UPMC PALLIATIVE AND SUPPORTIVE INSTITUTE

THE TABLET: PALLIATIVE CARE PHARMACY TIPS

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If you have a topic you would like the pharmacy team to answer, please send your suggestions to: lowrymf@upmc.edu

TODAY'S TOPIC:

Acetaminophen as adjunct for patients with cancer pain on high dose opioids

Background:

Management of pain in the cancer population relies heavily on pharmacologic therapy. Opioids have become the mainstay of treatment, given their resounding evidence to support their use. WHO Pain ladder suggests utilizing non-opioid adjuncts as first-line for mild cancer pain, and considering continuing as opioids are added to treatment regimen in setting of moderate-severe pain. Acetaminophen has been widely used as an adjunct option for cancer pain and we use it often in clinical practice with the goal of "opioid-sparing" and to target pain by a different mechanism. We know that the maximum pain relief obtainable from acetaminophen is from a 1000mg dose.

Importance:

Pain affects more than 70% of cancer patients and negatively affects quality of life. Palliative care clinicians should be aware of evidence related to adjunct medications to appropriately optimize pharmacotherapeutic regimens.

The Literature:

J Pain Symptom Manage. 2023 Sep;66(3):183-192.

Is Acetaminophen beneficial in patients with cancer pain who are on strong opioids? A Randomized controlled trial

Objective: To assess analgesic efficacy of acetaminophen in hospitalized cancer patients with moderate to severe pain receiving strong opioids

Methods: randomized, placebo-controlled, blind, parallel group clinical trial

- All cancer patients admitted to an internal medicine ward with acute moderate to severe (verbal numeric rating scale (VNRS) ≥4) cancer pain on strong opioids eligible
- Baseline pain assessed via visual analog scale (VAS) and VRNS
- Randomized to receive acetaminophen 1000mg IV every 6 hours or identical placebo
- Primary outcome: improvement in pain control from baseline (t=0) to 48 hours (t=2)
- Secondary outcomes: total MEDD at 48 hours, frequency of adverse effects

Results: (n=112); mean age 57.9 years old, 56% women

- 56.8% of patients on opioids prior to admission, most commonly: buprenorphine and tramadol
- Mean pain scores (VNRS and VAS) were significantly improved in both arms
- Mean MEDD increased from baseline to 24 hours and to 48 hours was not significant. *Mean MEDD were 56mg at baseline and between 70-79mg at 48 hours in each group*
- No differences in adverse effects between groups

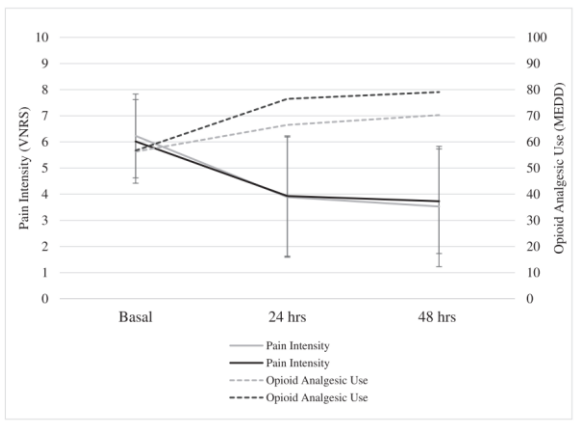

Fig. 2. Pain intensity (Pain Visual Numeric Rating Scale - VNRS) and opioid analgesic use (Morphine Equivalent Daily Dose - MEDD) over time by placebo vs. acetaminophen arm.

Conclusion: "We found that the addition of acetaminophen was not better than placebo for improving moderate to severe cancer pain in inpatients receiving strong opioids."

J Pain Symptom Manage. 2010 Mar;39(3):548-54.

Lack of benefit from paracetamol (acetaminophen) for palliative care patients requiring high-dose strong opioids: A Randomized, Double-blind, placebo-controlled, crossover trial

Objective: investigate potential analgesic benefits of 4g of paracetamol daily *for outpatient palliative care patients requiring high-dose opioids*

Methods: prospective, double-blind, randomized, crossover trial targeting cancer patients receiving palliative care, requiring *the equivalent of at least 200mg of oral morphine daily*

- Acetaminophen (APAP) 1000mg PO four times daily x 5 days, then 5 days of identical placebo
- Primary outcomes: pain score diary and breakthrough medication doses utilized
- Secondary outcomes: subjective ratings of nausea/vomiting, cognitive impairment, constipation, well-being

Results: (n=22 for analysis); average age 56.3 years, 54.5% male, all had primary diagnosis of cancer

- Mean opioid dose equivalent to 225mg morphine
- No difference in outcomes between groups: pain scores between groups (placebo: 3.59, APAP: 3.43), breakthroughs (placebo: 1.41, APAP: 0.99)

Conclusion: "The data presented in this article do not support the common palliative care practice of using 4 g of oral paracetamol daily as an adjunct to high-dose "strong" opioids for pain control in cancer patients receiving palliative care."

Palliat Med. 2003 Dec;17(8):724-5.

Is there an additive analgesic effect of paracetamol at step 3? A double-blind randomized controlled study

Objective: to determine whether paracetamol has an additive analgesic effect to *morphine in advanced cancer patients with well-controlled pain*

Methods: double-blind, randomized, placebo-controlled crossover design

- Randomized to receive APAP 1000mg PO QID x1 week or placebo, with 1-week crossover
- Outcomes: numerical rating scale (NRS: 0/10) and amount of PRN morphine used, quality of life questionnaire (on days 0,7,14)

Results: n=30, median age 70 years, median Karnofsky score 60

- Median total daily morphine dose was 70mg (range: 20-440mg)
- No difference in pain scores or quality of life

Conclusion: these data do not support routine use of paracetamol as adjunct with morphine in setting of mild/stable pain

Bottom Line:

- Data (inpatient & outpatient) does not support use of acetaminophen (IV or PO) as an adjunct to reduce pain scores or OME requirements for patients with cancer, already requiring OME ~50mg
- 48 hours would be sufficient to see a clinically significant difference as acetaminophen should reach steady state in < 24 hours
- Acetaminophen dosing may be burdensome for patients (two 500mg tablets, taken 4x/day), with limited clinically meaningful benefit
- Acetaminophen use may be effective when initially starting opioids or for patients requiring low doses of opioids (Step 2 WHO ladder) although once patients hit ~50mg OME mark, it might be reasonable to weigh risk of pill burden versus benefit of this adjunct therapy and consider deprescribing

CLINICAL PEARL: Acetaminophen seems to have limited benefit for cancer patients requiring opioids (≥~50mg OME) for pain