UPMC PALLIATIVE AND SUPPORTIVE INSTITUTE

THE TABLET: PALLIATIVE CARE PHARMACY TIPS

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TODAY'S TOPIC:

Calcitonin Use in Pain Management

Background:

Calcitonin is a hormone released by the thyroid gland in response to hypercalcemia and is FDA approved for postmenopausal osteoporosis treatment, hypercalcemia, and Paget's disease. It is available as an intranasal spray (200 units/actuation, dose: 1 spray in one nostril daily, FDA approved in 1995, cost ~$30/spray) and IM/SubQ injection (200 units/mL product, dose: 100 units IM/SubQ once daily, FDA approved in 1986, cost ~$500-1,000/vial). Calcitonin is used off-label as an analgesic for osteoporotic vertebral compression fractures (VCFs), phantom limb pain, complex regional pain syndromes (CRPS), and metastatic bone pain. As most of the literature focuses on calcitonin as an analgesic for acute pain following VCF, this issue of the Tablet will focus on the use of calcitonin as an analgesic for VCF and metastatic bone pain.

Importance:

VCFs and metastatic bone pain are prevalent among patients receiving palliative care, yet few guideline recommendations exist to guide clinicians on effective analgesics.

The Literature:

Cochrane Database Syst Rev. 2006 Jul 19;(3): CD003223.

Calcitonin for Metastatic Bone Pain: A Review (2015 updated review of a 2006 publication)

Objective: Determine the efficacy of calcitonin plus a rescue medication (i.e., opioid) in reducing metastatic bone pain compared placebo plus a rescue medication.

Methods: Systematic review using CENTRAL, MEDLINE (1966 - February 2015), EMBASE (1974 – February 2015) databases

- Included only double-blind RCTs with ≥ 4 weeks follow-up
- Studies were excluded if bisphosphonates were administered to participants prior to randomization
- 2 RCTs included in review, participants were all women with breast cancer and bone metastasis (n=90)
  - Both studies included determined "very low evidence" per GRADE
- Pain assessed via visual analog scale (VAS), with scale from 0 (no pain) to 10 (severe pain)

Included Study	Sample Size (participants)	Intervention	Follow-up Period
Roth et al., 1986	40	100 IU SubQ calcitonin daily x 28 days	1 month
Blomqvist et al., 1988	50	100 IU SubQ calcitonin daily x 3 months	1 year

Outcomes:

- Primary: Analgesic efficacy of calcitonin plus rescue medication, determined by:
  - Complete pain relief at ≥ 4 weeks follow-up
    - No definition for "complete pain relief" provided
  - Less or equal analgesia consumption
- Secondary: Pain intensity (measured via VAS), change in rescue medication usage from baseline to post-intervention, functional capacity (in Roth et al., measured by time spend in bed, defined as: fully active, capable of light activity, in bed < 50% of the time, in bed > 50% of the time, completely bedridden), adverse effects

Results:

Primary:

- From Roth et al., calcitonin was associated with complete pain relief compared to placebo at one month, but this difference was not statistically significant (RR 2.50, 95% CI 0.55 to 11.41).
- From Blomqvist et al., use of calcitonin did not significantly decrease analgesic consumption compared to placebo at one year follow up (RR 1.05, 95% CI 0.90 to 1.21).

Secondary:

- A greater number of adverse effects (primarily flushing and injection site pain) were reported by participants receiving calcitonin compared to placebo in both studies (RR 3.50, 95% CI 0.77 to 15.88).
  - Roth et al: 3 out of 25 participants receiving calcitonin and 1 of 25 participants receiving placebo reported injection site pain following administration
  - Blomqvist et al: 1 out of the 20 participants receiving calcitonin reported facial flushing
- No evidence found on calcitonin improving functional capacity or controlling complications from bone metastases. In Roth et al., no difference in time spent in bed was found between patients receiving placebo vs calcitonin.

Conclusion: Calcitonin may reduce metastatic bone pain in women with breast cancer after one month of use, although this difference was not statistically significant. Similarly, calcitonin was not found to significantly reduce the need for other analgesics and may cause mild, transient adverse effects.

JAMA. 2024 Sep 3;7(9):e2432041.

Conservative Treatments in the Management of Acute Painful Vertebral Compression Fractures: A Systematic Review and Network Meta-Analysis

Objective: Assess efficacy of conservative treatment options (pharmacotherapy or bracing) for acute pain management post-acute VCF compared to no treatment, placebo, or other conversative treatment modality.

Methods: Systematic review and network meta-analysis using PubMed, Embase, Scopus, and CINAHL databases

- Included only RCTs and prospective comparative studies (PCSs), excluded trials published before 1996
- Patients included had at least one painful, acute, osteoporotic VCF
- 20 international studies included in final analysis (16 RCTs and 4 PCSs) featuring 2,102 patients
  - Most studies graded "intermediate quality" via RoB2 criteria
  - All PCSs were graded "good quality" via Newcastle-Ottawa scale
  - Individual studies reported pain using VAS
- P-scores utilized to rank treatments on a continuous scale from 0-1
- In patients receiving calcitonin, various dosage forms of calcitonin were utilized, including dosage forms that are unavailable in the United States (i.e., calcitonin rectal suppository and IV infusion). Only one study utilized the salmon-derived calcitonin nasal spray used most frequently in practice in the United States.

Outcomes:

- Primary: Short-term pain (4 weeks) during activity (defined as walking, standing, rising from lying position)
- Secondary: Long-term (last follow up) non-specific pain

CLINICAL PEARL: Short-term use of calcitonin (< 30 days) *may* reduce pain associated with osteoporotic vertebral compression fractures or metastatic bone cancer pain and could be considered in patients with refractory pain to standard analgesics given current level of available evidence.

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Results:

Characteristics	RCTs (16 trials)	PCSs (4 trials)
Mean Age (yrs)	74	75
N (mean, per trial)	90	160
Time of Fracture	Immediate – 4 months post	Immediate

Primary:

- Calcitonin (SMD -4.86; 95% CI -6.87 to -2.86) was associated with decreased short-term pain during activity compared to placebo.
- Of the 20 trials included in the study, 2 directly compared calcitonin to placebo for short-term pain.
- Compared to other treatments (NSAIDs, teriparatide, and bisphosphonates), calcitonin was the most favored treatment (P-score = 0.92).

Secondary:

- Average follow-up period of 11.5 weeks
- Calcitonin (SMD -0.36; 95% CI -1.09 to 0.37) was not associated with decreased long-term non-specified pain compared to NSAIDs (no studies directly compared to placebo).
- Of the 20 trials included in the study, 1 directly compared calcitonin to NSAIDs for long-term pain.
- Calcitonin was less favored (P-score = 0.51) for reducing long-term pain compared to daily and weekly teriparatide (P-score = 0.83 and 0.78, respectively).

Osteoporosis Int. 2012 Jan 23;23(1):17-38.

Calcitonin for Treating Acute and Chronic Pain of Recent and Remote Osteoporotic Vertebral Compression Fractures: A Systematic Review and Meta-Analysis

Objective: Assess efficacy of calcitonin (subQ or intranasal) in older adults for acute (< 10 days) or chronic pain (> 3 months) related to a VCF compared to placebo or other treatment.

Methods: Systematic review and meta-analysis using Medline, Embase, and Lilacs databases

- Included only RCTs and PCSs with participants ≥ 60 years old living in a facility or community setting
- 13 studies were included in the qualitative analysis (all RCTs, n= 589) and 10 studies were included in final quantitative meta-analysis (all RCTs, n= 467)
  - Only 3 studies addressed all quality criteria outlined by the Cochrane Collaboration
  - 7 studies featured intranasal calcitonin ranging in dose from 100-200 IU daily

Outcomes:

- Primary: Analgesic efficacy of calcitonin measured via VAS
- Secondary: Adverse effects with calcitonin usage

Results:

- 6 studies analyzed acute pain from recent fracture and 7 studies analyzed chronic pain from a remote fracture

Primary:

- Acute Pain: Calcitonin significantly reduced acute pain at rest (SMD -3.39; 95% CI -4.02 to -2.76) and with mobility (SMD -2.60; 95% CI -4.07 to -1.13), with sustained results seen through 4 weeks.
- Chronic Pain: Calcitonin did not significantly reduce chronic pain at rest (SMD 0.17; 95% CI -1.46 to 1.12) after 3 months of treatment. A significant difference in pain scores in mobile patients was only seen at 6 months (SMD -0.49 95% CI -0.85 to -0.13).

Secondary:

- Calcitonin was associated with significantly more GI upset (RR 2.58, 95% CI 1.10 to 6.04) and flushing (RR 6.91, 95% CI 2.47 to 19.36) compared to placebo.
- NNTH (experience adverse effect): 12

Conclusion: For acute pain at rest or during mobility from a VCF, calcitonin significantly reduces pain scores compared to placebo. Patients with chronic pain are less likely to experience analgesia from calcitonin.

Bottom Line:

- Evidence to support the use of calcitonin as an analgesic for metastatic bone pain is limited; data from RCTs with follow up data ≥ 4 weeks exists only for women with breast cancer and bone metastases. It is unclear whether these results can be extrapolated to males, bone metastases caused by other cancer types, and calcitonin administered via intranasal route. Due to lack of data with calcitonin use > 1 month duration, I would not recommend patients use calcitonin for metastatic bone pain chronically.
- Calcitonin may be helpful to reduce acute pain (< 30 days post-fracture, not chronic pain) caused by VCFs. In practice, the nasal spray is more frequently used due to cost, tolerability, and patient preference. As each nasal spray contains 30 doses (one dose per day), I typically see patients complete a full 30 days of calcitonin. Of note, available data does not study calcitonin for use in the setting of VCFs in the palliative care population.
- Other literature suggests a time-to-benefit of 1-2 weeks of daily calcitonin use for analgesic benefits (Blau et al.); therefore, this timeline for potential benefit should be communicated to patients. It is hard to confirm this time to benefit period with the studies above as they used 1 month as the primary time point for analysis.
- It is important to counsel patients on the GI upset and flushing adverse effects associated with calcitonin use.
- At UPMC, the calcitonin injection is currently formulary-restricted to renal, endocrinology, or oncology. The calcitonin nasal spray is formulary.

References:

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3. Martinez-Zapata MJ, Roqué M, Alonso-Coello P, Català E. Calcitonin for metastatic bone pain. *Cochrane Database Syst Rev*. 2006;2006(3):CD003223. Published 2006 Jul 19. doi:10.1002/14651858.CD003223.pub2
4. Blau LA, Hoehns JD. Analgesic efficacy of calcitonin for vertebral fracture pain. *Ann Pharmacother*. 2003;37(4):564-570. doi:10.1345/aph.1C350

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