Bioequivalence Study of Two Commercial Products of 3mg Dinoprostone Vaginal Tablets

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Abstract: A randomized, parallel, active control, *in vivo* bioequivalence study (with clinical endpoint) determining the bioequivalence of two brands of dinoprostone 3 mg vaginal tablets was conducted in pregnant women at Jinnah Postgraduate Medical Center, Karachi. 3mg Dinoprostone vaginal tablet was administered with a second dose repeated after six hours if clinically prescribed. The bioequivalence was assessed by clinical endpoints and a safety analysis was also conducted for all dosed subjects. Maternal bishop score, CTG and neonatal APGAR score were noted. 90% Confidence Intervals for per protocol population was found well within the ±0.20 range. Test product (Glandin E2) and reference product (prostin E2) were found to be bioequivalent.

Keywords: APGAR score, Bioequivalence, Bishop score, CTG, Dinoprostone, prostaglandin, PGE2.

INTRODUCTION

Pharmacological and mechanical methods are currently used in clinical practice to modify the cervical status or for induction of labour at term pregnancy. Commonly used pharmacological agents for induction of labour are intravenous oxytocins and intracervical or intravaginal prostaglandin E2, administered separately or in combination while Dinoprostone (prostaglandin E2) is the preferred agent for cervical ripening and induction of labour at term [1] giving an overall success rate of induction as high as 44% [2].

Prostaglandins are unsaturated fatty acid derivatives produced endogenously that act locally on tissues at the site of their synthesis and are rapidly metabolized to inactive products [3]. After oral administration pharmacological preparations of prostaglandin E2 show a shorter half life and higher rate of maternal side effects as compared to vaginal applications [4]. Various pharmacological preparations of Dinoprostone are available in market manufactured by different pharmaceutical companies but therapeutic concentrations of active pharmacological agent are required at the site of action, a failure of which may results in induction failure.

This study is aimed to compare the bioequivalence of two commercial products of Dinoprostone 3mg vaginal tablets by using the Bishop's pelvic scoring system and mode of delivery to establish the test product as a generic replacement for the reference product; provided test product is found to be bioequivalent to reference product.

PATIENTS AND METHOD

The study was conducted on ninety (90) pregnant female subjects at the department of obstetrics and gynecology, Jinnah Postgraduate Medical Center, after being approved by the Institutional review board of Jinnah Postgraduate Medical Center, Rafiquee Shaheed road, Karachi 75510, Pakistan in compliance to ICH-GCP guidelines [5]. The study was single blinded and patients were unaware of the brand of Dinoprostone administered to them. This is a randomized, parallel designed study, employing two drug products (T=Test, R=Reference) given to two groups of equal size, consisting of pregnant women that were stratified as nulliparous and multiparous groups. Test product (T) was Dinoprostone (GLANDIN-E2) 3 mg Vaginal tablet; manufactured by Nabiqasim Industries (Pvt.) Ltd, Karachi, Pakistan, while reference formulation (R) was Dinoprostone (PROSTIN-E2) 3mg Vaginal tablet manufactured by SANICO NV, Veedijk,

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59 B-2300, Tumhout, Belgium and packed by Pfizer Laboratories Ltd. Pakistan.

The Study was comprised of 12 hours post dose observational period for the evaluation of primary end point; which was extended if fetal delivery was delayed till the time of delivery and restricted to patient admission in hospital for follow-up. After examination of the patients by Principal Investigator or her associates, those with no other co-morbidity and professionally advised for labor induction by administration of Dinoprostone 3mg vaginal tablet were selected for study. After seeking their written consent and evaluating them according to the inclusion and exclusion criteria, participants were chosen for the study and investigational drug administration was carried out.

The inclusion criteria were healthy females of age 18 to 35 year, gestational age ≥ 37 weeks with a medical or obstetrical indication for the Induction of labour, scheduled for induction of labor, singleton pregnancy, cephalic presentation, Parity ≤ 3, Intact membrane, Fetal reactive non-stress test, Bishop score less than or equal to 4 on admission, participants had no other epidemic/contagious disease, gave written consent for inclusion in the study and bore no contraindication for labour induction by Dinoprostone.

CBC, random blood sugar and CTG were performed before drug administration. CTG was repeated after two hours of first dose and before administration of the next dose. To ensure the well-being of both, mother and fetus, a CTG evaluation 2 - 6 hours after second dose, was also performed, if required. Vital signs of participants (blood pressure, pulse rate and temperature) were monitored during the study. APGAR scores of baby at one and five minutes after birth were determined. Cord blood was collected just after the birth and tested within half an hour. Initial single dose of 3mg vaginal Dinoprostone was inserted high into the posterior vaginal fornix [6]. The same dose was repeated after six hours of first dose if required and CTG found reactive. Patients were monitored for bishop score (after six hours of first and second dose), time & mode of delivery and vaginal irritation. Bishop score comprising of five parameters; dilation, effacement, fetal station, consistency and position [7]. The vaginal irritation were assessed and recorded thrice for each subject except those who delivered before 6 or 12 hours after the first dose, for whom these were lesser in number [7]. The recommended primary endpoint of the study for Dinoprostone was the proportion of subjects in the per protocol (PP) population identified as “treatment success” occurring during the 12-hour observation period after dosing of the assigned product. A “treatment success” was defined as; (i) Attainment of an increase of at least 3 in a Bishop score during the 12-hour observation period. (ii) The attainment of a Bishop score of ≥ 6 during the 12-hour observation period. (iii) Vaginal delivery occurring during the 12-hour observation period. The secondary outcomes included maternal (e.g. hyper-tonicity), foetal (e.g. foetal distress) and treatment related obstetrical adverse events, reported during the study.

The 90% confidence interval (CI) of the difference in the “treatment success rate” between the test product and reference drug product treatment groups at 12 hours after dosing of the assigned product was determined, using Yates’ correction. To establish the equivalence, based on the usual method used for binary outcomes, this 90% CI was decided to be contained within [-0.20, +0.20] for the dichotomous primary endpoint, using the PP study population [7].

RESULTS AND DISCUSSION

The study was conducted from March to June 2014.

The patients included in per protocol population (PP Population) were all Pakistani, had the mean age of 26.7±0.57 years and gestational age of 276 ±1.18 days. All, included multiparous and nulliparous pregnant female patients, were normotensive, at or near term and were professionally advised for the induction of labour (IOL). The subjects’ enrollment and flow is given in Figure **1** while the summary of demographic data of pp population is shown in Table **1** and Figure **2**.

This is the first bioequivalence study conducted to compare a local brand of Dinoprostone vaginal tablet (Glandin E2) with reference product (Prostin E2) to establish its equivalency. Bishop’s pelvic scoring system is most commonly used for cervical assessment prior to induction and cervical ripening with prostaglandin to reduce the incidence of failed induction and cesarean delivery [1]. Therefore, the bioequivalence in this study was determined by evaluating the change in bishop score measured after the Dinoprostone 3mg vaginal tablet insertion or by observing the mode and time of delivery as proposed by various studies and guidelines [7-9].

A “treatment success” was demonstrated by an increase of at least 3 in a Bishop Score or attainment of a bishop score of ≥ 6 or vaginal delivery occurring

Figure 1: Subjects' enrollment & flow chart.

Table 1: Demographic Data and Summaries of Baseline Characteristics of Two Treatment Groups (Test & Reference)

			Age (Years)	Weight (Kg)	Height (cm)	BMI (Kg/m^2)	BP_sys (mmHg)	BP_dias (mmHg)	Pulse (bpm)	RBS (mg/dl)	Gest_Age (days)
Nulliparous	Test	Mean	21	62	164	23	113	74	76	90	275
		s.e	0.97	2.99	1.05	1.07	2.89	1.76	2.68	8.93	3.95
	Ref	Mean	23	60	164	22	113	76	80	84	281
		s.e	1.04	3.52	2.4	0.75	2.86	2.02	1.6	5.37	6.13
Multiparous	Test	Mean	28.6	65.4	164.6	24.3	115.2	74.4	79.9	82.1	277.6
		s.e	0.91	2.38	0.81	0.85	0.98	1.34	1.58	4.42	1.73
	Ref	Mean	27.1	65	164.5	24.3	113.6	74.3	81.7	90	274.6
		s.e	0.74	1.91	0.58	0.72	1.28	1.58	0.86	4.08	1.52
Total	Test	Mean	26.8	64.6	164.5	24	114.7	74.4	79.1	84.2	277.1
		s.e	0.89	1.93	0.66	0.69	1.01	1.09	1.36	3.97	1.61
	Ref	Mean	26.2	64	164.4	23.8	113.4	74.6	81.3	88.9	276
		s.e	0.7	1.69	0.64	0.62	1.16	1.32	0.76	3.48	1.73

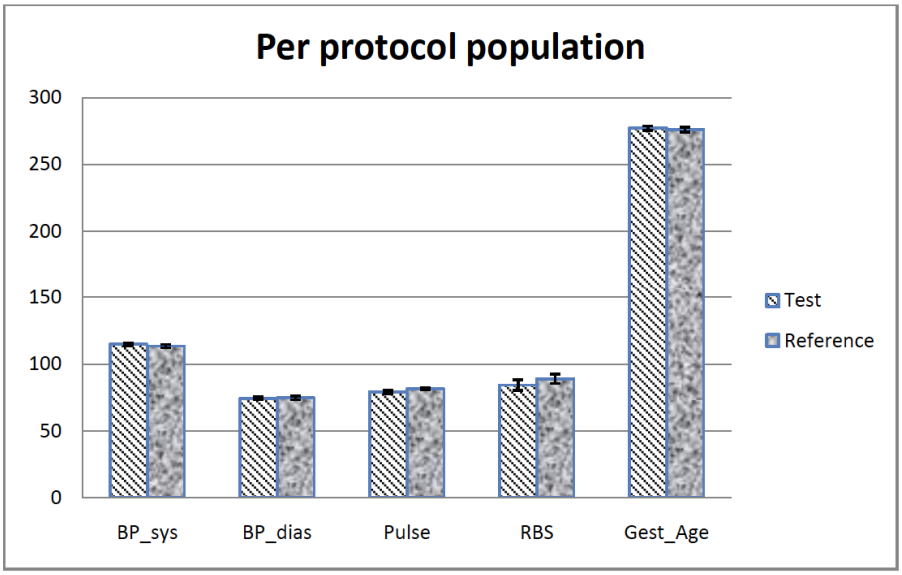

Figure 2: Mean Baseline Characteristics of PP-Population along with Standard Error.

during the 12 hour observation period. The treatment success regarding ratio of test to reference product for per protocol population was found to be 102.9% while for total population it was found to be 97.7%. In both cases the treatment success ratio of test to reference lies within the acceptable range of 80-120% and hence shows that test product is bioequivalent to reference product. The summary of outcomes for PP-population and 90% confidence interval are shown in Tables **2** and **3** respectively. The 90% confidence limits for all success rates are within the recommended criteria of ±0.20 (0.8-1.20) to establish the bioequivalence.

The rate of failed induction of labour leading to caesarean section in two groups of pp-population was insignificant. Total 9 out of 90 subjects underwent to EMLSCS for the delivery. The rate of caesarean section in test and reference treatment group is 8.88% (n=4) and 11.11% (n=5) respectively. While in PP-population the rate of caesarean section is almost similar for test and reference groups i.e 5.55% (n=2/36) and 5.71% (n=2/35) respectively. Earlier, Azra Naseem *et al.* has compared the intracervical foley'scatheter ballon versus prostaglandin E2 3 mg vaginal tablet for induction of labour and found that 8% of PGE2 patients underwent the caesarean which is close to our findings where 8.88% of glandin E2 receiving patients in total population underwent caesarean section [1]. Study by Taher *et al.* compared PGE2 vaginal tablet and gel for the induction of labour at term and found almost 10.84% patients with failed induction in PGE2 3mg vaginal tablet (prostin E2) [10]. Sadia waraich *et al.* in her study in patients with an indication for induction of labour assessed the efficacy and safety of intravaginal misoprostol for the induction of labour at term, in comparison to dinoprostone and found 26% rate of caesarean section in dinoprostone group which is higher than the result of our study where it is only 10% for all included subjects [11]. The Figure **3** shows the rate of caesarean section and mode of delivery in two groups of patients in our study.

The rate of meconium stained liquor for test and reference product is 6.66% (n=3/45) and 8.88% (n=4/45) respectively. A total of 7 (7.77%) subjects had

Table 2: Summary Outcomes of Per Protocol Population

Outcome	Test			Ref			Ratio of Test and Reference
	No. of Success	No. of Faliure	Success Ratio	No. of Success	No. of Faliure	Success Ratio	
Outcome 1	14	0	100%	13	2	87%	115.4%
Outcome 2	14	0	100%	12	3	80%	125.0%
Outcome 3	30	6	83%	33	2	94%	88.4%
Treatment Success	36	0	100%	34	1	97%	102.9%

Outcome 1: Attainment of an increase of at least 3 in a Bishop score during the 12-hour observation period. Outcome 2: The attainment of a Bishop score of ≥ 6 during the 12-hour observation period. Outcome 3: Vaginal delivery occurring during the 12-hour observation period.

Table 3: Classic Confidence Interval for Success Rates along with Standard Error, BE Limits and Bioequivalence Check

	Test			Reference				Confidence Interval		BE Check	
Population	Sample Size	Treatment Success	Success Rate	Sample Size	Treatment Success	Success Rate	Se	Lower Limit (L)	Upper Limit (U)	L ≥ -0.20	U ≤ 0.20
Complete	45	43	**0.96**	45	44	**0.98**	0.0378	-0.107	0.062	√	√
Per Protocol	36	36	**1**	35	34	**0.97**	0.0282	-0.046	0.103	√	√

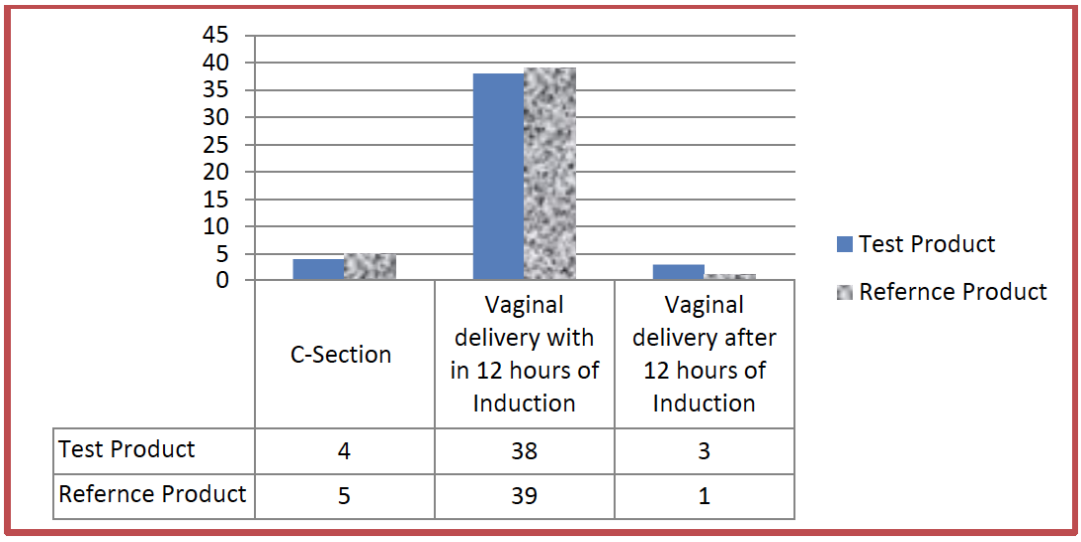

Figure 3: Mode of delivery in two Treatment Groups in all Subjects.

meconium stained amniotic fluid in this study. Out of these seven cases of meconium staining, three were recorded for multipara subjects and four for nullipara subjects.; while Afia Ansar *et al.* in her study had found 14 (34%) subjects out of 41 in Dinoprostone group with meconium staining (2). The fetal heart rate changes were also equal i.e. 2 (4.44%) babies in each group. In another study Evangelos G Papanikolaou *et al.* studied the comparison of misoprostol and Dinoprostone for elective induction of labour in nulliparous women at full term and found 9.6% meconium stained amniotic fluid and 12% altered fetal heart rate in Dinoprostone 3mg treatment group [12]. Hence, the meconium staining and change in fetal heart rate observed in this study corresponds well with the already reported values.

Neonatal outcomes regarding the APGAR score at 1st and 5th minutes and admission to neonatal unit were almost similar. 82 babies had excellent APGAR score at 5th minute. Seven babies were moderately depressed at five minutes' time but later on resumed stability and were discharged in good condition. Two babies found severely depressed (Low APGAR Score) at one and five minutes, required to be shifted to neonatal intensive care unit (NICU).

CONCLUSION

90% Confidence Intervals for per protocol population is found well within the ±0.20 range. Therefore Glandin E2 Vaginal Tablets (Test Product) and Prostin E2 Vaginal Tablets (Reference Product) are proved to be clinically equivalent. The study powers achieved for both full population and per protocol population were greater than 90%.

Difference between the numbers of subjects who experienced adverse events after Dinoprostone exposure in two treatment groups was not significant.. Both treatment groups showed only expected and earlier reported adverse events or serious adverse events.

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