Sex- and Age-related Differences in Morphine Requirements for Postoperative Pain Relief

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Background: Sex-related differences in the perception of pain and susceptibility to opioids remain a matter of debate. Intravenous morphine titration used to obtain pain relief in the immediate postoperative period is a unique clinical model for assessing the effect of sex on reported pain. Because of the wide variation in dose requirements for pain management, the authors conducted a prospective study in a large population and also assessed the effect of aging.

Methods: Intravenous morphine titration was administered as a bolus of 2 (body weight ≤ 60 kg) or 3 mg (body weight > 60 kg) during the immediate postoperative period. The interval between each bolus was 5 min. The visual analog pain scale (VAS) threshold required to administer morphine was 30, and pain relief was defined as a VAS score of 30 or less. Data are expressed as mean ± SD.

Results: Data from 4,317 patients were analyzed; 54% of the patients were male, and 46% were female. The mean morphine dose required to obtain pain relief was 11.9 ± 6.8 mg or 0.173 ± 0.103 mg/kg. Women had a higher initial VAS score (74 ± 19 vs. 71 ± 19; P < 0.001) and required a greater dose of morphine (0.183 ± 0.111 vs. 0.165 ± 0.095 mg/kg; P < 0.001). In contrast, no significant difference was noted in elderly (aged > 75 yr) patients (0.163 ± 0.083 vs. 0.157 ± 0.085 mg/kg).

Conclusion: Women experienced more severe postoperative pain and required a greater dose (+11%) of morphine than men in the immediate postoperative period. This sex-related difference disappeared in elderly patients.

SEX-RELATED differences in the perception of pain and susceptibility to opioids remain a matter of debate. Experimental studies show that there are sex-related differences in opioid analgesia, but there are discrepancies between animal and human studies. An outstanding feature of the clinical use of opioids is the extraordinary variation in dose requirements for pain management.

Therefore, we believed that only a study conducted in a large population could precisely answer the question of sex-related differences and that the responses would be clinically relevant despite individual variation. Any physiologic or pharmacologic sex-related difference may be markedly modulated by aging because gonadal hormonal secretions are deeply modified by the menopause in women and to a lesser degree by the andropause in men. However, no previous study has assessed the effect of aging on the sex-related differences on pain perception or the response to analgesic drugs.

The immediate postoperative period provides an interesting clinical model, mainly because the procedure of intravenous morphine titration enables precise control of doses of morphine to treat pain reported by the patient over a short period of time. Therefore, we decided to compare pain scores and postoperative morphine consumption in the postanesthesia care unit (PACU) between men and women. We tested the following hypotheses: (1) There are significant differences in postoperative pain perception and morphine consumption between men and women, and (2) these differences are modulated by aging.

Materials and Methods

This study was approved by our hospital ethical committee (Comité Consultatif de Protection des Personnes se Prêtant à la Recherche Biomédicale Pitié-Salpêtrière, Paris, France). Because data were recorded without any intervention and according to a protocol already used routinely our PACU, authorization was given to waive written informed consent. However, complete information on the postoperative management of pain, including intravenous morphine titration and pain assessment, was provided during the preoperative visit with the anesthesiologist. Some patients have been included in previous studies on morphine titration.

Intravenous Morphine Titration

All nurses in the PACU had been trained to assess pain using unidimensional scales and to perform morphine titration. They used the visual analog pain scale (VAS; 0–100, handheld slide rule type) 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) because these two methods are equivalent.

A strict protocol has been implemented in the PACU after a preliminary study determined the optimal regimen of morphine titration. 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 mor-

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phine, and the criteria to stop titration. After arrival of patients in the PACU, they were questioned, after tracheal extubation and the return of full consciousness, about the presence of pain (at least every 15 min before the onset of morphine titration) and asked to rate pain intensity on a scale (VAS). When the VAS score was greater than 30, intravenous morphine was titrated every 5 min by 3-mg increments (2 mg in patients weighing ≤ 60 kg), and pain was assessed every 5 min until pain relief, defined as a VAS score of 30 or less. 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 score of 0. When pain was too severe to obtain a VAS (patient refusal), it was assigned a score of 100. Clinical monitoring included respiratory rate measurements, oxygen saturation measured by pulse oximetry, sedation according to the Ramsay score, arterial blood pressure, and heart rate. Morphine titration was stopped if the patient had a respiratory rate lower than 12 breaths/min or an oxygen saturation by pulse oximetry lower than 95% or experienced a serious adverse event related to morphine administration (allegory with cutaneous rash and/or hypotension, vomiting, severe pruritus). In case of severe ventilatory depression (respiratory rate < 10 breaths/min), naloxone (intravenous bolus of 0.04 mg) was administered until the respiratory rate was greater than 12 breaths/min. As previously reported, a severe postoperative pain was defined as an initial VAS score of 70 or greater.

In the current study, nurses could not be blinded to the patient’s sex; thus, a possible bias could have occurred. Therefore, the data sheets of the first 1,050 patients were retrospectively assessed for potential protocol deviation, as previously reported. Moreover, we also looked for opioid dose administered during surgery in the last patients.

Patients
During the data collection period, consecutive patients who fulfilled the following criteria were included: (1) VAS score greater than 30 and (2) understanding of the unidimensional methods. Patients with minor pain (defined as a VAS score ≤ 30), with delirium or dementia, or who were non-French-speaking were not included in the study. Criteria for exclusion were interruption of morphine titration because of the occurrence of severe morphine-related adverse effects. Sedation was not considered a severe morphine adverse effect, as previously reported. Patients who received other analgesics (or regional anesthesia) as a rescue procedure because of lack of pain relief with morphine were also excluded. This decision was taken by the anesthesiologist, usually in patients requiring more than 10 boluses of morphine.

Morphine requirement (expressed as milligram per kilogram body weight) was the amount of morphine needed to obtain pain relief (VAS score ≤ 30) during intravenous morphine titration.

Statistical Analysis
Data are expressed as mean ± SD or median and 95% confidence interval. The Student t test was used to compare two means, the Mann–Whitney U test was used to compare two medians, and the Fisher exact method was used to compare two proportions.

The database was prospectively recorded for several research purposes. The decision to analyze sex differences was taken very early, but the decision to analyze the data base for sex differences was delayed until a large number of patients (> 4,000) had been included. Patients were divided into two groups according to their sex. The between group difference in morphine requirement and its 95% confidence interval were calculated. The following subgroup analyses were specified a priori: (1) exclusion of patients undergoing surgery related to their sex (i.e., hysterectomy, prostatectomy, breast surgery, genital surgery); (2) elderly (aged ≥ 75 yr) and nonelderly patients, who were separated into two groups (18–49 yr and 50–74 yr); and (3) according to the nature of the surgery, including groups in which at least 120 patients have been included.

All comparisons were two tailed, and a P value of less than 0.05 was required to rule out the null hypothesis. Statistical analysis was performed using a computer and NCSS 2001 software (Statistical Solutions Ltd., Cork, Ireland).

Results
Among 4,525 patients who fulfilled the criteria for inclusion, important data were lacking in 55 patients, and morphine titration was interrupted because of severe morphine adverse effects in 110 patients (2.4%) or administration of a rescue analgesic in 45 patients (1.0%). Therefore, data from 4,317 patients were analyzed in the study. The mean age was 50 ± 18 yr, the mean weight was 70 ± 14 kg, 2,334 patients (54%) were male, and 1,983 patients (46%) were female. They were admitted in the PACU after orthopedic surgery in 3,149 patients (73%), urologic surgery in 595 patients (14%), abdominal or gynecologic surgery in 266 patients (6%), vascular surgery in 121 patients (3%), and thoracic or cervicomaxillofacial surgery in 159 patients (4%). Local-regional anesthesia was performed in 267 patients (6%), and general anesthesia was performed in 4,050 patients (94%). In patients undergoing general anesthesia, 4,001 (99%) received sufentanil, 37 (0.9%) received remifentanil, and 12 (0.3%) received alfentanil.

The mean value of the initial VAS score was 72 ± 19 (median, 70). The mean morphine dose required to obtain pain relief was 11.9 ± 6.8 mg or 0.173 ± 0.105 mg/kg (median, 0.150 mg/kg). Pain relief was obtained after a
median of 4 boluses, with extremes ranging from 1 to 20 boluses.

Table 1 summarizes the differences between men and women. Women had a higher initial VAS and required a greater dose of morphine (difference, 0.019 mg/kg [95% confidence interval, 0.013–0.025], +11%). The evolution of VAS and the proportion of patients experiencing pain relief during morphine titration are shown in figure 1. The subgroup analysis is shown in figure 2. The significant difference between men and women was still observed after patients who received sex-related surgery were excluded. The difference was noted in most of the surgical procedures analyzed. In contrast, no significant difference was noted in elderly patients (fig. 2).

Table 2 shows that age modified morphine consumption in women but not in men (table 2).

We performed a quality control in the first 1,050 patients. Deviation of the protocol of intravenous morphine titration occurred in 38 patients, but no significant difference was observed between men and women (3.6 vs. 3.6%). The dose of sufentanil used in the preoperative period was collected in the last patients (n = 1,409). Women required a greater dose of sufentanil than men (0.698 ± 0.376 vs. 0.646 ± 0.412 μg/kg; difference, 0.052 μg/kg [95% confidence interval, 0.012–0.092], +8%).

**Discussion**

In the current study, we observed that women had significantly higher VAS scores and required more morphine during intravenous titration in the postoperative period than men. The magnitude of the difference in morphine requirements was estimated to be around 11%. This difference was not observed in elderly patients (aged ≥ 75 yr).

The VAS is the most commonly used tool to assess pain in the perioperative period and to measure outcome in clinical research. The VAS is sensitive to pharmacologic and nonpharmacologic procedures that alter the experience of pain and correlates well with pain verbal rating scales. In our study, we used the morphine dose required to obtain pain relief as an estimate of pain intensity. This measurement is not completely independent from the VAS measurement because the VAS is used to define pain relief. We have previously proposed two

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**Table 1. Comparison of Men and Women**

<table>
<thead>
<tr>
<th></th>
<th>Men (n = 2,344)</th>
<th>Women (n = 1,933)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, yr</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;75 yr</td>
<td>49 ± 18</td>
<td>52 ± 18</td>
<td>&gt; 0.001</td>
</tr>
<tr>
<td>&gt;75 yr</td>
<td>167 (7%)</td>
<td>207 (10%)</td>
<td>&gt; 0.001</td>
</tr>
<tr>
<td><strong>VAS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial</td>
<td>71 ± 19</td>
<td>74 ± 19</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Final</td>
<td>18 ± 16</td>
<td>18 ± 16</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Severe pain (VAS &gt; 60)</strong></td>
<td>1,340 (57%)</td>
<td>1,260 (63%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Incomplete pain relief</td>
<td>83 (4%)</td>
<td>74 (4%)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Weight, kg</strong></td>
<td>75 ± 13</td>
<td>65 ± 13</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>Morphine dose, mg</strong></td>
<td>11.5 ± 6.8</td>
<td>12.2 ± 6.9</td>
<td>0.002</td>
</tr>
<tr>
<td>mg/kg</td>
<td>0.165 ± 0.095</td>
<td>0.183 ± 0.111</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>Number of boluses</strong></td>
<td>4 (3-4)</td>
<td>4 (3-4)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD, median (95% confidence interval), or number (percentage).

NS = not significant; VAS = visual analog scale pain score.

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**Fig. 1.** Comparison of visual analog pain score (VAPS; A) and number of patients with complete pain relief (VAPS ≤ 30; B) in men and women. *P < 0.05.

**Fig. 2.** Comparison of morphine requirements in men and women. Odds ratio (95% confidence interval). OMR = osteosynthesis material removal; SRS = sex-related surgery; THP = total hip replacement.
ways in defining the severity of pain: The first is mainly related to the patient’s perception of pain, whereas the other depends largely on the amount of analgesics required to obtain pain relief. This last definition may be useful in clinical practice because it is related to the pharmacologic effort subsequently developed to obtain pain relief.

What are the possible sources of sex differences in acute pain? First, women seem to have a lower pain threshold and less tolerance to experimental pain than men. In healthy volunteers, a meta-analysis provided quantitative confirmation of this finding. For pain threshold and pain tolerance, male subjects had higher values than females for all types of noxious stimuli, although the largest effect sizes were obtained when pressure pain was compared across the sexes, followed by electrical pulses and finally thermal stimuli. Women exhibit greater sensitivity to laboratory pain compared with men, and this difference does not seem to be site specific. Using a topical capsaicin stimulation (tonic C fiber–mediated pain stimulus), Frot et al. showed that females rated pain as more intense and unpleasant than did males. This experimental pain model produces a mechanical hyperalgesia that also occurs during a surgical procedure. In the postoperative setting, Cepeda et al. showed that women exhibited more pain and had higher levels of pain intensity than men. Pain intensity on PACU arrival was significantly lower in men, whereas the pain intensity levels at the end of the study were similar. In contrast, Chia et al. observed no significant differences in pain intensity scores between men and women, either at rest or on movement except on the wards (second postoperative day). These authors concluded that the abdominal and thoracic surgical procedures were considered very painful and explained a similar level of pain intensity between women and men. However, this study was conducted in Taiwan with a Chinese population, and it should be noted that in other populations, pain perception and pain expression may also be explained by racial and cultural differences.

Second, there are sex-related differences in the effects of opioid analgesics. In our study, the dose of postoperative morphine and the dose of perioperative sufentanil, even when these doses were normalized for body weight, were higher in women than in men. According to several authors, women seem to be more sensitive to the effects of morphine as compared with males. Numerous studies have observed that men require a 20–40% higher dose of opioids to achieve adequate pain relief. However, these studies were performed using patient-controlled analgesia in the postoperative setting, and the difference in analgesic consumption between men and women may be related to psychological factors or personality traits, notably opioid side effect perception, that may have affected the use of patient-controlled analgesia device. Moreover, a major limitation of these studies is that the analgesic effects of the opioid were not measured in the patients. The authors focused their studies on opioid consumption, but this variable may be affected by factors other than pain intensity and pain relief. Lastly, most of the opioid requirements were not adjusted to the body weight. In contrast, other authors either did not demonstrate any significant sex-related differences or observed that women had larger consumption of morphine than men to achieve pain relief in the postoperative setting. In that study, women required 0.03 mg/kg (+30%) more morphine than men. Nevertheless, in this study, the sample size was relatively low (n = 277 men), the VAS score that defined pain relief was higher (> 40 out of 100), and the time interval (10 min) between each morphine bolus has been shown to be nonoptimal. In healthy volunteers receiving intravenous morphine, Sarton et al. observed that women showed greater morphine potency but slower onset and offset of analgesic effect, suggesting that sex differences in morphine-induced analgesia have a pharmacodynamic origin. Our results support the conclusions of Sarton et al. who demonstrated that the potency of morphine is decreased in the early phase of its administration because of a slower onset. Nevertheless, clinical extrapolation of laboratory results in healthy volunteers should be made with caution. In that study, the pain induced was not severe and the dose of morphine administered was low. Regardless, our study provides evidence, based on a large population, that women need more morphine to obtain pain relief in the early postoperative period, and this result was confirmed when looking at different types of surgery (fig. 2).

One of the main results of our study is the disappearance of sex-related differences in elderly patients (fig. 2). This result suggests that gonadal steroid hormone production may influence sensitivity to opioid analgesia. Gonadal hormones are known to modulate pain intensity. A decrease in pain threshold and an increase in morphine consumption has been observed in women with menstrual cycles, notably during the luteal phase.
However, no studies have been conducted to compare opioid analgesia at all stages of the menstrual cycle in any primate species. Our study, which indicates that sex-related differences disappear in elderly patients, favors the hypothesis of an important role of sexual hormones.

Some remarks must be included to assess the limitations of our study. First, the use of the 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 that varies only in intensity. 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. Second, the amount of morphine used to alleviate pain is not only dependent on the pharmacodynamics but also on the pharmacogenetics and pharmacokinetics. Further studies including morphine and morphine metabolite dosages are required to understand the different morphine requirements and measurement of pain in men and women. Some evidence has been recently provided that morphine-6-glucuronide, the main and active morphine metabolism, is not involved in sex-related differences.

Third, our results may not apply to the postoperative period after pain relief had been obtained by morphine titration. This period is more dependent on pharmacokinetics, as shown by the marked difference between elderly and young patients, which is not observed during intravenous morphine titration. Moreover, if the results of Sarton et al. obtained in the healthy volunteers apply to the postoperative setting, one can expect that sex-related difference in morphine consumption might be on the opposite site during this period, as previously noted.

Further studies are required to confirm this hypothesis. In conclusion, we observed that women experienced more pain and required greater doses of morphine than men during the immediate postoperative period to obtain pain relief. The magnitude of the increase in morphine requirements during intravenous morphine titration is estimated to be around 11%. This sex-related difference disappeared in elderly patients. Further research in both animals and humans is required to determine whether sex differences in pharmacokinetics and pharmacodynamics of morphine are mediated by sexual steroid hormones.

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