

RANDOMIZED, OPEN-LABEL CROSS-OVER STUDIES TO ASSESS THE POTENTIAL PHARMACOKINETIC INTERACTION OF WARFARIN OR DIGOXIN AND SEVELAMER CARBONATE

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Sevelamer carbonate (SC; Renvela[®]) was developed as a pharmaceutical alternative to sevelamer hydrochloride (SH). Studies have demonstrated that SH did not affect the bioavailability of warfarin or digoxin. After exposure to gastric contents, both SC and SH are similarly protonated salts of cross-linked poly(allylamine hydrochloride) and were expected to have similar drug-drug interactions. These studies were conducted to confirm that SC does not affect the pharmacokinetics of warfarin or digoxin.

These were randomized, open-label, cross-over studies in healthy volunteers. In the warfarin study, 18 subjects received 20 mg of warfarin alone or co-administered with 9.6 g of sevelamer carbonate powder. In the digoxin study, 18 subjects received 1 mg of digoxin alone or co-administered with 9.6 g of sevelamer carbonate powder.

The simultaneous administration of SC did not alter the mean plasma concentrations of warfarin or digoxin. The 90% CIs for C_{max} , $AUC_{(0-72)}$, and $AUC_{(0-inf)}$ were within the 80% to 125% range for warfarin. All values were within the 80% to 125% range for digoxin after excluding a subject with an anomalous C_{max} after digoxin alone.

Table 1: Geometric Means* for R-warfarin, S-Warfarin and Digoxin

	R-Warfarin		S-Warfarin		Digoxin	
	W + S	W	W + S	W	D + S	D
$AUC_{(0-inf)}$ (hr*ng/mL)	69122	63312	44359	42125	68.0	67.6
$AUC_{(0-72)}$ (hr*ng/mL)	42990	41566	31831	30879	50.7	52.0
C_{max} (ng/mL)	1168	1204	1125	1168	4.2	4.4

W: warfarin; S: sevelamer; D: digoxin

*Geometric mean based on least squares mean of log-transformed parameter values

In healthy volunteers, the co-administration of a single dose of sevelamer carbonate did not alter the pharmacokinetics of a single dose of warfarin or digoxin.