Letter to the editor:

ACENOCOUMAROL’S PHARMACOKINETIC: LINEAR OR NOT?

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Dear Editor,

Acenocoumarol, is a racemic mixture of the optical R (+) and S (-) enantiomers. R (+) enantiomer is several times more potent than the S (-) enantiomer (Godbillon et al., 1981). Acenocoumarol is rapidly absorbed following oral absorption with approximately 60 % of the dose available systemically (Trailokya, 2015). After a single dose of 10 mg, the peak plasma concentrations (Cmax) of acenocoumarol are reached within 1-3 h and the area under the plasma concentration-time curve (AUC) values are proportional to the dose in the dosage range of 8 to 16 mg (Sasso et al., 2012). The protein binding of acenocoumarol is 98 % (Trailokya et al., 2016). Acenocoumarol is mainly metabolized by CYP2C9 (Trailokya, 2015); 6- and 7-hydroxylation of both enantiomers of acenocoumarol are the major metabolites (Thijssen et al., 2000). The elimination half-life of acenocoumarol is 8 to 11 h (Sánchez et al., 2013). Approximately, 29 % of acenocoumarol excrete in feces and 60 % in urine. The starting dose of acenocoumarol usually ranged from 2 to 4 mg. Based on the prothrombin time, subsequent loading doses may be recommended (Trailokya, 2015).

Acenocoumarol is reported to exhibit a dose-proportional pharmacokinetics for the 8 to 16 mg doses (Trailokya, 2015). However, no information is available for the dose-proportionality of lower doses of acenocoumarol (i.e. 1 to 4 mg doses). We aimed to evaluate the dose-proportionality of acenocoumarol by performing a literature search and plotting a linear curve for AUC vs. dose from the available information.

Literature related to pharmacokinetics of acenocoumarol was searched in PubMed. A total of 115 from 1618 articles were identified related to acenocoumarol’s pharmacokinetics. From, 115 articles, 9 articles were identified as potentially relevant, as these articles reported the AUC values at different time points such as 24, 48, 72 h and at infinite time. These articles were finally considered for the evaluation of linearity of acenocoumarol pharmacokinetics. Various studies have reported the AUC0-48 and AUC0-∞ values of acenocoumarol for 1, 4, 10 and 12 mg dose (Table 1). No other information on AUC0-48 and AUC0-∞ were available with the 2, 8 and 16 mg dose. The pharmacokinetics data across these studies were used to generate a dose-proportionality curve (acenocoumarol dose vs. AUC0-48 or acenocoumarol dose vs. AUC0-∞). The dose-proportionality curves between AUC and acenocoumarol doses (AUC0-48 vs. dose, and AUC0-∞ vs. dose) are presented in Figure 1.
An R² of 1 indicates that the regression predictions perfectly fit the data. Therefore, from the value of R² (0.9988 for AUC₀-₄₈ vs. dose, and 0.9874 for AUC₀-∞ vs. dose), it is clear that acenocoumarol exhibits a dose-proportional pharmacokinetics.

REFERENCES


Table 1: AUC$_{0-48}$ and AUC$_{0-\infty}$ values of acenocoumarol from literature search

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>Subject (n)</th>
<th>AUC</th>
<th>Reference</th>
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<tr>
<td></td>
<td></td>
<td>0-24</td>
<td>0-48</td>
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<tr>
<td></td>
<td></td>
<td>R-AC</td>
<td>S-AC</td>
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<tr>
<td>1</td>
<td>28</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>24</td>
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<tr>
<td>10</td>
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Abbreviation denotes – AUC: area under the plasma concentration curve; R-AC: (R)-enantiomer of acenocoumarol; S-AC: (S)-enantiomer of acenocoumarol
Figure 1: Dose-proportionality curves between AUC and acenocoumarol doses (AUC_{0-48} vs. dose, and AUC_{0-\infty} vs. dose)