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Acetaminophen (Paracetamol) Improves Pain and Well-Being in People With Advanced Cancer Already Receiving a Strong Opioid Regimen: A Randomized, Double-Blind, Placebo-Controlled Cross-Over Trial

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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 rated 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.

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INTRODUCTION

Pain is common in patients with cancer, and estimates suggest that approximately 75% of people with advanced cancer suffer substantial pain.[1-3] The WHO acknowledged the importance of cancer pain by developing a three-step approach to its management: nonopioid analgesics such as acetaminophen (paracetamol) or a nonsteroidal anti-inflammatory drug (NSAID) for mild pain, the addition of a weak opioid (eg, codeine) if pain persists, and strong opioids if pain is severe.[4-6] Strong opioids are the mainstay of cancer pain management in the developed world.

Many people with cancer have persistent pain despite treatment with strong opioids. Standard recommendations are to titrate the dose of opioids to get the best balance between analgesia and side effects, both of which are dose-dependent. Typically, the optimal dose relieves pain substantially but not completely, because subjective side effects become troublesome. In the United Kingdom and Australia, acetaminophen (paracetamol) is frequently added to strong opioids to improve analgesia in such

patients.[7] In North America, acetaminophen is often used with weak opioids, but not with strong opioids.

Acetaminophen is commonly considered together with NSAIDs as a coanalgesic. Although the analgesic effects of acetaminophen and NSAIDs are comparable,[8] their mechanisms of action are thought to be different.[9] Acetaminophen shares none of the subjective side effects of NSAIDs, opioids, or other coanalgesics. It is safe and well tolerated in therapeutic doses. 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.[10]

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.[11-13]

The purpose of this study was to determine whether adding acetaminophen could improve pain and well-being in patients with advanced cancer and pain despite treatment with strong opioid regimen.

PATIENTS AND METHODS

The target population was ambulatory cancer patients with persistent pain despite a stable regimen of strong opioids. Participants were recruited from two tertiary referral cancer centers: the Princess Margaret Hospital in Toronto, Canada, and the Concord Repatriation and General Hospital campus of the Sydney Cancer Centre in Sydney, Australia.

Analgesia was considered stable if no changes were required during the previous 48 hours in either the opioid or nonopioid analgesics (NSAID or corticosteroid) and if no change was considered desirable over the next 96 hours. Participants could be on corticosteroids or NSAIDs, but must have started them more than 1 week earlier. Acetaminophen was not to be used for 24 hours before the study. Participants were encouraged to use breakthrough doses of opioids as required.

Participants were allowed to receive treatment with systemic anticancer treatment (cytotoxic chemotherapy or hormonal therapy) but were not allowed to have changed it or to have received radiotherapy for pain control in the 2 weeks before the study. Patients were not planned to start new anticancer treatment during the 96-hour study period. Patients with predominantly neuropathic pain were excluded, as were patients who were clinically jaundiced or with serum ALT, AST, or gamma-glutamyltransferase levels greater than 500 U/L.

Ethics approval was obtained from each of the participating institutions, and written, informed consent was obtained from all participants before randomization.

The study design was a double-blind, placebo-controlled, two-period cross-over trial (Fig 1). All participants received acetaminophen (1 g every 4 hours five times per day) for 48 hours and an identical-appearing placebo (using the same schedule) for 48 hours. The order (acetaminophen or placebo first) was randomly allocated by the study pharmacist at a remote location using a computer-generated randomization list.

Pain was the primary outcome and was rated with two measures: a verbal numeric scale (VNS) ranging from 0 (no pain at all) to 10 (the worst pain you can imagine), and a 10-cm linear visual analog scale (VAS) with similar anchors. Preferences, number of opioid breakthrough doses, and overall well-being were secondary measures of efficacy; nausea and vomiting, drowsiness, constipation, and cold sweats were secondary measures of adverse effects.

Pain and other symptoms were rated at baseline before patients started study treatment, then daily for 4 days while patients were receiving study treatment, and again on day 8 after completing study treatment using a study diary. Participants were telephoned daily to elicit the verbal numeric rating for pain and to remind them to fill in their diary. Preferences were rated on day 5 (the day after completing study treatment) by asking participants if they preferred the first 48 hours, the second 48 hours, or neither. Numbers of opioid breakthrough doses were recorded daily by patients. All other secondary outcomes were rated on 10-cm VASs. All self-ratings are expressed on a range from 0 (least) to 10 (most).

The original analysis plan was amended because of slow accrual and a smaller than planned sample size. The original plan

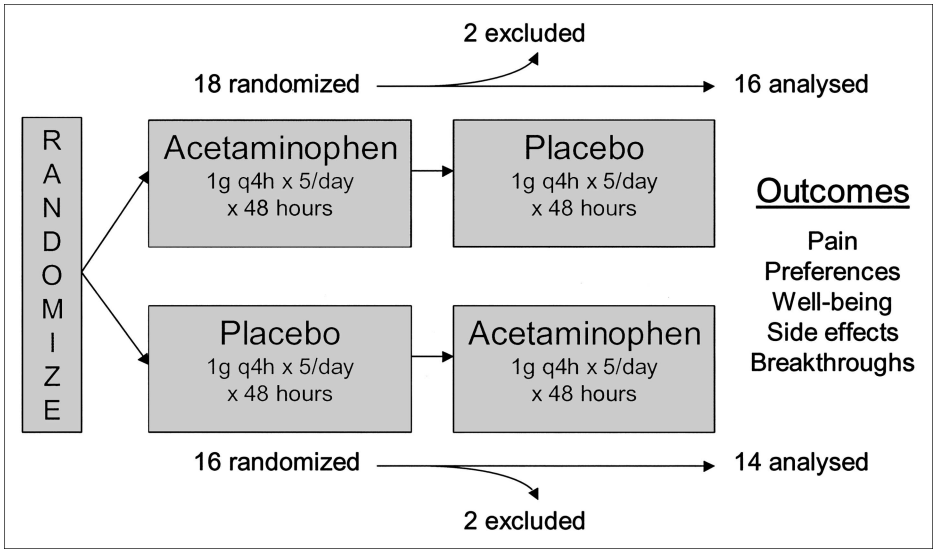

Fig 1. Schema.

specified three primary outcomes: pain, preferences, and opioid breakthroughs. The planned sample size of 50 patients (43 with complete data) was designed to have an 80% power to detect a 7% difference (0.7 on a scale from 0 to 10) with a one-sided type I error of 0.0167. The justification for one-sided *P* values was the extensive data supporting the effectiveness of acetaminophen as an analgesic. The type I error rate was to be set at 0.0167 rather than 0.05 to account for three primary outcomes. The trial was stopped after randomization of 34 patients (30 with complete data) because of slow accrual.

The amended analysis plan was specified before examining or unblinding the data. Pain was considered most important and was made the primary outcome. We decided to give equal weight to the two measures of pain (VNS and VAS), using them to support and corroborate one another. All other outcomes were considered secondary. Preferences were analyzed by comparing the number of participants preferring acetaminophen to the number preferring placebo using McNemar's test. All *P* values are two-sided, and .05 was specified as the notional level for statistical significance.

The cross-over data were analyzed according to the method of Hills and Armitage using analyses of variance to examine for treatment, period, order, and carryover effects.[14] All analyses were based on scores from days 2 and 4 to avoid any possible carryover effect and obviate the need for a washout period. These analyses were carried out for pain, overall well-being, side effects, and the number of breakthrough doses of opioid. The data for each outcome (on days 2 and 4) was checked for normality. Where the data were not normal, the analysis was repeated after logit transformation: ln(yi/[100 − yi]). This transformation and analysis gave results that were consistent with the simpler untransformed analyses.

RESULTS

Complete data were available for 30 participants. Thirty-four patients were randomly assigned, but four were excluded because they took insufficient study medication: one patient in each arm took no study drug, and one patient in each arm took less than 50% of the study drug. We excluded these participants before unblinding the randomization code and without knowledge of their outcomes.

The participants' baseline characteristics are listed in Table 1 and are typical of ambulatory oncology patients. All had troublesome pain attributable to cancer despite a stable regimen of strong opioids. Most had moderate pain: the median VNS for pain was 4, with an interquartile range of 2 to 5 on a scale from 0 to 10.

All participants were on oral opioids (morphine, n = 23; hydromorphone, n = 7). The median regular daily opioid dose in oral morphine equivalents was 200 mg (range, 20 to 2,100 mg). Half the participants were using corticosteroids and/or NSAIDs as coanalgesics.

The average scores for pain and overall well-being were better on the days people took acetaminophen than on the days they took placebo (Fig 2). As planned, all statistical comparisons were based on scores from days 2 and 4 to avoid any possible carryover effect and obviate the need for a washout period. The average difference between acetaminophen and placebo in VNS for pain on days 2 and 4 was 0.4 ($P = .03$; 95% CI, 0.1 to 0.8) and in VAS for pain on days 2 and 4 was 0.6 ($P = .09$; 95% CI, −0.1 to 1.3). VNS for pain was at least one point better while receiving acetaminophen than while receiving placebo in 12 patients but was at least one point better while receiving placebo than while receiving acetaminophen in only four patients. VAS for pain was at least one point better for 12 patients receiving acetaminophen but for only three patients receiving placebo. The average difference between acetaminophen and placebo in VAS for overall well-being on days 2 and 4 was 0.7 ($P = .05$; 95% CI, 0.0 to 1.4). VAS for overall well-being was at least one point better for 12 patients receiving acetaminophen but for only three patients receiving placebo.

More patients preferred acetaminophen (n = 14) than placebo (n = 8), but many had no preference (n = 8), and this difference was not statistically significant ($P = .3$). There were no differences between acetaminophen and placebo in the number of breakthrough doses of opioid used.

There were no demonstrable differences between acetaminophen and placebo in nausea and vomiting, drowsiness, constipation, or cold sweats. There were no period, order, or carryover effects.

DISCUSSION

Acetaminophen improved pain and overall well-being in people already on a stable regimen of strong opioids, half of whom were also taking corticosteroids, NSAIDs, or both. The observed improvements were small, real, and clinically important. The average improvements in pain and overall well-being were modest at 0.4 to 0.7 points on a 10-point scale. However, these averages comprise some patients who seemed to benefit a lot and others who seemed not to benefit at all. Approximately a third of the participants had improvements of one or more points on a scale from 0 to 10. Empirical research suggests that differences of this magnitude are clinically important.[15,16]

Many placebo-controlled trials show that acetaminophen improves analgesia in people with dental and surgical pain; however, we found no other studies of acetaminophen in people with persistent cancer pain despite strong opioids. Acetaminophen reduced dental pain when used alone or in combination with weak opioids.[17,18] Acetaminophen improved pain, satisfaction, and opioid requirements when added to parenteral patient-controlled analgesia in people with postoperative pain.[19] Acetaminophen reduced pain and morphine requirements in women after abdominal hysterectomy[20] and in children after day-surgical procedures.[21] Propacetamol hydrochloride, an intravenous prodrug of acetaminophen, reduced morphine requirements for people undergoing orthopedic

Table 1. Patient Characteristics

	Arm A (n = 16)		Arm B (n = 14)		Overall (n = 30)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
Age, years						
Median	65		52		62	
Range	50-80		42-75		42-80	
Sex						
Male	12	75	9	64	21	70
Female	4	25	5	36	9	30
Primary site						
Prostate	6	38	4	29	10	33
Breast	3	19	3	21	6	20
Colorectal	1	6	2	14	3	10
Lung	2	13	0	0	2	7
Myeloma	1	6	1	7	2	7
Other	3	18	4	29	7	23
Metastatic	15	94	14	100	29	97
Previous treatment						
Chemotherapy	7	44	8	57	15	50
Radiation	11	69	10	71	21	70
Current treatment						
Chemotherapy	5	31	7	50	12	40
Radiation	0	0	0	0	0	0
Opioid drug used						
Morphine	11	69	12	86	23	77
Hydromorphone	5	31	2	14	7	23
Regular daily opioid dose, oral morphine equivalents						
Median	250		150		200	
Range	20-2,100		40-600		20-2,100	
Co-analgesic use						
NSAID alone	1	6	5	36	6	20
Corticosteroids alone	4	25	2	14	6	20
Both corticosteroids and NSAIDs	3	18	1	7	4	13
Pain sites						
Chest	7	44	0	0	7	23
Back	6	38	6	43	12	43
Limbs	4	25	8	57	12	40
Pelvis	4	25	5	36	9	30
Abdomen	1	6	0	0	1	3
Other	5	31	2	14	7	23
Source of pain						
Bone	11	69	11	79	22	73
Soft tissue, lymph nodes or skin	4	25	2	14	6	20
Visceral, liver/spleen/kidney	1	6	1	7	2	7
Other	2	13	1	7	3	10
Coexisting incident pain	3	19	2	14	5	17

Abbreviation: NSAID, nonsteroidal anti-inflammatory drug.

procedures in three randomized trials and lowered pain scores in two such trials.[22-24]

The main strengths of our study are its double-blind, placebo-controlled, cross-over design, multiple outcome measures, and pragmatic inclusion criteria. The design provides substantial protection against bias as the explanation for the results. The consistency of the results across multiple outcome measures supports the conclusion that the effects are real. Our aim was to recruit people who had troublesome pain despite optimization of their opioids and other coanalgesics. The people included were typical of ambulatory patients with cancer pain, and the results should be widely applicable.

The main limitations of our study are its small sample size, short duration, and moderate levels of pain at baseline. Recruitment of participants was harder and slower than expected, but consistent with other studies of palliative interventions. The study was stopped before it reached its

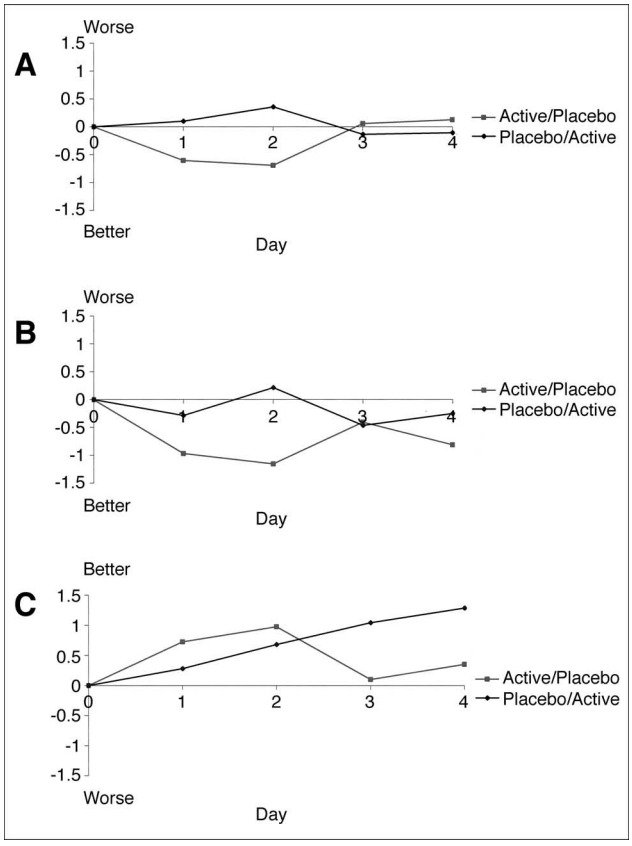

Fig 2. Profiles of mean changes from baseline on a scale from 0 to 10. (A) Visual analog scale for pain; (B) verbal numeric scale for pain; (C) visual analog scale for overall well-being.

planned sample size because of slow accrual. In Australia, accrual was limited by clinicians' reluctance to remove patients from treatment with acetaminophen, whereas in Canada, accrual was limited by clinicians' reluctance to treat patients with acetaminophen. The duration of treatment was deliberately kept short to minimize the effects of disease progression and other interventions. It would be good to know whether the beneficial effects of acetaminophen continue beyond 48 hours, but there is no reason to expect that they would not. Because participants had to be treated with a stable opioid regimen, most had moderate, relatively well-controlled pain, and the extent that their pain could improve was limited.

We considered a washout period when the trial was designed, but decided against it. Instead, we chose to base all analyses on scores collected on days 2 and 4, the second 24 hours of each period. Acetaminophen has a half-life of 1 to 3 hours, so we expected no residual effects 24 hours after the last dose. We found no evidence of a carryover effect in any of our analyses (tested by looking for interactions between treatment and order). Visual examination of the data from day 2 to day 3 do not suggest any carryover effect either (Fig 2).

The main advantages of acetaminophen are its effectiveness, lack of side effects, simplicity, and low cost. The main disadvantages are that its effect is modest and there are many tablets to swallow. The modest average effectiveness of acetaminophen in this trial partly reflects people in whom it made little or no difference. People who feel no better on acetaminophen can stop it. The dose we tested (10 tablets per day, or 1g every 4 hours while awake) is based on the half-life of acetaminophen and the usual dosing intervals for short-acting morphine. A lower dose of eight tablets per day (1g every 6 hours) is commonly used with long-acting opioids. Extended-release formulations also require six to eight tablets per day. All these schedules require many tablets to swallow, but people can try acetaminophen and decide whether the degree of analgesia justifies the number of tablets.

Controlling cancer pain is a major global problem. Many patients with cancer have persistent pain despite an optimized regimen of opioids and coanalgesics. Many others use insufficient opioids and/or NSAIDs because of side effects, price, unavailability, or prejudice. Acetaminophen improved pain and well-being without major side effects in people with cancer and persistent pain despite a strong opioid regimen. Its addition is worth considering in all such patients.

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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