

PHARMACOKINETIC EVALUATION OF RISPERIDONE IN HEALTHY BLACK VOLUNTEERS IN, ZARIA, NIGERIA

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Background: The pharmacokinetic evaluation of risperidone is important due to its importance in the management of crippling and debilitating mental illnesses in all ages and races, its long dosage regimen, coupled with reports of inter-individual variations in its pharmacokinetic parameters.

Objective: The aim of this study is to determine the pharmacokinetic profile of risperidone in healthy black volunteers.

Methods: Eighteen (18) healthy male volunteers were recruited for the pharmacokinetic study. Each subject received a single dose of risperidone (2 mg) tablet and blood samples were collected at specified intervals (0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 12 and 24 hours) and the pharmacokinetic parameters for each volunteer was generated using the Kinetica 5.0 software by feeding in the extrapolated plasma concentrations.

Results: The mean \pm SEM pharmacokinetic parameters observed after oral administration of risperidone (2 mg) to the 18 healthy human volunteers were; C_{max} (ng/ml) = 20.80 ± 1.55 , t_{max} (h) = 1.67 ± 0.11 , k_a (h⁻¹) = 1.92 ± 0.15 , $t_{1/2a}$ (h) = 0.40 ± 0.03 , k_e (h⁻¹) = 0.61 ± 0.12 , $t_{1/2e}$ (h) = 1.99 ± 0.32 , AUC_{0-t} (ng.h/ml) = 60.06 ± 0.76 , $AUC_{0-\infty}$ (ng.h/ml) = 71.86 ± 9.52 , V_d (L) = 75.83 ± 8.43 and Cl (L/h) = 41.57 ± 6.56 .

Conclusion: Large inter-individual differences were observed in some pharmacokinetic parameters especially in the elimination phase and this can be attributed to differences in hepatic metabolism and protein binding among the participants.

Keywords: Risperidone, pharmacokinetics, inter-individual variations, metabolism, black volunteers.

Introduction

Risperidone, a new generation atypical antipsychotic, is the first of its kind introduced into the pharmaceutical market in its generic form. It alleviates both positive and negative symptoms of schizophrenia and causes fewer side effects. Its affordability, efficacy and safety has made it a drug of choice in the management of schizophrenia and the acute manic phase of bipolar disorder.[1,2]

The absolute oral bioavailability of risperidone is 70% and it has a volume of distribution of 1 – 2 L/kg. The non-competitive protein binding of risperidone is 90% and it is extensively metabolized in the liver. It is rapidly distributed in the brain tissues.[3] The half-life of risperidone is 3 hours in extensive metabolizers, and 20 hours in poor metabolizers. It is excreted approximately 70% in urine and 14% in faeces.[4]

Risperidone is primarily metabolized by cytochrome P450 (CYP) 2D6 into the active metabolite 9-hydroxyrisperidone via 9-hydroxylation. It also undergoes CYP 3A4- mediated first-pass metabolism in the small intestine.[5]

Genetic variations in cytochrome P450 enzymes, which are the predominant enzyme system involved in human drug metabolism results in changes in the pharmacokinetics of drugs. The P450 enzymes have the ability to exhibit substantial inter-individual variation in basal expression and/or activity, leading to differences in the rates of drug elimination and subsequently response. This inter-individual variation can result from a myriad of factors, including genetic variation in the promoter or coding regions, variation in transcriptional regulators, alterations in

microRNA that affect P450 expression, and ontogenic changes due to exposure to xenobiotics during the developmental and early postnatal periods.[6] Several single and multiple dose pharmacokinetic studies have been carried out on risperidone in healthy volunteers and patients with diverse mental illnesses and attitude disorders. A pharmacokinetic study after oral administration of 4 mg risperidone in healthy human volunteers carried out in Romania reported mean peak plasma concentration of 27 ng/ml. This study also reported peak plasma concentration of as low as 10 ng/ml in one subject presenting typical risperidone adverse event, thereby inferring a very rapid CYP2D6 conversion of risperidone to its metabolite.[7]

A study of serum concentration of risperidone in children and adolescents (mean age: 13 ± 3.1 years) carried out in Brazil reported as regards CYP2D6 genetic status of 67 patients, that 64.2 % were extensive metabolizers and 35.8 % were poor metabolizers and that the mean serum concentration of risperidone was 6.5 ± 4.9 ng/ml.[8]

A systematic review of therapeutic drug levels of second generation antipsychotics in youth revealed highly variable results in studies of aripiprazole, olanzapine, and risperidone, thus indicating that more research is needed on plasma levels with these drugs.[9]

Several studies [10-12] have compared variations in pharmacokinetic parameters of drugs ranging from common over-the-counter analgesics to cardiovascular drugs in whites and blacks

The aim of this study was to evaluate the pharmacokinetics of risperidone in healthy black volunteers, which has not been reported in literature.

Materials and Methods

Methods

HPLC (Agilent, Germany), Centrifuge (Mettler Gallenkamp, England), Analytical balance (Mettler Gallenkamp, England), Risperidone reference standard (Sigma Aldrich, Germany), Clozapine reference standard (Sigma Aldrich, Germany), Risperidone tablets; Risperdal® (Jassen-Cilag, Germany), Methanol (HPLC grade; Merck, Germany), Acetonitrile (HPLC grade; Merck, Germany), EDTA collection tubes.

Study design

An open-labelled, single-dose, randomized, fasting, study design was conducted in 18 healthy Black male volunteers.

Study setting

The research study was carried out at the research laboratory of the Department of Pharmaceutical and Medicinal Chemistry, Ahmadu Bello University, Zaria, Nigeria.

Study Participants

A total of 18 healthy male volunteers (age between 18 and 40 years; body mass index (BMI) in the range of 18 – 25 kg/m³) were recruited by adopting the following exclusion criteria: allergic reactions to risperidone or other ingredients in the formulation, subjects having history of diseases that could affect bioavailability of risperidone (such as, gastrointestinal, liver, renal diseases), history of regular alcohol consumption, smoking (more than 10 cigarettes per day) or having participated in other clinical experiments within 1 month prior to our study. All volunteers were examined physically and their vital signs, medical and drug histories were documented.

Data Collection

Drug administration and sample collection

Each subject was administered with a single dose risperidone 2 mg tablet with 240 ml of water after an overnight fast. They maintained an upright seating position for at least 30 min. Blood sample (6 ml) was collected via venipuncture at the forearms before dosing and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 12 and 24 hours after the drug administration and transferred into EDTA coated plastic tubes. Risperidone can be detected in plasma from 0.25- 0.5 hrs after dosing, necessitating the first blood sample collection after dosing to be at 0.25 hrs. The sample collection is carried out over 24 hrs, because 24 hrs after a single dose of risperidone 2 mg, risperidone becomes undetectable in plasma. At 2 hours post-dosing, a 500 ml of glucose drink (Lucozade® drink) was given to each subject and a meal of rice and beef was provided at 4 hours after the drug administration.

Preparation and analysis of plasma samples

The blood samples were centrifuged at 4500 rpm for 10 minutes and the plasma which separated out on the upper layer was collected and stored in plain collection tubes in the refrigerator at - 20° C. Subsequently, 1 ml of the pre-prepared thawed plasma was extracted with 5ml of acetonitrile, the mixture was centrifuged at 4000 rpm for 5 minutes and the supernatant was injected into the HPLC machine for analysis to produce a chromatogram under

the following chromatographic conditions (ChemisilODS C18, 35 °C (column); methanol: acetonitrile, 60:40 (mobile phase); 10 µl (injection volume); 1.0 ml/min (flow rate); 280 nm (detection wavelength).

Pharmacokinetic analysis

The peak height ratios obtained from the chromatogram were used to extrapolate plasma concentrations at specified times (0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 12 and 24 hours). The pharmacokinetic parameters for each volunteer was generated using the Kinetica 5.0 software by feeding in the extrapolated plasma concentrations.

Ethical approval

Ethical approval for the research was obtained from the Ahmadu Bello University Committee on Use of Human Subjects for Research (ABUCUHSR/2016/003). All volunteers completed and signed the informed and voluntary consent form of the ABU Research Ethics Committee (ABUCRHS).

Results

The 18 participants were all black males with a mean age of 23.5 ± 1.4 years. The average Body Mass Index (BMI) was 21.31 ± 0.42 kg/m³. The blood pressure and body temperature of the participants were monitored during the study and were found to be within accepted ranges.

The mean \pm SEM pharmacokinetic parameters observed after oral administration of risperidone (2 mg) to the 18 healthy human volunteers were; C_{max} (ng/ml) = 20.80 ± 1.55 , t_{max} (h) = 1.67 ± 0.11 , k_a (h⁻¹) = 1.92 ± 0.15 , $t_{1/2a}$ (h) = 0.40 ± 0.03 , k_e (h⁻¹) = 0.61 ± 0.12 , $t_{1/2e}$ (h) = 1.99 ± 0.32 , AUC_{0-t} (ng.h/ml) = 60.06 ± 0.76 , $AUC_{0-\infty}$ (ng.h/ml) = 71.86 ± 9.52 , V_d (L) = 75.83 ± 8.43 and Cl (L/h) = 41.57 ± 6.56 .

Table 1: Pharmacokinetic parameters of risperidone (2 mg) in healthy black volunteers (n= 18)

Volunteer (Code No)	Age (years)	C_{max} (ng/ml)	t_{max} (h)	k_a (h ⁻¹)	$t_{1/2a}$ (h)	k_e (h ⁻¹)	$t_{1/2e}$ (h)	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	V_d (L)	Cl (L/h)
1	25	24.46	2.00	1.56	0.45	0.17	4.15	101.97	139.07	84.60	14.38
2	24	12.42	2.00	1.32	0.53	0.78	0.88	22.09	25.50	113.96	88.89
3	21	19.64	1.50	2.05	0.34	0.37	1.89	65.17	70.04	77.18	28.56
4	23	23.99	1.00	2.71	0.26	1.83	0.38	22.45	24.81	44.05	80.61
5	23	20.29	2.00	1.54	0.45	1.24	0.56	30.36	31.94	50.50	62.62
6	25	15.94	2.00	1.52	0.46	0.30	2.34	62.26	74.85	89.07	26.72
7	24	18.94	1.00	3.08	0.23	0.17	4.13	47.96	61.73	190.58	32.40
8	23	11.28	2.00	1.25	0.55	0.94	0.74	23.52	25.63	82.98	78.03

9	21	21.20	1.50	2.03	0.34	0.36	1.94	96.88	108.96	51.37	18.36
10	25	19.70	1.00	3.15	0.22	1.57	0.44	19.05	22.35	56.84	89.48
11	23	15.91	1.00	2.03	0.34	0.56	1.23	35.93	42.46	83.87	47.10
12	25	14.48	2.00	1.45	0.48	0.21	3.31	72.64	98.36	97.09	20.34
13	25	34.22	2.00	1.54	0.45	0.35	2.00	99.11	110.26	51.83	18.14
14	24	19.37	1.00	3.09	0.22	1.03	0.67	30.06	30.94	62.76	64.64
15	23	20.94	2.00	1.43	0.48	0.30	2.34	65.51	77.50	86.02	25.81
16	21	19.02	2.00	1.37	0.51	0.32	2.19	85.45	98.99	63.95	20.21
17	25	36.51	2.00	1.66	0.42	0.35	1.97	118.47	130.23	36.57	15.36
18	23	26.04	2.00	1.74	0.40	0.15	4.70	82.20	119.81	41.73	16.69
MEAN	23.5	20.80	1.67	1.92	0.40	0.61	1.99	60.06	71.86	75.83	41.57
SD	1.4	6.59	0.45	0.65	0.11	0.51	1.35	32.35	40.40	35.77	27.82
SEM	0.3	1.55	0.11	0.15	0.03	0.12	0.32	0.76	9.52	8.43	6.56
%CV	6.1	31.68	27.22	33.80	27.36	83.38	67.55	53.86	56.22	47.17	66.91
MINIMUM	21	11.28	1.00	1.25	0.22	0.15	0.38	19.05	22.35	36.57	14.38
MAXIMUM	25	36.51	2.00	3.15	0.55	1.83	4.70	118.47	139.07	190.58	89.48
MIN-MAX	4	25.23	1.00	1.90	0.33	1.68	4.32	99.42	116.72	154.01	75.10

Key: *c_{max}* – Peak plasma concentration; *t_{max}* – Time to attain peak plasma concentration; *k_a*- Absorption constant; *t_{1/2a}*- Absorption half-life; *k_e* – Elimination constant; *t_{1/2e}* – Elimination half-life; *AUC*- Area under the curve; *V_d*- Volume of distribution; *Cl*- Clearance, *SD*- Standard deviation; *SEM*- Standard error of mean; *%CV*- Percentage coefficient of variation.

Discussion

The large inter-individual difference which was described in a previous study ^[13] during therapeutic drug monitoring of risperidone was observed in this study, with peak plasma concentrations (*C_{max}*) ranging from 11.28 to 36.52 ng/ml and total area under the curve (*AUC_{0-∞}*) ranging from 22.35 to 139.07 ng.h/ml. Variations in age has been identified as the major source of inter-individual variability ^[13], however this does not appear to be the case in this study, because a narrow age range of volunteers was employed (21- 25 years). Studies on inter-individual differences in metabolism have recognized that both intrinsic (genetics, age, sex, and disease states) and extrinsic (diet, chemical exposures from the environment, and sunlight) sources/factors. ^[14] Therefore, genetic variation of cytochrome P450 enzymes in the volunteers and extrinsic sources may be responsible for the large inter-individual differences observed in this study.

Extensive literature review did not produce any pharmacokinetic study of risperidone in black healthy human volunteers in order to carry out comparisons. However, a couple of studies have been carried out on the pharmacokinetics of risperidone in Asians and South Americans after administration of a single oral dose of 2 mg risperidone. A pharmacokinetic study of risperidone carried out in Chile reported a mean C_{max} and $AUC_{0-\infty}$ values of 25.32 ng/ml and 88.23 ng.h/ml respectively in Chilean male volunteers^[15], while another study in Thailand⁴ reported a mean C_{max} and $AUC_{0-\infty}$ values of 15.73 ng/ml and 229.73 ng.h/ml respectively in Thai male volunteers. Another pharmacokinetic study in Thai volunteers but with a 4 mg oral dose of risperidone reported mean C_{max} and AUC_{0-48h} values of 31.11 ± 17.24 ng/ml and 160.64 ± 152.89 ng.h/ml.^[16] These reports show large variations in the C_{max} and $AUC_{0-\infty}$ values of risperidone (2 mg) in healthy human volunteers in different races.

It has been reported that pharmacokinetic differences can occur between racial and ethnic groups especially with drugs that undergo gut or hepatic first-pass metabolism, extensive protein binding, hepatic metabolism, renal tubular secretion and have high volume of distribution.^[17] Risperidone undergoes first-pass metabolism, extensive protein binding, hepatic metabolism, and has a high volume of distribution, thus explaining the pharmacokinetic differences that occur between the different racial groups.^[3] This correlates with result in this study because it was observed that variation in pharmacokinetic parameters was higher in the elimination phase compared to the absorption phase. This may be attributed to variations in clearances of risperidone by the CYP2D6 or CYP3A4 pathway, due to differences in genetic composition of the enzymes.^[11] Alterations in the expression and/or activity of these enzymes result in changes in elimination/clearance of risperidone.^[6]

Conclusion

The pharmacokinetic profile of risperidone in healthy black volunteers was determined. Elimination rate constant and clearance showed inter-individual variations.

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