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Research Article

Cost-minimization analysis of various pharmaceutical alternatives of clopidogrel bisulfate

Ahmed Yahya[1], Ata-ul-Razzaq Khan[1], Wahab Usaid Naeem[1], Sajid Bashir[1], Babar Murtaza[1], Aqeel Aslam[1*]

[1]Faculty of Pharmacy, University of Sargodha, Sargodha, 40100 Pakistan.

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ABSTRACT

Cardiovascular disease is the most common cause of death throughout the world. Various therapies are available but the increased cost of treatment is of great concern especially in developing countries. Clopidogrel is used extensively for various cardiac conditions but has a high price. Cost-minimization analysis (CMA) differentiates alternative therapies based on price, given that all of the interventions have exactly the same health effects and must be bioequivalent when it comes to health benefits and adverse effects. Dissolution studies, using four marketed products, were conducted using a six stage, type II dissolution apparatus. Samples were analyzed at 240nm using a UV-VIS spectrophotometer. Concentration values of each sample, taken after 30 minutes were calculated from the calibration curve constructed with Clopidogrel Bisulfate. ANOVA was used to analyze any significant differences between the means of active dissolved. Plavix was found to have the highest percentage release of 97% but Ogrel had the least SEM of 3.9 with a percentage release of 95%. Lowplat and Pidogrel, although showed average percent releases of greater than 85%, their SEM and standard deviations were large showing widespread variations in unit contents. ANOVA gave a p>0.05, indicating a non-statistically significant difference between the means of active dissolved hence proving bioequivalence. CMA (cost minimization analysis) concluded that Ogrel may be used instead of the more expensive Plavix.

Keywords: Clopidogrel bisulfate; Cost minimization analysis; Bioequivalence; Heart disease; Ogrel; Plavix

INTRODUCTION:

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality throughout the world (Smith, 2010, Go *et al*., 2013). On average, every year 610,000 people die of heart disease of which approximately 370,000 are Coronary Heart Disease patients (Alwan, 2011). It was approximated that in the year 2010, a total of $315.4 billion were spent directly and indirectly on CVD and stroke (Go *et al*., 2014). Studies showed that Pakistani population has one of the greatest risks of coronary artery disease throughout the world (Raza *et al*., 2013, Jafar *et al*., 2007). Cardiovascular diseases may be treated with drugs that interfere with the function of platelets. These drugs are of three types, employed acutely, chronically or used as preventive measure. Clopidogrel, a relatively new drug, is utilized for the acute treatment and primary prevention of certain heart diseases, including unstable angina, heart attacks, and coronary angioplasty. Its cardio protective effects stem from its inhibition of one of many platelet aggregation mechanisms (Nurden and Herbert, 2009). Clopidogrel is usually co-administered with aspirin to decrease the risk of vascular events (Wang *et al*., 2013). On regular use in post-myocardial infarction or stroke patients, Clopidogrel has been shown to be effective (Niruntraporn *et al*., 2007).

As health resources are limited, increased attention is being given to the assessment of healthcare measures in terms of money. This is achieved by comparing costs and consequences of

***Corresponding Author :** Aqeel Aslam,*
Address: Faculty of Pharmacy, University of Sargodha, Sargodha, Pakistan
***E-mail:** aqeelaslam01@gmail.com*
***Phone#** +92 334 7556742*

alternative interventions (Drummond, 2005). Cost-minimization analysis (CMA) differentiates alternative therapies based on price, given that all of the interventions have exactly the same health effects and must be bioequivalent when it comes to health benefits and adverse effects (Calvet *et al*., 2012). Bioequivalence refers to comparable bioavailability under similar experimental conditions shown by pharmaceutical equivalent or alternative products (Shargel *et al*., 2007). As Clopidogrel belongs to the BCS (Biopharmaceutics Classification System) class II, bioavailability depends on dissolution, which is the rate-determining step (Chavda *et al*., 2010).

Clopidogrel is highly used and has a high acquisition cost (Niruntraporn *et al*., 2007). Various multisource products are available in the market with varying prices (Table 1). All products are being prescribed extensively by local practitioners; therefore the economic impact on patients as well as the institutions is significant. The aim of the study is to establish bioequivalence between different multisource products of Clopidogrel bisulfate and run a Cost-Minimization Analysis to asses if the local products can be used interchangeably with the international innovator product without compromising health effects.

Table 1: Prices of different brands of Clopidogrel Bisulfate

Brand	Pack Price (Rs.)	Units	Unit Price (Rs.)
Ogrel	280	28	10
Pidogrel	100	10	10
Lowplat	140	10	14
Plavix	700	28	25

MATERIALS AND METHODS

Materials

Clopidogrel Bisulphate (99.17%) was a gift from Highnoon Laboratories Ltd which was used to construct the standard curve.

Brands Used

Four (4) brands of Clopidogrel tablets, namely Ogrel, Pidogrel, Lowplat, Plavix, were generously provided by Tahir heart institute's pharmacy in Chenab Nagar. They were randomly marked from C1-C4. The samples were properly checked for their manufacturing license numbers, batch numbers, manufacturing dates and expiry dates. The labeled active ingredient was 75 mg of Clopidogrel and all were packaged in strip or in blister. The samples were carefully collected such that no more than four months had passed since the date of their production. The strip or blister packs were stored at 25±2°C for four weeks before the dissolution study in order to assess any organoleptic change (Kabir *et al*., 2009).

Dissolution studies

Dissolution test of Clopidogrel tablets was carried out in a six station USP type II apparatus (Paddle type) at 37± 0.5 °C at 50 rpm speed using 900 ml 0.1M Hydrochloric acid, at pH=2, as a dissolution medium. The dissolution study was performed according to USP-NF 30 guidelines. Samples were withdrawn after 30 minutes for determination of released Clopidogrel concentrations by using a UV-VIS spectrophotometer (SHIMADZU Corporation, JAPAN) at 240 nm wavelength against a blank. This absorption of each sample was used to determine the concentration using the calibration curve constructed. The data was tabulated and analyzed.

ANALYSIS

The amount of active in milligrams, dissolved in different Clopidogrel tablets, dissolution profiles at 30 minutes (t30 min, %) and were analyzed for significant differences by one-way analysis of variance (ANOVA). The statistical analysis was conducted using MS Office Excel 2013.

RESULTS AND DISCUSSION

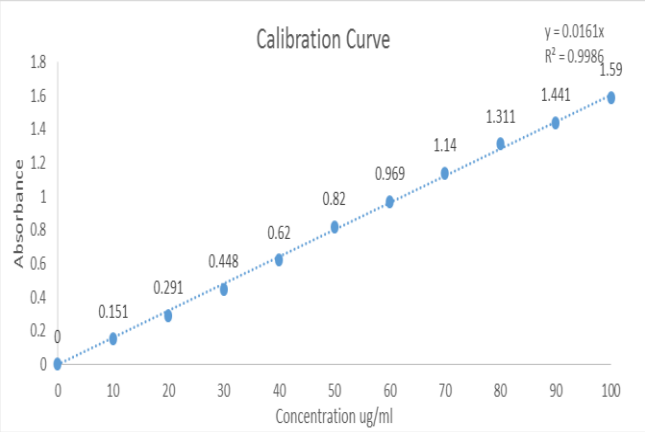

Figure 1: Calibration curve – Clopidogrel Bisulfate

Figure 1 depicts a calibration curve that was constructed using the Clopidogrel Bisulfate. The equation of the regression line is y=0.0161x with an R^2 of 0.9986. The R^2 value clearly shows that the line model fits the observations. This equation of the line was used to determine the percentage releases of the test products.

Figure 2 shows the percent of labeled amount of active released along with the standard error of the mean (SEM) of the various products of Clopidogrel that were tested in the study. Plavix (Sanofi-Aventis) showed the greatest release among all the products. On average, 97±4.7% of the active was dissolved. None of the Plavix tablets had a percent release of less than 85%.

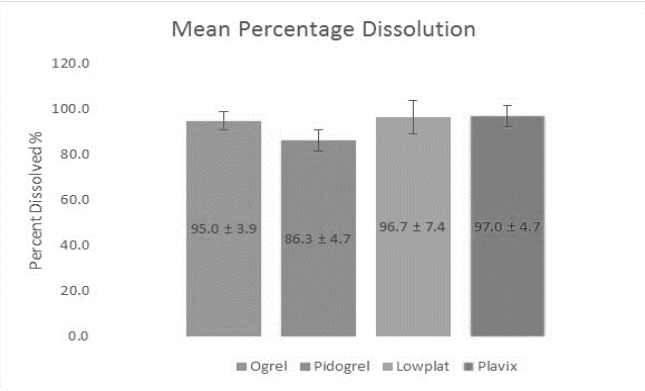

Figure 2: Average Percent Drug Dissolution

Ogrel (Bosch) showed excellent release of 95% with the lowest SEM of 3.9% and the lowest standard deviation. It was seen that although all four products passed the minimum requirement of the assay, Ogrel tablets had the best uniformity in its amount of active in each unit. Pidogrel (Highnoon) and Lowplat (PharmEvo), although showed an average release of greater than 85% but as indicated by their SEMs, the percent dissolution of individual units varied a lot.

The amount of drug present in each tablet was determined spectrophotometrically and all the brands met the official standard of USP, which specifies that the content should not be less than 90% and more than 110% (Gomez *et al*., 2004) as shown in Table 2. Disintegration is a crucial step for immediate release dosage forms since the rate of disintegration affects the dissolution and subsequently the therapeutic efficacy of the medicine in vivo (Shah and Amidon, 2014). Generally, a drug will be released rapidly as the tablet disintegrates. British Pharmacopeia specifies

Table 2: Assay* of commercial brands of Clopidogrel tablets

Sample	Amount of drug (mg)	Potency (%)	Remarks
Ogrel	73.4	97.9	Complied
Pidogrel	68.3	91.1	Complied
Lowplat	70.9	94.5	Complied
Plavix	74.1	98.8	Complied

*Claimed potency is 75mg per tablet. Accepted range of average drug content per tablet according to BP & USP is from 67.5 mg to 82.5 mg.

that uncoated tablets should disintegrate within 15 min and film coated tablet disintegrate within 30 min. All the brands (coated and uncoated) complied with the BP specifications for disintegration as all the test formulations dissolved within specified disintegration time (DT) of 30 minutes. Thus, quick onset of action

may be expected from these brands, as faster dissolution will ensure rapid absorption from the GI tract.

For the assessment of the difference of the means of milligrams of active dissolved, One-Way ANOVA was applied, which gave a p value of 0.46. This clearly shows that there is not a significant statistical difference between the means of amount of drug dissolved. Thus it is safe to assume that all products are bioequivalent and thus eligible for CMA.

Use of very expensive drugs, which are not affordable due to price, negatively affect therapeutic outcomes (Giwa and Tayo, 2013). Considering the high standard deviation and SEMs of Lowplat and Clopidogrel, Ogrel can be considered a suitable alternative to the highly expensive Plavix. The unit cost of Plavix is 2.5 times more than Ogrel but release rates are comparable. Keeping in view the high cost and daily use of clopidogrel, it better suits patient as well as hospital to prescribe a brand which costs less but is equally effective. Studies have shown that the high cost may lead to non-compliance of therapy by patients (Giwa *et al*., 2008).

Pharmacoeconomic analysis has widespread applications and is used to select drugs from a range of options, for formularies (Shafie and Hassali, 2011). The selection is based on price differences, given that all products have similar clinical effect. The therapy having lower cost is beneficial for both hospital and patients (Giwa and Tayo, 2013).The saved money can thus be allocated else ware and patients may be more compliant towards their therapy as it becomes more affordable.

CONCLUSION

Economic evaluation, such as cost minimization analysis of drug therapy is of paramount importance in policy and decision making to facilitate more rational choices/prescription. All the stakeholders need to be enlightened and work collaboratively in this regard. Ogrel can be used instead of the high priced Plavix, to save finances.

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