

Evaluation of Clinical Outcome and Estimation of Effect of Serum Creatinine Levels in Parkinson's Patients with the Administration of Ropinirole

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Abstract: *Parkinson's disease is a long term degenerative disorder of the central nervous system that mainly affects the motor system. Dopamine agonists are used in the treatment of parkinson's disease. Ropinirole is a dopamine agonist used in the treatment of parkinson's disease. The present review is aimed on the evaluation of clinical outcome and estimation of serum creatinine levels in parkinson's patients with the administration of ropinirole. The clinical monitoring of serum creatinine levels is done to estimate the safety and efficacy of ropinirole in the treatment of Parkinson's disorder. After the study it was found that the serum creatinine levels were significantly increased in patients administered with ropinirole and the levels remained normal in patients administered with ropinirole. The review provides information regarding the side effects, drug interaction of ropinirole and also the comorbidities of the disease. The review states the use of other anti parkinson's drugs instead of ropinirole i.e. levodopa or the dose may be reduced.*

Keywords: Parkinson's disease, Creatinine, Ropinirole, Dopamine agonists, Levodopa

1. Introduction

Parkinson's disease (PD) is a long-term degenerative disorder of the central nervous system that mainly affects the motor system. The symptoms generally come on slowly over time. Early in the disease, the most obvious are shaking, rigidity, slowness of movement, and difficulty with walking. Thinking and behavioural problems may also occur. Dementia becomes common in the advanced stages of the disease.^[1] Depression and anxiety are also common occurring in more than a third of people with PD. Other symptoms include sensory, sleep, and emotional problems. The main motor symptoms are collectively called "parkinsonism", or a "parkinsonian syndrome". The motor symptoms of the disease result from the death of cells in the substantia nigra, a region of the midbrain.

Ropinirole is a dopamine agonist prescribed for mainly Parkinson's disease, RLS and extrapyramidal symptoms. It can also reduce the side effects caused by selective serotonin reuptake inhibitors, including Parkinsonism syndrome as well as sexual dysfunction and erectile dysfunction caused by either SSRIs or antipsychotics.^[4] Ropinirole acts as a D₂, D₃, and D₄ dopamine receptor agonist with highest affinity for D₂.

For Parkinson's disease, the maximum recommended dose is 24 mg per day, taken in three separate doses spread throughout the day. The maximum dose recommendations of ropinirole for subjects with end stage renal disease (ESRD) should be reduced by 25% compared with those recommended for subjects with normal renal function. A 25% dose reduction represents a more straightforward dosage regimen in terms of available tablet strength, compared with a 30% dose reduction

- Creatinine is a chemical waste molecule that is generated from muscle metabolism.
- Creatinine is produced from creatine, a molecule of major importance for energy production in muscles.
- Approximately 2% of the body's creatine is converted to creatinine every day.
- Creatinine is transported through the bloodstream to the kidneys. The kidneys filter out most of the creatinine and dispose of it in the urine.
- Because the muscle mass in the body is relatively constant from day to day, the creatinine production normally remains essentially unchanged on a daily basis.^{[3][4]}

Normal levels of creatinine in the blood are approximately 0.6 to 1.2 milligrams (mg) per deciliter (dL) in adult males and 0.5 to 1.1 milligrams per deciliter in adult females. (In the metric system, a milligram is a unit of weight equal to one-thousandth of a gram, and a deciliter is a unit of volume equal to one-tenth of a liter.)

The study involves the rise in serum creatinine levels while taking ropinirole as an anti Parkinson's drug. A rise in serum creatinine levels has been shown in some studies

Hanaa M. Roshdy^[5] et al (2015) conducted a study on "Cytogenetic, Biochemical and Histopathological Effects of Ropinirole on Albino Male Mice". Ropinirole is a synthetic, nonergot derivative receptor agonist that has selective activity for the D₂ class of dopamine receptors. Ropinirole is approved for the therapy of symptomatic Parkinson's disease and restless legs syndrome. The effects of ropinirole in doses equal and above the maximum recommended doses for human has not been adequately studied. dependent. The biochemical analysis were examined in the liver and kidney of treated males. The results showed that there were significant increases in the frequencies of MDA, ALT, AST, urea, uric acid and

Volume 6 Issue 7, July 2017

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creatinine levels in all treated groups compared with the control males and these increase were dose-dependent. Moreover, the pathological analysis examined in the liver and kidney tissues of treated and control males showed that there were vascular degeneration of hepatocytes reduction of cellular in filtration and dilation of main blood vessels in liver tissue and intestinal hemorrhage and thickening of the parietal wall of Bowman capsule was observed in renal tissue and these effects were dose-dependent.

Pauline Anderson^[6] et al (2015) conducted a study on "Creatinine Study in Parkinson Disease Terminated early". Despite early promise and a great deal of interest in creatinine monohydrate as a possible treatment of Parkinson disease, a large new double-blind, placebo-controlled trial found that this treatment does not improve clinical outcomes in patients with this neurologic disorder. The new findings "do not support the use of creatinine" in patients with early Parkinson disease treated with background dopaminergic therapy, the study authors, with corresponding author Karl Kieburtz, MD, MPH, from the University of Rochester Center for Human Experimental Therapeutics, New York, conclude. The trial was terminated early for futility on the basis of an interim analysis of 955 participants who had completed 5 years of follow-up.

Kulisevsky. J^[7] et al (2010) conducted a study on "Tolerability and Safety of Ropinirole versus Other Dopamine Agonists and Levodopa in the Treatment of Parkinson's Disease". The present study evaluated the tolerability and safety of ropinirole against those of other dopamine agonists (bromocriptine, cabergoline, pramipexole, rotigotine, pergolide) and placebo in monotherapy and adjuvant therapy with levodopa in the treatment of Parkinson's disease, as reported in the peer reviewed medical literature. A systematic review of the medical literature was carried out for relevant English language articles in the MEDLINE database and Cochrane Library from January 1975 to November 2008. The searches were limited to either double-blind clinical trials or randomized clinical trials that included both patients with early Parkinson's disease receiving dopamine agonist monotherapy, and patients at a later stage on combined treatment with levodopa. In all the included studies, dopamine agonists, including ropinirole, exhibited a higher incidence of adverse events than placebo. Ropinirole showed an adverse event profile similar to other dopamine agonists. Consideration of the clinical characteristics of each patient and the differences in the incidence of adverse events related to each dopamine agonist, may help to optimize the dopamine agonist therapy.

Stephane Thobois^[8] et al (2006) conducted a study on "Proposed dose equivalence for rapid switch between dopamine receptor agonists in Parkinson's disease". Progressive reduction of the dose of one dopamine receptor agonist and simultaneous, progressive dose escalation of another is a frequently used strategy for controlling motor symptoms of Parkinson's disease (PD) or avoiding specific adverse events. Rapid switch has been proposed as an alternative that might reduce the need for such major limitations as the possible exacerbation of symptoms and the need to monitor patients for several

weeks. However, the equivalence of doses of dopamine receptor agonists before and after switching drugs remains empirical because few clinical trials have addressed this issue. Six studies comparing 2 dopamine agonists and 4 studies analyzing the switch between dopamine agonists were selected. The proposed conversion factors were 1:6 for bromocriptine to pramipexole, 1:6 for pergolide to ropinirole, 10:6 for bromocriptine to ropinirole, 10:1 for bromocriptine to pergolide, and 10:1 to 10:1.5 for bromocriptine to pramipexole.

Rascol^[9] et al (2000) conducted a study on "Ropinirole as Compared with Levodopa in Parkinson's Disease". The study summarize the results of their study by stating that Parkinson's disease is best managed with ropinirole alone as the initial treatment, with levodopa used as a supplemental, second step if necessary. This recommendation is based on their finding that the risk of dyskinesias (medication-induced chorea) is lower with ropinirole. If a reduced risk of dyskinesia is to be the basis for making a recommendation with such broad implications, then the magnitude of the problem must warrant this concern. They reviewed the medical records of 350 randomly chosen patients with Parkinson's disease who were seen in the past year at our clinic, all of whom were receiving carbidopa-levodopa as primary treatment. Eighty-three of the patients (24 percent) had dyskinesias rated as moderate or severe (a score of 2 or higher on items 32 and 33 of the Unified Parkinson's Disease Rating Scale [UPDRS]). Of the patients who had been treated for 5 years or less, only 7 percent had clinically significant dyskinesias, and of the 246 patients who had been treated for up to 10 years, only 12 percent had clinically significant dyskinesias. Parkinson's disease can be managed well with levodopa therapy, without the use of adjunctive agonist therapy, over a five-year period. Our experience suggests that the risk of dyskinesias is a weak basis for a treatment recommendation with such broad clinical and financial implications. Although early use of an agonist makes sense in patients with early-onset Parkinson's disease, for patients in their 60s, 70s, or 80s, carbidopa-levodopa remains the best treatment

Sethi KD^[10] et al (1998) conducted a study on "Ropinirole for the treatment of early Parkinson disease: a 12-month experience". The objective of the study was to evaluate ropinirole hydrochloride as dopaminergic monotherapy in patients with early Parkinson disease. A 6-month extension of a double-blind, placebo-controlled study. Patients who successfully completed the initial 6-month study could enter the 6-month extension study (ropinirole, n = 70; placebo, n = 77). The efficacy variables were the number of patients who successfully completed the 12-month study and did not require supplemental levodopa, the number of patients requiring supplemental levodopa, and the proportion of patients having an insufficient therapeutic response. The result of the study shows that ropinirole was effective and well tolerated as monotherapy for 12 months in patients with early Parkinson disease

2. Methodology

Study Design

Prospective experimental study

Volume 6 Issue 7, July 2017

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Study Population

Patients diagnosed with Parkinson's disease

Study Site

Tertiary care setting; Department of neurology; Pushpagiri Medical College Hospital, Thiruvalla.
 Pushpagiri College of Pharmacy, Thiruvalla.

IEC Number

PCP/E3/01A/03/2016

Study Period

6 months

Sample Size of the Study

About 100 patients to be diagnosed with parkinson's disease.

$$N = [2S_p^2 [Z_{1-\alpha/2} + Z_{1-\beta}]^2] / \mu_d^2$$

$$P^2 = +S_2$$

$$S_p^2 = \frac{S_1^2 + S_2^2}{2}$$

Where,

- S_1^2 - Standard deviation in the first group.
- S_2^2 - standard deviation in the second group.
- μ_d^2 - Mean difference between the sample.
- α - Significance level.
- $1-\beta$ - Power.

3. Study Criteria

Inclusion Criteria

Group 2 (Patients administered with ropinirole)

- 1) Patients of all age groups except paediatrics.
- 2) Both male and female patients.
- 3) Both OP & IP patients.
- 4) Patients who are willing to sign informed consent form.
- 5) Patients with Parkinson's disease taking ropinirole.

Group 1(Patients administered with levodopa)

- 1) Patients of all age groups except paediatrics.
- 2) Both male and female patients.
- 3) Both OP & IP patients.
- 4) Patients who are willing to sign informed consent form.
- 5) Patients with Parkinson's disease taking levodopa.

Exclusion Criteria (Group 2 And Group 1)

- 1) Patients not willing to sign informed consent form.
- 2) Patients taking drugs that affect renal function.
- 3) Alcoholic patients.
- 4) Paediatric patients.
- 5) All patients who have a chance to show altered serum creatinine such as kidney disease, protein energy, malnutrition etc.

4. Brief Procedure of Study

A prospective experimental study was carried out in collaboration with Dept. of Neurology. Pushpagiri Medical College and Research, Institute, Thiruvalla which offers

neurologic services. All patients received a brief introduction regarding the study and confidentiality of data. 100 patients were selected for the study. A written informed consent was obtained from patient /care giver. A well designed data collection form was used to collect informations such as demographic details of patient, etiology, past medication history, current medication, dose, frequency, adverse drug reactions and family history.

About 3 ml of residual blood was obtained from the laboratory. Serum was separated by centrifugation and was used for the estimation of serum levels of creatinine. The experiment was a control based study. The patients were selected based on the inclusion and exclusion criteria. The concentration was analysed by using analytical kits in semi-auto analyser. The results obtained from the experiment was compared with the normal range of creatinine in blood. The common side effects and drug interaction of the drug was studied based on each patient.

Efficacy of ropinirole and its effect in serum creatinine levels was determined after the collection of samples from patients receiving ropinirole treatment and patients receiving levodopa.

Procedure for Determination of Serum Creatinine

ELITech Clinical Systems CREATININE JAFFE is intended for the quantitative in vitro diagnostic determination of creatinine in human serum.

Method

Colorimetric, Jaffe-Kinetic

Principle

The rate of formation of coloured complex between creatinine and alkaline picrate is measured. The effect of interfering substances are reduced using the kinetic procedure.

Reagent Composition

Reagent 1: R1 Picric acid	8.73mmol/L
Reagent 2: R2 Sodium hydroxide Disodium phosphate	312.5mmol/L 12.5mmol/L
Standard: Std Creatinine	2mg/Dl

Procedure

Wavelength 505cm
 Temperature 37degree celsius

Read against distilled water

	BLANK	CALIBRATON	TEST
Reagent R1	125µL	125µL	125µL
Distilled Water	25µL	-	-
Standard	-	25µL	-
Sample	-	-	25µL

Mix and wait 4 minutes and 43 seconds, then add:

Reagent R2	125µL	125µL	125µL
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Mix and after 24 seconds of incubation, read the variation of the absorbance (ΔA) during 106 seconds. The sample is tested using an auto analyser.

5. Results and Discussion

a) Age

In this study, most of the study population falls under the age group 65-79. The mean age of the patients were found to be 53%

b) Gender

In this study, the majority of the Parkinson's patients were males (53%) followed by females (47%).

c) Family History Of Brain Disorder

In the study of 100 patients, 59% patients were having a positive family history and 41% were not having family history of brain disorder.

d) Drug Interaction

The study explains the drug interaction of ropinirole with pregabalin (44%), acetaminophen (34%) and alprazolam (22%). In this the drug, ropinirole interacts seriously with pregabalin (44%).

e) Comorbidities

In the study of 100 patients, 45% were having a comorbidity of depression, 29% were having a comorbidity of sleep disorder and 26% were having a comorbidity of anxiety.

f) Side Effects

In the 100 patients of group 2 administered with ropinirole, 62% shows syncope as side effect, 56% shows hallucination

as side effect, 52% shows insomnia as side effect and 30% shows diarrhoea.

g) Serum Creatinine Level

The group 1 patients (patients administered with levodopa) shows normal serum creatinine level and the group 2 patients (patients administered with ropinirole) shows above normal serum creatinine level. The normal levels of creatinine in males is 0.5-1.1mg/dl and in females is 0.6-1.2mg/dl. As per the study the patients taking ropinirole showed an increase in the serum creatinine levels i.e. group 2 when compared to patients taking other anti parkinson's drugs i.e. group 1.

Effect of Ropinirole On Serum Creatinine Level

- In the study of 100 patients, the patients were categorised into two groups, there is a significant increase in the serum creatinine levels in the patients with Parkinson's disease taking ropinirole, i.e., group 2. In the control group, the serum creatinine levels of Parkinson's patients were normal, i.e., patients taking levodopa
- The mean creatinine level in group 1 (patients administered with levodopa) is 0.77mg/dl.
- The mean creatinine level in group 2 (patients administered with ropinirole) is 2.64mg/dl.
- The values were significant, i.e., the $p < 0.001$.
- Therefore, the study shows that the patients administered with ropinirole for Parkinsonism has higher serum creatinine levels than the patients administered with other levodopa.

Group 1- Patients Administered With Levodopa
Group 2- Patients Administered With Ropinirole

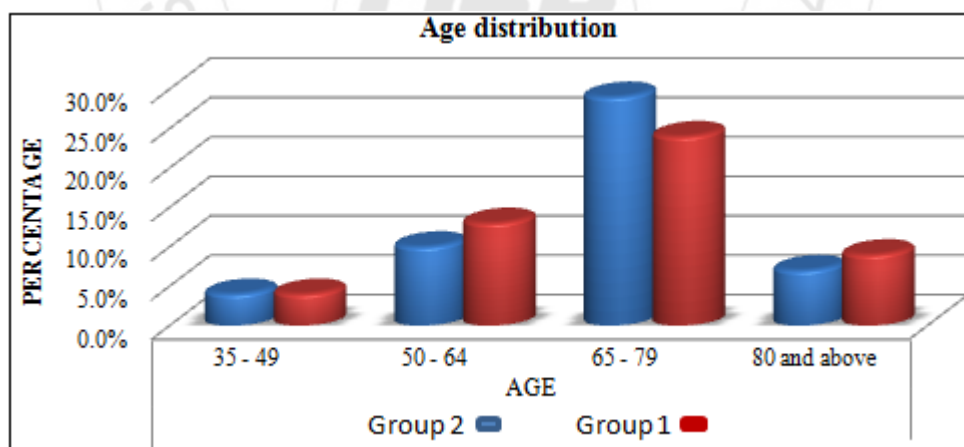


Figure 1

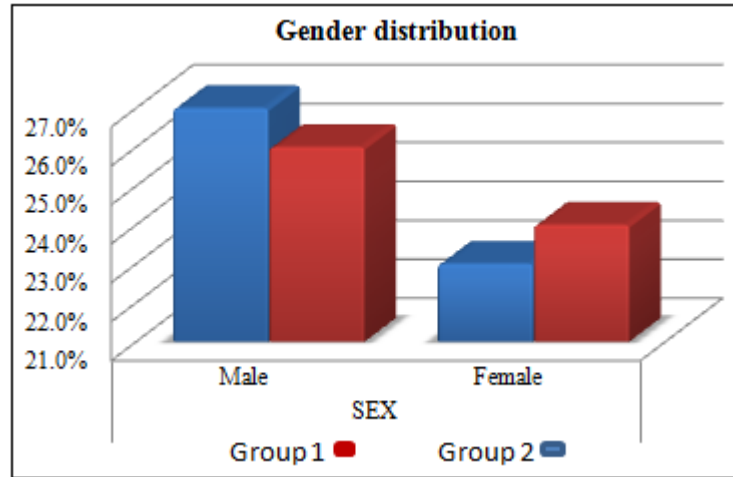


Figure 2

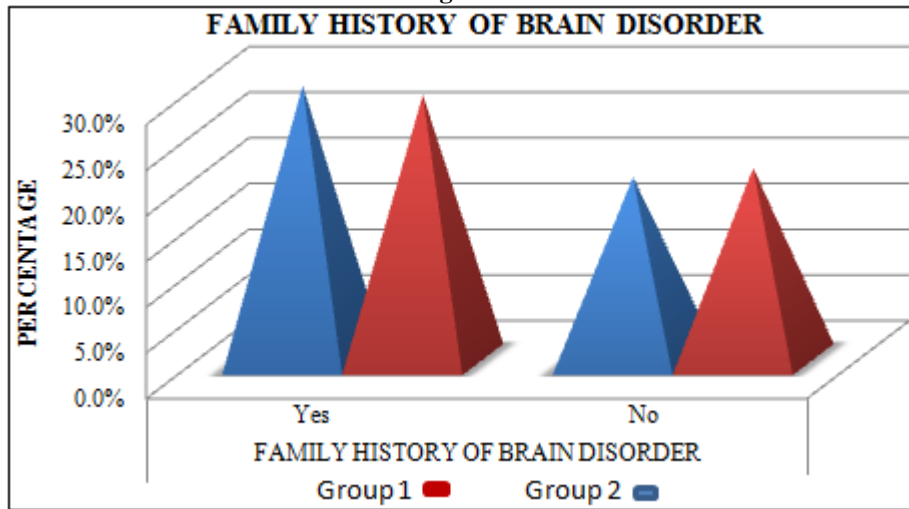


Figure 3

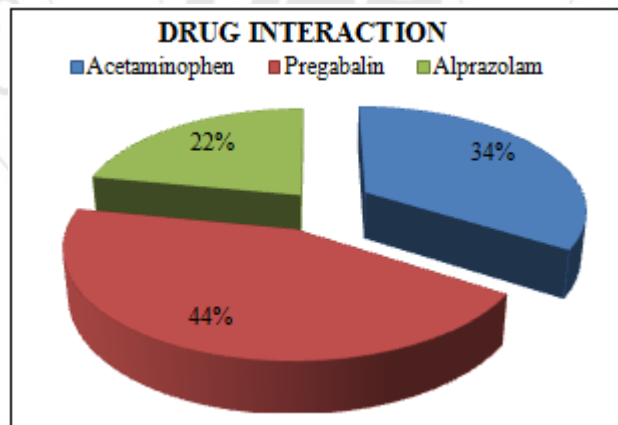


Figure 4

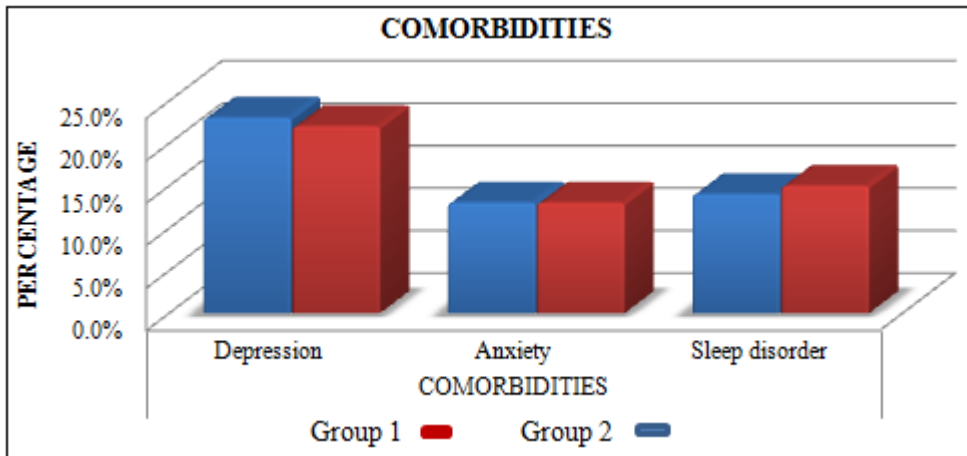


Figure 5

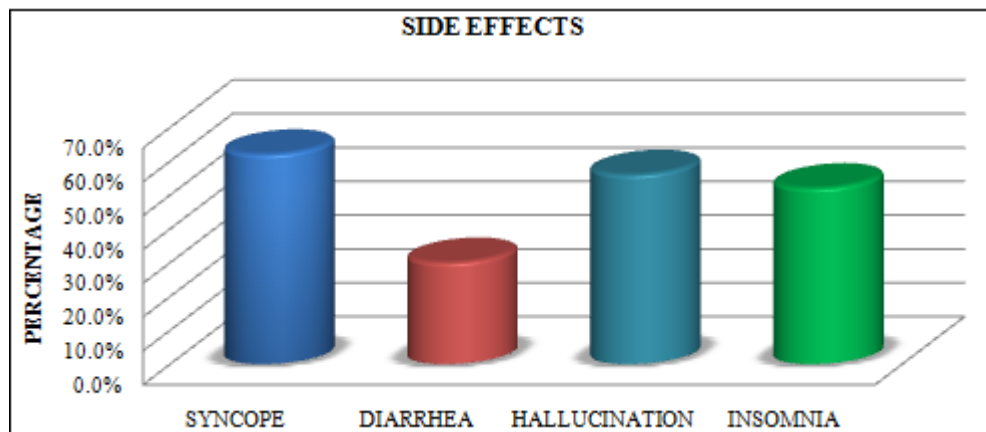


Figure 6

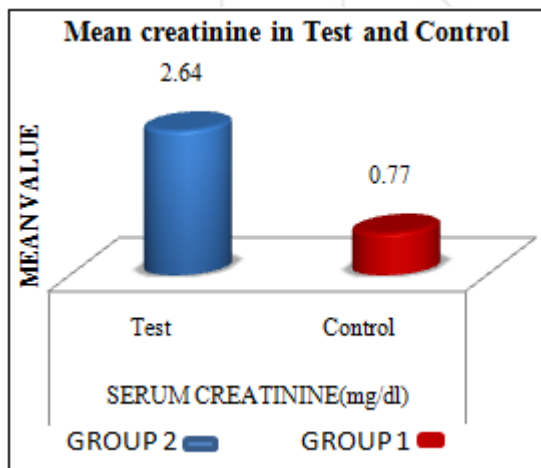


Figure 7

6. Conclusion

Ropinirole is a dopamine agonist. It is used in the parkinson's patients below the age of 70 and slowness or stiffness of an arm or leg as the major symptom. The studies regarding the elevation of serum creatinine with the treatment of ropinirole are very rare. The effect of serum creatinine elevation with administration of ropinirole can be magnified by carrying out further studies and assessments. Levodopa was the drug included in the study to compare with ropinirole. The clinical outcome, side effects and drug interaction were assessed. The dose was reduced and proper

clinical monitoring should be carried out during ropinirole therapy for Parkinson's disease.

7. Future Scope

The study can be referred to the estimation of serum creatinine levels with the administration of ropinirole.

References

- [1] Comella CL, Stebbins GT, Brown-Tom SN, Goetz CG. Physical therapy and Parkinson's disease: a controlled clinical trial. *Neurology*, 44, 1994, 376-378.
- [2] Lida M, Miyazaki I, Tanaka K, Kabuto H, Iwata-Ichikawa E, Ogawa N: Dopamine D2 receptor-mediated antioxidant and neuroprotective effects of ropinirole, a dopamine agonist. *Brain research*, Volume 838, Issues 1-2, 14 August
- [3] Allen PJ (May 2012). "Creatine metabolism and psychiatric disorders: Does creatine supplementation have therapeutic value?". *Neurosci Biobehav Rev.* 36 (5): 1442-62. doi:10.1016/j.neubiorev.2012.03.005
- [4] Gross JL, de Azevedo MJ, Silveiro SP, Canani LH, Caramori ML, Zelmanovitz T (January 2005). "Diabetic nephropathy: diagnosis, prevention, and treatment". *Diabetes Care.* 28 (1): 164-76.
- [5] Hanaa M. Roshdya, Mahrousa M. Hassananea, Salwa M. Kassema, Nermeen M. Shaffieb. Cytogenetic, Biochemical and Histopathological Effects of

- Ropinirole on Albino Male Mice'. *Int. J. Pharm. Sci. Rev. Res.*, 30(1), January – February 2015; Article No. 29, Pages: 160-168
- [6] Pauline Anderson, Laurie Barclay, MD. Creatinine Study in Parkinson Disease Terminated Early. CME/CE Released: 5/5/2015; Valid for credit through 5/5/2016
- [7] Jaime Kulisevsky, Javier Pagonabarraga. Tolerability and Safety of Ropinirole versus Other Dopamine Agonists and Levodopa in the Treatment of Parkinson's Disease Meta-Analysis of Randomized Controlled Trials. February 2010, Volume 33, Issue 2, pp 147–161
- [8] Thobois S. Proposed dose equivalence for rapid switch between dopamine receptor agonists in Parkinson's disease: a review of the literature. *Clin Ther.* 2006 Jan;28(1):1-12.
- [9] Rascol et al. (May 18 issue. Ropinirole as Compared with Levodopa in Parkinson's Disease. *Engl J Med* 2000; 343:884-885 September 21, 2000 DOI: 10.1056/NEJM200009213431211 the new England journal of medicine
- [10] Sethi KD¹, O'Brien CF, Hammerstad JP, Adler CH, Davis TL, Taylor RL, Sanchez-Ramos J, Bertoni JM, Hauser RA. Ropinirole for the treatment of early Parkinson disease: a 12-month experience. Ropinirole Study Group. 1998 Sep;55(9):1211-6.

