Predicting morphine related side effects in the ED: An international cohort study☆

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Study objectives: Morphine is the reference treatment for severe acute pain in an emergency department. The purpose of this study was to describe and analyse opioid-related ADRs (adverse drug reactions) in a large cohort of emergency department patients, and to identify predictive factors for those ADRs.

Methods: In this prospective, observational, pharmaco-epidemiological international cohort study, all patients aged 18 years or older who were treated with morphine were enrolled. The study was done in 23 emergency departments in the US and France. Baseline numerical rating scale score and initial and total doses of morphine titration were recorded. Logistic regression analysis was used to study the effects of demographic, clinical and medical history covariates on the occurrence of opioid-induced ADRs within 6 h after treatment.

Results: A total of 1128 patients were included over 10 months. Median baseline initial pain scores were 8/10 (7–10) versus 3/10 (1–4) after morphine administration. Median titration duration was 10 min (IQR, 8–30). The occurrence of opioid-induced ADRs was 25% and 2% were serious. Patients experienced mainly nausea and drowsiness. Medical history of travel sickness (odds ratio [OR], 1.7; 95% confidence interval [CI], 1.01–2.86) and history of nausea or vomiting post morphine (OR, 3.86; 95% CI, 2.29–6.51) were independent predictors of morphine related ADRs.

Conclusion: Serious morphine related ADRs are rare and unpredictable. Prophylactic antiemetic therapy could be proposed to patients with history of travel sickness and history of nausea or vomiting in a postoperative setting or after morphine administration.

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1. Introduction

Most international guidelines and clinical consensus recommend intravenous morphine for the management of severe acute pain in the emergency department setting [1–3]. Aggressive titration protocols have been proposed to overcome poor response to morphine for some patients [4]. Studies focus on improving the efficacy of opioid analgesia; however very few studies were exclusively based on improving safety. The incidence of opioid-induced ADRs (adverse drug reactions) in an emergency department setting in the literature varies between 11% and 23% [5–10]. The clinical response to opioids is, however, highly variable and occurrence of ADRs could be affected by factors not related to the dose [11]. An appealing strategy should be to find easily identifiable characteristics of patients that predict response to opioids and to use these factors to modify interventions. In 2009, a study of 277 patients failed to detect any associated factors; however it had a small sample size [12]. Our goal was then to find identifiable characteristics that
predict patient response to opioids and use that information to modify interventions. The present study was so designed to describe and analyse opioid related ADRs in a large cohort of emergency department patients at multiple sites, and to identify predictive factors for those ADRs.

2. Patients and methods

2.1. Study design

This was a prospective, pharmacoepidemiological international clinical observational study, done in 23 emergency departments in the US and France. This study was registered at ClinicalTrials.gov (identifier NCT01654055). Enrolment began in the United States in July, 14th 2010 and in France in October, 17th 2011. Enrolment concluded when the desired number of patients was reached in May, 31th 2012. The study was approved by the Institutional Review Board at Beth Israel Deaconess Medical Center, Boston, MA and by the institutional review board in France (Comité consultatif sur le traitement de l’information en matière de recherche dans le domaine de la santé). Standardised information was read then given to eligible patients. Oral consent was obtained from every patient, as patient's full informed written consent was waived by the ethics committees.

2.2. Setting

The study was performed in 23 rural and urban academic and non-academic medical centres in the US and France. One was a US emergency department with an annual census of 55 000 patients, the others were French Emergency departments with annual census varying from 20 000 to 60 000 patients. The decision to provide morphine analgesia, including titration of subsequent doses, was the responsibility of physicians, according to local and national standards of care. In all centres, physicians regularly undergo comprehensive education programs concerning the ethical conduct of research and the treatment of acute pain.

2.3. Selection of participants

All patients aged 18 years or older who were treated with morphine were considered for entry into the study. Included patients had to be conscious without life threatening illness. We excluded patients who received morphine during or after an orotracheal intubation, patients with altered level of consciousness, patients who have already been included or patients who were unable or unwilling to give consent. All patients who had an allergy to opioids were also not included.

The choice of morphine dose and titration protocol was at the discretion of the treating physician, based on individual knowledge and experience of each physician, and also based on the cause and intensity of pain, the dose could be adapted individually for each patient.

2.4. Data collection and processing

Clinicians were asked to identify patients in the ED who were to receive morphine. Each patient was approached and verbal consent was requested. A standardised questionnaire was administered asking about history of motion sickness, morphine administration or postoperative nausea/vomiting. For patients with a history of morphine administration, we recorded the supposed morphine related nausea/vomiting. All vital signs including non-invasive monitoring of blood pressure, heart rate, respiratory rate, and oxygen saturation by pulse oximetry (SpO2) were routinely recorded in each service at baseline and at regular intervals during ED stay. Labs for organ dysfunction were not routinely obtained.

In each centre, patients reported their pain using a Numerical Rating Scale (NRS); subjects were asked to provide a whole-integer pain score in which 0 was defined as “no pain” and 10 was defined as the “worst pain imaginable.” Baseline characteristics were also collected, including gender, age, initial NRS score, cause (including traumatic vs non-traumatic pain), location of pain, and medical history. Self-reported weight was used to calculate the weight-based doses of morphine. All drugs used, initial dose, and total dose of morphine titration were also recorded.

2.5. Outcome measures

The primary outcome variable was the occurrence of opioid-induced ADRs within 6 h after treatment, which is a standard emergency department length of stay. Possible ADRs were predefined as either deterioration of patient’s vital signs (respiratory rates <10/min, oxygen desaturation <95%, heart rate <50/min) or new or worsening nausea, vomiting, dizziness, sedation, pruritus, drowsiness, confusion, urticaria, headache or need to use naloxone. All these specific outcomes had to be assessed by the treating physician during and at the end of the first 6 h of care, by interrogation and clinical examination. All these symptoms had to be reported on a specific document for each patient. Among the possible opioid-induced ADRs reported, a specific pharmacological analysis was secondarily performed by independent physicians trained in pharmacology. We used the French method of causal relationship assessment [13]. The causality assessment method of Begaud et al. is based on seven criteria, which are separated into two groups (chronology and symptoms or signs). It is carried out independently for each drug taken. The criteria of chronology include time lapse between the administration of the drug and the reaction, the effect of drug cessation and drug reintroduction. The clinical criteria involve symptoms, possible contributing factors (if validated), another possible differential diagnosis and results of reliable and specific laboratory tests. These scores result in five final possible causality scores: ‘unlikely’, ‘possible’, ‘probable’, ‘likely’, and ‘very likely’. Thus, for the final analysis, we considered only ADRs with a score assessed at least as ‘possible’ [13,14]. This causality assessment method take into account the following criteria: time to onset, dechallenge and rechallenge, search for non-drug related causes, risk factor(s) for drug reaction, reaction at site of administration or validated laboratory test in favor of drug causation, previous report of similar drug event association and/or symptoms evocative of a drug causation.

2.6. Statistical analysis

Data were entered using the Microsoft Excel program 2007 (Microsoft, Redmond, WA). All data were entered and checked twice.

Statistical analysis was conducted using STATA/SE 12.0. Qualitative variables were expressed as frequency and percentage (%). Quantitative variables were expressed as means with standard deviations and medians with interquartile ranges (IQRs). Univariate and multivariate analyses were performed to identify predictive factors of opioid related ADRs. Variables with a P-value of <0.20 in the univariate analysis were included in a stepwise, multivariable, logistic regression analysis. In addition, gender and age were included in the multivariate analysis. Odds ratios (ORs) were reported with 95% confidence intervals (CIs). P < 0.05 was considered statistically significant.

According to the data available in the literature [4,10], a minimum of 11% of patients receiving morphine in an emergency setting experiences an ADR. To obtain these 100 patients, 910 patients had to be included. A logistic regression of a binary response variable (Y) on a binary independent variable (X) with a sample size of 910 observations achieves 97% power at a 0.05 significance level to detect in Prob (Y = 1) from the baseline value of 0.150 to 0.250. This change corresponds to an odds ratio of 1.889.

3. Results

During the 10 months of the study, 1156 potential subjects were approached from 23 emergency departments. Twenty-eight subjects...
were excluded (2.5%) for a total of 1128 subjects (Fig. 1). Their main characteristics are presented in Table 1. The cause of pain was traumatic in 387 (34%) subjects. The median dose of morphine was 0.05 mg/kg (IQR, 0.04–0.07) for initial dose, and 0.10 mg/kg (IQR, 0.06–0.13) for total cumulative dose. Median titration duration was 10 min (IQR, 1–30).

Median baseline initial pain scores were 8/10 (7–10) versus 3/10 (1–4) after morphine administration.

ADRs were reported for 292 (25.9%) subjects, but 10 were classified as ‘unlikely’ (due to the occurrence of the event before morphine administration), for a final count of 282 (25%) morphine-induced ADRs; out of these, 103 were classified as ‘possible’, 119 as ‘probable’ and 60 as ‘likely’. The type and the consequences of ADRs are presented in Table 2. Twenty three patients (2%) experienced a serious ADR: a respiratory distress with desaturation <90% or bradypnea, reversible after tactile stimulation and/or oxygenation. No naloxone administration was reported.

The results of the univariate and multivariate analyses are presented in Table 3. These demonstrate that the medical history of travel sickness (adjusted odds ratio [AOR], 1.7; 95% confidence interval [CI], 1.01–2.86) and history of nausea or vomiting post morphine (AOR, 3.86; 95% CI, 2.29–6.51) were independent predictors of morphine related ADRs. According to our model, initial and total doses of opioids were not associated to occurrence of ADRs. There was no predictor of severe ADRs.

4. Limitations

The incidence of ADRs in our dataset is higher than in other published studies, suggesting a reporting or selection bias and possible overestimation of true ADR frequency. We think that this may have been related to the main endpoint of the study as physicians were more likely to include patients with adverse events than other ones. Also, subjects may have been more likely to report milder symptoms as they were being specifically asked about them for a research study. Regardless, this effect increases the statistical power to compare risk factors in the final analysis. The second point is that the data was only collected for 6 h for everyone. That means we deliberately chose to assess only the immediate adverse events (those seen in the emergency departments). As an intravenous administration, the peak of plasma morphine is observed within minutes, and most of the severe adverse events have an immediate occurrence. Morphine half-life varies from 4 to 6 h, based on individual factors, and we thought that 6 h would be sufficient for observing most immediate adverse events.

![Fig. 1. Flow diagram of study participants.](image-url)
Pharmacovigilance study provides valuable means for detection, quantification, and support for this study.

Some studies focused on morphine related nausea and vomiting prevention in emergency departments, using various antiepileptics such as metoclopramide or low-dose naloxone [19-21]. None of these studies was positive, partly related to an overall low incidence of adverse events. Nevertheless, there is poor literature about prophylactic administration of antiepileptics following the administration of iv morphine for acute pain management in the emergency setting. We found only one study concerning this topic about metoclopramide [15]. Routine metoclopramide administration might expose patients to a risk of harm which is not justifiable given a lack of evidence of benefit. On the other hand, identifying patients at risk may change the strategy of antiepileptics administration in the ED and could allow demonstrating a real benefit for those patients. Based on our results, we think that prophylactic antiepileptic therapy could be proposed to patients with a history of travel sickness and a history of nausea or vomiting postoperatively or post morphine. Some further research could aim to determine if in this population, a systematic treatment could be proposed.

A multimodal approach to treating pain has been advocated [22-24]. The combination of synergistic analgesics such as nonsteroidal anti-inflammatory drugs may offer more intense analgesia and limit the amount of morphine necessary. However, this does not necessarily translate to a reduction of ADRs. There are nevertheless a few studies that looked at multimodal pain management and found a reduction in opioid ADRs, and no increase in ADRs from the use of NSAIDs [25].

In our study, we did not found age as predictive factor for opioid related ADRs. Because of the large variation in dose requirements for pain management and because titration strictly adapts the dose to the pain, there is no evidence that a titration protocol should also take into account the age of the patients. Moreover, titration is performed over a short period in which age-related changes in pharmacodynamics and pharmacokinetics might be less important. In another prospective study, Aubrun et al. demonstrated that the same protocol of intravenous morphine titration could be used in young and elderly patients in a postoperative setting without a significant increase in morphine-related ADRs [26].

Another interesting result is that the initial and total doses of opioids used were not related to ADRs. This is consistent with previously published studies on opioid efficacy in emergency department settings [5-10] which all described mild to moderate adverse events that were not related to dose. These studies were not powered sufficiently to detect significant ADRs.

5. Discussion

The occurrence of opioid-induced ADRs was 282 of 1128 subjects included (25%) and twenty three patients (2%) have experienced a serious ADR: respiratory distress with desaturation <90% or bradypnea. Factors associated with the occurrence of adverse events were medical history of travel sickness (odds ratio [OR], 1.7; 95% confidence interval [CI], 1.01–2.86) and history of nausea or vomiting post morphine (OR, 3.86; 95% CI, 2.29–6.51).

This paper presents the largest published cohort for morphine-induced ADRs in an emergency department setting. Our data suggests that serious morphine-related ADRs are rare and unpredictable. Patients experience mainly nausea and drowsiness and having had either postoperative or post-morphine nausea or travel sickness increases the risk of suffering similar ADRs again.

Concern about opioid ADRs is an often cited barrier to provide adequate doses. Some studies [5,7,9] have shown that morphine in out-of-hospital clinical practice is effective when used alone. An important result of our study is that a high initial opioid dose (>0.1 mg/kg) was not associated with a larger number of ADRs. These results are consistent with other works published by our research team [7,12]. One study demonstrated that even a 0.15 mg/kg dose of morphine is not associated with a statistically or clinically significant increase in ADRs [16]. In another study, Fletcher et al. evaluated the event of perioperative administration of two doses of morphine for postoperative analgesia after remifentanil-based anaesthesia [17]. They found that a large dose of morphine (0.25 mg/kg compared to a 0.15 mg/kg) slightly improved postoperative analgesia but was responsible for postoperative respiratory depression. Of course, these results from a postoperative setting with doses much greater than typical recommended doses cannot be extrapolated to a typical emergency department setting.

Morphine is the most commonly used parenteral opioid in US emergency department practice [18], as in France [1]. Our present study reinforces the safety of morphine in the emergency department setting. We found that very few ADRs were clinically significant or could not be easily managed. Four patients had a prolongation of their hospitalisation in the ED due to adverse reactions. We deeply think that our pharmacovigilance study provides valuable means for detection, quantification and maybe morphine ADR reduction, reducing overall healthcare costs in the process.

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6. Conclusion

Serious morphine related ADRs are rare; patients receiving morphine experience mainly nausea and drowsiness. Age, gender, and initial and total opioid doses are not related to ADR occurrence. Prophylactic antiepileptic therapy could be proposed to patients with a history of travel sickness and history of nausea or vomiting postoperatively or post morphine.

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