agents such as biperiden, benzhexol (Trihexiphenidyl), orphenadrine, benztropine, promethazine and amantadine. Trihexiphenidyl is a reference drug for treating EPS, and the dose prescribed is associated with that of the Antipsychotic agent used.

Some studies have found that concomitant treatment with Anticholinergics can attenuate the therapeutic effect of antipsychotic drugs treatment [4,5]. All anticholinergics can exacerbate tardive dyskinesia but are probably not a predisposing factor in its development [5,6]. The present study however showed efficacy of anticholinergic drugs given prophylactically or therapeutically. A hormonal effect such as Hyperprolactinemia is treated by substituting one Antipsychotic with other or by using Dopamine agonist drugs such as Bromocriptin and Cabergoline. Cabergoline is the reference drug for treating Hyperprolactinemia [7,8]. EPS and Hyperprolactinemia, as a consequence of using Antipsychotic drugs are the most important causes for patients not complying with the psychiatric treatment. This study aimed at assessing the occurrence of these side effects after usage of risperidone and evaluation of their resolution with standard reference drugs.

Materials and Methods

In the present Clinical study Risperidone 0.5, 1, 2, 3 and 4 mg tablets; Cabergoline 0.5 and 1 mg tablets; Propranolol 40 mg tablets; Diazepam 5 mg and Risperidone + Trihexiphenidyl (X + 2 mg) where X = 2, 3, 4 mg tablets were used.

A prospective, single centric, open-label study was performed on schizophrenic patients. The study was conducted at Astha clinic, Ahmedabad, Gujarat outpatient department of psychiatry from December 2012 to April 2013.

IRB approval of the study was obtained. The consent

of the patients and their relatives obtained and all formal procedures were completed. The purpose of the study was explained to all the participants. Patients who met the inclusion and exclusion criteria were included in the study.

Thirty one Schizophrenic patients treated with Risperidone were assessed to determine the occurrence of Extrapyramidal symptoms and Hyperprolactinemia, using Simpson Angus Rating Scale (SAS), Barnes Akathisia Rating Scale (BARS) & Abnormal Involuntary Movement Scale (AIMS) as follows:

Simpson and Angus rating scale [9] was used for extrapyramidal effects, comprising ten items in a scale from zero (absent) to four (severe). Each item brings instructions to assess and specify severity of each symptom.

Barnes akathisia scale [10] was made up of three items with the following classifications: objective evaluation from zero (absent) to three (constant akathisia);

subjective assessment that has two subitems, restlessness perception and discomfort associated with restlessness, from zero (absent) to three (severe); Global akathisia evaluation from zero (absent) to five (severe), and it was developed to measure dyskinetic symptoms in patients taking antipsychotic drugs.

Abnormal Involuntary Movement Scale (AIMS) [11,12] was used to measure dyskinetic symptoms in patients taking antipsychotic drugs comprising 12 items, on five-point severity scale ranging from 0 to 4. Total scores are not generally reported. Instead, changes in global severity and individual areas can be monitored over time. Ten items cover the movements themselves, divided into sections rating global severity and those related to specific body regions; two items concern dental factors that can complicate the diagnosis of dyskinesia. In the presence of extended neuroleptic exposure and the absence of other conditions causing dyskinesia, mild dyskinetic movements in two areas or moderate movements in one area suggest a diagnosis of tardive dyskinesia. The scale can be administered by trained raters. It can be completed in less than 10 minutes. Good psychometric properties have been reported.

Questionnaire of women's and children's hospital Government of South Australia were used to assess the symptoms of EPS & Hyperprolactinemia (baseline, after 15 days, monthly for two months).

Management of EPS was done using antiparkinsonian drug Trihexiphenidyl, β blocker propranolol & diazepam, Inj. Prometazine HCl and Clozapine. Whereas management of Hyperprolactinemia was done using dopamine agonist drug Cabergoline. Evaluation of their management was done using Health monitoring Questionnaire (baseline, after fifteen days, monthly for two months) & Prolactin blood level test.

Clinical outcome of the study was measured in terms of survival, complete recovery and survival with minor symptoms.

Data were obtained from the patient's chart, through interviews with patients, who voluntarily agreed to participate in the study after signing an informed consent form, using questionnaire forms Prepared by the researchers. The data collected was grouped, and subjected to statistical analysis and tabulated. The results are presented in absolute and percent numbers, as figures and tables.

Statistical Analysis

Data analysis had been done using percentage evaluation of data obtained in result.

Results

Thirty one patients under treatment with Risperidone who met the all inclusion and none of the exclusion criteria were participated in the study. Out of 31 patients 20 patients were found with ADRs while 11 were without any ADRs. In order to facilitate data analysis, it was decided to group the results into following categories:

- As shown in the Table 1, among 31 patients studied, 14(45.16%) were male and 17(54.83%) were female.
- As shown in Table 2, among 31 patients studied, 17 (54.83%) developed EPS; 2 (6.45%) Developed Hyperprolactinemia; 1 (3.22%) developed

EPS + Hyperprolactinemia; were as 11(35.48%) didn't developed EPS & Hyperprolactinemia.

- As shown in the Table 3, among 17 patients who developed EPS, majority of them (15) belong to Parkinsonism and only some patients (2) belong to Akathisia. Whereas none of the patients developed Dystonia and Tardive dyskinesia.

- As shown in the Table 4, 3 patients who developed Hyperprolactinemia were treated with cabergoline and Risperidone + Trihexiphenidyl and after drug treatment patients shows the complete recovery of Hyperprolactinemia.

- (The normal values for prolactin for Males: 2 - 18 ng/mL for females: 2 - 29 ng/mL)

- Table 5 shows the Recommended Daily Dose and Dose in present Clinical study of the drugs used for the treatment of EPS and HYPERPROLACTINEMIA.

- As shown in Table 6, among 20 patients who developed EPS, Hyperprolactinemia, EPS + Hyperprolactinemia; 15 were received Risperidone + Trihexiphenidyl, 2 received Cabergoline, 1 received Risperidone + Trihexiphenidyl & Cabergoline, 1 received propranolol and 1 received diazepam.

- As shown in the Table 7, amongst 17 patients of EPS; 15 shows complete recovery; 2 were survival with minor symptoms and 2 Hyperprolactinemia patients shows complete recovery.

Treatment of patients developed extrapyramidal symptoms and hyperprolactinemia: All the patients who developed extrapyramidal symptoms were treated with Trihexiphenidyl in case of Parkinsonism and with propranolol or diazepam in case of akathisia. All the patients who developed hyperprolactinemia were treated with cabergoline.

Clinical outcome of patients who developed extrapyramidal symptoms and hyperprolactinemia: Outcome of the patients who developed extrapyramidal symptoms and hyperprolactinemia were measured in terms of survival, complete recovery and

Table 1: Distribution of patients according to sex.

Sex	Number of patients	Percent
Female	17	54.83%
Male	14	45.16%
Total	31	100%

Table 2: Distribution of patients according to the development of Extrapyramidal Symptoms (EPS) and hyperprolactinemia.

Type of patients	Male	Female	Total	Total percent
Those who developed EPS	9	8	17	54.83%
Those who developed Hyperprolactinemia	0	2	2	6.45%
Those who developed EPS and Hyperprolactinemia	0	1	1	3.22%
Those who didn't develop EPS and Hyperprolactinemia	5	6	11	35.48%
Total	14	17	31	100%

Table 3: Distribution of the patients according to types of extrapyramidal symptoms.

Extrapyramidal symptoms	Male	Female	Total
Dystonia	0	0	0
Akathesia	1	1	2
Parkinsonism	8	7	15
Tardive dyskinesia	0	0	0
Total	9	8	17

Table 4: Distribution of the patients who developed hyperprolactinemia with prolactin concentration and side effect management therapy.

Sr. No.	Risperidone Treatment		Prolactin concentration (ng/ml)	Cabergoline treatment mg/wk	Risperidone + Trihexiphenidyl (mg/day)	Prolactin concentration (ng/ml) after drug treatment
	Dose mg	Days to Peak PRL				
1.	3 mg	13 days	96.5	0.5	-----	10.3
2.	3 mg	15 days	110.9	0.5	-----	6.10
3.	2 mg	14 days	163.8	1.0	3 mg + 2 mg	18.2

Table 5: Recommended vs actual doses of, antiparkinsonian drug, dopamine agonist drug, muscle relaxant drug and β blocker drug.

Drugs	Recommended Daily Dose	Dose in present Clinical study
Trihexiphenidyl (Antiparkinsonian)	Maintenance: 5-15 mg/day in 3-4 divided doses Maximum dose: 15 mg/day	Risperidone + Trihexiphenidyl (X + 2 mg)
Cabergoline (Dopamine agonist)	1 mg (up to 4.5 mg)/wk	0.5 mg once a wk/ twice a wk
Propranolol (B-blocker)	40 mg bid-tid	40 mg once a day
Diazepam (Muscle relaxant)	2-15 mg daily in divided doses	5 mg twice a day

(X = 2, 3, 4 mg)

Table 6: Distribution of the patients who are on drug therapy for the management of extrapyramidal symptoms and hyperprolactinemia according to the sex.

Drug Therapy	Male	Female	Total
Risperidone + Trihexiphenidyl	8	7	15
Cabergoline	0	2	2
Risperidone + Trihexiphenidyl, Cabergoline	0	1	1
Propranolol	0	1	1
Diazepam	1	0	1
Total	9	11	20

Table 7: Clinical outcome of patients treated.

Outcome	Extrapyramidal symptoms	Hyperprolactinemia	Extrapyramidal symptoms & Hyperprolactinemia
Survival	17	2	1
Complete recovery	15	2	1
Survival with minor symptoms	2	0	0

survival with minor Symptoms. "Survival" means that the patient who developed adverse effects and also survived after the treatment. Complete recovery" was defined as the survival with resolution of adverse effect after the drug treatment. "Survival with minor symptoms" meant that the patients survived but symptoms like mild tremors & mild rigidity persisted.

Discussion

The striking finding was that the patients who were on Risperidone drug showed EPS in 54.83% patients; majority of them (88.23%) developed Parkinsonism and rest of the patients (11.77%) developed Akathisia whereas none of the patients developed Dystonia and Tardive dyskinesia. There was no significant difference in occurrence of EPS based on gender. Hyperprolactinemia occurred in small percentage (11.76%) of females who participated in the study.

In the present clinical study fixed dose combination of risperidone and trihexiphenidyl (X + 2 mg) was given twice a day or one tablet in morning and half tablet in evening which meant 3 to 4 mg of Trihexiphenidyl per day. This implies that Trihexiphenidyl provides an effective treatment of the side effect even at lower level of recommended daily dose of drug. This finding clearly establishes efficacy of the drug in reversing EPS & negates the reports questioning its efficacy. Treatment of Risperidone + Trihexiphenidyl is continued for longer time. In some cases doctors even prescribed combination of Risperidone + Trihexiphenidyl as a pre-emptive measure for EPS. Such patients were not included in the study. Trihexiphenidyl brought about resolution of most patients with Parkinsonism (88.24%) and partial resolution in remaining patients where tremors & rigidity persisted.

In the present clinical study propranolol 40 mg was given once a day as treatment for Akathisia. This implies that propranolol provides effective treatment of side effects at doses much lower than recommended daily dose of drug. In the present clinical study diazepam 5 mg was given twice a day as treatment for akathisia. This implies that diazepam provides effective treatment of side effects at recommended dose. Propranolol and diazepam brought about the resolution of akathisia. Cabergoline brought about satisfactory reso-

lution of HP and associated symptoms in all the cases. In the present clinical study cabergoline 0.5 mg tablets was given once a week or twice a week as treatment for hyperprolactinemia. This implies that cabergoline provides effective treatment of hyperprolactinemia at recommended dose.

Duration of the study was only five months. Longer duration of follow up is required to assess the Extrapyramidal side effects and Hyperprolactinemia of atypical antipsychotic Risperidone as it is used for a long term treatment. Sample size of the study was small. This was because all the Schizophrenic patients have prescribed typical antipsychotics and other atypical antipsychotics besides Risperidone which resulted in comparing lesser number of patients treated with Risperidone. Acute dystonia and Tardive dyskinesia could not be studied because they did not develop. Only a few patients showed Hyperprolactinemia in present study. Further research in the same area with larger sample size and long term follow-ups would be useful. The propensity of other antipsychotic drugs to induce adverse effects should be studied in comparison to Risperidone.

In conclusion, about 58, 43 percent of the patients receiving risperidone drug exhibited extrapyramidal side effects, majority of them being Parkinsonism. It was found that patients treated with 3-4 mg of Risperidone which is on the middle-lower side of recommended therapeutic dose of 4-6 mg/day as maintenance dose also developed EPS (maximum dose: 16 mg/day). A small percentage of female (11.76%) who participated in the study developed hyperprolactinemia. All the side effects were adequately resolved by the conventional drugs even at lower levels of the recommended dose improving the compliance of the treatment. Trihexiphenidyl provides an effective treatment of the side effect even at lower level of recommended daily dose of drug.

Author contributions

The principal investigator of the present study was Dr. Dharmesh Patel who diagnosed disease and adverse effects associated with it and treated the symptoms by giving medications. He helped in this study by providing direct patients interactions with patients at his Clinic. The co-investigator of the study was Dr. Jayant B. Dave

who is the guide of dissertation study and gave very useful suggestions throughout out the study. The other co-investigator of the study was Asha K. Patel who carried out the whole study and collected all the data related to study as a part of her dissertation study and prepared all the results and reports after necessary interaction with and guidance of the guide and principal investigator.

Acknowledgements

The authors acknowledge the support and cooperation received from Sanjivani Hospital, Satellite hospital and Astha Clinic Ahmedabad for the conduct of the study.

References

1. Saeb-Parsy K, Assomull RG, Khan FZ, Kelly EA (1999) Instant pharmacology. London: John Willy & Sons 95-98.
2. Goldman LS, Gilman A, Brunton L, Lazo J, Parker KL (2006) The pharmacological basis of therapeutics. (11th Edn). USA: McGraw-Hill 29: 25.
3. Kane JM (2001) Extrapyramidal side effects are unacceptable. Eur Neuropsychopharmacology 11: S397-S403.
4. Kaplan & Sadock (2009) Synopsis of Psychiatry tenth edition. 992-995.
5. Johnstone EC, Crow TJ, Ferrier IN, Frith CD, Owens DG, et al. (1983) Adverse effects of anticholinergic medication on positive schizophrenic symptoms. Psychol Med 13: 513-527.
6. Jeste DV, Caligiuri MP (1993) Tardive dyskinesia. Schizophr Bull 19: 303-315.
7. Di Sarno A, Landi ML, Cappabianca P, Di Salle F, Rossi FW, et al. (2001) Resistance to cabergoline as compared with bromocriptine in hyperprolactinemia: prevalence, clinical definition, and therapeutic strategy. J Clin Endocrinol Metab 86: 5256-5261.
8. De Luis DA1, Becerra A, Lahera M, Botella JI, Valero, et al. (2000) A randomized cross-over study comparing cabergoline and quinagolide in the treatment of hyperprolactinemic patients. J Endocrinol Invest 23: 428-434.
9. Simpson GM, Angus JW (1970) A rating scale for extrapyramidal side effects. Acta Psychiatr Scand Suppl 212: 11-19.
10. Barnes TR (1989) A rating scale for drug-induced akathisia. Br J Psychiatry 154: 672-676.
11. Miyamoto S, Merrill DB, Lieberman JA, Fleischacker WW, Marder SR (2008) Antipsychotic Drugs. In Psychiatry, Third Edition. Edrs. Allan Tasman, Gerald Kay, Jeffrey A. Lieberman, Michael B. First and Mario Maj. John Wiley & Sons, Ltd.
12. Daniel DG, Igan MF, Wolf SS. Neuropsychiatric Aspects of Movement Disorders. In Comprehensive Textbook of Psychiatry. Vol 7, Kaplan HI and Saddock BJ (eds), Williams & Wilkins, Baltimore, MD, USA.

Copyright: ©Dave et al. This is an Open Access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.