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Vitamin D Metabolome (VDM) Profiles after Single and Repeated Doses of Extended-release Calcifediol (ERC) in Hemodialysis (HD) Patients

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1 INTRODUCTION

Circulating 1,25-dihydroxyvitamin D (1,25D) levels are low in HD patients and presumed unresponsive to 25-hydroxyvitamin D (25D) repletion due to loss of renal CYP27B1 (cytochrome P450 25D-1α-hydroxylase). Serum 1,25D normalization has been demonstrated with regular dosing of oral ERC during HD.[1] ERC raises serum 25D sufficiently high (≥50 ng/mL) to drive hormone production by extra-renal CYP27B1.[2,3]

2 OBJECTIVE

To examine potential changes in the VDM profile after single and repeated ERC doses in HD patients.

3 METHODS

VDM profiles were studied in 26 adults requiring thrice-weekly HD during 24-hour periods after the first and last ERC doses in a 6-month phase 2 trial. Participants were randomized 3:1 to ERC (n=19) or placebo (n=7). Dosing began with 900 µg on Day 1 and continued with 300 µg/HD from Day 8 to 184. Serum obtained at -12, -3, 0, 4, 8, 12, 16, 20 and 24 hours post-dose was assayed for calcifediol ($25D_3$), total and free 25D, 1,25D, 24,25-dihydroxyvitamin D_3 ($24,25D_3$), vitamin D binding protein (DBP), corrected calcium (Ca) and phosphorus (P). Data were analyzed using mixed-effects models with repeated measures to estimate geometric mean time-courses, changes from baseline (BL), and metabolite:calcifediol ratios at each time point.

4 BASELINE CHARACTERISTICS

Parameter	All Participants (N=20)	ERC (N=15)	Placebo (N=5)
Age, years	58.6 (12.1)	57.9 (12.3)	60.8 (12.5)
Female, n (%)	7 (35.0)	6 (40.0)	1 (20.0)
Race, n (%) White Black or African American	 15 (75.0) 5 (25.0)	 12 (80.0) 3 (20.0)	 3 (60.0) 2 (40.0)
Hispanic or Latino, n (%)	5 (25.0)	3 (20.0)	2 (40.0)
Body weight, kg	97.1 (30.8)	96.9 (35.6)	97.8 (9.1)
BMI, kg/m^2	33.3 (9.1)	33.5 (10.3)	32.4 (4.6)
25D, ng/mL	28.2 (13.7)	23.7 (9.6)*	40.2 (15.8)
1,25D, pg/mL	10.2 (5.0)	9.4 (4.5)*	12.6 (6.1)
Free 25D, ng/mL	5.2 (1.9)	4.6 (1.4)	7.0 (2.0)
$24,25D_3$, pg/mL	<0.54	<0.54	<0.54
DBP, µg/mL	324.7 (46.8)	330.3 (51.4)	308.0 (26.0)
iPTH, pg/mL	562.1 (173.7)	587.2 (161.4)	486.6 (206.4)
Calcium, mg/dL	8.9 (0.5)	9.0 (0.4)	8.6 (0.8)
Phosphorus, mg/dL	4.6 (1.0)	4.5 (1.0)	4.9 (1.2)

Note: Six participants did not complete the study (4 in ERC group; 2 in placebo group) due to reasons unrelated to study procedures; Mean (SD) for continuous parameters; * p<0.01

Figure 1. Single Dose PK Data (Day 1)

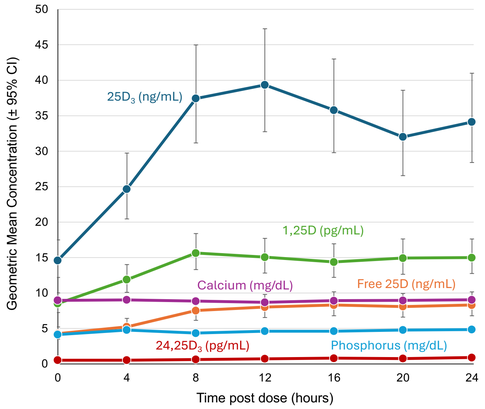
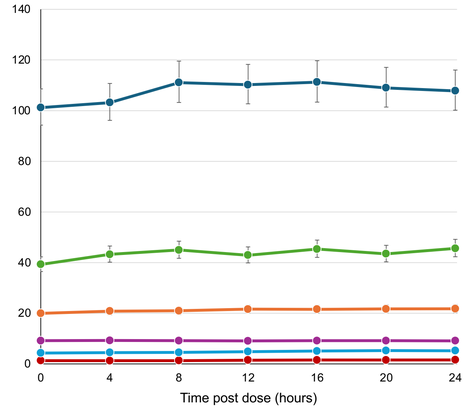


Figure 2. Repeat Dose PK Data (Day 184)



5 RESULTS

- Day 1: Mean (95% CI) calcifediol rose maximally after the initial 900 µg dose by 24.7 (8.7-51.8) ng/mL or 27.4 pg/mL/µg at 12 hours (Figure 1).
- Interim Treatment Period: Serum calcifediol increased with repeated 300 µg doses at each HD to steady-state at 101.2 (94.3-108.6) ng/mL.
- Day 184: Mean calcifediol rose maximally after the last 300 µg dose by 9.0 (1.8-16.8) ng/mL or 30.0 pg/mL/µg at 12 hours (Figure 2).
- Free 25D and 1,25D increased in constant proportions equal to 0.02% and 0.04% of the calcifediol concentrations, respectively, after both single and repeated doses. Serum $24,25D_3$ also increased but with proportions decreasing from 2.3% to 1.3%.
- DBP, Ca and P remained unchanged vs. placebo.

6 CONCLUSIONS

ERC therapy produced dose-proportional increases in circulating concentrations of total and free calcifediol and 1,25D, decreases in $24,25D_3$ ratios and no changes in DBP, Ca or P. Increases in 1,25D likely resulted from substrate-driven production by extra-renal CYP27B1.

1. Bishop CW, Ashfaq A, Choe J, et al. Extended-release Calcifediol Normalized 1,25-Dihydroxyvitamin D and Prevented Progression of Secondary Hyperparathyroidism in Hemodialysis Patients in a Pilot Randomized Clinical Trial. Am J Nephrol 2025; DOI: 10.1159/000546615.
2. Bishop CW, Ashfaq A, Choe J, et al. Managing Dysregulated Vitamin D Metabolism in CKD: Time to Update Conventional Wisdom? Kidney360 2025; DOI 10.34067/KID.0000000982.
3. Strugnell SA, Sprague SM, Ashfaq A, et al. Rationale for Raising Current Clinical Practice Guideline Target for Serum 25-Hydroxyvitamin D in Chronic Kidney Disease. Am J Nephrol 2019; DOI: 10.1159/000499187.

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