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

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Introduction

When the patent of a new drug is due, generic drug copies 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 effectiveness of the branded drug and its 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 bestselling drug with clinical trials available was selected (Plavix®), whose active ingredient is clopidogrel bound with hydrogen sulphate salt.

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.

Results

Table 1. Literature review summary

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>patients</th>
<th>time (day)</th>
<th>agent studied and salt</th>
<th>Conclusion</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jeong, 2010</td>
<td>20</td>
<td>PCI</td>
<td>30</td>
<td>clopidogrel hydrogen sulphate</td>
<td>No significant difference in the antiplatelet effect between the two drugs</td>
<td>Short duration, small sample size</td>
</tr>
<tr>
<td>Komova, 2013</td>
<td>53</td>
<td>PCI</td>
<td>8</td>
<td>clopidogrel hydrogen sulphate</td>
<td>No differences in platelet aggregation and pharmacodynamic response between the two drugs</td>
<td>Short duration, small sample size</td>
</tr>
<tr>
<td>Di Girolamo, 2010</td>
<td>24</td>
<td>healthy</td>
<td>7</td>
<td>clopidogrel sulphate</td>
<td>The same variability between the two drugs</td>
<td>Healthy volunteers</td>
</tr>
<tr>
<td>Neuberger, 2009</td>
<td>21</td>
<td>healthy</td>
<td>23</td>
<td>clopidogrel hydrogen sulphate and besylate</td>
<td>No overall significant difference in the antiplatelet effect between the two different clopidogrel formulas</td>
<td>Healthy volunteers</td>
</tr>
<tr>
<td>Borasczyk, 2012</td>
<td>150</td>
<td>PCI</td>
<td>30</td>
<td>clopidogrel hydrogen sulphate and besylate</td>
<td>The same variability between an intrasubject variation between the two different clopidogrel formulas</td>
<td>Short duration, not use of control and not option to use a different way to measure the platelet function</td>
</tr>
<tr>
<td>Zibberhansli, 2012</td>
<td>60</td>
<td>PCI</td>
<td>40</td>
<td>clopidogrel hydrogencitrate, hydrochloride and besylate</td>
<td>No overall significant difference in the antiplatelet effect between the two drugs</td>
<td>Short duration, small sample size</td>
</tr>
<tr>
<td>Hamilos, 2015</td>
<td>101</td>
<td>stable coronary disease</td>
<td>3</td>
<td>clopidogrel hydrogen sulphate and besylate</td>
<td>The polymorphism that cause poor antiplatelet function did no difference between two clopidogrel salts</td>
<td>Short duration, small sample size</td>
</tr>
</tbody>
</table>

Conclusions

- From the result of the literature review, it can be concluded that the statistical difference of +/- 20% of AUC in 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 pharmacokinetic 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 sick to account that both type of patients must have genetic traits as similar as possible in order to minimize the factors that could influence bioequivalence.

References