The importance of bioequivalence in generic drugs. An example: Clopidogrel

Silvia Millet Rafel, Biotechnology Degree, Universitat Autònoma de Barcelona, Tutor: Nuria Maria Vivas Sabido

Introduction

When the patent of a new drug is due, generic drug clones come into the market. Generic drugs are enforced to have the same active ingredients, route of administration, and dosage form as the branded product but there are no specific requirements for the salts. Thus generic drugs must prove to be bioequivalent to the branded drug before they can be authorised and marketed.

Objective

- Verify whether there is or not a difference regarding the effectivity of the branded drug and their generics and also if they can be considered interchangeable.
- Examine the usage of different salts within the various generic formulations to check if they could modify the properties of the drug composition and its effectiveness and safety.

Methodology

The methodology consisted on the review through literature research of journal articles based on the case of a drug approved in the Spanish market. In detail a commercial best-selling drug with clinical trials available was selected (Plavix®), whose active ingredient is clopidogrel binded with hydrogen sulphate salt.
As for the generic drug clones, the approval for selling them into the market comes with three distinct salts (besylate, hydrochloride and hydrogen sulphate), therefore studies accounting for each type of salt have been reviewed to confirm if there is any relationship between the salt and the bioequivalence.

What bioequivalence means?

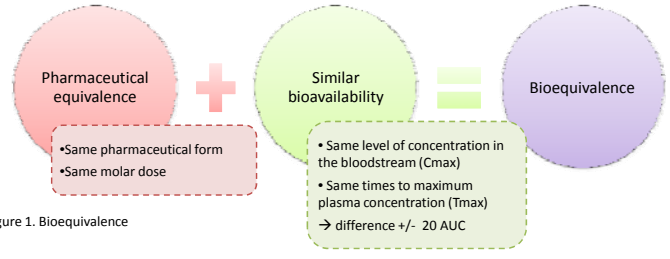

Figure 1. Bioequivalence

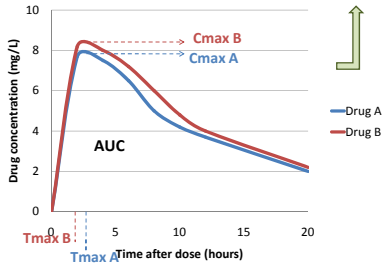

Figure 2. Bioavailability: Drug concentration versus time. *AUC*: curves for two drug products. area under the curve of the drug's concentration in the blood with respect to time

Platelets in Acute coronary syndrome (ACS)

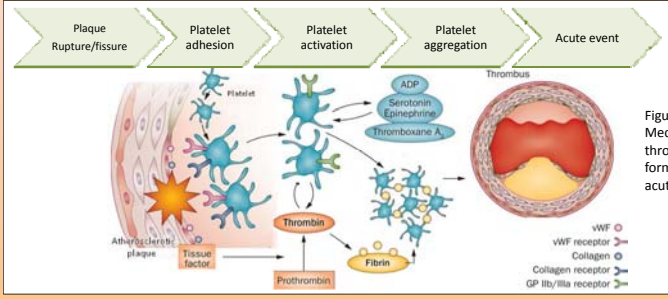

Figure 3. Mechanism of thrombus formation and acute event[1]

The Clopidogrel characteristics

- Clopidogrel is a drug used as the primary choice for the treatment and prevention of ACS
- Clopidogrel is part of the platelet antiaggregant group.
- Clopidogrel is a derivative of tienopyridine a prodrug which requires to be activated through the multiples hepatic cytochromes (CYP) P450s mainly the CYP3A4 and CYP3A4 isoform and the isoenzyme CYP2C19 in order to perform its platelet antiaggregant activity.

This activity is performed via a selective and irreversible bonding with the platelet P2Y12 receptor of the adenosine diphosphate (ADP). As a consequence, the activation of the complex glycoprotein (GPIIb-GPIIIa) that is fired through ADP as the molecule in charge of the platelet antiaggregation, is inhibited.

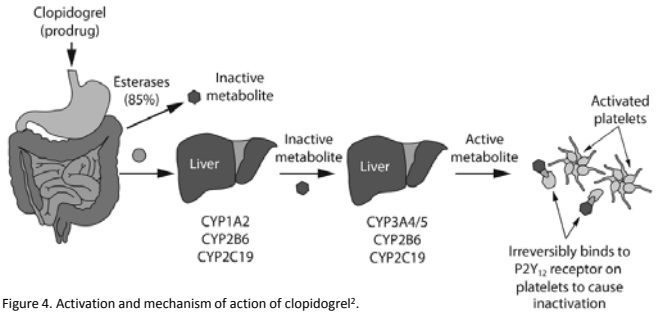

Figure 4. Activation and mechanism of action of clopidogrel[2].

- It has been identified some variability against responses that can be associated with extrinsic or intrinsic factors.

The most important factor is related to the following genetic variations:

- polymorphism of the gene platelet P2Y12 receptor
- Polymorphism of different CYP isoenzymes

Results

Table 1. Literature review summary

Study	N	patients	time (day)	agent studied and salt	Conclusion	Limitations
Jeong, 2010[3]	20	PCI	30	clopidogrel hydrogen sulphate	No inter-therapy differences in platelet reactivity with the two drugs Poor agreement inter-therapy in platelet functions measurements between the two drugs	Short duration and small sample size
Komosa, 2015[4]	53	PCI	8	clopidogrel hydrogen sulphate	No differences in platelet aggregation and pharmacodynamic response between the two drugs The same variability between the two drugs	Short duration and small sample size
Di Girolamo, 2010[5]	24	healthy	7	clopidogrel hydrogen sulphate	No differences in pharmacodynamic and pharmacokinetic in the two drugs	Short duration, small sample size and healthy volunteers
Neubauer, 2009[6]	21	healthy	23	clopidogrel hydrogen sulphate and besylate	No overall significant difference in the antiplatelet effect between the drugs The same variability inter-individual an intraindividual between the two different clopidogrel formulas	Healthy volunteers
Borsiczky, 2012[7]	150	PCI	30	clopidogrel hydrogen sulphate and besylate	No overall significant difference in the antiplatelet effect between the two drugs The same variability inter-individual an intraindividual between the two different clopidogrel formulas	Short duration, not use a control and not option of use a different way to measure the platelet function
Oberhansli, 2012[8]	60	PCI	40	clopidogrel hydrogensuphate, hydrochloride and besylate	No overall significant difference in the antiplatelet effect between the two drugs The same variability inter-individual an intraindividual between the two different clopidogrel formulas	Short duration and small sample size
Hamilos, 2015[9]	101	stable coronary disease	1	clopidogrel hydrogen sulphate and besylate	No overall significant difference in the antiplatelet effect between the two drugs The polymorphisms that cause poor antiplatelet function did no difference between two clopidogrel salts	Short duration and small sample size

Conclusions

- From the result of the literature review, it can be concluded that the statistical difference of +/- 20% of AUC in the bioavailability of the bioequivalence studies does not change the effectiveness of the generic drug against the branded one.
- Branded and generic drugs are fully interchangeable: No differences in the pharmacokinetics and pharmacodynamic effects between the generic and the branded drugs were found.
- The fact that different salts were used on the branded and the generic drug equivalent is independent of the bioavailability.
- A recommendation for the bioequivalence studies would be the selection of patients both healthy and with diseases. It is also important to take into account that both type of patients must have genetic traits as similar as possible in order to minimize the factors that could influence bioavailability.

References

1. Franchi, F& Angiolillo, D. J. (2014) Novel antiplatelet agents in acute coronary syndrome. Nat. Rev. Cardiology. 2015, 12:30–47
2. Tynes CR, Livingston B, Patel H, Arnold JJ. Clinical Investigation Chiral Stability of an Extemporaneously Prepared Clopidogrel. 2008;25–9..
3. Jeong YH, Koh JS, Kang MK, Ahn YJ, Kim IS, Park Y, et al. The impact of generic clopidogrel bisulfate on platelet inhibition in patients with coronary artery stents: Results of the ACCEL-GENERIC study. Korean J Intern Med. 2010;25(2):154–61.
4. Komosa A, Siller-Matula J, Kowal M. Comparison of the antiplatelet effect of two clopidogrel bisulfate formulations: Plavix and generic-Egitromb, Platelets2015 ;26(1):43-47.
5. Di Girolamo G, Czerniuk P, Bertuola R, Keller G a. Bioequivalence of two tablet formulations of clopidogrel in healthy Argentinian volunteers: a single-dose, randomized-sequence, open-label crossover study. Clin Ther [Internet]. Excerpta Medica Inc.; 2010;32(1):161–70.
6. Neubauer H, Krüger JC, Lask S, Endres HG, Pepinghege F, Engelhardt A, et al. Comparing the antiplatelet effect of clopidogrel hydrogensulfate and clopidogrel besylate: A crossover study. Clin Res Cardiol. 2009;98(9):533–40.
7. Borsiczky B, Sarszegi Z, Konyi A, Szabados S, Gaszner B. The effect of clopidogrel besylate and clopidogrel hydrogensulfate on platelet aggregation in patients with coronary artery disease: A retrospective study. Thromb Res [Internet]. Elsevier Ltd; 2012;129(6):700–3
8. Oberhänsli M, Lehner C, Puricel S, Lehmann S, Togni M, Stauffer JC, et al. A randomized comparison of platelet reactivity in patients after treatment with various commercial clopidogrel preparations: The CLO-CLO trial. Arch Cardiovasc Dis [Internet]. Elsevier Masson SAS; 2012;105(11):587–92.
9. Hamilos M, Saloustros I, Skalidis E, Igoumenidis N, Kambouris M, Chlouverakis G, et al. Comparison of the antiplatelet effect of clopidogrel hydrogenosulfate and clopidogrel besylate in patients with stable coronary artery disease. J Thromb Thrombolysis [Internet]. 2015.