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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 (C_{max}) 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 AUC_{0-48} and $AUC_{0-\infty}$ values of acenocoumarol for 1, 4, 10 and 12 mg dose (Table 1). No other information on AUC_{0-48} and $AUC_{0-\infty}$ 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. AUC_{0-48} or acenocoumarol dose vs. $AUC_{0-\infty}$). The dose-proportionality curves between AUC and acenocoumarol doses (AUC_{0-48} vs. dose, and $AUC_{0-\infty}$ vs. dose) are presented in Figure 1.

An R^2 of 1 indicates that the regression predictions perfectly fit the data. Therefore, from the value of R^2 (0.9988 for AUC_{0-48} vs. dose, and 0.9874 for $AUC_{0-\infty}$ vs. dose), it is clear that acenocoumarol exhibits a dose-proportional pharmacokinetics.

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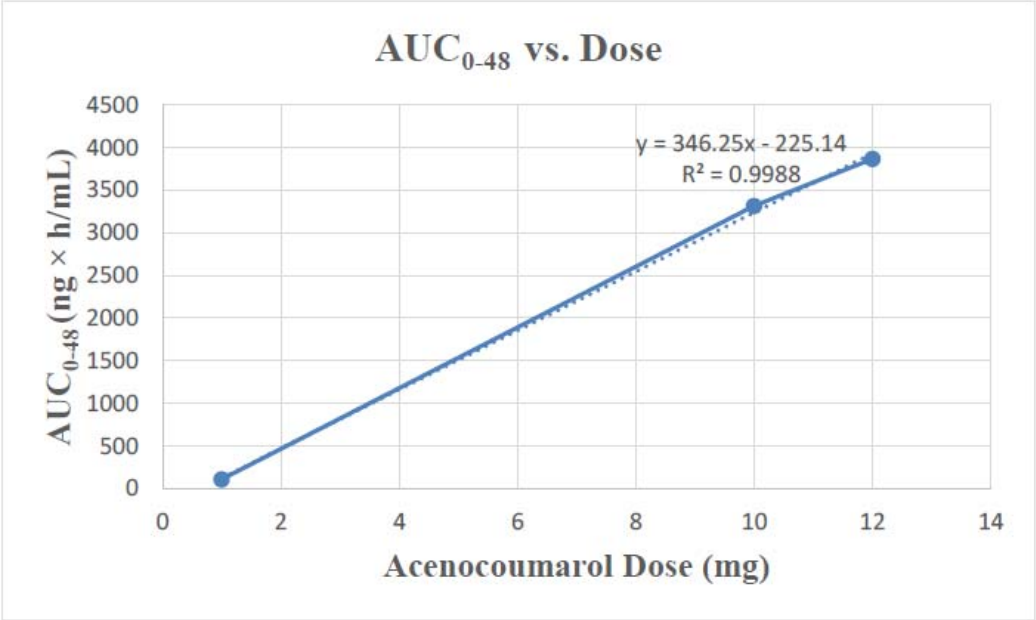
Table 1: AUC_{0-48} and $AUC_{0-\infty}$ values of acenocoumarol from literature search

Dose (mg)	Subject (n)	AUC								Reference
		0-24		0-48		0-72		0-∞		
		R-AC	S-AC	R-AC	S-AC	R-AC	S-AC	R-AC	S-AC	
1	28	-	-	107	-	-	-	126	-	Public Assessment Report, Acenocoumarol, 2013
4	24	1364.38	-	-	-	-	-	1786	-	Sasso et al., 2012
10	12	-	-	3315	289	-	-	3807	361	Rolan et al., 2003
10	18	-	-	-	-	2529	169	-	-	Huang et al., 2008
10	12	-	-	-	-	3831	382.4	3962	387.3	Sunkara et al., 2004
10	6	-	-	3458	479	-	-	-	-	Masche et al., 1999
10	7	-	-	3400	-	-	-	-	-	Thijssen and Hamulyàk, 1989
10	5	-	-	-	-	-	-	3900	-	Thijssen and Baars, 1983
12	8	-	-	3866.36	-	-	-	-	-	Popovic et al., 1994

Abbreviation denotes – AUC: area under the plasma concentration curve; R-AC: (R)-enantiomer of acenocoumarol; S-AC: (S)-enantiomer of acenocoumarol



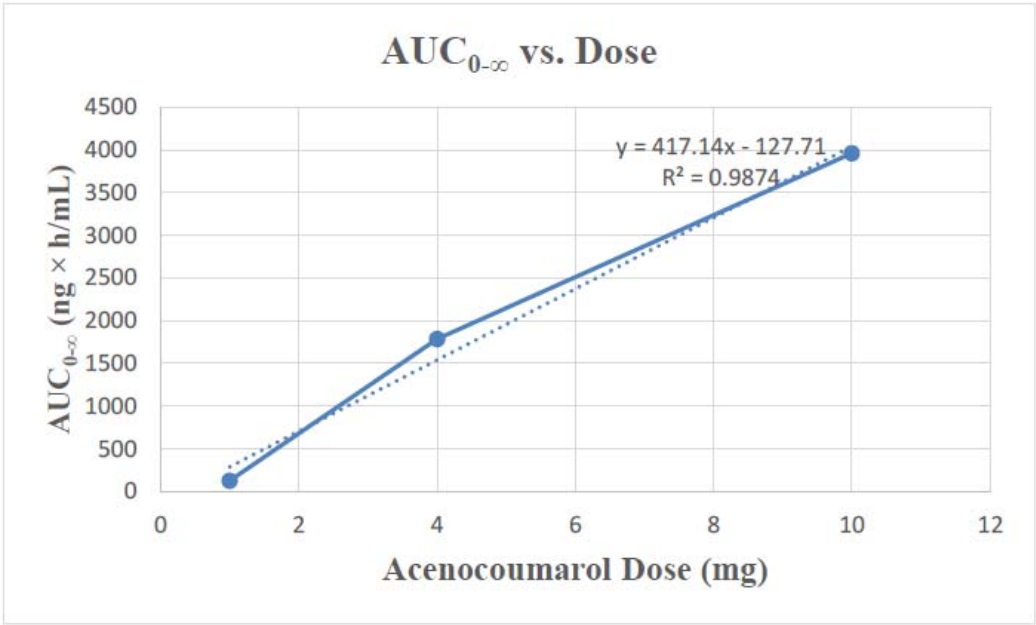


Figure 1: Dose-proportionality curves between AUC and acenocoumarol doses (AUC_{0-48} vs. dose, and $AUC_{0-\infty}$ vs. dose)