Journal Watch

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Question: Is there any use for Acetaminophen as an analgesic adjunct for a patient on a Strong (step 3 or higher of the WHO analgesic ladder) Opioid?

Abstract:

Purpose: To determine whether adding regular acetaminophen (paracetamol) could improve pain and well-being in people with advanced cancer and pain despite strong opioids.

Patients and Methods: Participants took acetaminophen for 48 hours and placebo for 48 hours. The order (acetaminophen or placebo first) was randomly allocated. Pain was the primary outcome. Preferences, number of opioid breakthrough doses, overall well-being, nausea and vomiting, drowsiness, constipation, and cold sweats were secondary outcomes. Patients related themselves daily with visual analog scales (VAS) and a verbal numeric scale (VNS) for pain, all scaled from 0 to 10.

Results: Thirty patients completed the trial. The oral opioid was morphine in 23 patients and hydromorphone in seven patients. The median daily opioid dose in oral morphine equivalents was 200 mg (range, 20 to 2, 100 mg). Nonsteroidal anti-inflammatory drugs, corticosteroids, or both were used by 16 patients. Pain and overall well-being were better for patients receiving acetaminophen than for those receiving placebo. The mean difference was 0.4 (95% CI, 0.1 to 0.8; P = .03) in VNS for pain, 0.6 (95% CI, -0.1 to 1.3; P= .09) in VAS for pain, and 0.7 (95% CI, 0.0 to 1.4; P = .05) in VAS for overall well-being. More patients preferred the period they took acetaminophen (n = 14) than the period they took placebo (n = 8), but many had no preference (n = 8). There were no differences in the other outcomes.

Conclusion: Acetaminophen improved pain and well-being without major side effects in patients with cancer and persistent pain despite a strong opioid regimen. Its addition is worth considering in all such patients.

Comments

Strengths/uniquness:

- Allocation Concealment ("The order (acetaminophen or placebo first) was randomly allocated")
- Addresses some of the many of the challenges of palliative-care research (eg, the need for short study times, easy assessments, and telephone follow-up).
Funding: Foundation plus some industry funding. Supported by a grant from the Cancer Council, New South Wales, Australia, and Janssen Cilag (Drug company that makes Haldol®, Fentanyl®)

Weaknesses:
- No intention to Treat Analysis (34 Randomized but 30 Analyzed)
- Small sample size. The trial was stopped after randomization of 34 patients (30 with complete data) because of slow accrual.
- Inapplicability to this specific practice environment. The study used high doses of acetaminophen that are not generally used (1 g every 4 hours five times per day). The justification for this dosing schedule was that "Hepatic toxicity is the only serious complication, but this is rare with doses less than 8 g/d, even in patients with chronic liver disease."

Results:
- The only significant result in favor of adding Acetaminophen to the analgesic regimen was an average difference of 0.4 (using an 11-point verbal numeric scale for pain assessment) on two assessment days (P = .03. The clinical benefit was not mentioned.
- No other pain management end points (Visual Analog Scale for pain, patient preference, and need for breakthrough medications) were statistically different.
- The overall well-being experienced by patients while on acetaminophen which is the softest outcome measure determinants, was assessed. The average increase in overall well-being was significant (P = .05). However we need to keep in mind that the determinants of well-being are multifactorial.
- It is not clear that how much Opioid will be spared by adding Acetaminophen. The authors of the paper suggest:
  
  The rationale for adding acetaminophen to a strong opioid regimen is to improve the balance between analgesia and side effects by either increasing analgesia without adding side effects or by maintaining analgesia with less side effects from opioids, NSAIDs, or other drugs.

  Furthermore, there was no difference in the balance between analgesia and adverse effects as measured by nausea and vomiting, drowsiness, and constipation scores.
- The palliative patients have to swallow an additional 10 large tablets a day for an uncertain clinical outcome. Some might argue that this is a burdensome treatment
- This study would need to be repeated in a larger number of patients. Also it would be helpful if the patients are separated according to the daily morphine-equivalent dose.

Relevance to Palliative Care:
The study shows a small (0.4 on an 11-point verbal numeric scale) analgesic gain that is statistically significance. One would question the clinical significance of this pain relief. Nonetheless, overall the study supports the claim that acetaminophen can be a viable adjunct for a select group of palliative patients already on a strong opioid.