Demonstration of relative bioavailability of newly developed and innovator drug metaxalone 800 mg in healthy subjects under fed condition

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Abstract

The notable unbiased of this research work was to evaluate the well-being and effectiveness of metaxalone by administering the newly developed test and reference drug. A two-period, two-categorization, crossover bioavailability study in fed conditions. Eleven participants were dosed and completed the trial successfully. The drugs were administered by way of a schedule. Samples collected in both periods for pharmacokinetic evaluation. Plasma samples analyzed using a validated method. Pharmacokinetic parameters for investigational and reference products were calculated using the metaxalone drug concentration and safety of the participants monitored by measurement of vital sign. Relative estimation factors calculated for Cmax, Tmax, area under the curve (AUC) t, AUC inf, K el, half-life, and 90% confidence intervals applied for to check for whether reference and test products are equivalent. The experimental part of the study was completed with no major adversarial event. No losses or stern adverse events transpired throughout the course of the experiment. The assessment product is analogous to reference product in relation to degree and extent of absorption. The outcome of this study indicates the newly developed drug is equivalent to the innovator drug and medication was well tolerated by all participants.

Key words: Fed condition, liquid chromatography–mass spectrometry, metaxalone, oral bioavailability, pharmacokinetics

INTRODUCTION

Metaxalone helps to lessen the muscle contractions. Metaxalone is used together with rest and physical remedy to take care of skeletal muscle circumstances such as discomfort or harm.

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The action of drug is unknown and it was due to communal dominant of the nervous system dejection. Metaxalone is not proficient in generating tightening of striated muscle, the motor nerve fiber and a muscle fiber or the axon of a neuron. It is an additional therapy to relaxation, bodily treatment then extra actions to alleviate the uneasiness of critical and painful musculoskeletal complaints.

Uttermost plasma absorptions of metaxalone yield roughly 3 h subsequently a 400 mg oral dose below abstained conditions. Increase of 400 mg dosage to 800 mg leads to surge in drug concentration as specified by highest

drug concentration in plasma (Cmax) and area under the curve (AUC).[1,2] To appraise the food special effects showed in 42 healthy volunteers by administering 400 mg metaxalone tablet in fasting state and subsequently a typical high-fat mealtime. Likened to fasting conditions, the existence of extraordinary fat breakfast augment the Cmax by 177.5% and greater than before AUC that is 123.5% and 115.4%, correspondingly. Time for highest drug attentiveness (Tmax) deferred by 1 h and terminal half-life diminished 6.6 h in served condition equated to abstained.[3,4]

In an additional food influence, the analogous approach, 800 mg metaxalone and 400 mg of two tablets given to the study participants associated to abstained condition, the intake of a meal that is high in fat during the juncture of drug intake amplified Cmax 193.6% and enhanced AUC 146.4% and 142.2%, one-to-one time for highest drug attentiveness (Tmax) behind by 4.9 h from 3.0 h and the terminal half-life was reduced by 4.2 h from 8.0 h in nourished condition matched to fasting state. The half-life of metaxalone in nursed condition might be extra indicative of the disposition half-life, as advanced plasma concentrations attained. Similar food effect study results revealed when metaxalone 800 mg tablet was given to individual instead of metaxalone 400 mg double dose. Upsurge in metaxalone familiarity may be consistent to reduction in half-life probably indicate additional act of drug absorption indicates intake of a meal that is high in fat.

The degree of proteins within the blood binding and total bioavailability of metaxalone is unknown. Drug is processed by the liver and expelled in the urine as unidentified small molecules.[5,6]

Frequent adversarial reactions to metaxalone comprise lethargy, faintness, nuisance, anxiety, nausea, and intestinal upset. Additional adverse reactions significantly reduced renal or hepatic function.[6-10]

In the present study, newly developed formulation compared with marketed dug by evaluating the safety and efficacy parameters based on the pharmacokinetic parameter, vital signs, hematology, and chemical laboratory examination.

MATERIALS AND METHODS

Chemicals and reagents
Acetonitrile, ammonium formate, water, methanol used of high-performance liquid chromatography quality and ethyl acetate, and formic acid used of analytical reagent grade. Fresh frozen human plasma (K3-EDTA as anticoagulant) used during validation was supplied by Bangalore Blood Bank.

Overall study design and plan
A two-period, two-categorization, crossover study under fed conditions. The study has been accepted by the autonomous ethics agency (Approval No: 257/09) and took consent prior involved in exploration work. A whole of 11 study contributors accomplished the assessments.

There was a 28-day selection phase earlier to the medicating day. Participants were administered the drug in each period. The drugs were administered as per the randomization schedule. Eleven participants were dosed and completed the trial successfully. Blood samples were collected throughout the treatment periods for pharmacokinetic evaluation. Safety of the participants was monitored by the measurement of vital signs.

The plasma samples taken from the 11 participants who finished the study were considered for measurements. Relative factors for the investigational and innovator product planned from the concentration of analyzed drug concentration from participant plasma samples. Ninety percent of confidence interval (CI) for the ratio of geometric least squares mean (LSM) of the estimated pharmacokinetic parameters, Cmax, AUC t, and AUC inf of investigational and reference product computed for metaxalone.

Discussion on choice of the control groups
Bioequivalence study, a crossover design premeditated in accordance with the CPMP guideline. Based on the pharmacokinetics of the drug, bioequivalence study was planned on 11 participants under fed conditions. Peak plasma level of the metaxalone occurs roughly 3 h after dosing. Based on that, a washout period of 7 days was considered to be adequate. The pharmacokinetic profile of the newly developed formulation was considered comparative to that of the reference formulation and the bioequivalence was evaluated for metaxalone. With a crossover fashion, each participant represented as own control. Hence, no control group was required for the study.

Selection of the study population
Participants ready to partake in the experimental were examined proceeding to their admission, in directive to evaluate the aptness by fulfilling complete inclusion and none of the rejection criteria. Screening, the participants were questioned for acceptable medical history in addition to clinical examination, sitting blood pressure, heart rate, 12-lead electrocardiogram, medical lab test evaluation, chest X-ray (posteroanterior view), nonreactive HIV antibody screen and negative screen for hepatitis B surface antigens, and HCV antibodies and syphilis. This process was accompanied within 28 days past to the dose administration in period-I.

Treatments administered
An overnight fast of minimum 10 h proceeding to serving uniform high fat breakfast, one tablet was orally

given with 240 ml of water in sitting position, followed by the investigation of hand and mouth. Participants were not allowed to lie down for 3 h after the drug administration. Subsequently, the participants merely permitted engaging in usual activities while evading severe physical action.

Collection of blood samples for pharmacokinetic measurements

Based on the protocol, overall 22 blood samples (4 mL each) were collected from the study participants. The blood samples were collected before administration of standardized high-fat breakfast while the other samples collected at 1.00, 2.00, 2.50, 3.00, 3.50, 4.00, 4.33, 4.67, 5.00, 5.33, 5.67, 6.00, 6.50, 7.00, 8.00, 10.00, 12.00, 16.00, 20.00, 24.00, and 36.00 h following drug intake during both periods. The blood samples collection was done using an adaptor/syringe by a permanently extant cannula in the upper limb between the elbow and the wrist vein of the participants. The samples before dosing taken within 1 h preceding to dosing and the after dosing obtained within the planned time. The obtained samples from the participants moved to prelabeled and precooled vacutainers containing (K_3EDTA) as the anticoagulant.

Summary of analytical method

The plasma samples were scrutinized using a corroborated LC-MS/MS method.[11-14] The analysis performed and concentrations are used for efficacy analysis. Calibration curves of metaxalone concentrations extending from 50.03 ng/mL to 6003.18 ng/mL, respectively, were used for concluding the metaxalone drug concentrations in the samples.[15-18]

RESULTS

Efficacy evaluation
Data sets analyzed
The study was planned to obtain data from 11 evaluable participants and all participants completed the trial successfully and plasma samples were analyzed.

Demographic and other baseline characteristics

A sufficient number of participants, who were most likely to meet the requirements for this study and were willing to participate in the study after obtaining the consent, were checked-in for the trial. Eleven participants were dosed who fulfilled the complete inclusion and none of the rejection criteria and mean ± standard deviation of age, weight, and height and Body mass index were 22 ± 3, 55.6 ± 7, 163 ± 5.6, and 20.7 ± 2.1, respectively.

Measurements of treatment compliance

All the participants took the drug in the study. Dosing verification was done by trained study personnel, by the scrutiny of the participants' mouth (using a torch and spatula),

immediately after the drug administration in each period. All the participants complied with the treatment based on this evaluation. Individual dispensed container for each participant labeled with two identical labels, one of which was stuck on the dosing sheet of the respective CRF (Case Record Form), which further confirmed compliance to correct treatment allocated. The estimation of the drug in the experimental samples of the participants, whose plasma samples were evaluated.

Analysis of efficacy
Clinical pharmacokinetics analysis
The drug absorption, distribution, metabolism, and excretion were measured using WinoNonlin Software for individual participants from the drug concentration versus the time of metaxalone. The mean metaxalone relative estimation factors for reference drug-A and test drug-B are briefed in Tables 1 and 2, and the mean concentration-time profile for reference product-A and test product-B are presented in Figures 1 and 2.

Interpretation of data

Arithmetical examination done by SAS release 9.1. The analysis of variance, using general linear model procedure, made on the log-transformed relative estimation factors AUC t, AUC inf, and Cmax on alpha level of 0.05. The Fisher analysis of variance model encompassed sequence, treatment, and period as fixed effects, and participant nested within sequence as a random effect. Consistent with the two one-sided tests for bioequivalence, 90% CI ratios of (Test/Reference) resulted by the involution of the CI established for the LSM differences among formulations found. All the pharmacokinetic parameters established are not noteworthy.

The descriptive of statistical exploration is given in Table 3. The mean Cmax of test and reference drug is 1811.60 and 3137.32 ng/mL, reported Tmax of test and reference drug is 9.61 and 7.52 h, and AUC t and AUC inf of test and reference drug is 15732.91, 22265.87 and 15279.42, 27098.12, respectively. Reported Tmax, Thalf, and Kel of test and reference drug is 9.61, 5.49, and 0.14513 and 7.52, 3.92, and 0.20822, respectively.
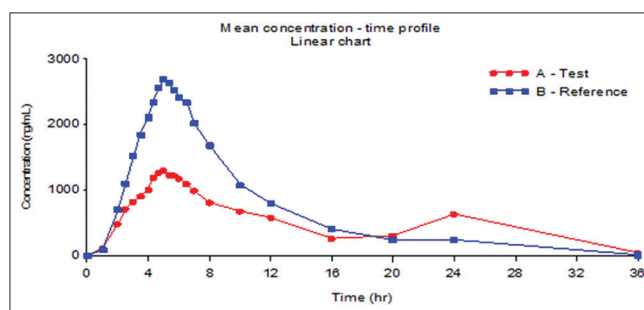

Figure 1: The mean concentration – time profile for reference product-A and test product-B (linear chart)

Table 1: Mean pharmacokinetic parameters of test drug

Parameter	Unit	n	Mean±SD	CV (%)	Minimum	Median	Maximum
AUCt	ng*h/mL	21	15,732.91±9139.20	58.09	5155.69	13,395.62	47,904.81
AUCinf	ng*h/mL	13	15,279.42±6471.27	42.35	6052.17	14,341.51	30,659.98
Cmax	ng/mL	21	1811.60±683.74	37.74	647.55	1826.88	3239.36
Tmax	H	21	9.61±7.19	74.81	2.50	7.00	24.00
Thalf	H	13	5.49±2.34	42.67	3.08	5.07	10.55
Kel	1/h	13	0.14513±0.05123	35.30	0.06569	0.13662	0.22510

SD: Standard deviation, AUC: Area under the curve, Cmax: Maximum plasma concentration, Tmax: Time to maximum plasma concentration, CV: Coefficient of variation

Table 2: Mean pharmacokinetic parameters of reference drug

Parameter	Unit	n	Mean±SD	CV (%)	Minimum	Median	Maximum
AUCt	ng*h/mL	21	22265.87±17835.26	80.10	2572.86	16963.01	73315.21
AUCinf	ng*h/mL	16	27098.12±18383.09	67.84	2799.15	24478.29	74285.11
Cmax	ng/mL	21	3137.32±2773.14	88.39	353.74	2326.06	9144.28
Tmax	h	21	7.52±5.50	73.11	2.50	5.00	24.00
Thalf	h	16	3.92±1.67	42.52	1.70	3.71	8.46
Kel	1/h	16	0.20822±0.09154	43.96	0.08196	0.18704	0.40758

SD: Standard deviation, CV: Coefficient of variation, AUC: Area under the curve, Cmax: Maximum plasma concentration, Tmax: Time to maximum plasma concentration

Table 3: Summary of statistical analysis

Parameter	90% confidence limits (%)		Intra-subject variability (%)
	Lower	Upper	
lnAUCt	88.30	110.01	12.93
lnAUCinf	90.68	109.67	10.69
lnCmax	93.87	110.93	7.01

AUC: Area under the curve, Cmax: Maximum plasma concentration

Safety evaluation

Adverse events

Overall, three adverse events listed throughout the trial refer Table 4; all the adverse events remained trivial in nature and were stable. No diseases or severe adverse events reported throughout the study.

Before the enrollment of the participants, the laboratory parameters were assessed which included tests for complete blood count, biochemistry, urine, immunological tests, and electrolytes.

At screening, the majority of the participants showed values, which were normal. All the out-of-range parameters were reviewed by the clinician and were found to be clinically in acceptable range (nonsignificant) and the participants partaken in the study. All immunology factors were negative for participants who were enrolled in the trial. The assessments encompassed are of full blood profile, hepatic function, and kidney function. The values observed for the laboratory parameters were assessed for individual participants and found satisfactory. Patients treated with skeletal muscle relaxants between-group changes were not statistically meaningfully dissimilar. Outcomes remained comparable irrespective of age, sex, and baseline severity.[19,20]
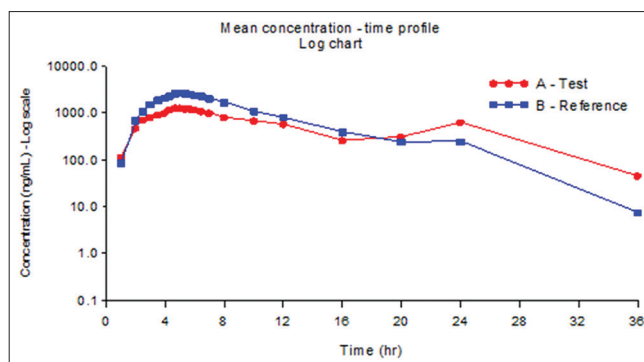

Figure 2: The mean concentration – time profile for reference product-A and test product-B (linear chart)

Clinical interpretations interrelated to safety

The clinical examination was carried out after check-in, prior check-out in both phases and at the study completion and values found to be within acceptable ranges. There were no clinically relevant changes in the vital signs noted during check-in, after dosing, roughly at 4, 8, and 24 h afterward medication and earlier check-out in two phases of the study and at the study finishing point. All participants' vital signs found within the clinically acceptable ranges.

DISCUSSION

Study medication was well-tolerated by all participants. The result of this study indicates that investigational product is analogous to the innovator product. All the adverse events remained trivial in nature and were stable.

Overall, the experimental part of the study concluded with no significant adverse event. The newly developed

Table 4: List of adverse events

Period	Adverse event	Severity
1	Abdominal pain	Mild
2	Head ache	Mild
2	emesis	Mild

drug is very well bearded by all partakers, after intake of metaxalone one dose. The harmful prevalence that occurred throughout the study was mostly mild in nature and was resolved. No bereavements or calumnious occurred all over the course of the experimental portion. The clinical laboratory values were considered to be within clinically acceptable ranges. The outcome of this study indicates the newly developed drug is equivalent to the innovator drug and medication was well-tolerated by all participants.

Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. SKELAXIN (Metaxalone) Prescribing Information. Bristol: King Pharmaceuticals; 2006 August. https://www.accessdata.fda.gov/drugsatfda_docs/label/2006/013217s046lbl.pdf.

2. Shargel L, Wu-Pong S, Yu AB. Applied Biopharmaceutics and Pharmacokinetics. 6th ed. New York, NY, USA: McGraw-Hill; 2012.

3. Abdou HM. Dissolution, Bioavailability and Bioequivalence. Ch. 26. Easton, Pa, USA: Mack Printing Company; 1989.

4. Li Y, Delcher C, Reisfield GM, Wei YJ, Brown JD, Winterstein AG. Utilization patterns of skeletal muscle relaxants among commercially insured adults in the United States from 2006 to 2018. Pain Med 2021;22:2153-61.

5. Moore KA, Levine B, Fowler D. A fatality involving metaxalone. Forensic Sci Int 2005;149:249-51.

6. Bruce RB, Turnbull L, Newman J, Pitts J. Metabolism of metaxalone. J Med Chem 1966;9:286-8.

7. Cashin AG, Folly T, Bagg MK, Wewege MA, Jones MD, Ferraro MC, *et al.* Efficacy, acceptability, and safety of muscle relaxants for adults with non-specific low back pain: Systematic review and meta-analysis. BMJ 2021;374:n1446.

8. Poklis JL, Ropero-Miller JD, Garside D, Winecker RE. Metaxalone (skelaxin)-related death. J Anal Toxicol 2004;28:537-41.

9. Gruszecki AC, Kloda S, Simmons GT, Daly TM, Hardy RW, Robinson CA. Polydrug fatality involving metaxalone. J Forensic Sci 2003;48:432-4.

10. Otto M, Cepek L, Ratzka P, Doehlinger S, Boekhoff I, Wiltfang J, *et al.* Efficacy of flupirtine on cognitive function in patients with CJD: A double-blind study. Neurology. 2004; 62(5):714-8.

11. Causon R. Validation of chromatographic methods in biomedical analysis. Viewpoint and discussion. J Chromatogr B Biomed Sci Appl 1997;689:175-80.

12. Braggio S, Barnaby RJ, Grossi P, Cugola M. A strategy for validation of bioanalytical methods. J Pharm Biomed Anal 1996;14:375-88.

13. Nirogi RV, Kandikere VN, Shukla M, Mudigonda K, Shrivastava W, Datla PV. Quantification of metaxalone in human plasma by liquid chromatography coupled to tandem mass spectrometry. J Anal Toxicol 2006;30:245-51.

14. Jemal M. High-throughput quantitative bioanalysis by LC-MS/MS. Biomed Chromatogr 2000;14:422-9.

15. Nowatzke W, Woolf E. Best practices during bioanalytical method validation for the characterization of assay reagents and the evaluation of analyte stability in assay standards, quality controls, and study samples. AAPS J 2007;9:E117-22.

16. Bansal S, DeStefano A. Key elements of bioanalytical method validation for small molecules. AAPS J 2007;9:109-14.

17. Zhao L, Li Q, Shu C, Wang K, Ding L. Quantitative determination of Metaxalone in human plasma by LC-MS and its application in a pharmacokinetic study. Asian J Pharm Sci 2016; 11(5): 668-72.

18. Tiwari A, Bag P, Sarkar M, Chawla V, Chawla PA. Formulation, validation and evaluation studies on metaxalone and diclofenac potassium topical gel. Environ Anal Health Toxicol 2021;36:e2021001-0.

19. Abril L, Zamora C, Cordero M, Williams AR, Friedman BW. The relative efficacy of seven skeletal muscle relaxants. An analysis of data from randomized studies. J Emerg Med 2022;S0736-8.

20. Vuletić L, Khan MZ, Špoljarić D, Radić M, Cetina-Čižmek B, Filipović-Grčić J. Development of a clinically relevant dissolution method for metaxalone immediate release formulations based on an IVIVC model. Pharm Res 2018;35:163.