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SAFETY AND MULTIPLE DOSE PHARMACOKINETICS OF PALIPERIDONE ER IN INDIAN SCHIZOPHRENIC PATIENTS

HR Mehta*[1], AS Srivastava [1], SK Shah [1], DS Patel [1], PG Labana [1], AK Ramani [1], PB Patel [2]and BB Patel [3]

Clinical Research Group, Torrent Research Centre [1], Village-Bhat, Gandhinagar, Gujrat, India

Department of Pharmacology, ISTAR, A R College of Pharmacy [2], Vallabh Vidyanagar, Gujrat, India

Department of Pharmacology, Shri Sarvajanik Pharmacy College [3], Mehsana, Gujrat, India

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Correspondence to author:

Hiren Mehta

Clinical Research Group,
Torrent Research Centre,
Gandhinagar, Gujrat, India
Email-
hirenpharm@rediffmail.com

ABSTRACT

Paliperidone is a new active substance, belonging to the class of atypical antipsychotic, and is the active metabolite of a well-known active substance, risperidone that has been used for the last 3 years. A randomized, double-blind, multicentric, study to evaluate the safety and efficacy of Paliperidone ER compared to Olanzapine in patients with Schizophrenia was conducted in Indian schizophrenic patients. Pharmacokinetic Evaluation in Indian schizophrenic patients randomized to Paliperidone ER was an open label extension, pharmacokinetic (PK) study of previously conducted phase III trial. The doses of paliperidone 3, 6, 9, and 12 mg were administered during the study. Paliperidone concentrations were measured up to 36 hours post dose after administration of paliperidone ER 30 minutes after dinner to the patients who continued the medication after completion of phase III clinical trial. The mean C_{min}, C_{max}, AUC (tau) for paliperidone ER 3 mg, 6 mg, 9 mg, 12 mg were found to be [6.71 ng/ml, 23.59 ng/ml, 349.50 hr*ng/ml]; [28.88 ng/ml, 57.77 ng/ml, 1040.86 hr*ng/ml]; [17.25 ng/ml, 71.05 ng/ml, 1032.17 hr*ng/ml]; [34.35 ng/ml, 96.75 ng/ml, 1812.40 hr*ng/ml] respectively. Paliperidone ER was very well tolerated during the pharmacokinetics study.

INTRODUCTION: Schizophrenia is a devastating illness with significant psychological, physical, social, and economic impacts [1, 2]. Although the disease course is variable; it is most often chronic as characterized by ongoing function impairment and the frequent recurrence of acute psychotic symptom [3]. The general goal of treatment aims to quickly reduce symptom severity, improve patient functioning, and prevent recurrences of symptomatic episodes and associated deterioration of functioning. Antipsychotic medication is the primary intervention for the stabilization of acute episodes and the prevention of symptom recurrence in patients with schizophrenia [4, 5]. The atypical antipsychotics are associated with lower risk of reversible and irreversible movement disorders than conventional antipsychotic [4-8]. There is also evidence to suggest that atypical antipsychotic have an advantage in their ability to delay time to relapse [5, 6-9].

Paliperidone is a new active substance, belonging to the class of atypical antipsychotics, and is the active metabolite of a well-known active substance, risperidone. Risperidone is extensively metabolized to 9-hydroxy-risperidone (i.e. paliperidone) via CYP2D6 and the exposure after administration of risperidone is often presented in terms of “active moiety”, which is the sum of risperidone and 9- hydroxy-risperidone plasma levels. Paliperidone (9-OH-risperidone) is a receptor monoaminergic antagonist that exhibits the characteristic dopamine type 2 (D_2) and serotonin (5-hydroxytryptamine 5-HT) type 2A (5-HT2A) antagonism of antipsychotic drugs. Paliperidone is the major active metabolite of risperidone which is a widely used atypical antipsychotic approved for the treatment of schizophrenia and other psychiatric disorders. The current study was basically undertaken to evaluate the pharmacokinetic (PK) parameters of paliperidone ER in Indian schizophrenic patients.

MATERIALS AND METHODS:

Subjects: Total 15 Indian schizophrenic patients had participated in an on- going clinical trial: A randomized, double-blind, multicentric, study to evaluate the safety and efficacy of Paliperidone ER compared to Olanzapine in patients with Schizophrenia with Pharmacokinetic Evaluation in patients randomized to Paliperidone ER..At the end of phase-III trial all the completed patients were unblinded and they continued treatment after completion of trial. Patients who were willing to participate in open label extension pharmacokinetic study and those who gave their informed consent were recruited in the present pharmacokinetic study.

Total 15 patients from four centers across the India participated in the pharmacokinetic study having age of 18 to 65 years. The study was conducted at Investigator’s Site 1) A522/GovindMarg, Near Rumgta hospital, Malvia nagar, Jaipur, SMS Medical College) Shakunt Psychiatry Clinic, A/244, Popular Plaza, 132 Feet Ring Road, Satellite. Ahmedabad) Trishul Hospital, 611, K. K. Nagar, Madurai) "Santvan"-Psychiatric Clinic, Chitta Khana Chawk-Junagadh. Consenting patients were considered eligible if they satisfied the following main inclusion criteria: Patients (male or female aged between 18-65 years) with diagnosis of schizophrenia, who had completed the trial and continuing treatment as per study & randomized to paliperidone ER were participated in the study. Exclusion criteria included compliance check for the trial medication (Paliperidone ER) as consumed over the last one week, current dose

of Paliperidone ER (each capsule = Paliperidone ER 3 mg), any clinical significant abnormal post study safety evaluation after completion of phase III trial. Patients with history of allergy or hypersensitivity to drugs were kept away from the trial. Use of depot antipsychotic 120 days prior to the screening was given to the patients.

Electroconvulsive treatment within 3 months before screening or had involuntary admission to psychiatric hospital, pregnant women or nursing mother, women of child bearing age unwilling to use barrier contraceptives. Patients with DSM-IV axis I diagnosis other than schizophrenia, within 6 months of screening were not included. Patients with significant risk of suicidal or aggressive behavior within last four weeks, history of Tardive Dyskinesia or Neuroleptic Malignant Syndrome, subjects with serum ALT, AST, bilirubin, alkaline phosphatase of > 2X ULN. Subject with serum creatinine > ULN.

History of current gastro-intestinal diseases influencing drug absorption, except for appendicectomy or if the patient have any medical condition that may hamper/alter the ADME of study medication. Virology hepatitis B virus surface antigen (HBsAg), hepatitis C virus antibodies (HCV Ab), human immunodeficiency virus 1/2 (HIV), and urine drug screening. All patients provided written informed consent to participate in the trial, according to the ethical principles stated in the Declaration of Helsinki, the applicable guidelines for the International Conference of Harmonization–Good Clinical Practice (ICH-GCP), and the applicable laws and regulations of India. The study protocol was approved by the National Regulatory Authority (DCGI), India and Independence Ethics Committee before the start of the study.

Study Design: The study followed a protocol of open-label, extension of the completed multicentric clinical trial with randomized, an open label extension design. In the study, oral doses (3, 6, 9, and 12 mg) of Paliperidone ER were administered to 15 Indian schizophrenic patients. Those patients who completed the trial were administered with same oral dose of paliperidone ER that they have been prescribed continuously after completion of phase- III trial.

For PK study, patients were confined to hospital at least 4 hours before dosing until after 36 hours post dose blood draw in four sites across the India. After administration of the study drug, Standardized meals (i.e. breakfast, Lunch, Snacks, Dinner and Breakfast) were provided approximately 12.00, 16.00, 20.00, 24.00 and 36.00 hours post dose respectively. Water was not be accessible to the patients 2 hours post dose except during administration of the dose. Patients remained in sitting/semi-reclining position for at least first 2 hours after study drug administration.

A total of (10 x 5 ml) of venous blood samples were collected at 0.00 (pre-dose) and at 3.00, 6.00, 9.00, 12.00, 16.00, 20.00, 23.00, 24.00 and 36.00 after study drug administration. An extra 0.5ml heparinised blood sample was discarded before each in-house sample from indwelling cannula. Heparin-lock technique was used to prevent clotting of the blood in the indwelling cannula. The blood samples were collected in polypropylene tubes containing 5 IU diluted heparin for each ml of blood. Each sample was centrifuged and plasma

separated and stored in refrigerator (deep freezer) till it is transported. The Plasma samples were transported to the temperature controlled environment. Sample kept in frozen condition (-70°C ± 20°C) until it was analysed.

Safety Monitoring: The safety and the general tolerability of the drug were judged based on adverse events (AEs), vital signs, physical examinations, and laboratory tests. All observed or volunteered AEs were recorded after administration of each dose with regard to their time of onset, severity, duration, and possible relationship to the study drug. Vital signs (blood pressure, heart rate, and oral body temperature) of the patients were recorded at the time of enrollment; pre-dose, at 3.00, 7.50, 22.00, 24.00 and 36.00 post dose and whenever necessary and at the time of discharge. After completion of 36 hours after dosing, a physical examination was carried out.

Analytical Methods: The concentration of paliperidone in plasma was determined by means of a validated liquid chromatography/tandem mass spectrometry (LC/MS/MS) method. The method was validated for linearity and selectivity and be able to determine paliperidone with sufficient selectivity and accuracy. A limit of quantification was set to quantify the levels of drug adequately in plasma. The method validation had to include a pre-study validation with determination of stability of the stock solutions and of the analyte in the biological matrix under processing conditions and during the entire period of storage, specificity, accuracy, precision, limit of quantification, and response function, as well as online validation with control samples at three concentration levels. All samples of the same patient had measured in a single analytical run in order to eliminate the influence of the inter-assay variance on the assessment. Paliperidone and risperidone plasma concentrations were determined by an LC-MS/MS assay, based on Method A published by Remmerie et al. (2003) [10]. The data support the accurate and precise quantitation of paliperidone and risperidone in 500 µl of heparin plasma over a concentration range of 0.1 - 250 ng/ml with a lower limit of quantification of 0.1 ng/ml and with acceptable accuracy and precision [11].

Pharmacokinetic Evaluation: The plasma concentration-time data of Paliperidone for each patient was analyzed with the noncompartmental method using validated WinNonlin® Professional software (Version 5.2, Pharsight, Cary, North Carolina). Pharmacokinetic parameters for Paliperidone included maximum observed concentration (C_{max}), Minimum Blood Concentration (C_{min}), Area Under the Concentration – time curve during dosing interval ($AUC\ \tau_{(tau)}$)or within a 36-hour dosing interval (AUC0-36), T_{max} and AUC_{last}.

Statistical Analysis: Single dose pharmacokinetic parameters had expressed as arithmetic mean, geometric mean, and standard deviation (SD) unless noted. A nonlinear power model was used to assess dose proportionality using SAS Version 9.1.3 (SAS Institute, Inc, Cary, North Carolina).

RESULTS AND DISCUSSION: The study was undertaken recruiting total 15 patients and all the patients completed the study as per protocol. The plasma samples separated from the collected blood were then subjected to

quantification of paliperidone as means of validated method as per international acceptance criteria. Following tables describes pharmacokinetic parameters as well as previously reported adverse events during the phase-III clinical trial of those patients who are recruited into this Pharmacokinetic study. The causality of the AEs is discussed later in this section. Due to the limitation of the sample size of this current study, the relationship of AEs could not be established with paliperidone plasma concentrations.

Pharmacokinetic Parameters:

TABLE 1:PALIPERIDONE ER 3 mg

DOSE	T_{max} (hr)	C_{min} (ng/mL)	C_{max} (ng/mL)	AUC τ *(tau)* (hr*ng/mL)	AUC_{last} (hr*ng/mL)
3 mg	12.00	1.304	18.625	249.923	365.543
	9.00	7.999	27.746	398.238	541.638
	12.00	15.977	37.772	630.879	856.101
	20.00	1.540	10.214	118.952	200.204
N	4	4	4	4	4
Mean	13.250	6.7050	23.5893	349.4976	490.8711
SD	4.7170	6.91598	11.85988	219.55809	280.57344
Min	9.000	1.3040	10.2140	118.9520	200.2040
Median	12.000	4.7695	23.1855	324.0800	453.5900
Max	20.000	15.9770	37.7720	630.8785	856.1005
CV%	35.6	103.1	50.3	62.8	57.2
Geometric Mean	12.688	4.0025	21.1308	293.9790	429.2013

Total 4 patients were administered with Paliperidone ER 3 mg; Peak Trough Ratio for Paliperidone ER 3 mg was 3.5

TABLE 2:PALIPERIDONE ER 6 mg

DOSE	T_{max} (hr)	C_{min} (ng/mL)	C_{max} (ng/mL)	AUC τ *(tau)* (hr*ng/mL)	AUC_{last} (hr*ng/mL)
6 mg	9.00	34.062	76.872	1246.049	1788.005
	9.00	49.789	73.508	1553.718	2151.792
	16.00	10.836	46.493	694.403	1227.959
	16.00	20.820	34.191	669.255	1046.787
N	4	4	4	4	4
Mean	12.500	28.8768	57.7660	1040.8563	1553.6358
SD	4.0415	16.87788	20.78229	433.30074	508.48823
Min	9.000	10.8360	34.1910	669.2550	1046.7870
Median	12.500	27.4410	60.0005	970.2260	1507.9820
Max	16.000	49.7890	76.8720	1553.7180	2151.7920
CV%	32.3	58.4	36.0	41.6	32.7
Geometric Mean	12.000	24.8707	54.7458	973.9298	1491.2581

Total 4 patients were administered with Paliperidone ER 6 mg; Peak Trough Ratio for Paliperidone ER 6mg was 2

TABLE 3: PALIPERIDONE ER 9 mg

DOSE	T_{max} (hr)	C_{min} (ng/mL)	C_{max} (ng/mL)	AUC τ *(tau)* (hr*ng/mL)	AUC_{last} (hr*ng/mL)
9 mg	0.00	33.898	90.352	1388.924	1763.270
	23.00	20.283	37.192	678.165	1053.015
	9.00	6.561	51.035	638.311	894.193
	6.00	14.739	71.969	1027.990	1458.712
	9.00	10.664	23.649	409.378	809.674
	24.00	17.380	152.126	2050.278	3481.062
N	6	6	6	6	6
Mean	11.833	17.2542	71.0538	1032.1741	1576.6541
SD	9.6212	9.49007	46.34770	605.33425	1000.37122
Min	0.000	6.5610	23.6490	409.3780	809.6740
Median	9.000	16.0595	61.5020	853.0773	1255.8633
Max	24.000	33.8980	152.1260	2050.2775	3481.0615
CV%	81.3	55.0	65.2	58.6	63.4
Geometric Mean	-	15.1980	59.5072	896.3865	1377.3024

Total 6 patients were administered with Paliperidone ER 9 mg; Peak Trough Ratio for Paliperidone ER 9mg was 4.8

TABLE 4:PALIPERIDONE ER 12 mg

DOSE	T_{max} (hr)	C_{min} (ng/mL)	C_{max} (ng/mL)	AUC τ *(tau)* (hr*ng/mL)	AUC_{last} (hr*ng/mL)
12 mg	12.00	34.345	96.745	1812.396	2562.174
N	1	1	1	1	1
Mean	12.000	34.3450	96.7450	1812.3955	2562.1735
SD	-	-	-	-	-
Min	12.000	34.3450	96.7450	1812.3955	2562.1735
Median	12.000	34.3450	96.7450	1812.3955	2562.1735
Max	12.000	34.3450	96.7450	1812.3955	2562.1735
CV%	-	-	-	-	-
Geometric Mean	12.000	34.3450	96.7450	1812.3955	2562.1735

One patient was administered with Paliperidone ER 12 mg; Peak Trough Ratio for Paliperidone ER 12mg was 2.8

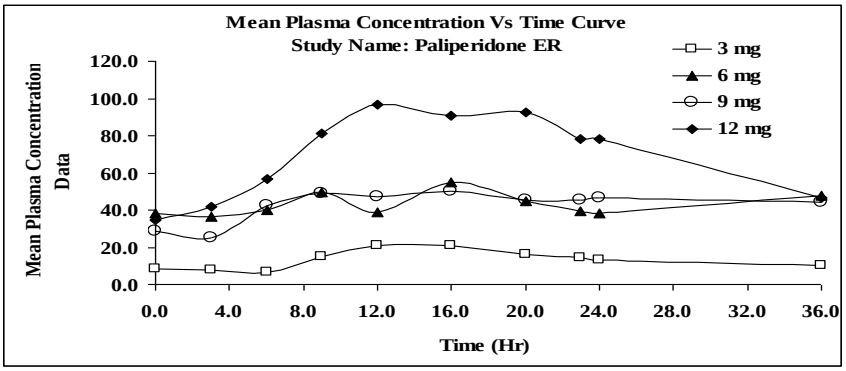

FIGURE 1: MEAN PLASMA CONCENTRATION GRAPHS

Mean (SD) plasma paliperidone ER concentration- time profiles from 0.0 to 36.00 hours following single oral administration of 3 to 12 mg paliperidone

Safety Profile: All 15 patients enrolled in trial, successfully completed the study. The dose of orally administered Paliperidone ER from 3 to 12 mg was safe and well tolerated. Out of total 15 patients enrolled in the current PK study, four patients experienced adverse events during the Phase-III clinical trial. Total 12 AEs were reported amongst these four patients. All the reported AEs were mild to moderate in intensity and were not serious as per investigator judgment. As described in table 5, the AEs were classified as per SAFTEE (A Structured Instrument for Collecting Adverse Events Adapted for Clinical Studies) for relationship to treatment drug. Almost 50% of AEs were classified as 'almost certain' and rest other were either classified as 'possible' or 'probable' related to the treatment drug. None of the patients were withdrawn from the study due to safety reason and all the reported AEs were resolved after appropriate follow ups by investigators.

TABLE 5: ADVERSE EVENTS

Dose	C_{max} (ng/mL)	AUC_TAU (hr*ng/mL)	ADVERSE EVENTS	DURATION	SEVERITY	SERIOUSNESS	RELATION TO STUDY DRUG
6 mg	73.508	1553.718	Increased sleep	7 days	Mild	Not Serious	Almost certain
			Increased appetite	7 days	Mild	Not Serious	Almost certain
			weight gain	20 days	Mild	Not Serious	Probable
9 mg	37.192	678.165	EPS	7 days	Mild	Not Serious	Probable
			Increased appetite	30 days	Mild	Not Serious	Possible
			Increased salivation	15 days	Mild	Not Serious	Almost certain
			slowness	15 days	Mild	Not Serious	Probable
			EPS	2 days	Mild	Not Serious	Probable
6 mg	46.493	694.403	Slowness	14 days	Moderate	Not Serious	Almost certain
			Leg pain	14 days	Moderate	Not Serious	Almost certain
			Drug induced parkinsonism	9 days	Moderate	Not Serious	Almost certain
3 mg	18.625	249.923	Diarrhea	14 days	Mild	Not Serious	Possible

Furthermore, all the reported AEs are expected or suspected as per available literature of innovator drug. The pharmacokinetic parameters of paliperidone ER 3mg to 12mg manufactured by TPL, India as described in table 1 to 4 are comparatively high as compared to the international branded product. Available data of adverse events AND reported events during the clinical trial revealed that paliperidone ER tablets (3 mg, 6 mg, 9 mg) manufactured by Torrent Pharmaceuticals Ltd shows comparable safety profile with international branded product in spite of higher systemic bioavailability.

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