Original Contribution

Intravenous morphine titration to treat severe pain in the ED☆

Virginie Lvovschi MD, Frédéric Aubrun MD, PhD, Pascale Bonnet MD, Anna Bouchara MD, Mouhssine Bendahou MD, Béatrice Humbert, Pierre Hausfater MD, Bruno Riou MD, PhD†

Department of Emergency Medicine and Surgery, and Department of Anesthesiology and Critical Care, Centre hospitalo-universitaire Pitié-Salpêtrière, Assistance Publique-Hôpitaux de Paris; Université Pierre et Marie Curie-Paris 6, 75013 Paris, France

Received 26 April 2007; revised 12 October 2007; accepted 12 October 2007

Abstract
Purpose: We assessed the safety of intravenous morphine titration in the emergency setting.
Methods: A total of 621 consecutive adult patients admitted in the ED with acute severe pain (visual analogue scale pain score ≥ 70) were included. Intravenous morphine titration was administered as a bolus of 2 (body weight ≤ 60 kg) or 3 mg (body weight > 60 kg) with 5-minute interval between each bolus. Pain relief was defined as a visual analogue pain score of 30 or lower.
Results: The dose of morphine administered was 0.16 ± 0.10 mg/kg and the median number of boluses was 3. Pain relief was obtained in 512 (82%) patients. Morphine-induced adverse events occurred in 67 patients (11%) without severe adverse event. Titration was interrupted before pain relief had been obtained in 107 (17%) patients. In the remaining 514 patients, pain relief was obtained in 507 (99%) patients. Two variables were significantly associated with no pain relief: major protocol deviation (odds ratio, 17.3; 95% confidence interval, 10.0-30.1) and morphine-induced adverse effect (odds ratio, 13.0; 95% confidence interval, 6.7-25.3).
Conclusion: Intravenous morphine titration is a safe and effective option for severe pain when used according to a strict protocol.

© 2008 Elsevier Inc. All rights reserved.

☆ Authors’ contributions: Virginie Lvovschi took part in data acquisition and verification, interpretation of the results, emergency physician training, and drafting of the manuscript. Frédéric Aubrun took part in the study conception and interpretation of the results. Pascale Bonnet and Mouhssine Bendahou took part in data acquisition and emergency physician training. Anna Bouchara took part in data acquisition and verification, and interpretation of the results. Béatrice Humbert took part in nurse training and administrative support. Pierre Hausfater took part in interpretation of the results and revision of the manuscript. Bruno Riou took part in study conception, statistical analysis, interpretation of the results, and drafting of the manuscript. All authors contributed to the final version of the manuscript.
† Corresponding author. Service d’Accueil des Urgences, CHU Pitié-Salpêtrière, 47 Boulevard de l’Hôpital, 75651 Paris Cedex 13, France. Tel.: +33 1 42 16 22 59; fax: +33 1 42 16 22 69.
E-mail address: bruno.riou@psl.aphp.fr (B. Riou).

0735-6757/$ – see front matter © 2008 Elsevier Inc. All rights reserved.
doi:10.1016/j.ajem.2007.10.025
Intravenous morphine titration to treat severe pain in the ED

1. Introduction

Acute pain relief is now a standard requirement of effective clinical practice in the ED [1]. However, despite important progress in pain management, undertreatment of pain in the ED remains an unresolved and major problem [2-4]. Intravenous administration of opioids is widely used for acute pain relief in the immediate postoperative period and use of small intravenous boluses of morphine (intravenous morphine titration) allows a rapid titration of the dose needed for complete pain relief [5,7]. However, several barriers have prevented its application in the ED including, high admission numbers, inadequate training in pain relief, lack of continuity of care, and concern about opioid adverse effects, not to mention concerns that have been repeatedly refuted such as fear of psychological addiction or impairment of clinical diagnostic accuracy [8]. The main consequence is that even the most recent clinical trials have investigated therapeutic options that would have been considered as unacceptable in other settings [9,10]. In contrast, intravenous morphine titration has been recently advocated for acute cancer pain control, suggesting that this technique can also be applied outside the post-anesthesia care unit [11,12]. Moreover, although the safety of the technique has not been assessed in the emergency setting, intravenous morphine titration is now used on a routine basis in some ED [13].

Therefore, the goal of our study was to test the hypothesis that intravenous morphine titration is an efficient and safe means of obtaining complete and rapid pain relief in the ED. We used a protocol for adult patients, which has been demonstrated to be efficacious, safe, and simple to perform for nurses in the postoperative period [5-7].

2. Material and methods

We used an observational prospective cohort design. The study protocol was approved by our institutional review board (Comité de Protection des Personnes se Prêtant à la Recherche Biomédicale Pitié-Salpêtrière, Paris, France). Because the protocol was considered as routine care applied to all patients, authorization to waive written informed consent was granted.

2.1. Patients

All patients were older than 18 years. Inclusion criteria were admission to the ED with severe pain defined as a visual analog scale (VAS) pain score of 70 or higher, as previously reported [6]. Exclusion criteria were allergy or contra-indication to morphine (chronic respiratory insufficiency, drug addiction), pregnancy, and lactation. Patients with chronic pain (>3 months) and/or previous administration of opioids (within 1 month) were excluded from that analysis and thus not recorded, although they could receive intravenous morphine in the ED, including using this protocol. Patients with delirium or dementia, who did not understand the pain scales, or who were not French speaking were also excluded.

2.2. Study protocol

The VAS (0-100, handheld slide-rule type) [14] was shown and explained to the patients. All nurses in the ED had been trained to assess pain using unidimensional scales and to perform morphine titration. They used the VAS and a special form for data collection. When patients had difficulties in manipulating the VAS, nurses were allowed to use a numerical rating scale (from 0 to 100) [5], as these 2 methods are equivalent [15]. A strict protocol has been implemented in the ED and was similar to that used in our post-anesthesia recovery room for many years [5-7]. This protocol defined the dose of intravenous boluses of morphine, the interval between boluses, the absence of limitation on the total dose, the VAS threshold required to administer morphine, and the criteria to stop titration. Immediately after arrival of patients in the ED, they were questioned by the triage nurse about the presence of pain and asked to rate pain intensity on a scale. When the VAS was greater than 70, intravenous morphine was titrated every 5 minutes by 3-mg increments (2 mg in patients weighing ≤60 kg) and pain was assessed every 5 minutes until pain relief, defined as a VAS score of 30 or lower [5-7]. When the patient was asleep, no attempt was made at arousal. In this situation the patient was considered as having adequate pain relief and was assigned a VAS score of 0. When pain was initially too severe to obtain a VAS (patient refusal), it was scored 100. Clinical monitoring included respiratory rate measurements, pulse oximetry (SpO2), sedation according to the Ramsay score [16], arterial blood pressure, and heart rate. Morphine titration was stopped if the patient had a respiratory rate lower than 12 breaths per minute and/or an SpO2 lower than 95%, and/or experienced a serious adverse event related to morphine administration (allergy with cutaneous rash and/or hypotension, vomiting, severe pruritus), as previously described [5-7]. In case of severe ventilatory depression (respiratory rate <10 breaths per minute), naloxone (intravenous bolus of 0.04 mg) was administered until the respiratory rate was greater than 12 per minute. The only modifications to the protocol used in our post-anesthesia care unit [5-7] were additional safety rules. These were (1) validation by the physician when more than 5 and 10 boluses were required; (2) no exit from the ED within 1 hour after the end of titration, except for radiological examination; and (3) no exit from the hospital within 2 hours after the end of titration.

2.3. Adverse effects

The occurrence of the following adverse effects was recorded: nausea and vomiting, respiratory depression
(respiratory rate <12 breaths per minute and/or SpO₂ <95% and/or requirement for oxygen), urinary retention requiring urine drainage, itching, sedation (Ramsay scale >2), allergy, and dizziness. Nausea, vomiting, pruritus, urinary retention, and respiratory depression, allergy, and dizziness were considered as morphine-related adverse effects. Only severe respiratory depression requiring administration of naloxone and/or assisted ventilation was considered as a severe adverse effect. Sedation was not considered as a morphine-related adverse event, as previously reported [5-7]. Detailed instructions were provided by our protocol to treat severe respiratory depression (see above) and nausea/vomiting (metoclopramide then ondansetron in case of failure). No systematic prevention of nausea/vomiting was performed because of the low expected incidence [13].

2.4. End points

The main end points were the incidence of morphine-induced adverse effect and severe respiratory adverse effects. The secondary end points were the number of patients with appropriate pain relief, the dose of morphine administered, the number of patients with protocol deviation.

2.5. Deviation from the protocol

All data sheet were retrospectively assessed for potential protocol deviation, as previously described [17]. These deviations were classified as follows: error in the dose of boluses (minor if only 1 error), error in the timing (minor if only 1 error of <5 minutes), administration of morphine despite pain relief (VAS <30), and inappropriate termination (VAS ≥30). Assessment of the monitoring (respiratory rate and SpO₂) was analyzed separately. Inadequate monitoring was considered when at least 2 consecutive measurements of either respiratory rate or SpO₂ were lacking.

2.6. Statistical analysis

We expected that the incidence of morphine-induced adverse effects should be less than 20% and the incidence of severe morphine adverse effects should be less than 2%. Thus, we calculated that at least 300 patients would be needed to contain the 95% confidence interval (CI) of the incidence within these limits.

Data are expressed as mean ± SD or median and 95% CI. The Student t test was used to compare 2 means, the Mann-Whitney U test was used to compare 2 medians, and the Fisher exact method was used to compare 2 proportions. For multiple comparisons, analysis of variance and Newman-Keuls test, Kruskal-Wallis multiple comparison Z value test, and Fisher exact method with Bonferroni correction were used when appropriate. We performed a multivariate analysis to assess variables associated with no pain relief (VAS ≥30) using backward logistic regression. Interactions were not tested. The Spearman coefficient matrix correlation was used to identify significant collinearity (>0.70) between variables. The odds ratio and 95% CI of variables selected by the logistic model were calculated. The discrimination of the model was assessed using the receiver operating characteristic (ROC) curve and the calculation of the area under the ROC curve. The percentage of patients correctly classified by the logistic model was calculated using the best threshold determined by the ROC curve. Calibration of the model was assessed using the Hosmer-Lemeshow statistics.

All comparisons were 2 tailed and a P value of less than .05 was required to rule out the null hypothesis. Statistical analysis was performed using a computer and the NCSS 2004 software (Statistical Solutions Ltd, Cork, Ireland).

3. Results

A total of 625 consecutive patients were included in the study. Important data were lacking in 4 patients, and, thus, 621 patients were considered for analysis.

There were 340 (55%) men and 281 (45%) women, the mean age was 42 ± 16 years (extremes, 18-106), and the mean weight was 71 ± 15 kg. The cause of pain was traumatic in 114 (18%) patients and nontraumatic in 507 (82%) patients. The location of pain in nontraumatic causes was the spine (n = 165, 27%), abdomen and pelvis (n = 239, 38%), thorax (n = 20, 3%), head (n = 43, 7%), diffuse cancer pain (n = 13, 2%), and other various locations (n = 27, 4%). Other analgesics were used in 210 (35%) patients, mostly acetaminophen (n = 124, 20%) and nonsteroidal anti-inflammatory drugs (n = 128, 21%).

Fig. 1 Distribution of intravenous morphine boluses administered (n = 327). The black column indicates the median.
The median delay between arrival in the ED and the onset of morphine titration was 28 minutes (95% CI, 25-32 minutes). The initial VAS was 84 ± 11 and the final VAS was 27 ± 23. The mean dose of morphine administered was 10.5 ± 6.4 mg (extremes, 2-46 mg), that is, 0.15 ± 0.10 mg/kg (extremes, 0.03-0.80). The median number of boluses administered was 3 (95% CI, 3-4) (Fig. 1) and the median duration of titration was 15 minutes (95% CI, 15-20). Pain relief was obtained in 511 (82%) patients (95% CI, 79-85). Pain relief required significantly more morphine in patients with traumatic cause (n = 114, 0.17 ± 0.12 mg/kg) than in those with abdominal pain (n = 239, 0.15 ± 0.09 mg/kg) or in those with spine pain (n = 165, 0.15 ± 0.08 mg/kg). Other causes of pain could not be explored because of a low number of patients.

Morphine-induced adverse events occurred in 67 (11%) patients (95% CI, 9%-13%) (Table 1). Severe morphine-induced adverse events occurred in no patient (95% CI, 0%-0.6%). Other adverse events occurred in 2 patients (displacement of the intravenous line). Sedation was noted in 60 (10%) patients (95% CI, 8%-12%). During the titration, the respiratory rate slightly decreased (from 21 ± 6 to 19 ± 4, \( P < .05 \)) and the \( \text{SpO}_2 \) also (from 98 ± 4% to 97 ± 5%). There was no significant difference between patients who experienced morphine adverse effects and those who did not (Table 2).

Morphine titration was interrupted before pain relief had been obtained in 107 (17%) patients (95% CI, 14%-21%). The reasons for this interruption were the occurrence of an adverse effect (n = 41, 7%), interference with the care (n = 32, 5% mainly radiological examination), patient refusal (n = 2, 0.5%), and inappropriate interruption by the physician (n = 36, 6%). In the remaining 514 patients without interruption of the titration process, pain relief was obtained in 507 (99%) patients with a mean dose of 10.4 ± 6.2 mg, that is, 0.15 ± 0.09 mg/kg, and 3 (95% CI, 3-3)

### Table 1  Morphine-induced adverse effects

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>n (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea/vomiting</td>
<td>26 (4.2)</td>
<td>2.9%-6.1%</td>
</tr>
<tr>
<td>Allergy</td>
<td>1 (0.2)</td>
<td>0%-0.9%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>4 (0.6)</td>
<td>0.3%-1.6%</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>17 (2.7)</td>
<td>1.7%-4.3%</td>
</tr>
<tr>
<td>Respiratory depression</td>
<td>16 (2.6)</td>
<td>1.6%-4.1%</td>
</tr>
<tr>
<td>Severe respiratory depression</td>
<td>0</td>
<td>0%-0.6%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>18 (2.9)</td>
<td>1.8%-4.5%</td>
</tr>
<tr>
<td>Any adverse events</td>
<td>67 (10.8)</td>
<td>8.6%-13.5%</td>
</tr>
</tbody>
</table>

### Table 2  Comparison of patients with and without morphine-induced adverse effects

<table>
<thead>
<tr>
<th></th>
<th>No adverse effect (n = 554)</th>
<th>Adverse effect (n = 67)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>41 ± 16</td>
<td>44 ± 14</td>
</tr>
<tr>
<td>Men</td>
<td>309 (56%)</td>
<td>31 (46%)</td>
</tr>
<tr>
<td>Women</td>
<td>245 (44%)</td>
<td>36 (54%)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>71 ± 14</td>
<td>71 ± 15</td>
</tr>
<tr>
<td>Initial VAS</td>
<td>84 ± 11</td>
<td>85 ± 11</td>
</tr>
<tr>
<td>Dose of morphine (mg)</td>
<td>10.4 ± 6.3</td>
<td>10.8 ± 7.3</td>
</tr>
<tr>
<td>Dose of morphine (mg/kg)</td>
<td>0.15 ± 0.09</td>
<td>0.16 ± 0.11</td>
</tr>
<tr>
<td>Number of boluses</td>
<td>3 (3-3)</td>
<td>3 (3-4)</td>
</tr>
<tr>
<td>Cause of pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Traumatic</td>
<td>100 (18%)</td>
<td>14 (21%)</td>
</tr>
<tr>
<td>Nontraumatic</td>
<td>454 (82%)</td>
<td>53 (79%)</td>
</tr>
</tbody>
</table>

Values are shown as mean ± SD, median (95% CI), or number (percentage) where appropriate.

No significant difference between groups.

$P < .05$). There was no significant difference between patients who experienced morphine adverse effects and those who did not (Table 2).

Morphine titration was interrupted before pain relief had been obtained in 107 (17%) patients (95% CI, 14%-21%). The reasons for this interruption were the occurrence of an adverse effect (n = 41, 7%), interference with the care (n = 32, 5% mainly radiological examination), patient refusal (n = 2, 0.5%), and inappropriate interruption by the physician (n = 36, 6%). In the remaining 514 patients without interruption of the titration process, pain relief was obtained in 507 (99%) patients with a mean dose of 10.4 ± 6.2 mg, that is, 0.15 ± 0.09 mg/kg, and 3 (95% CI, 3-3)

### Table 3  Comparison of patients with minor and major deviation from the protocol and those without

<table>
<thead>
<tr>
<th></th>
<th>No deviation (n = 350)</th>
<th>Minor deviation (n = 137)</th>
<th>Major deviation (n = 134)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>41 ± 15</td>
<td>43 ± 17</td>
<td>41 ± 16</td>
</tr>
<tr>
<td>Men</td>
<td>180 (51%)</td>
<td>83 (61%)</td>
<td>77 (58%)</td>
</tr>
<tr>
<td>Women</td>
<td>170 (49%)</td>
<td>54 (40%)</td>
<td>57 (43%)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>70 ± 15</td>
<td>72 ± 13</td>
<td>71 ± 14</td>
</tr>
<tr>
<td>Initial VAS</td>
<td>83 ± 11</td>
<td>84 ± 11</td>
<td>85 ± 12</td>
</tr>
<tr>
<td>Final VAS</td>
<td>23 ± 19</td>
<td>23 ± 18</td>
<td>42 ± 31 * ***</td>
</tr>
<tr>
<td>Dose of morphine (mg)</td>
<td>8.6 ± 4.7</td>
<td>12.4 ± 7.0 *</td>
<td>13.4 ± 7.7 * ***</td>
</tr>
<tr>
<td>Dose of morphine (mg/kg)</td>
<td>0.13 ± 0.08</td>
<td>0.18 ± 0.11 *</td>
<td>0.19 ± 0.11 *</td>
</tr>
<tr>
<td>Number of boluses</td>
<td>3 (3-4)</td>
<td>4 (3-4) *</td>
<td>5 (4-5) * **</td>
</tr>
<tr>
<td>Morphine-induced adverse effect</td>
<td>36 (10%)</td>
<td>22 (16%)</td>
<td>9 (7%) **</td>
</tr>
<tr>
<td>Sedation</td>
<td>39 (11%)</td>
<td>13 (9%)</td>
<td>8 (6%)</td>
</tr>
<tr>
<td>Pain relief</td>
<td>320 (91%)</td>
<td>124 (91%)</td>
<td>68 (51%) * **</td>
</tr>
</tbody>
</table>

Values are shown as mean ± SD, median (95% CI), or number (percentage) where appropriate.

* $P < .05$ vs no deviation.

** $P < .05$ vs minor deviation.

$P < .05$). There was no significant difference between patients who experienced morphine adverse effects and those who did not (Table 2).

Morphine titration was interrupted before pain relief had been obtained in 107 (17%) patients (95% CI, 14%-21%). The reasons for this interruption were the occurrence of an adverse effect (n = 41, 7%), interference with the care (n = 32, 5% mainly radiological examination), patient refusal (n = 2, 0.5%), and inappropriate interruption by the physician (n = 36, 6%). In the remaining 514 patients without interruption of the titration process, pain relief was obtained in 507 (99%) patients with a mean dose of 10.4 ± 6.2 mg, that is, 0.15 ± 0.09 mg/kg, and 3 (95% CI, 3-3)

### Table 4  Variables associated with inadequate pain relief (defined as a VAS pain score >30) (N = 621)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Pain relief (n = 512)</th>
<th>Inadequate pain relief (95% CI)</th>
<th>Odds ratio</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major protocol deviation</td>
<td>68 (13%)</td>
<td>66 (61%)</td>
<td>17.3 (10.0-30.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Morphine-induced adverse effect</td>
<td>36 (7%)</td>
<td>31 (28%)</td>
<td>13.0 (6.7-25.3)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

The Hosmer-Lemeshow test was significant (14.9, $P < .05$) indicating inadequate calibration of the model. The percentage of appropriately classified patients was 82%, indicating adequate discrimination. The variables were not correlated ($r = 0.37; <0.70$).
4. Discussion

In the present study, we demonstrated that intravenous morphine titration can be safely used in the emergency setting to treat acute severe pain, with an incidence of morphine-related adverse effects of 11% and an incidence of severe respiratory adverse effects of 0 (95% CI, <0.6%). Complete pain relief was obtained in 82% of our patients, the efficacy reaching 99% in patients in whom the titration process could be completed.

An outstanding feature of the clinical use of opioids is the extraordinary variation in the dose requirements for pain management [6], explaining why titration of the dose to the effect is so important. It is generally recognized that intravenous morphine titration is a very efficient technique to obtain complete pain relief in most patients in the postoperative period [5-7,17]. Some interesting comparisons between our patients in the ED and those in the postoperative period can be made. In patients with acute severe pain (VAS >70), the mean dose of morphine was not markedly different (0.16 vs 0.19 mg/kg) as well as the median number of boluses needed to obtain pain relief (3 vs 4) [6]. These results should be interpreted as a strong argument to treat severe pain appropriately in the ED and explain why a fixed low dose of morphine failed to control pain [9]. The proportion of patients with pain relief was lower in the emergency setting than in the postoperative setting (82% vs 95%). This difference was obviously related to interruptions of the titration process, which was related to the need to perform either radiography or computed tomography scan in these emergency cases, but also to an inappropriate interruption by some emergency physicians. We interpreted these last interruptions as persistent reluctance to use high intravenous doses of opioids and expect that this practice should progressively disappear. In patients without interruption of the process, intravenous morphine titration succeeded in obtaining pain relief in most of the cases.

The incidence of morphine-induced adverse effects was acceptable and not markedly different from that observed during the postoperative period (11% vs 14%) [17]. The incidence of nausea/vomiting was low and close (5% vs 4%) to that previously reported with lower doses of morphine in the emergency setting [13]. No severe respiratory adverse effect was noted. This result is not surprising as nociceptive inputs are thought to counter-balance the respiratory depressant effect of the opioids [18]. Nevertheless, these good results were obtained after appropriate training of the staff and with close clinical monitoring (respiratory rate and SpO2). Moreover, we interrupted titration in case of sedation which can be considered as a predictive signal of respiratory depression [5-7,19]. In a previous study, we observed dissociated effects of morphine on the time course of sedation and analgesia with sedation occurring first, followed by analgesia [19]. Sedation cannot be arbitrarily attributed to the occurrence of an adequate level of analgesia because, among patients in whom morphine titration is discontinued because of sedation, 25% still exhibit a level of VAS above 50 [19]. Moreover, sedation has been shown to be associated with the frequent need for rescue analgesia after (and despite) an intravenous morphine titration [20]. However, we think that interruption of titration when sedation occurs is a safe option. It should be emphasized that there was no significant difference between patients with or without morphine-induced adverse effects (Table 1), particularly concerning the dose of morphine.

The proportion of protocol deviation was high (44%) in our study, far higher than that previously observed in the postoperative period (4%) [17], although 58% of them were considered as minor deviations probably without any detectable clinical consequences. Nevertheless, this proportion is close to that recently observed in the prehospital setting (43%) [21]. This high incidence emphasizes the difficulties in strictly applying such a protocol in a crowded emergency setting. Similarly, the clinical monitoring was judged as insufficient in 15% of our patients. Despite these high incidences of errors, no severe adverse event occurred, suggesting that the whole process of intravenous morphine titration was safe in the ED. Nevertheless, as severe adverse events rarely occur during intravenous morphine titration (incidence of <0.01% [5]), we think that safety can only be increased by careful supervision of the adherence of the staff to safety rules.

We observed that patients with major protocol deviation experienced more frequently inadequate pain relief (Table 3). These patients also required more morphine and thus had a longer duration of morphine titration, therefore increasing the probability to observe a protocol deviation. With the use of multivariate analysis, only 2 variables were found to be associated with inadequate pain relief: a major protocol deviation and a morphine-induced adverse effect (Table 4). Therefore, our study confirms recent results obtained in the prehospital setting and in emergency conditions [21].
suggesting that poor compliance with titration protocol is associated with a greater rate of inadequate pain relief.

5. Limitations

Some remarks must be included to assess the limitations of our study. First, the use of VAS assumes that pain is a unidimensional experience. Although intensity is a very important dimension of pain, it is clear that pain refers to a variety of sensations that cannot be categorized under a single linguistic label which varies only in intensity [22]. Nevertheless, it should be pointed out that VAS has been widely accepted because of its ease and brevity of administration, its minimal intrusiveness, and its conceptual simplicity [22]. Second, only morphine was studied. We choose this opioid because it is the standard opioid against which others are judged. In addition, it is well known by every physician and nurse in the ED, has a long duration of action, and has a low cost. However, as morphine was titrated to effect, observation of marked differences in efficacy/safety between opioids could not be expected. Third, most of our patients received morphine only and a synergistic action could have been expected with other analgesics. Nevertheless, it should be pointed out that association with analgesics such as acetaminophen may not be important as we have shown that this analgesic slightly decreases morphine consumption without any significant decrease in morphine-related adverse effects [23]. This is not the case with nonsteroidal anti-inflammatory drugs that have been demonstrated to decrease the incidence of morphine-induced adverse effects [24,25]. Fourth, some studies have proposed to administer a loading dose of morphine before titration [26]. The results we recently obtained in the postoperative period do not support that proposal, as we observed an increase in morphine-induced adverse effects [27]. Fifth, as few of our patients were elderly (4%), our results should be interpreted with caution in this frail subpopulation. However, it should be pointed out that elderly patients are at particularly high risk of undertreatment of pain in the ED [28]. Moreover, we have recently demonstrated that intravenous morphine titration can be safely administered without any modification to the protocol in elderly patients during the postoperative period [17]. Sixth, the bolus was not precisely adapted to body weight for the following reasons: (1) the protocol was more simple as the nurses administered either 3 or 2 mg per bolus; (2) a precise adaptation to body weight is not necessary in a titration process, particularly when the dose required is so variable from one patient to another. Nevertheless, it should be pointed out that a precise adaptation of the bolus dose is obviously required in children and maybe in morbidly obese adult patients. Lastly, although this cohort represents consecutive patients receiving intravenous morphine titration, we must recognize that a high screening failure rate probably occurred. Nevertheless, our good results should probably facilitate a higher routine use of this technique now in our ED.

6. Conclusion

Intravenous morphine titration may be a simple and efficacious option to avoid undertreatment of acute severe pain in the emergency setting, given a strict protocol, close clinical monitoring, and appropriate training of the staff. Poor compliance with titration protocol is associated with a greater rate of inadequate pain relief.

Acknowledgment

We thank the nurses and the emergency physicians of the ED of CHU Pitié-Salpêtrière, Paris, France for their work on this study and Dr DJ Baker, DM, FRCA (Department of Anaesthesiology, CHU Necker-Enfants Malades, Paris) for reviewing the manuscript. The study was supported by a research grant from the Fondation Hôpitaux de Paris-Hôpitaux de France.

References


