

## Opioid Dose Titration for Severe Cancer Pain: A Systematic Evidence-Based Review

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### ABSTRACT

Dosing strategies to achieve rapid analgesia in patients with severe or crescendo cancer pain are important. A systematic review of research trials for treatment of severe or crescendo cancer pain was conducted; nine studies were identified. Eight trials were prospective; two were randomized between different dosing strategies. Dosing frequency predicted onset to analgesia regardless of baseline opioid dose. None of the trials were associated with evidence of respiratory depression. The studies all suffered significant methodological problems limiting broad conclusions. Until better data exist, opioid dose titration for severe/crescendo pain will be guided by expert opinion and experience.

### INTRODUCTION

SEVERE OR CRESCENDO PAIN is common in advanced cancer and typically requires aggressive dosing with oral or parenteral opioids. Titration strategies involve planned dose escalation at fixed or variable dosing intervals and/or titration by a loading dose followed by maintenance doses of oral or parenteral opioid.<sup>1-3</sup> There are currently no evidence-based guidelines to aid clinicians in the procedure of dose titration that optimizes clinical outcome with minimal risk. In 2003 the Federation of French Cancer Centers attempted to establish clinical practice guidelines based on a literature review and found only a few randomized trials with weak conclusions.<sup>4</sup> A systematic review of opioid dosing strategies for severe or crescendo pain in advanced cancer has not been reported in the English literature. A systematic review requires both a methodology for literature review to avoid bias and a method of

grading evidence for establishing guidelines. The goal of this paper is to systematically review opioid titration trials for cancer pain published in the English literature in hopes of establishing evidence based guidelines for opioid titration in severe cancer pain.

### METHODS

For the purpose of this review, severe pain is defined as uncontrolled or continuous crescendo pain. Published studies of opioid dose titration strategies were accessed through PubMed, Ovid Med (Ovid Technologies, New York, NY) and the Cochrane Reviews using the following search words; titration, opioid, cancer pain, dosing. Other studies were obtained through references from published articles. Only studies whose primary objective was the rapid titration of opioids for poorly controlled continuous pain in non-

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postoperative cancer patients were selected; trials that provided regular opioid dosing with provision of opioids for breakthrough pain or dose escalation for breakthrough pain only, were excluded. Unpublished studies, abstracts, and studies not available through MEDLINE searches were not reviewed.

Articles were classified on the basis of methodology as either a Class A trial (randomized controlled trial), Class B (cohort study), Class C (non-randomized trial with concurrent or historical controls or population based study), or Class D (cross-sectional study or case series). The pretitration opioid dose, dosing strategy, method of determining analgesia, assessment schedule, time to analgesia, side effects, and patient demographics were abstracted from each article.

We attempted to base our recommendations on the Method of Guyatt and coworkers.<sup>5</sup> Unfortunately, given the weakness of the available datum, these criteria were not descriptively useful. Thus, we adopted the following grading scale from the Institute for Clinical Systems Improvement<sup>6</sup>:

**Grade I** The evidence consists of results from studies of strong design for answering the question addressed. The results are both clinically important and consistent with minor exceptions at most. The results are free of significant doubts about generalizability, bias, and flaws in research design. Studies with negative results have sufficiently large samples to have adequate statistical power.

**Grade II** The evidence consists of results from studies of strong design for answering the question addressed, but there is uncertainty attached to the conclusion because of inconsistencies among the results from different studies or because of minor doubts about generalizability, bias, research design flaws, or adequacy of sample size. Alternatively, the evidence consists solely of results from weaker designs for the question addressed, but the results have been confirmed in separate studies and are consistent with minor exceptions at most.

**Grade III** The evidence consists of results from studies of strong design for answering the question addressed, but there is substantial uncertainty attached to the conclusion because of inconsistencies among the results from different studies or because of

serious doubts about generalizability, bias, research design flaws, or adequacy of sample size. Alternatively, the evidence consists solely of results from a limited number of studies of weak design for answering the question addressed.

**Grade IV** The support for the conclusion consists solely of the statements of informed medical commentators based on their clinical experience, unsubstantiated by the results of any research studies.

## RESULTS

Nine trials were identified from the search criteria, including eight prospective and one retrospective trial<sup>7-15</sup> (Table 1). Six trials were single-arm trials (Class D) and two trials were randomized (Class A).<sup>9,14</sup> Different trials used different pain rating scales including visual analogue scale (VAS), verbal rating scale (VRS), numerical rating scale (NRS), and pain descriptors (e.g., moderate-severe). The definition of acute or severe pain was not consistent across trials, including: pain score of 8 or more (NRS 0-10) lasting for at least 6 hours; of 5 or more (NRS 0-10); less than 7 (NRS 0-10); greater than 80 (NRS 0-100); pain of 80-100 (VAS 0-100); 3 or more (VRS 1-7), "uncontrolled pain," "inadequate pain relief," and "moderate to severe pain."

The method and timing of pain assessment also varied widely, ranging from patient self-assessment every 2-10 minutes, four times per day, or only once daily assessment. In the patient controlled analgesia (PCA) studies, patient diaries were assessed morning, noon, evening, and night or daily.<sup>12,13</sup>

Analgesics used prior to opioid titration differed widely. In five trials, patients had received only nonsteroidal anti-inflammatory drugs (NSAIDs) or weak opioids (dextropropoxyphene and codeine) prior to titration. At the other extreme, in one trial of nine patients, the average pretitration morphine dose was 3.36 g. The number of patients who were receiving potent opioids was not provided in one study.<sup>15</sup>

All nine trials used different titration schedules including intravenous titration,<sup>7-9</sup> PCA of either morphine or fentanyl,<sup>11,12</sup> and oral dose titration.<sup>13-15</sup> The outcome measures used to gauge titration efficacy included "the absence of pain," "pain relief and comfort," "initial signs of signif-

TABLE 1. SUMMARY OF OPIOID TITRATION TRIALS PUBLISHED IN THE ENGLISH LITERATURE

<i>Study</i>	<i>Methodology</i>	<i>Pretrial opioid</i>	<i>Pain assessment and response</i>	<i>Dose</i>	<i>Number of patients</i>	<i>Mean time to analgesia</i>
Hagen et al. <sup>7</sup>	Prospective case study	Morphine	NRS (0–10) Response $\leq 5$	IV morphine 10–20 mg/15 min double q30 minute if no relief	9	89 min
Kumar A	Retrospective case series	NSAIDs, a weak opioid	NRS (0–10) Response complete pain relief	IV morphine 1.5/10 min IV + metoclopramide	491	<100 minutes for complete pain relief
Kumar B	Prospective randomized	NSAIDs, weak opioids	NRS (0–10) Response complete pain relief	IV versus oral 1.5/10 min IV + metoclopramide versus 5–10 mg PO q4H	62	84% at 1 hr (IV) versus 26% at 1 hr (PO)
Mercadante et al. <sup>10</sup>	Prospective case series	NSAIDs weak and potent opioid	NRS (0–10) Response initial onset to significant analgesia	IV morphine 2 mg/2 min	49	9.7 min
Radbruch et al. <sup>11</sup>	Prospective case series	Weak opioids	NRS (0–100) Response not defined by pain scale	PCA morphine 1 mg/5 min lockout	28	300 minute (range 100–620 minutes)
Zech et al. <sup>12</sup>	Prospective case series	Oral morphine and SC morphine	VAS (0–100) Response not defined by VAS	PCA Fentanyl 50 $\mu$ 5/min lockout	20	In 24 hours VAS 68 to 34 (mean change in VAS)
Klepstad et al. <sup>13</sup>	Prospective case series	Codeine/APAP Dextropropoxyphene/APAP	VRS (1–7) VAS (0–100)	Oral Morphine 10 q4h $\times$ 6 doses Increase by 33%–50% q24 hours	40	2.3 day
Klepstad et al. <sup>14</sup>	Randomized controlled, double-blinded	Codeine Dextropropoxyphene	VAS (0–100) VRS (1–7) Response 3 or less (VRS)	Morphine IR vs. SR 60 mg/d titrated 90–120–180–270–360 mg	128	2.1 day (IR) 1.7 day (SR)
Lichter <sup>15</sup>	Prospective case series	Weak or potent opioids (not morphine)	Qualitative description of pain relief and comfort	Oral morphine oral 5 > 10 > 15 > 20 > 30 > 40 > 60 > 80 120 > 160–200 at 4-hr intervals at home Oral q2h same schedule in hospice	50 22 in home care 28 in hospice	26 hr home 6h hospice

IR, immediate release; SR, sustained release; NRS, numerical rating scale; NSAIDs, nonsteroidal anti-inflammatory drugs; IV, intravenous; VAS, visual analogue scale; PCA, patient-controlled analgesia; SC, subcutaneous; PO, per os (orally); VRS, verbal rating scale.

icant analgesia," or a numerical score of 5 or less (NRS 0–10). The PCA and oral titration trials considered either a pain score of less than 30 (NRS 0–100) or less than 3 (VRS 1–7) as success.

### *Individual trials*

The trial by Hagen et al.<sup>7</sup> was a prospective pilot study of nine subjects, mean age 50 (range, 31 to 70 years). Pain was assessed using a numeric rating scale (0–10). Patients entered this trial with a NRS of 8 or greater lasting at least 6 hours. The pretrial analgesic was morphine, with a median dose of 1530 mg (range, 48–16,800 mg). The treatment strategy consisted of 10–20 mg intravenous morphine over 15 minutes, and doubled at 30-minute intervals until pain control was achieved. Treatment efficacy was considered a pain score of 5 or less (NRS 0–10). The mean dose to achieve analgesic benefit was not provided. All patients responded; the mean time to response was 89 minutes (range, 4–215 minutes). No toxicity was reported.

The study by Kumar and Nassema<sup>8</sup> was a retrospective study of 491 patients. Patient ages ranged from 18 to 89 years. Criteria for entry was a pain score of greater than 5 (NRS 0–10) on a weak opioid or nonsteroidal anti-inflammatory drug (NSAID). Treatment consisted of 1.5 mg of morphine intravenously every 10 minutes until complete relief of pain. Treatment response was defined as "complete analgesia." Of 482 patients, 380 (79%) had total pain relief. Doses for complete relief ranged from 1.5–15 mg for 94% of responders (range, 1.5–60 mg). Response was seen in 79% of patients, all within 100 minutes. There was no difference in response based on the type of pain. Forty-five of 61 patients in the "aching" pain group responded, 41 of 54 in the "burning" pain group, 14 of 20 in the "lacinating" pain group, and 16 of the 22 "prickling" pain group responded. Side effects included nausea and vomiting (7), breathlessness (3) and drowsiness; drowsiness occurred in 32% of the entire group and 22% of complete responders.

A second trial by the same group was a prospective randomized controlled trial comparing an intravenous morphine titration schedule to oral morphine, administered every 4 hours.<sup>9</sup> Sixty-two subjects were enrolled; two thirds were between the age of 40 and 70. The entry criterion was a pain score greater than 5 (NRS 0–10). Prior analgesics were acetaminophen and NSAIDs. The

treatment strategy was (1) parenteral morphine, 1.5 mg every 10 minutes until complete pain relief compared to (2) oral morphine 5–10 mg every 4 hours. The definition of treatment response was "complete pain relief." The mean parenteral morphine dose to achieve complete pain relief was 4.5 mg (range, 1.5–34.5 mg). By 1 hour, 26 of 31 (84%) patients receiving parenteral morphine and 8 of 31 (26%) treated with oral morphine responded ( $p < 0.001$ ). By 24 hours all patients treated with parenteral morphine had responded and 26 of 31 (84%) oral morphine treated patients responded ( $p = 0.55$ ). Side effects included rash and pruritis in the parenteral treated group. In the oral morphine group, 1 patient developed intractable vomiting; drowsiness developed in 11 patients on the parenteral morphine treatment arm.

The trial published by Mercandante et al.<sup>10</sup> was a prospective case series involving 49 patients (45 evaluable) with a mean age of 58 (range, 53–62 years). The criterion for entry was a pain score greater than 7 (NRS 0–10). Prior analgesics included oral morphine (14 patients), fentanyl (1 patient); an undisclosed number of patients were also receiving NSAIDs. The treatment strategy consisted of intravenous morphine 2 mg every 2 minutes until "initial signs of significant analgesia." All patients responded, the mean morphine dose at the time of response was  $8.5 \text{ mg} \pm 2.0$ , occurring in  $9.7 \pm 2.3$  minutes. Responses were independent of pain mechanism and unrelated to prior opioid exposure. Side effects included drowsiness (2 patients), pruritis (2 patients), nausea (3 patients), emesis (2 patients), and dizziness (2 patients).

The study by Radbruch et al.<sup>11</sup> was a prospective case series involving three pain clinics. Twenty-eight patients with a mean age of 56 (range, 32–79 years) were assessed using an NRS (0–100). The entrance criterion was "severe pain"; the mean NRS at study entry was 67. Patients received only weak opioids prior to study entry. Treatment consisted of PCA using 1 mg of morphine as a PCA dose with a 5-minute lockout interval. The criteria for treatment response was not clearly defined. Pain assessment in 15 patients demonstrated "sufficient analgesia," defined in this subgroup as a pain score less than 30 (NRS 0–100); the mean time to response was 300 minutes (range, 100–620 minutes). The mean dose in the first 24 hours was 32 mg (range, 4–78 mg), resulting in a mean pain score reduction from 67 to

22. Side effects included constipation (15 patients), vomiting (7 patients), nausea (16 patients); the authors felt that some of these toxicities were present prior to morphine administration.

The study by Zech et al.<sup>12</sup> was a prospective case series involving 20 patients with a mean age of 56 (range, 40–68 years). The entrance criterion was very great or maximum conceivable severe pain score ( $\geq 80$  VAS 0–100) on oral or parenteral weak opioids. However most at the time of study were on potent opioids, hence the discrepancy between VAS scores ( $> 80$  on weak opioids and 68 upon starting PCA fentanyl). The treatment strategy was fentanyl 50  $\mu\text{g}$  by PCA with a 5-minute lockout interval. Efficacy was measured by a five-point pain relief scale (0 = 100% relief and 4 = no relief); pain was assessed by daily patient self-reported pain score (VAS). The mean daily VAS decreased from 68 (40–95) to 34 (20–45); the mean total fentanyl dose in the initial 24 hours was 1.5 mg (range 0.25–3.60 mg). There was a statistically significant decrease in VAS after 1 day of treatment ( $p < 0.01$ ). Side effects included constipation, nausea, vomiting, anorexia, dry mouth, fatigue, sweating, and dizziness; the authors attributed much of these toxicities to the weak opioids used prior to study entry.

The first trial by Klepstad et al.<sup>13</sup> was a prospective case series involving 40 patients (35 evaluable) with a median age of 66 (range, 34–86 years). The criterion for entrance was inadequate pain, measured by VAS (0–100) and VRS (1–7); patients were receiving acetaminophen combined with weak opioids (codeine or dextropropoxyphene). A 2-day premorphine washout phase used ketobemidone, a  $\mu$  binding opioid, as needed, followed by titration with immediate release oral morphine. The treatment strategy consisted of oral morphine 10 mg every 4 hours times 6 doses with a planned daily escalation of 33%–50% until pain relief. Initial VAS was 32 (range, 25–39) and VRS 3.6 (range, 3.2–4.0). Efficacy was defined as a VRS of 3 or less not requiring more than two rescue doses per day. All patients responded. The mean dose at response was  $97 \pm 20$  mg (range, 60–180 mg) and the time to response was  $2.3 \pm 0.6$  days (range, 1–6 days). The VAS at the end of the titration was 16 (range, 11–21) and VRS 2.6 (range, 2.2–2.9). Side effects were nausea, vomiting, constipation and sedation; titration was delayed in 9 patients as a result of fatigue.

The second study by Klepstad et al.<sup>13</sup> was a

prospective, randomized, double-blinded, double-dummy comparison of immediate and sustained release oral morphine. Forty patients (34 evaluable) were enrolled. The mean age in the immediate-release morphine group was 66 (range, 61–71 years) and 62 (range, 57–66 years) in the sustained release morphine group. Entrance criteria included pain unrelieved by optimal doses of weak opioids (codeine and dextropropoxyphene) and NSAIDs. Both a VAS (0–100) and a VRS (1–7) were used to assess response similar to their first study. The treatment strategy consisted of once-daily sustained-release morphine or every 4-hour placebo or 4-hour immediate-release morphine and once-daily placebo. Similar to their first study, a 2-day washout period using ketobemidone was required before starting morphine titration. Starting doses were 60 mg of daily morphine with a planned daily dosage increase of 33%–50%. Response was defined as a pain score of 3 or less (VRS 1–7). The mean daily dose administered in the immediate-release morphine group was  $94 \pm 23$  mg and  $82 \pm 14$  mg for immediate release and sustained-release morphine, respectively. Time to response was 2.1 days  $\pm 0.6$  and 1.7 days  $\pm 0.6$  for immediate- and sustained-release morphine, respectively ( $p > 0.05$ ). None of the patients dropped out because of a lack of efficacy. Side effects were assessed by a quality-of-life instrument; fatigue was reported more frequently with immediate-release than sustained-release morphine ( $p < 0.05$ ).

The study by Lichter et al.<sup>15</sup> was a prospective case series involving 50 patients either in home care or in a hospice; the mean patient age was not provided.<sup>14</sup> The intensity of pain was determined by the treating physician; a pain scale was not used. The entry criterion was severe pain on weak or potent opioids other than morphine. The treatment strategy was 5–20 mg of oral morphine with a planned dose titration every 4 hours for home care patients, and titration every 2 hours for inpatient hospice patients; intramuscular morphine was used for some patients. The every 4-hour dose at the time of response was 15–60 mg for home care patients. The dose was not reported for inpatient hospice patients. Time to response was 26 hours for home care (range, 12–72 hours) and 6 hours for inpatient hospice patients (range, 4–12 hours). Side effects were not listed, however, it was noted that drowsiness, sedation, and respiratory depression were not observed.

## DISCUSSION

The discipline of hospice and palliative care prides itself on the ability to relieve severe or crescendo pain safely and reliably. In fact, optimal pain relief is often used as a defining aspect of this domain of medical care. This review is an effort to develop an evidence based opioid titration strategy for severe or crescendo pain in cancer patients. Unfortunately, the datum is too meager to justify anything other than expert opinion (grade IV recommendations). All trials suffer from methodological problems that make comparison between trials impossible. The patient populations were heterogeneous, definitions of severe pain differed significantly as did pain assessment methods and prior analgesic therapy.

While no evidence-based recommendations can be made regarding the optimal dosing strategy of severe pain, the review does demonstrate that all reported methods were safe, no patient in any trial developed central nervous system depression to the point of respiratory depression. Moreover, regardless of the regimen, the majority of patient's had their pain relieved within 24 hours (level III-D). The datum suggests, not surprisingly, that onset to analgesia is fastest for parental dosing schedules (level III-A). Finally, one double-blind, randomized controlled study found no difference between using sustained and immediate release oral opiates for acute pain (level III-A).

It is clear that additional research is needed to answer the important question of opioid dose titration for severe pain. Prior to such research, it is also clear that standards need to be established among pain and palliative medicine researchers for the definition of severe pain, pain assessment research methods, and definitions of analgesic success. Once established, the field can move forward with prospective trials to determine the optimal dosing strategy for both oral and parenteral dosing.

Such studies need to be multi-institutional for patient numbers, randomized based on presently known dosing protocols, and stratified based on previous opioid exposure. Outcome measures would include time to analgesia, dose requirement, toxicity, and patient satisfaction. Variables that would be of interest to study would be oral and parenteral dosing interval and PCA demand versus continuous plus demand strategies.

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