The Oral Calcilytic Encaleret Reduced Urinary Calcium While Maintaining Blood Calcium in Individuals with Post-Surgical Hypoparathyroidism

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Background

The actions of PTH and the calcium-sensing receptor (CaSR) on renal calcium handling are intertwined

- PTH activity and CaSR activation have opposing effects on renal calcium reabsorption
- CaSR activation impacts PTH secretion, confounding the ability to isolate the PTH-independent effects of renal CaSRs on calcium regulation

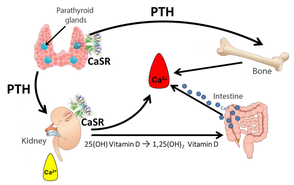

Figure 1: PTH and the CaSR regulate blood and urinary calcium

Calcilytics: Antagonists of the CaSR

- Encaleret is an investigational oral calcilytic (negative allosteric modulator of the CaSR).
- In post-menopausal women and patients with Autosomal Dominant Hypocalcemia Type 1 (ADH1) due to activating *CASR* variants, calcilytics ↑blood calcium,↑PTH, and ↓urine calcium (Caltabiano et al., *Bone*, 2013; Gafni et al., *NEJM*, 2023).
- In patients with functioning parathyroid glands, calcilytics reduce fractional calcium excretion through the combined effects of increased PTH and direct inhibition of renal CASRs.

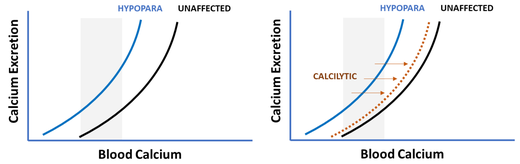

Figure 2: Calcium excretion curve in unaffected (black) vs. hypoparathyroid (blue) individuals. Calcilytics shift the curve towards normal (orange). (Figure adapted from Peacock et al., *Endocrinol Metab Clin North Am,* 2018)

Calcilytics in Post-surgical Hypoparathyroidism (PSH)

- Current treatment of PSH is inadequate:
- Calcium and active vitamin D requires a balance between blood calcium, urinary calcium, and symptoms.
- Approved and investigational PTH analogs require daily injections.
- Hypothesis: Encaleret administration to individuals with PSH may reveal the PTH-independent effects of CaSR modulation on renal calcium handling and clarify the potential therapeutic role of calcilytics as an orally administered alternative in PSH.

Study Design

- 10 adults with PSH
- Proof-of-principle, open-label design
- 5-day inpatient with encaleret 162 mg BID (high dose)
- Calcitriol stopped Day -1 -> individualized calcium and calcitriol titration
- Key endpoints: Fractional Excretion of Calcium (FECa), blood calcium, urine calcium

Study Participants

Table 1: Baseline Characteristics

Baseline Characteristics	Median (range); n (%)
Age	52 (26-69)
Female	9 (90%)
Time since surgery (years)	6.5 (1-12)
Corrected calcium (mg/dL, nl 8.4-10.2)	8.4 (7.9-9.3)
Intact PTH (pg/mL, nl 15-65)	8.8 (3.2-14.5)
25OH-Vitamin D	45 (38-52)
24h Urine Calcium (mg/24h, nl <250)	397 (204-853)
Nephrocalcinosis/nephrolithiasis	4 (40%)
Supplement Doses	
Elemental Calcium (mg/day)	1100 (85-3600)
Calcitriol (mcg/day)	0.5 (0.25-1.5)

*Measurements fasting immediately prior to first encalcert
**Home regimen, averaged over 1 week

Adverse Events

Table 2: Adverse Events (AEs)

AEs	Total=33; n(%)
Mild	26 (79%)
Moderate	7 (21%)
Severe	0 (0%)

- No serious AEs
- Treatment-related AE: Mild hypercalcemia and mild headache in 1 participant.

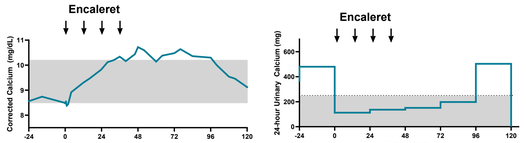

Figure 3: Albumin-corrected blood calcium and 24-hour urinary calcium in participant with hypercalcemia. Despite hypercalcemia, urine calcium was maintained <200 mg/24hr until the drug effect wore off.

Results

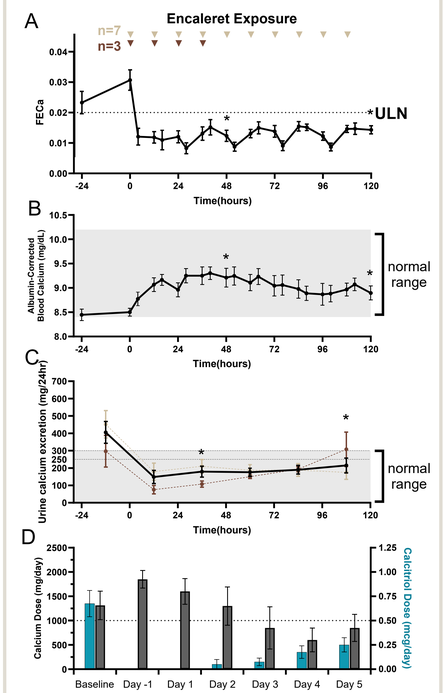

Figure 4: (A) Fractional excretion of calcium (FECa), a measure of renal calcium handling, decreased on encaleret, reflecting a decrease in (C) urinary calcium despite higher (B) albumin-corrected blood calcium levels. (D) Calcium and calcitriol doses were titrated to maintain mid-normal blood calcium levels. 7 participants received encaleret for 5 days and 3 participants for 2 days. Encaleret stopped due to hypercalcemia (n=1) or planned observation of off-drug effect (n=2). Mean±SEM; ULN = upper limit of normal
*p<0.05, 48hr or 120hr compared to baseline at 0hr

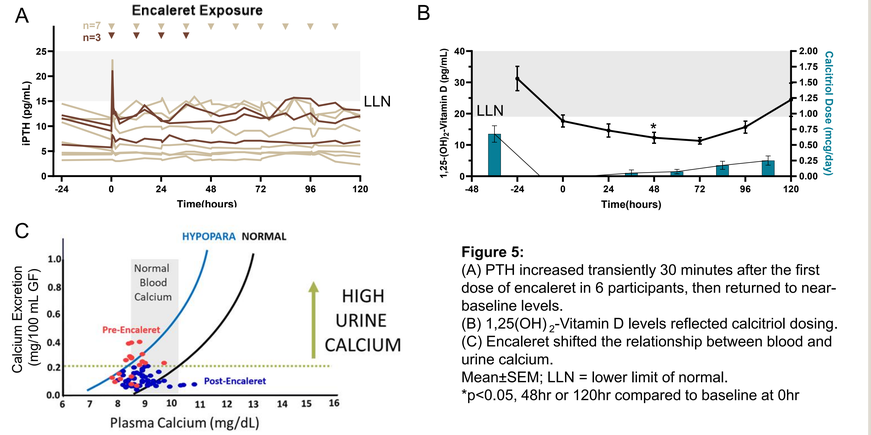

Figure 5:
(A) PTH increased transiently 30 minutes after the first dose of encaleret in 6 participants, then returned to near-baseline levels.
(B) 1,25(OH)$_2$-Vitamin D levels reflected calcitriol dosing.
(C) Encaleret shifted the relationship between blood and urine calcium.
Mean±SEM; LLN = lower limit of normal.
*p<0.05, 48hr or 120hr compared to baseline at 0hr

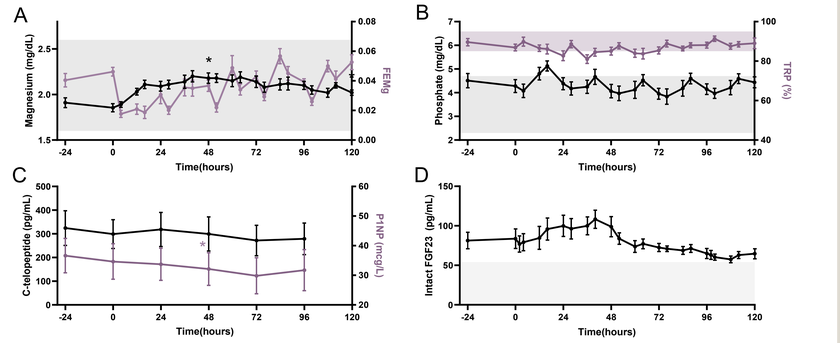

Figure 6: Encaleret administration was associated with (A) increase in blood magnesium (black) and decrease in FEMg (non-significant, purple) followed by return to baseline. (B, D) Blood phosphate (black), tubular reabsorption of phosphate (TRP, purple) and FGF23 did not significantly change. (C) C-telopeptide (black) was unchanged and P1NP (purple) slightly decreased on encaleret. Shaded gray or purple = normal range
*p<0.05, 48hr or 120hr compared to baseline at 0hr

Conclusions

- Encaleret treatment resulted in a rapid and sustained reduction in fractional excretion of calcium from the protocol-defined baseline (Day –1) in nine participants with post-surgical hypoparathyroidism.
- Apart from a small and transient rise after the initial dose, PTH levels remained low suggesting encaleret's sustained effect likely occurred independent of PTH, primarily driven by renal CaSR inhibition.
- CaSR inhibition did not appear to impact 1,25-(OH)$_2$-Vitamin D levels.
- Preliminary results from this Phase 2 study support continued evaluation of encaleret as an orally administered therapy for the treatment of patients with PSH.