Original Article

Safety and Effectiveness of Intravenous Morphine for Episodic Breakthrough Pain in Patients Receiving Transdermal Buprenorphine

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Abstract

Supplemental dosing of an opioid is the main treatment suggested to manage breakthrough pain in cancer patients. The intravenous route has been proven to be safe and effective, providing rapid analgesia in patients receiving oral morphine. Transdermal buprenorphine (TTS-BUP) is increasingly used in cancer pain management, but this drug has been labeled as a difficult drug to use in combination with other opioids. The aim of this open-label study was to verify the safety and effectiveness of intravenous morphine (IV-MO) for the treatment of episodic pain in cancer patients receiving TTS-BUP. A consecutive sample of 29 cancer patients, who were treated with TTS-BUP, reported an acceptable basal analgesia, and presented with episodic pains were selected for the study. The IV-MO dose was one-fifth of the morphine equivalent oral daily dose calculated using a ratio of TTS-BUP/oral morphine of 1:75, and a morphine IV/oral ratio of 1:3. For each episode, pain intensity and opioid-related adverse effects were recorded when severe pain occurred (T0), and 15 minutes after. One hundred six breakthrough events in the 29 patients (3.7 episodes per patient, on average) were recorded during admission. The mean pain intensity decreased from an initial value of 7.3 (confidence interval [CI] 95% 7.0–7.5) to 2.9 (CI 95% 2.5–3.3) 15 minutes after IV-MO. Ninety-eight episodes (92.4%) were considered treated successfully, defined as a reduction of more than 33% within 15 minutes; 88 of these episodes (83.0%) had more than 50% pain intensity decrease. No differences in age, gender, pain mechanism, and time of events were found. Eight episodes (7.5%) did not respond effectively within 15 minutes, and required further doses. The occurrence of adverse effects for each episode treated was not frequent and intensity was not relevant. IV-MO was effective and safe in most cancer patients receiving TTS-BUP who experienced pain exacerbation. J Pain Symptom Manage 2006;32:175–179.

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Intravenous morphine, transdermal buprenorphine, opioids, breakthrough pain, cancer pain

Introduction

Although buprenorphine (BUP), a partial mu-receptor agonist, has been used for at least 30 years in the treatment of cancer-related pain, this drug has never gained popularity. The reasons include the adverse event profile of the parenteral and sublingual formulations, the presumed ceiling effect for analgesia, and possible problems if used with other opioids due to its potential antagonist activity when administered to a patient already receiving a full agonist drug.[1] Thus, BUP has been labeled as an atypical opioid, difficult to place on the World Health Organization "analgesic ladder," and less easy to use clinically than other strong opioids.[2]

Recently, BUP has been formulated as a transdermal patch. With this delivery system, peaks in plasma concentration due to rapid absorption are unlikely and the more constant concentrations may provide a clinical advantage.[1,3,4]

No data exist on the treatment of breakthrough pain in patients receiving transdermal BUP (TTS-BUP). Traditional short-acting opioids are commonly used for this purpose. Intravenous morphine (IV-MO) has been reported to be safe and effective in treating breakthrough episodes, using a dose proportional to the basal dosage of oral morphine, in patients receiving oral morphine for their basal pain control.[5] As the use of BUP in association with other opioids has been of concern because of a possible antagonistic effect which might reduce analgesia or induce withdrawal symptoms rather than decrease the intensity of a pain flare, the aim of this open-label study was to evaluate the safety and effectiveness of IV-MO in advanced cancer patients who were receiving TTS-BUP.

Methods

A consecutive sample of 29 cancer patients admitted to a pain relief and palliative care unit were recruited for the study. Patients were receiving TTS-BUP for their basal pain and reported acceptable analgesia. Patients requiring four or more breakthrough doses were excluded. Breakthrough pain had to exceed a pain score of 7/10, so that patients with fluctuations of pain with no clear cut peaks of pain intensity were also excluded. Institutional approval and informed consent were obtained.

According to the department policy, an intravenous line was established on admission for emergency treatment of symptoms and hydration, if required. Patients were encouraged to call when their pain became severe (more than seven on a 0–10 numerical pain scale) and a bolus of IV-MO was administered over 5 minutes

The IV-MO dose was one-fifth of the morphine equivalent oral daily dose, using the following conversion ratios: IV-MO:oral MO was 1:3 and TTS-BUP:oral MO was 1:75.[5] For example, a daily dose of TTS-BUP of 52.5 μg/hour (about 1.2 mg/day), was considered equivalent to 90 mg of oral MO. This corresponded to 30 mg of IV-MO (1:3 ratio), so that the final dose (one-fifth of the daily dose) for the episodic pain was to be 6 mg. As the TTS BUP doses used were 35, 52.5, and 70 μg/hour, the equivalent boluses of IV-MO were 4, 6, and 8 mg, respectively. Written orders were given and IV-MO was administered by nurses.

For each episode, pain intensity was recorded using a numerical scale from 0 to 10, and opioid-related adverse effects were described using a scale from 0 to 3 (absent, slight, moderate, severe). Data were collected by nurses trained in symptom measurement as part of their daily activity. Daily doses of TTS-BUP were also recorded. Data were recorded at time of the flare (T0) and 15 minutes after (T1). Patients who did not respond satisfactorily 15 minutes after IV-MO (reduction in pain intensity greater than 33%), or were unsatisfied, were considered unresponsive and received further treatments (a half dose of IV-MO). According to previous experience with IV-MO, 15 minutes was considered an acceptable time for evaluating effects. Patients with a pain reduction of at least 33% 15 minutes after IV-MO injection were considered to have a clinical benefit.[6]

Statistical Analysis

Frequency analysis was performed using the Chi-squared test. The paired Wilcoxon