Effect of Kidney Disease and Vitamin D Repletion on Drug Transporter Activity

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INTRODUCTION

- Chronic kidney disease (CKD) patients exhibit changes in renal and nonrenal clearance of drugs[1-3]
- 1,25-dihydroxyvitamin D_3 (VitD) has been implicated in the regulation of several xenobiotic drug transporters[4]
- VitD deficiency is highly prevalent across all stages of CKD, necessitating repletion[5]
- We hypothesize that changes to drug transport in CKD patients may by affected by vitamin D status (depletion vs repletion)

OBJECTIVE

- To elucidate the effect of VitD status (deplete vs replete) on drug transporter phenotypes in patients with normal kidney function and CKD

METHODS

- VitD deplete (< 30 ng/mL) subjects (n=32) with normal kidney function and CKD were enrolled
- Probes were used to characterize transport phenotypes
  - Fexofenadine (FEX) to characterize nonspecific transport (i.e. P-gp, OATP)
  - Olmesartan (OLM) to characterize anionic transport (i.e. OAT, OATP)
  - N-methylnicotinamide (NMN) to characterize cationic transport (i.e. OCT2, MATE1/2-K)[6]
- Subjects received a drug "cocktail" of FEX 60 mg PO + OLM 10 mg PO before and after repletion
- Repletion therapy: 5,000 IU cholecalciferol PO QD x 12 weeks
- 9 blood samples and 2 urine samples collected over 48 h and 12 h, respectively
- FEX and OLM PK parameters calculated using noncompartmental methods (WinNonlin, vx.x.)
- NMN kinetic parameters calculated using trapezoidal rule and interval excretion method

RESULTS

Figure 1. Plasma concentration-time profiles of fexofenadine

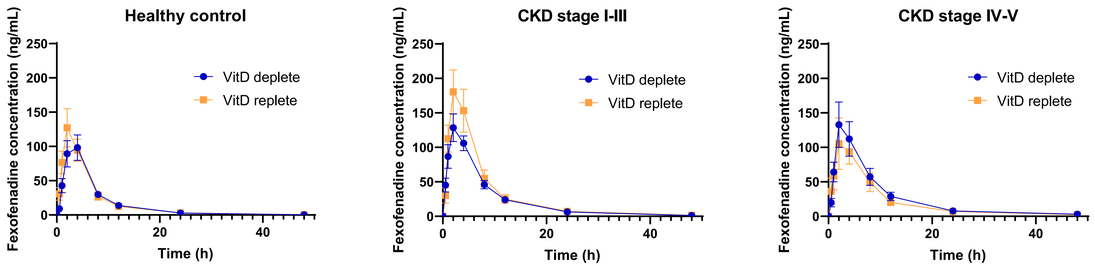


Figure 2. Plasma concentration-time profiles of olmesartan

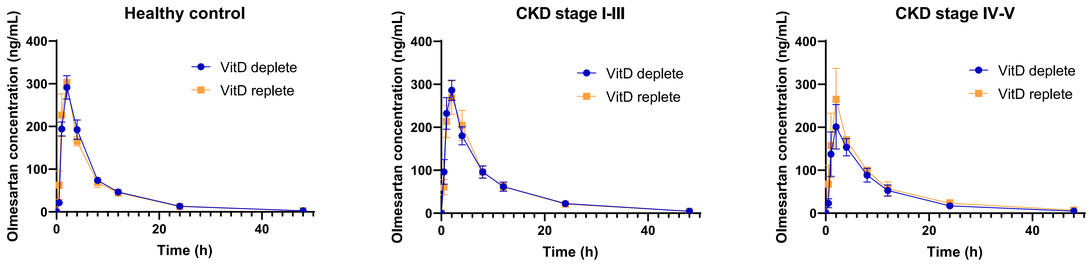
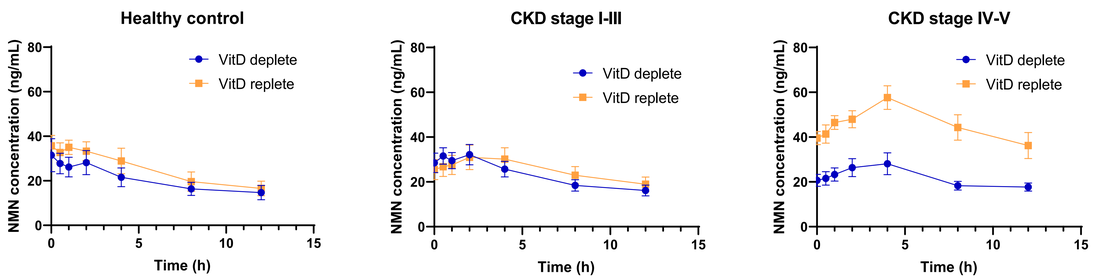


Figure 3. Plasma concentration-time profile of N-methylnicotinamide



RESULTS

Table 1. Change in PK parameters of FEX, OLM, and NMN after vitamin D repletion

	Healthy control (n = 9)	CKD Stage I-III (n = 15)	CKD Stage IV-V (n = 8)
FEX	No change	↑ $AUC_{0-\infty}$ 29% [a] ↑ C_{max} 52% [a]	No change
OLM	No change	No change	No change
NMN	↑ AUC_{0-12} 23% [ns] ↓ CL_R 28% [ns]	↑ AUC_{0-12} 11% [ns] ↓ CL_R 14% [ns]	↑ AUC_{0-12} 111% [ns] ↓ CL_R 49% [ns]

[a] $p < 0.05$ by Wilcoxon-ranked sums test or paired t-test, [ns] not significant

PK parameters of FEX and OLM assessed: area under the concentration-time curve from 0 to infinity, $AUC_{0-\infty}$; apparent clearance, CL/F; elimination half-life, $t_{1/2}$; maximum concentration, C_{max}; time to C_{max}, t_{max}
Kinetic parameters of NMN assessed: area under the concentration-time curve from 0 to 12 h, AUC_{0-12}; renal clearance, CL_R; amount excreted in the urine, A_e

CONCLUSIONS

- ↑ $AUC_{0-\infty}$ and C_{max} of FEX with VitD repletion in CKD stage I-III may be due to changes in intestinal or hepatic OATP uptake or P-gp efflux, and is probably largely due to ↓ intestinal P-gp efflux and ↑ FEX bioavailability. Changes in FEX were not seen in CKD stage IV-V, potentially due to interactions with disease-related changes to P-gp/OATP activity and FEX PK[2].
- No changes were observed in any OLM PK parameters, suggesting that VitD status does not significantly affect net renal and hepatic anionic transport irrespective of kidney function. Notably, our data do not reflect previously reported changes in OATP function[3] or OLM PK[7] in CKD versus normal kidney function. The reason for this discrepancy is unclear.
- ↑ AUC_{0-12} and ↓ CL_R of NMN suggest ↓ OCT2 and/or MATE1/2-K activity with VitD repletion, especially in patients with severe CKD. However, this requires further validation due to limitations of NMN as an endogenous transport probe (niacin intake, stress exposure, nutritional and biosynthetic factors, etc).

REFERENCES

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FUNDING

This study was supported by NIH/NIGMS R01 GM107122 and CTSA Grants UL1 TR001857 (University of Pittsburgh) and UL1 TR002535 (University of Colorado).

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