Original Article

Dose-Response Relationship Between Opioid Use and Adverse Effects After Ambulatory Surgery

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Abstract
This health outcomes analysis based on data from a randomized, double-blind, placebo-controlled trial determined dose-response relationship between opioid use and related symptoms. All patients received intravenous fentanyl on demand for pain predischarge, and oral acetaminophen 500 mg/hydrocodone 5 mg every 4–6 hours as needed postdischarge for up to 7 days postsurgery. Patients completed an opioid-related Symptom Distress Scale (SDS) questionnaire every 24 hours postdischarge for 7 days, which assessed 12 opioid-related symptoms by 3 ordinal measures: frequency, severity, and bothersomeness. Clinically meaningful events (CMEs) were defined based on the responses to this questionnaire. Opioid use was converted to morphine equivalent dose (MED). The dose-response relationship between composite SDS scores and MED on Day 1, on Days 0 and 1, and on Days 1–4, was assessed. SDS scores for all 12 symptoms within the 3 dimensions were significantly associated with MED on Day 1 (F-value = 1.56; P = 0.04), as well as cumulative MED used on Days 0 and 1 (F-value = 1.85; P < 0.01). Patients with a specific CME used a higher MED than those without a CME on Day 1 (P < 0.001). Between Days 1 and 4, patients with a higher number of patient-CME-days used a significantly higher MED. Regression analyses suggested that once the MED reached a threshold, approximately every 4 mg increase in MED was related to 1 additional patient-CME-day (P < 0.01). A dose-response relationship empirically exists between MED and directly assessed opioid-related CMEs after ambulatory laparoscopic cholecystectomy. Once daily MED reaches a threshold, every 3–4 mg increase will be associated with 1 additional clinically meaningful opioid-related symptom, or 1 additional patient-day with an opioid-related CME. J Pain Symptom Manage 2004;28:35–46. © *2004 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.*

Key Words
Opioid dose reduction, opioid-related adverse effects, ambulatory surgery, opioid dose-response relationship

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Accepted for publication: November 3, 2003.

0885-3924/04/$–see front matter
doi:10.1016/j.jpainsymman.2003.11.001

Introduction

Ambulatory surgery constituted 60–70% of all surgery performed in North America in the early 1990s.[1] Over the past decade, the percentage of surgical procedures being performed in outpatient centers has significantly increased.[2,3] In response, managing postoperative pain has become a focus area of research.

Opioids are very effective analgesics for postoperative pain management, but numerous studies published during the last decade have demonstrated that opioid analgesics are significantly associated with adverse drug effects, including nausea and vomiting, respiratory depression, urinary retention, pruritus, fatigue, and central nervous system (CNS) effects such as headache, somnolence, drowsiness, and dizziness.[3–6] For example, the reported incidence of postoperative nausea and vomiting after laparoscopic cholecystectomy surgery is 25–40% when no prophylactic antiemetic is provided.[7,8] Urinary retention is a well-known adverse effect of opioid analgesics, with an average of 17.5% of patients reporting some form of urinary retention in studies assessing this symptom.[4] Additionally, a high incidence of fatigue or tiredness,[3] pruritus,[4] and common CNS effects, such as sleep impairment, dizziness, sedation, somnolence, and headache, have been demonstrated with the use of opioid analgesics.[4]

Although opioid analgesic-related adverse events are common, there is a paucity of well-designed studies correlating postoperative adverse events to dose of opioid analgesia. The literature inconsistently reports adverse reactions associated with opioids. Furthermore, although it has been suggested that most opioid-associated adverse events are dose-related,[4,9] to our knowledge no well-designed studies have empirically proved such a relationship. Establishing a dose-response relationship is important to provide theoretical guidance to opioid dose-sparing therapeutic strategies, which are considered desirable in managing postoperative pain. The purpose of this study was to establish the relationship between opioid dose, as represented by the morphine equivalent dose (MED), and 12 common opioid-related adverse effects, as represented by a Symptom Distress Scale (SDS) score and clinically meaningful events (CMEs), after ambulatory surgery. Both immediate responses (one day postoperatively) and longer-term responses (1–4 days) were examined.

Methods

Study Design

This is a health outcomes analysis based on data from a randomized, double-blind, placebo and active comparator-controlled, parallel-group clinical trial among patients who required elective ambulatory laparoscopic cholecystectomy surgery (LCS).[10] Acceptable indications for LCS included acute or chronic cholecystitis, gallstones with a history of pancreatitis (not currently active), and gallstones with a history of jaundice (without current bile duct obstruction). The active arm received intravenous parecoxib 40 mg administered 30–45 minutes preoperatively, and valdecoxib 40 mg every day orally up to Day 4 and as needed on Days 5 to 7 postsurgery. The comparator arm received placebo in place of parecoxib and valdecoxib. General anesthesia was induced with propofol 1–2 mg/kg and fentanyl 2–5 (μg/kg followed by a non-depolarizing neuromuscular blocking drug to facilitate tracheal intubation. Anesthesia was maintained with sevoflurane 1–3% end-tidal concentrations. No local anesthetic was administered either intravenously or at the surgical site. Neuromuscular blockade was reversed with neostigmine and glycopyrrolate. All patients received a prophylactic dose of ondansetron 4 mg intravenously (IV) 10–20 minutes prior to the end of surgery to prevent postoperative nausea and vomiting. The tracheal tube was removed after the patient was able to maintain adequate ventilation and follow commands.

The study included four periods: 1) the pretreatment period—from the screening visit (Day −14) to the time of preoperative dosing with study medication on the day of surgery (Day 0); 2) the intraoperative period—Day 0, from the time of dosing with study medication to the end of surgery (tracheal extubation); 3) the early postoperative period—Day 0, first 4 hours beginning 10 minutes after awakening (T0–T240 minutes); and 4) the oral dosing period—T240 minutes on Day 0 through Day 7. All patients received standard of care intravenous fentanyl on demand for the treatment of pain in the early postoperative period. During the oral

dosing period, patients experiencing insufficient pain relief were allowed to take supplementary hydrocodone 5 mg/acetaminophen 500 mg (Vicodin®; 1–2 tablets orally every 4–6 hours as needed, with a maximum number of 6 tablets for Day 0 and 8 tablets for Days 1 to 7).

During the early postoperative and oral dosing periods, the cumulative opioid dose required by patients, pain intensity, daily activities interfered with by pain, and opioid-related symptoms were directly assessed. For the purposes of this study, we first focused on opioid dose use on Days 0 and 1 after surgery and correlated it with opioid-related symptoms within the first 48 hours after surgical procedure. To assess the longer-term dose-response relationship during the recovery period after surgery, the study also analyzed data between Days 1 and 4 after the operation.

Assessment of Opioid-Related Symptoms

In the oral dosing period, or postoperative Days 1 to 7, opioid-related symptoms were assessed daily with an opioid-related SDS adapted from the Memorial Symptom Assessment Scale.[11] A total of 12 opioid-related symptoms were assessed, including nausea, vomiting, constipation, difficulty passing urine, difficulty concentrating, drowsiness or difficulty staying awake, feeling light-headed or dizzy, feeling confused, feelings of general fatigue or weakness, itchiness, dry mouth, and headache. Pain and diarrhea were also assessed in the questionnaire but were excluded from this analysis because they were not considered to be opioid-related symptoms. Three dimensions were used to determine the symptom experience: severity of the symptom, on a 4-point Likert scale ranging from "slightly severe" (1) to "very severe" (4); frequency, on a 4-point Likert scale, ranging from "rarely" (1) to "almost constantly" (4); and bothersomeness, on a 5-point Likert scale, ranging from "not at all" (1) to "very much" bothered (5). On Days 1 and 2, opioid-related symptom assessment was made over the telephone. For the remaining days, assessments were made via patient diary at bedtime.

Study Sample

One hundred ninety-three (193) patients who fulfilled the requirements of the clinical trial were included in this analysis. Analyses were conducted among all eligible patients in the clinical trial, regardless of treatment group, to provide empirical evidence of a dose-response relationship between MED and opioid-related adverse effects. In this way, the study was able to double the sample size and increase the MED range for this cohort.

Data Analysis

Opioid Use. Dosages of supplementary intravenous fentanyl and oral hydrocodone per patient during the study period were converted to the MED. Briefly, fentanyl 50 μg every hour and hydrocodone 15 mg every 4 hours is equivalent to morphine 15 mg every 4 hours.[12] Therefore, morphine 1 mg is equivalent to fentanyl 13 μg or hydrocodone 1 mg. MED was calculated for the aforementioned time periods.

Creating Individual and Composite Symptom Distress Scale (SDS) Scores. SDS scoring was performed using the methodology of Portenoy et al.[11] Values for frequency and severity for each symptom were scored from 1 to 4. For bothersomeness, reported values of 1 to 5 were scaled to a range roughly similar to the frequency and severity domains: "not at all" was scored as 0.8, "a little bit" as 1.6, "somewhat" as 2.4, "quite a bit" as 3.2, and "very much" as 4.0. If a patient did not experience the symptom in the past 24 hours, a score of 0 was assigned to each domain. The average SDS score for each symptom was calculated by taking the mean of the patient-reported scores for each of the 3 symptom distress dimensions. The overall composite SDS score was the mean of each of the 12 individual symptoms' SDS score. By taking the mean score of all 12 symptoms in each dimension, dimension-specific composite SDS scores for frequency, severity, and bothersomeness were also created.

Creating Clinically Meaningful Events (CMEs). A CME was defined based on the level of patient response to each symptom in the 3 measured dimensions; frequency, severity, and bothersomeness. For each study symptom, a patient with a response of "frequently" to "almost constantly" for the frequency dimension, "moderate" to "very severe" for the severity dimension, or "quite a bit" to "very much bothered" for the bothersomeness dimension was considered to

have a CME.[13] In addition, 3 summary CME measures, patients with at least 1, 2, or 3 CMEs, were created based on individual CMEs.

Statistical Analysis

Dose-Response Relationship Between MED and SDS Scores on Day 1. The SDS scores on Day 1 for individual symptoms as well as for overall symptom frequency, severity, and bothersomeness was described by mean and SD. The overall symptom distress score for all 12 symptoms was also described. Association of Day 1 SDS scores with MED on Day 1, and on Days 0 and 1, were first determined by multiple analysis of variance (MANOVA), adjusting for potential confounding factors. Patient characteristics, clinical features, and operation-related variables significantly associated with SDS score ($P < 0.10$) in a series of univariate analyses were considered potential confounders. These included race, major medical history, open gall bladder during surgery, and treatment. Age and sex were also included as potential confounders. The dose-response relationship between composite SDS scores and MED, both on Day 1 and on Days 0 and 1, was assessed by multiple regression, adjusting for potential confounders.

Dose-Response Relationship Between MED and CMEs on Day 1. The numbers of patients with a CME for each specific opioid-related symptom and with at least 1, 2, or 3 CMEs on Day 1 were described by percentage. The relationship between Day 1 MED and opioid-related CMEs on Day 1 after LCS was determined by 2 methods. The first method compared MED between patients with a specific opioid-related CME and patients without that event by *n*-way ANOVA, after adjusting for potential confounders. The weighted average (by sample size) was also calculated over all symptoms and compared between patients with and without a specific opioid-related CME by *n*-way ANOVA. The second method used multiple linear regression to test the dose-response relationship between MED used on Day 1 only and the number of CMEs patient experienced on Day 1. Because MED taken on the day of surgery (Day 0) might have had a residual impact on CMEs the following day (Day 1), the aforementioned analyses were also conducted based on the total cumulative MED on Days 0 and 1.

Dose-Response Relationship Between MED and Patient-Days with CMEs Between Days 1 and 4. To investigate the association between MED and opioid-related adverse effects in the entire recovery period after LCS, the study tested the dose-response relationship between cumulative MED used between Days 1 and 4 and the number of patient-days with a CME. To perform this analysis, symptom-specific CMEs were first assessed based on the SDS score each day during the 4-day period. Then, the total number of patient-days with CMEs for a given symptom for each patient was calculated, ranging from 0 to 4 days. Patients with 3 or 4 days with a CME were combined due to low counts. Mean MED for each number of patient days with CME for a given symptom was calculated and compared by *n*-way ANOVA, adjusting for potential confounders. By combining all symptom-specific CMEs, we also created 3 summary measures of patient-days with CMEs: patient-days with at least 1, 2, or 3 CMEs, between Days 1 and 4. Linear regression was used to test the average dose-response relationship between cumulative MED between Days 1 and 4 and the number of patient-days with a symptom specific CME. Furthermore, by summing the number of patient-days with CME for all 12 study symptoms, we also created a composite measure of total patient-CME-days. Linear regression was used to assess the relationship between cumulative MED between Days 1 and 4 and total patient-CME-days.

All statistical analyses were performed using SAS (v. 8.02, SAS Institute Inc., Cary, NC).

Results

Description of Study Sample

Table 1 shows patient characteristics and clinical features within all study patients, and reports levels of pain severity and the cumulative MED used in the different treatment periods of the study.

Distribution of SDS Scores

The distribution of SDS scores for each individual opioid-related symptom and composite SDS scores for all opioid-related symptoms

Table 1
Patient Characteristics

Variables	All patients (n = 193)
Age (years) Mean ± SD	45.4 ± 14.1
Sex—Female, *n* (%)	156 (81)
Patient health status (ASA Class), *n* (%)	
I	63 (33)
II	113 (58)
III	17 (9)
Pain severity (range 0–10),[a] Mean ± SD	
Day 0	5.1 ± 2.7
Day 1	4.6 ± 2.6
Days 1 to 4	3.2 ± 2.1
Mean intraoperative fentanyl dose (μg), Mean ± SD	131.0 ± 46.4
Cumulative morphine equivalent dose (mg), Mean ± SD	
Up to 240 minutes post-operation	12.8 ± 9.0
On operation day (Day 0)	23.1 ± 14.4
On Day 1 after operation	14.8 ± 13.4
On both Day 0 and Day 1	37.9 ± 25.0
Between Day 1 and Day 4 after operation	39.0 ± 38.1
Cumulative morphine equivalent dose (mg), Median (range)	
Up to 240 minutes post-operation	11.2 (0–51)
On operation day (Day 0)	20.0 (0–79)
On Day 1 after operation	10.0 (0–80)
On both Day 0 and Day 1	34.1 (0–122)
Between Day 1 and Day 4 after operation	30.0 (0–175)

[a]Pain scores are based on responses to the "worst pain in the past 24 hours," using the Brief Pain Inventory measured on a scale of 0 to 10, where 0 = no pain, 10 = worst pain possible.

assessed on Day 1 are listed in Table 2. Feelings of general fatigue or weakness resulted in the highest SDS score, followed by dry mouth, drowsiness or difficulty staying awake, headache, nausea, feeling light-headed or dizzy, itchiness, and difficulty passing urine. The composite SDS score for symptom frequency was a little higher than for symptom severity or bothersomeness. Similar results were observed for the proportion of patients with CMEs for each study symptom (Table 2).

Dose-Response Relationship Between MED and SDS Scores

MANOVA determined the overall relationship between MED and SDS scores. After adjusting for confounders, SDS scores for all 12 individual symptoms and dimensions (frequency, severity, bothersomeness) were significantly associated with MED on Day 1 (F-value = 1.56; $P = 0.04$), as well as cumulative MED used on Days 0 and 1 (F-value = 1.85; $P < 0.01$).

The association between MED and SDS scores was assessed using linear regression. Due to the limited sample size and having a wide range of SDS scores for individual symptoms, the study only estimated the dose-response relationship between composite SDS scores (frequency, severity, bothersomeness, overall) and MED. After adjusting for potential confounders, the study found that composite SDS scores for frequency, severity, and bothersomeness and for overall SDS score were significantly associated with cumulative MED. The effect of each 1 mg increase in MED on SDS score on Day 1 was similar for the dimension-specific SDS scores and for overall SDS score (range 0.0049–0.0058, $P < 0.05$). When the cumulative MED used during Day 0 and Day 1 was used instead of only Day 1, the effects of each 1 mg increase in MED on SDS score were smaller, ranging from 0.0037 to 0.0041 for all patients ($P < 0.01$) (data not shown).

Dose-Response Relationship Between MED and CMEs on Day 1 and on Days 0–1

n-way ANOVA was used to compare the MED between patients with a CME for a given opioid-associated symptom and those without a CME. In general, patients with a specific CME used a higher dose of morphine than those without the CME. The average MED among patients with a CME was 18.1 mg MED (SE = 0.6) on Day 1 only and 45.2 mg (SE = 1.3) on both Day 0 and Day 1, whereas average MED used among those without a specific CME were 14.3 mg (SE = 0.1) on Day 1 only ($P < 0.0001$) and

Table 2
Distribution of Opioid-Related SDS Score and CMEs on Day 1 After Surgical Procedure

	All Patients (n = 193)	
	Mean ± SD	n (%) with CME
SDS score based on individual symptoms		
Nausea	0.36 ± 0.8	20 (10)
Vomiting	0.11 ± 0.5	8 (4)
Constipation	0.18 ± 0.6	10 (5)
Difficulty passing urine	0.19 ± 0.7	12 (6)
Difficulty concentrating	0.13 ± 0.5	6 (3)
Drowsiness or difficulty staying awake	0.54 ± 0.9	35 (18)
Feeling light-headed or dizzy	0.34 ± 0.7	18 (9)
Feeling confused	0.02 ± 0.2	0 (0)
Feeling of general fatigue or weakness	1.06 ± 1.1	73 (38)
Itchiness	0.30 ± 0.7	13 (7)
Dry mouth	0.96 ± 1.2	58 (30)
Headache	0.44 ± 0.9	28 (14)
With at least one symptom	N/A	123 (64)
With at least two symptoms	N/A	71 (37)
With at least three symptoms	N/A	39 (20)
Composite SDS score		
How often did you experience it	0.46 ± 0.4	N/A
How severe was it	0.34 ± 0.3	N/A
How bothersome was it	0.36 ± 0.4	N/A
Overall score	0.39 ± 0.4	N/A

Range for SDS score 0 to 4 where 0 = no symptom, 4 = most frequent, most severe, or most bothersome.

36.9 mg (SE = 0.3) on both Day 0 and Day 1 ($P < 0.0001$). The average differences in MED between patients with and without a given CME were 3.7 mg for dose used on Day 1 only and 8.3 mg for dose used on Day 0 and Day 1 (4.2 mg per day).

More than 36% of patients had CMEs for more than one symptom; patients with or without a specific symptom might also have other symptoms. Consequently, comparing the average MED among patients with a specific CME with those without such a CME might underestimate or overestimate the difference in MED between the two groups. Therefore, the dose-response relationship between MED and number of symptoms with a CME was determined by regression analyses. Table 3 indicates that patients with higher numbers of symptoms with CMEs used more opioid analgesics. The analyses based on the MED used on Day 1 suggested that once MED reached a threshold (10.6 mg of daily dose), approximately every 3 mg increase of MED was associated with an additional symptom with a CME. The MED based on opioid use on Days 0 and 1 was approximately 6 mg (3 mg per day) per additional symptom with a CME after reaching a threshold of 29 mg (Table 3) (Figure 1a and b).

Dose-Response Relationship Between MED and Patient-Days with CMEs Between Days 1 and 4

Table 4 presents the distribution of average MED by the number of patient-days with a CME for each specific opioid-related symptom. In general, MEDs were significantly higher among patients with a higher number of days with a CME for a specific symptom than among patients with a lower number of days with a CME. The table also indicates that patients with higher MED had a significantly higher number of days with multiple CMEs. For example, the average MED was 77.0 mg for patients with at least 3 CMEs for three or more days, whereas the average MED was only 33.3 mg for patients with no days of three or more CMEs during the same time period. Multiple regression analyses between MED and number of patient-days with CMEs for a specific symptom showed that out of the 12 symptoms assessed, the dose-response relationship was statistically significant for 8 symptoms among all study patients (Table 4). The regression analysis also indicated that the number of patient-days with multiple CMEs was

Table 3
MED (mg) Used and Number of Clinically Meaningful Symptoms Experienced on Day 1

	Based on Day 1 Dose				Based on Day 0 and Day 1 Dose			
	Comparison of Means	Effect Estimate of One Additional Clinically Meaningful Symptom on Dose			Comparison of Means	Effect Estimate of One Additional Clinically Meaningful Symptom on Dose		
No. CMEs	Least Square Mean ± SE[a]	Baseline (α) (mg)	Effect Estimate (β) (mg)[b]	Effect Estimate (β_{adj}) (mg)[c]	Least Square Mean ± SE[a]	Baseline (α) (mg)	Effect Estimate (β) (mg)[b]	Effect Estimate (β_{adj}) (mg)[c]
No event	11.0 ± 1.5	10.6	3.5	3.0	31.0 ± 2.7	29.1	7.2	5.9
1 event	14.8 ± 1.7				36.3 ± 3.1			
2 events	15.6 ± 2.2				41.7 ± 3.9			
≥3 events	20.8 ± 2.1				49.1 ± 3.7			

[a]Least square mean MEDs (mg) calculated by *n*-way ANOVA, adjusting for age, sex, race, significant medical history, open gall bladder, and among all patients, treatment.
[b]Unadjusted regression analysis ($P < 0.001$).
[c]Adjusted regression analysis, controlling for age, sex, race, significant medical history, open gall bladder, and among all patients, treatment ($P < 0.001$).

significantly associated with MED ($P \leq 0.001$ for all three summary measures, Table 4). These regression analyses also suggested that levels of the dose-response relationship differed by individual symptoms.

The study also determined the relationship between MED use between Days 1 and 4 and total number of patient-CME-Days. Table 5 and Figure 1c show that patients with higher numbers of patient-CME-days used a significantly higher MED between Days 1 and 4. The regression suggested that once MED between Days 1 and 4 reached a threshold (20.6 mg), approximately every 4 mg increase in MED was related to one additional patient-CME-day ($P < 0.01$).

Discussion

In clinical management of postoperative pain, patients treated with opioid analgesics often present with one of two common situations: either pain is controlled but the patient experiences some intolerable adverse effects, or pain is not adequately controlled and it is impossible to increase the opioid analgesic dose because of adverse effects.[14] Some previous studies, using multimodal treatment strategies to reduce opioid use, have been unable to demonstrate a relationship between opioid dose reduction and reduction of opioid-related adverse effects.[15,16] A study in which propacetamol was administered with postoperative morphine did not demonstrate any significant reduction in opioid-related side effects compared with morphine alone, including nausea, respiratory depression, and urinary retention.[16] From this, Aubrun et al.[16] suggested that the proposed benefits of multimodal analgesia, at least with respect to opioid-related adverse effects, may be erroneous. However, there is much recently published literature to support the concept of multimodal analgesia to improve patient outcomes, part of which includes reducing opioid-related adverse effects.[4,17–19] The ability to demonstrate such a relationship is important to support treatment strategies that reduce postoperative opioid use.

The current study found that symptom distress, as measured by SDS score, is significantly associated with opioid dose. On average, each milligram increase in daily MED is associated with an approximate 0.005 to 0.006-point increase in overall composite SDS score. To interpret this relationship for clinical practice, the study used the concept of CME to establish the dose-response relationship between morphine daily dose and CMEs for individual symptoms. Using three approaches, the study found that on average, an approximate 3–4 mg increase in MED was related to 1 additional CME. Specifically, the average MED for patients with a specific CME was 4 mg higher than for patients without any CMEs, and approximately each 3 mg increase in daily MED was associated with one additional CME after reaching a threshold level (10.6 mg). Furthermore, using the concept of patient-CME-days, the study found that during the recovery period (Days 1 to 4) after ambulatory LCS once the cumulative MED reached about 20 mg, each 4 mg increase in MED was associated with an additional patient-CME-day.

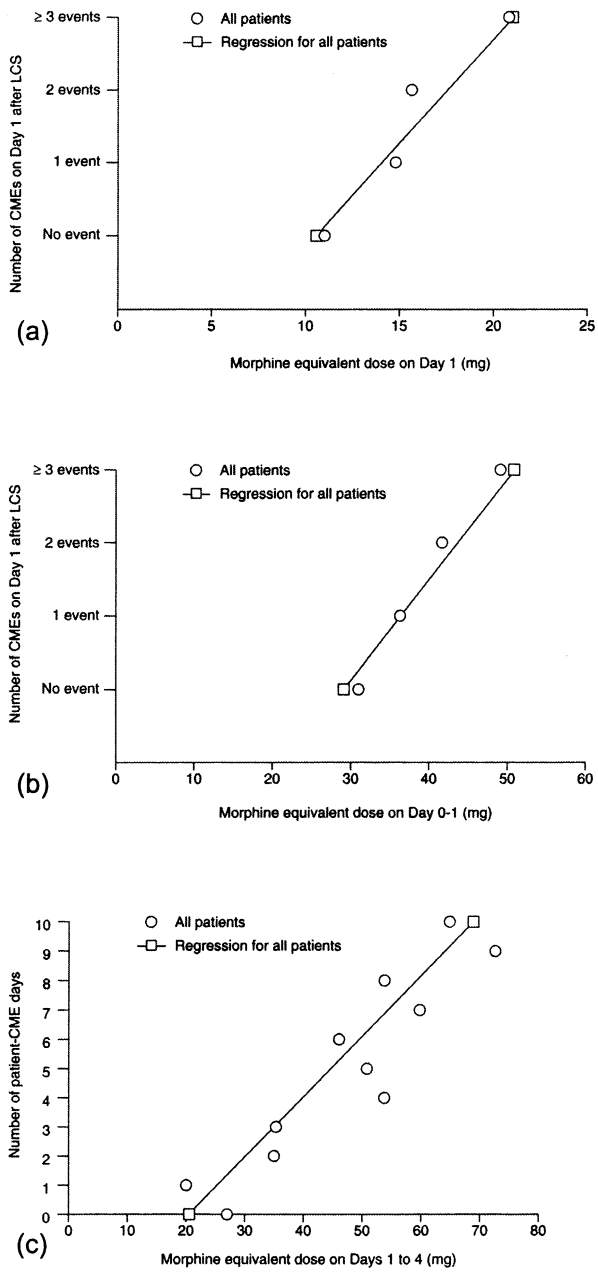

Fig. 1. Dose-response relationship between MED (mg) used and number of CMEs on Day 1, on Day 0 and 1, and Days 1 to 4 after LCS. Multiple regression analysis demonstrates that the number of patients with multiple CMEs was significantly associated with MED for all patients on (a) Day 1 postsurgery ($Y = 10.6 + 3.5X$), and on Days 0 and 1 (b) ($Y = 29.1 + 7.2X$) ($P < 0.001$). Additionally on postoperative Days 1 through 4 the number of patient-days with multiple CMEs was significantly associated with MED for all patients ($Y = 20.6 + 4.8X$; $P < 0.001$).

The findings of this study have significant clinical value in postoperative pain management. Because most adverse events associated with opioids are dose-related,[4] opioid-sparing strategies are desirable. The findings of this study provide guidance in the use of co-therapies. It suggests the dose at which an opioid analgesic could be coadministered with a nonopioid analgesic to obtain optimal pain control with limited adverse effects. The study findings may also help in the design of clinical trials for evaluating the benefit of opioid-sparing effects of a particular analgesic.

The time when opioid-related symptoms occur can vary greatly. For example, urinary retention and constipation may develop more slowly and become symptomatic a day or more after surgery, whereas nausea occurs relatively early. Therefore, assessment of an opioid-related adverse effect at a fixed time may miss the peak occurrence of some events, which may significantly affect the sensitivity of a dose-response relationship analysis. The study used two different approaches to overcome these challenges. Firstly, by combining study adverse effects, namely, creating composite SDS scores and number of CMEs, using the average relationship for all study symptoms, the study was able to reduce the impact of symptom variance due to time of occurrence for individual adverse effect. Secondly, using the patient-event-time method, the study evaluated the longer-term (up to four days after operation), dose-response relationship between cumulative MED and specific opioid-related CMEs. This analysis estimated the average impact over a reasonable time period after surgical procedure. Combining each study event and using cumulative MED over a four-day period increased the robustness of the longitudinal relationship. This second approach showed that levels of dose-response relationship between MED and different CMEs were significantly different.

Symptoms included in this study are the common adverse effects related to the use of opioid analgesics reported in the literature. However, this is not a complete list. For example, respiratory depression was not included in the SDS questionnaire for two reasons: 1) this effect is the least commonly reported opioid-associated adverse event,[4] and 2) without an appropriate monitoring method, the reliability

Table 4
Association Between Cumulative MED Between Days 1 and 4 and Number of Days with CMEs

	Least Square Mean MED by Number of Days Patients with CMEs								
	0 Days		1 Day		2 Days		3 Days		
Symptom	*n* (%)	$MED_{mg} \pm SE$	*n* (%)	$MED_{mg} \pm SE$	*n* (%)	$MED_{mg} \pm SE$	*n* (%)	$MED_{mg} \pm SE$	Effect Estimate (β) (mg)
Nausea	157 (81)	36.9 ± 4.1	23 (12)	36.8 ± 8.1	6 (3)	80.9 ± 15.0	7 (4)	87.2 ± 13.9	13.7[a]
Vomiting	182 (94)	38.2 ± 4.2	9 (5)	39.2 ± 13.0	0 (0)	N/A	2 (1)	64.9 ± 26.7	6.0
Constipation	139 (72)	33.1 ± 4.4	27 (14)	45.3 ± 7.3	14 (7)	52.5 ± 9.9	13 (7)	72.6 ± 10.7	11.1[a]
Difficulty passing urine	168 (87)	37.9 ± 4.2	18 (9)	30.2 ± 9.0	4 (2)	92.8 ± 18.2	3 (2)	80.5 ± 20.9	11.5[b]
Difficulty concentrating	177 (92)	37.5 ± 4.2	11 (6)	54.8 ± 11.8	5 (3)	57.8 ± 17.0	0 (0)	N/A	12.6
Drowsiness or difficulty staying awake	143 (74)	35.6 ± 4.3	33 (17)	50.3 ± 7.2	14 (7)	54.6 ± 10.6	3 (2)	35.6 ± 21.2	8.2[b]
Feeling light-headed or dizzy	159 (82)	34.2 ± 4.3	25 (13)	52.0 ± 8.0	6 (3)	64.4 ± 14.7	3 (2)	77.0 ± 21.4	14.3[a]
Feeling confused	190 (98)	37.5 ± 4.1	3 (2)	98.6 ± 21.1	0 (0)	N/A	0 (0)	N/A	61.1[c]
Feeling of general fatigue or weakness	83 (43)	34.1 ± 4.9	49 (25)	36.8 ± 6.3	31 (16)	43.6 ± 7.5	30 (16)	54.9 ± 7.6	5.9[c]
Itchiness	157 (81)	36.9 ± 4.4	17 (9)	44.4 ± 9.3	13 (7)	48.3 ± 11.1	6 (3)	51.7 ± 15.5	5.2
Dry mouth	121 (63)	33.4 ± 4.4	42 (22)	48.5 ± 6.5	19 (10)	47.4 ± 9.1	11 (6)	61.7 ± 11.4	8.0[c]
Headache	146 (76)	37.7 ± 4.4	30 (16)	41.9 ± 7.5	10 (5)	49.8 ± 12.7	7 (4)	46.5 ± 15.0	2.9
At least 1 of the above	36 (19)	27.4 ± 6.3	34 (18)	27.5 ± 6.6	50 (26)	39.5 ± 5.9	73 (38)	56.0 ± 5.5	9.1[a]
At least 2 of the above	80 (41)	28.8 ± 4.8	54 (28)	41.1 ± 5.8	30 (16)	46.3 ± 6.9	29 (15)	67.5 ± 7.7	10.0[a]
At least 3 of the above	126 (65)	32.3 ± 4.2	39 (20)	49.2 ± 6.7	17 (9)	62.8 ± 9.2	11 (6)	77.0 ± 11.3	13.4[a]

Least square mean MEDs calculated by *n*-way ANOVA, adjusting for age, sex, race, significant medical history, open gall bladder, and among all patients, treatment.
[a] $P < 0.001$;
[b] $P < 0.05$;
[c] $P < 0.01$; multiple regression between patient-days with a CME and cumulative MED Days 1 to 4, adjusting for age, gender, race, significant medical history, open gall bladder, and among all patients, treatment.

Table 5
Association Between Cumulative MED Between Days 1 and 4 and Number of Patient-CME-Days

	All Patients (n = 193)				
	Comparison of Means		Effect Estimate of One Additional Patient-CME-Day		
Number of Patient-CME-Days	n (%)	Mean ± SE[a]	Baseline (α) (mg)	Effect Estimate (β) (mg)[b]	Effect Estimate (β_{adj}) (mg)[c]
0	36 (19)	27.0 ± 6.3	20.6	4.8	4.3
1	19 (10)	20.0 ± 8.3			
2	27 (14)	35.0 ± 7.3			
3	26 (13)	35.3 ± 7.6			
4	13 (7)	53.8 ± 10.7			
5	18 (9)	50.8 ± 8.7			
6	13 (7)	46.1 ± 10.3			
7	10 (5)	59.8 ± 11.7			
8	4 (2)	53.0 ± 17.7			
9	6 (3)	72.6 ± 14.4			
10+	21 (11)	64.8 ± 8.7			

[a]Least square mean MEDs (mg) calculated by n-way ANOVA, adjusting for age, sex, race, significant medical history, open gall bladder, and among all patients, treatment.
[b]Unadjusted regression analysis ($P < 0.001$).
[c]Adjusted regression analysis, controlling for age, sex, race, significant medical history, open gall bladder, and among all patients, treatment ($P < 0.001$).

of patient self-reported respiratory depression is very low.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used as coanalgesics to reduce morphine therapy,[20–23] but their use in the postoperative setting can be limited due to a high risk of gastropathy,[24,25] and increased bleeding due to inhibition of platelet aggregation.[26] COX-2 specific inhibitors have an improved upper gastrointestinal and platelet safety profile[27–29] and provide one option for postoperative pain management to reduce postoperative opioid use.[30–32] For example, compared to the standard of care, use of intravenous parecoxib 40 mg preoperatively, and postoperative oral valdecoxib 40 mg daily, can significantly reduce the amount of opioid analgesic use by 30%, postoperative pain by 30%,[10,33–35] SDS score by 35%, and incidence rate of opioid-related CMEs by approximately 40%.[36]

A few limitations related to the current study should be noted. The study was based on the data from a well-controlled clinical trial conducted among patients who had ambulatory LCS. Because the severity of postoperative pain and dosage required to manage postoperative pain varies significantly among different surgical procedures, the results of the study should not be generalized to other surgical procedures in clinical practice, such as inpatient surgery, where greater amounts of opioids may be administered. Additional studies should be conducted for different surgical procedures to establish such a relationship. In addition, the study is based on data from a well-controlled clinical trial. Due to the nature of clinical trials, inclusion and exclusion criteria of patients, surgical procedures, and postoperative management may be significantly different from real-life clinical practice. Therefore, it is necessary to exercise caution if applying the findings of this study to clinical practice.

In conclusion, a dose-response relationship empirically exists between MED and directly assessed opioid-related CMEs after ambulatory LCS. Once the daily MED reaches a threshold, every 3–4 mg increase in MED will be associated with one additional clinically meaningful opioid-related symptom, or one additional patient-day with an opioid-related CME.

Acknowledgments

This work was sponsored in part by Pfizer Inc., 5200 Old Orchard Road, Skokie, IL 60077, and 100 Route 206 North, Peapack, NJ 07977 USA.

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