ANALYSIS OF PULSE RATE VARIABILITY DURING BIOEQUIVALENCE STUDIES IN HEALTHY VOLUNTEERS.

Saeed Ahmed Lakho[*1], Ijaz Ahmed[2], Afaq Ahmed Siddiqui[3], Arslan Ahmer[4], Zaheer Ahmed Mughal[5], Attia Ayoob[6], Madan Lal Maheshwari[7]

ABSTRACT:

OBJECTIVE: The objective of this study was to evaluate the impact of bioequivalence studies on vital organs and their working ability during the procedure. **PLACE AND DURATION:** Pharma Professional Services, Karachi, October 2018 to September 2019. **METHODOLOGY:** A group of 93 volunteers were tested for pulse rate up to 12 hours during BE studies. All the data contained were from 4 BE studies carried out at volunteers of Sindh, Pakistan. As per standard protocols on different times before drug administration and after 1, 2, 4, 8 and 12 hours of drug administered, all this data was collected for pulse rate of volunteers. All these studies were containing same procedures such as 3 hours fasting and then meals as per schedule. This study is always carried out to check the physical status of volunteer's. All the data which were gathered were analyzed using SPSS 22.0 version. The tests which were performed to evaluate this data was analysis of variance (ANOVA). **RESULTS:** The normal ranges of the pulse rate were selected and then it was observed from the results that all of these volunteers remained stable and their pulse rate were in normal range. **CONCLUSION:** From the above results of study it is concluded that healthy volunteers of BE studies during the process of BE studies have normal autonomic condition which in turn gives the normal pulse rate.

KEYWORDS: Pulse rate variability (PRV), bioequivalence (BE) studies, SPSS, ANOVA.

1. Department of Pharmaceutical Chemistry, Faculty of Pharmacy and Pharmaceutical Sciences, University of Karachi, Karachi, Sindh, Pakistan.
2. Department of Pharmaceutical Chemistry, Faculty of Pharmacy and Pharmaceutical Sciences, University of Karachi, Karachi, Sindh, Pakistan
3. Professor, Faculty of Pharmacy and Pharmaceutical Sciences, University of Karachi, Sindh, Pakistan
4. Institute of Pharmaceutical Sciences, Peoples University of Medical and Health Sciences for Women Nawabshah, Sindh, Pakistan.
5. Institute of Pharmaceutical Sciences, Peoples University of Medical and Health Sciences for Women Nawabshah, Sindh, Pakistan.
6. Consultant, Department of cardiology, PMCH Nawabshah.
7. Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Sindh Jamshoro.

CORRESPONDENCE: Saeed Ahmed Lakho, Ph.D student in Department of Pharmaceutical Chemistry, Faculty of Pharmacy and Pharmaceutical Sciences, University of Karachi, Karachi, Sindh, Pakistan.
Email: saeed.lakho@usindh.edu.com 03040298434

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INTRODUCTION

As this study was about pulse rate or heart rate variability (HRV) which is defined as a vital process of beat-to-beat changes which is being produced during heart rate because of the communication of pulse charge created by the directions of autonomic nervous system (ANS) on the sinus node (SN) in the cardiac muscles.[1] If the pulse rate raises, the period of each total cycle of the heart including both the contraction phase and relaxation phase decreases. At a normal pulse rate of 72 beats per minute, the period of contraction is about 0.40 of the entire cycle. [2] Differences in SA node impulse creation are represented by pulse rate variability (PRV) resulting from RR intervals. This rhythmic process, also said as respiratory sinus arrhythmia (RSA), varies with the parts of respiration, cardio-acceleration during inspiration, and cardio-deceleration during expiration. The pulse rate varies in different age groups and among different ethinic groups. Transmission of AV node may give the variability in RR intervals but it does not deteriorate conditions of heart or body. The condition of heart can be assured by monitoring AV transmission capacity also. There are presences of techniques such as spectral analysis which can be utilized to differentiate in between basic cause of HRV, because this rhythmicity of the pulse occurs at same times. Age, area, ethnicity, environment, and sex etc. can have some impact on PRV.[3-5] It is also different during exercise and normal conditions.[6] It has been measured by different instruments.[7] It is also reported to vary in different pathological conditions i.e. apnea condition and also in sleeping time.[8] We have gathered a data of BE studies which were conducted in local population of Sindh, Pakistan. This is first study reported so far in this era. No one earlier has published this kind of study. These data are always gathered during BE studies in each study but never published. Our group aims to show the normal vitals have been shown during these studies especially in this study, PRV has been counted. PRV was examined in this time domain as per recommendations of the North American society

of pacing and electrophysiology (NASPE) and Task Force of the European Society of Cardiology (ESC) [9].

MATERIAL AND METHODS

Instruments: Operon GmbH digital machine was utilized to note down the electrocardiograph (ECG) which has color LCD screen (4.3 inch) having options of manual as well as auto printing. It has tendency of measure ECG of single subject in 10 to 15 seconds. Beurer automatic blood pressure monitor machine was utilized for measurement of pulse rate. It has tendency to measure pulse rate and heartbeat at same time.

Methodology: Data from random selection of Ninety three 93 healthy male volunteers having normal ECG and other pathological reports were included who had participated in 4 different BE studies. Ages of these volunteers were between 18 and 50 years having mean age of 29±13 years. From heart disease point of view we gathered history of diseases and no one had any previous disorder or disease of heart. All the volunteers who were already selected for these studies were good in health, having no criminal record, and non smokers. All the requirements were met when these studies were being conducted and all the volunteers whose data were taken have been given codes during these studies. Before start of each study the written consents were taken from these volunteers. This is the non-interventional study which is descriptive. The sampling of the individuals by non-probability convenience was randomly selected. All erroneous obscurity were editable and on any problem were rectified in the present data. During sinus rhythm, temporal variation during beat to beat rhythm was expressed as PRV. The variation in pulse rate reflects variations in sympatho-vagal activity of ANS.

RESULTS

All the values for pulse rate were said to be in normal ranges. The average values of pulse rate at different time domains were found to be close with each other and with standard deviation from the sampled population of all volunteers. It was observed from the results that average value at 4th hour time interval of pulse rate is matching with mean value of 12th hour except confidence interval (CI) values which differ from each other. In each CI the true significance of pulse rate is positioned at 95% confidence level.

The collected data has been evaluated by using SPSS-22. The variables such as mean, standard deviation; ANOVA were expressed and utilized for comparison each other and with standard or normal values. The p value <0.05 was believed significant during data analysis. It can be concluded from the results which were found after One-way ANOVA, that the pulse rate did not exceeds or lowers down then normal range within the volunteers during stay in BE studies. Another homogeneity test carried out using same software. It was observed from the test that among the sample, variances are not equivalent and the result was said to be statistically significant. The results of this test can be seen in table 2. The mean values which were calculated at different time intervals were compared by using ANOVA F-Test. The present data when statistically analyzed gave the equation:

F = 11.216 (p = 2.55E-10) This equation <5% significance level of α) significant results with test of homogeneity of variance ep = 2.66E-10. Statistically speaking, all the average values of PRV at different time domains were observed to be different with each other. From all these results it is supposed that equal variance is also found to be significant.

	Mean	Std. Dev.	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
				Lower Bound	Upper Bound		
0 Hour	72.44	4.36151	.44986	71.5428	73.3295	60.00	82.00
1 Hour	74.48	4.62515	.47705	73.5314	75.4260	64.00	86.00
2 Hour	73.20	5.00662	.51639	72.1767	74.2276	64.00	88.00
4 Hour	75.87	4.98219	.51387	74.8519	76.8928	64.00	88.00
8 Hour	76.52	5.17797	.53407	75.4607	77.5818	65.00	90.00
12 Hour	75.70	3.84325	.39640	74.9150	76.4893	69.00	89.00
Total	74.70	4.89643	.20618	74.2972	75.1071	60.00	90.00

Table Number 1: The descriptive statistics shows at different time interval like mean, standard deviation and confidence interval at 95% confidence level with minimum and maximum values.

ANOVA Pulse_Rate

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	1232.638	5	246.528	11.216	.000
Within Groups	12265.319	558	21.981		
Total	13497.957	563			

Robust Tests of Equality of Means Pulse_Rate

	Statistic[a]	df1	df2	Sig.
Brown-Forsythe	11.216	5	539.032	.000

a. Asymptotically F distributed.

DISCUSSION

The physiological range of pulse rate which is considered to be normal is between 70 and 80

beats per minute in healthy human beings. The pulse rate is a illustration of incorporated response of the cardiovascular system in different conditions. The aim of this study was to document the reference values for pulse rate in bioequivalence studies. This is first time that such kinds of studies have been carried out in Pakistan. Sztajzel has termed the pulse rate measurement as the simple way for checking autonomic nervous system. He has checked pulse rate of healthy volunteers of Swiss origin. [10] The Quintana et al., have mentioned pulserate value in healthy volunteers but they have taken a small group of population i.e.n=24. [11] In same manner, Ramaekers et al., have studied pulse rate variability of healthy volunteers on day time and night time. [12] Previously, Alamgir Khan et al., have studied about heart rate variability studies in healthy volunteers of Pakistan. They have conducted study on 37 volunteers. In this study they have carried out a 24 hour time study.[13] In this study we have conducted a data on measurement of pulse rate variability in healthy volunteers in different periods during bioequivalence studies. In first, pulse rate have been measured in 3 hours fasting. 3 hours after taking drugs, the volunteers were given breakfast and then one hour after this again pulse rate was measured. In all these time intervals we have checked and compared the values by different tests. This kind of studies can be done for more time intervals. And also the effect of other parameters can be seen also. This test does not show full autonomic nervous system analysis but only make an effort for further studies in future.

CONCLUSION

From the above results of study it is concluded that healthy volunteers of BE studies during the process of BE studies have normal autonomic condition which in turn gives the normal pulse rate.

ETHICS APPROVAL: The ERC gave ethical review approval

CONSENT TO PARTICIPATE: written and verbal consent was taken from subjects and next of kin

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CONFLICT OF INTEREST: No competing interest declared.

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