Anaesthesia dosage and opioid administration in morbidly obese patients
Postoperative intravenous morphine titration

F. Aubrun¹*, J.-X. Mazoit² and B. Riou³

¹ Department of Anesthesiology and Critical Care, Université Claude Bernard Lyon 1, Groupe Hospitalier Nord, Hôpital de la Croix Rousse, Lyon, France
² Department of Anesthesiology and Critical Care, Université Paris-Sud 11, Hôpital Bicêtre, Le Kremlin Bicêtre, France
³ Department of Emergency Medicine, Université Pierre et Marie Curie, Groupe Hospitalier Pitié-Salpêtrière, Paris 6, France

* Corresponding author: Département d’Anesthésie-Réanimation, Groupe Hospitalier Nord, Hôpital de la Croix Rousse, 103, Grande-Rue de la Croix Rousse, 69317 Lyon Cedex 04, France. E-mail: frederic.aubrun@chu-lyon.fr

Editor’s key points

- Titration of morphine i.v. is used widely for treatment of pain in post-anaesthesia care unit.
- The careful use of a protocol should minimize the adverse effects of morphine.
- Distinguishing between adequate pain relief and morphine-induced sedation can be difficult.
- It can be used with caution in the elderly, children, and obese patients.

Summary. Relief of acute pain during the immediate postoperative period is an important task for anaesthetists. Morphine is widely used to control moderate-to-severe postoperative pain and the use of small i.v. boluses of morphine in the post-anaesthesia care unit allows a rapid titration of the dose needed for adequate pain relief. The essential principle of a titration regimen must be to adapt the morphine dose to the pain level. Although morphine would not appear to be the most appropriate choice for achieving rapid pain relief, this is the sole opioid assessed in many studies of immediate postoperative pain management using titration. More than 90% of the patients have pain relief using a protocol of morphine titration and the mean dose required to obtain pain relief is 12 (7) mg, after a median of four boluses. Sedation is frequent during i.v. morphine titration and should be considered as a morphine-related adverse event and not evidence of pain relief. The incidence of ventilatory depression is very low when the criteria to limit the dose of i.v. morphine are enforced. Morphine titration can be used with caution in elderly patients, in children, or in obese patients. In practice, i.v. morphine titration allows the physician to meet the needs of individual patients rapidly and limits the risk of overdose making this method the first step in postoperative pain management.

Keywords: analgesia, postoperative, analgesic techniques, i.v., analgesics opioid, morphine, pain, acute, titration

WHY using opioids with caution in obese patients. ?

ESA Mulier 2015
Dose adjustment of anaesthetics in the morbidly obese

J. Ingrande and H. J. M. Lemmens*

Department of Anesthesia, Stanford University School of Medicine, 300 Pasteur Drive, Room H3576, Stanford, CA 94305, USA

* Corresponding author. E-mail: hlemmens@stanford.edu

Key points

- Morbidly obese patients require special dosing regimens.
- Lean body weight is the optimal scalar for most i.v. opioids and anaesthetics.
- Knowledge of the altered pharmacological behaviour of anaesthetic drugs is essential for optimal management of the morbidly obese.

Anaesthesiologists must be prepared to deal with pharmacokinetic and pharmacodynamic (PD) differences in morbidly obese individuals. As drug administration based on total body weight can result in overdose, weight-based dosing scalars must be considered. Conversely, administration of drugs based on ideal body weight can result in a sub-therapeutic dose. Changes in cardiac output and alterations in body composition affect the distribution of numerous anaesthetic drugs. With the exception of neuromuscular antagonists, lean body weight is the optimal dosing scalar for most drugs used in anaesthesia including opioids and anaesthetic induction agents. The increased incidence of obstructive sleep apnoea and fat deposition in the pharynx and chest wall places the morbidly obese at increased risk for adverse respiratory events secondary to anaesthetic agents, thus altering the PD properties of these drugs. Awareness of the pharmacology of the commonly used anaesthetic agents including induction agents, opioids, inhalation agents and neuromuscular blockers is necessary for safe and effective care of morbidly obese patients.

Keywords: anaesthetics, i.v., pharmacokinetics; anaesthesia, inhalation, pharmacokinetics; obesity, morbid

LBW is the optimal scalar for most i.v drugs
Knowledge is essential for morbidly obese patients

ESA Mulier 2015
Opioids dosing in morbidly obese.

- Fentanyl (dose on LBW)
  - Clearance is higher and increases with LBW
  - Increased CO in obese -> **lower conc during early distribution even when dosed on LBW**

- Sufentanyl (dose above LBW but TBW is too high)
  - Highly lipophilic -> increased distribution volume and elimination half-life, but plasma clearance comparable
  - **Plasma conc are freq lower** than in non obese patients

- Remifentanil (dose on LBW)
  - Rapidly metabolized, organ dependent clearance.
  - If infusion is based on TBW -> **higher plasma conc** than non obese
  - If infusion is based on LBW -> **faster recovery** than non obese
How does TBW IBW IBW-adj LBW relate for a certain length to TBW?


A patient's ideal body weight (as described by Devine 1974) may be calculated according to the following equation:

Ideal BW (men) = 50 + 2.3 * (height over 60 inches)
Ideal BW (women) = 45.5 + 2.3 * (height over 60 inches)

Adjusted body weight

This calculator uses an adjustment factor of 0.4, or 40%, to provide an adjusted body weight in patients who are more than 20% of their ideal body weight. This adjustment uses the following equation:

AdjustedBW = IdealBW + (0.4 * (ActualBW - IdealBW))

Nutritional body weight

This calculator uses an adjustment factor of 0.25, or 25%, to provide a nutritional body weight in patients who are more than 20% of their ideal body weight. Note that some references will use a nutritional body weight on the basis of BMI, rather than percent ideal body weight. This adjustment uses the following equation:

NutritionalBW = IdealBW + (0.25 * (ActualBW - IdealBW))

Lean body weight

A more accurate measure of lean body weight may be the LBW2005 equation, which unlike the Devine 1974 equation, has been derived and validated from actual patient data. Although this equation is less cited in the literature and less commonly used in practice, it may be a useful alternative in the clinical setting for patients who are particularly short (height < 60 inches) or particularly obese. The LBW2005 uses the following equations:

LBW2005 (men) = \( \frac{9.27 \times 10^3 \times \text{ActualBW}}{6.68 \times 10^3 + (216 \times \text{BMI})} \)

LBW2005 (women) = \( \frac{9.27 \times 10^4 \times \text{ActualBW}}{8.78 \times 10^3 + (244 \times \text{BMI})} \)

Body mass index (BMI)

BMI is a commonly used measure of obesity outside of the medical setting, but is rarely used within the medical community for clinical decisions. One downfall of the body mass index metric is that it cannot differentiate between lean body weight ("muscle mass") and adipose tissue (fat) because it only takes into account height and weight. The following equation is used to calculate BMI:

\[ \text{BMI} = \frac{\text{Weight in kg}}{(\text{Height in meters})^2} \]
Remifentanil Pharmacokinetics in Obese versus Lean Patients

Talmage D. Egan, M.D.,* Bernou Huizinga, M.D.,† Samir K. Gupta, Ph.D.,‡ Rudy L. Jaarsma, M.D.,†, Richard J. Sperry, M.D., Ph.D.,§ James B. Yee, M.D., Ph.D.,‖ Keith T. Muir, Ph.D.¶

Background: Remifentanil is a short-acting opioid whose pharmacokinetics have been characterized in detail. However, the impact of obesity on remifentanil pharmacokinetics has not been specifically examined. The goal of this study was to investigate the influence of body weight on remifentanil pharmacokinetics.

Methods: Twelve obese and 12 matched lean subjects undergoing elective surgery received a 1-min remifentanil infusion after induction of anesthesia. Arterial blood samples were collected for determination of remifentanil blood concentrations. Each subject’s pharmacokinetic parameters were estimated by fitting a two-compartment model to the concentration versus time curves. Nonlinear mixed-effects population models examining the influence of lean body mass (LBM) and total body weight (TBW) were also constructed. Clinical simulations using the final population model were performed.

Results: The obese patient cohort reached substantially higher remifentanil concentrations. The individual pharmacokinetic parameters of a two-compartment model were not significantly different between the obese versus lean cohorts (unless normalized to TBW). The final population model scaled central clearance and the central and peripheral distribution volumes to LBM. The simulations illustrated that remifentanil pharmacokinetics are not grossly different in obese versus lean subjects and that TBW based dosing in obese patients can result in excessively high remifentanil concentrations.

Conclusions: The essential findings of the study are that remifentanil’s pharmacokinetics are not appreciably different in obese versus lean subjects and that remifentanil pharmacokinetic parameters are therefore more closely related to LBM than to TBW. Clinically this means that remifentanil dosing regimens should be based on ideal body weight (or LBM) and not TBW. (Key words: Body weight; obesity; opioids; pharmacokinetics; remifentanil.)
Remifentanyl

Faster recovery in obese patients when dosed on LBW

<table>
<thead>
<tr>
<th>Infusion rate (min)</th>
<th>Lean patient 80%</th>
<th>Obese Patient 80%</th>
<th>Lean Patient 50%</th>
<th>Obese Patient 50%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to decrease (min)</td>
<td>80% decrement time</td>
<td>50% decrement time</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Obese TBW dosing
Lean TBW dosing
Lean LBW dosing
Obese LBW dosing

Fig. 1. The raw concentration versus time data. The obese subjects’ data are plotted with a solid line; lean subjects are represented by the dashed line. Remifentanil concentration is shown on a log scale.

Fig. 6. A computer simulation of a typical remifentanil “balanced” anesthetic (i.e., remifentanil in combination with nitrous oxide, inhaled vapor, or propofol) when the dosage regimen is calculated based on LBM or TBW for both obese and lean patients (1 μg/kg bolus injection followed by an infusion of 0.5 μg·kg⁻¹·min⁻¹ for 15 min and 0.25 μg·kg⁻¹·min⁻¹ for an additional 105 min). Note that TBW-based dosing in an obese patient results in dramatically higher concentrations.
Opioid dosing peri-operative

- doses to achieve: analgesia < balanced anesthesia < full sympathicolysis

  - Fentanyl: 10 ug=1mg M+  
    - 1 – 2  
    - 2 – 20  
    - 20 – 50 ug/kg

  - Sufentanyl: 1 ug=1mg M+  
    - 0.1 – 0.2  
    - 0.2 – 8  
    - 8 – 30 ug/kg

  - Remifentanil: 0.5ug=1mg M+  
    - 0.025 – 0.1  
    - 0.1 – 0.5  
    - 0.5 – 2 ug/kg/min

- Analgesia post operative or anesthesia under spont breathing

- Balanced anesthesia with inhalation or propofol

- Full sympathicolysis with opioid only (stress free)
Intra-operative remifentanil might influence pain levels in the immediate post-operative period after major abdominal surgery

E. G. Hansen1,4, T. H. Duedahl2,6, J. Rømsing2, K.-L. Hilsted3 and J. B. Dahl3
1Department of Anaesthesiology, Herlev University Hospital, Herlev, 2The Danish University of Pharmaceutical Sciences, Copenhagen, and 3Department of Anaesthesiology, Glostrup University Hospital, Glostrup, Denmark

Thoracic epidural with bupivacaine 30 mg/h perop -> 10 mg/h postop
Remifentanyl 0.4 ug/kg/min or placebo perop
PCA morphine postop together with thoracic epidural
How to avoid opioids per-operative?

- Stress free anesthesia with full sympathicolysis without opioids
  - Locoregional anesthesia
  - Dexmedetomidine (1 - 2 ug/kg/h)
  - Or lidocaine (3 - 4 mg/kg/h)
  - Magnesium alone not enough (10 - 20 mg/kg/h)

- Balanced anesthesia without opioids
  - multimodal sympathicolysis
    - Dexmedetomidine 0.25 – 0.5 ug/kg idem ug/kg/h
    - + Lidocaine 1.5 mg/kg (or procaine) 1 mg/kg/h
    - + Magnesium 40 mg/kg 5 mg/kg/h
  - + Hypnosis with
    - inhalation 0.8 - 1 MAC
    - Or Propofol 12 mg/kg/h

ESA Mulier 2015
Further opioid reduction by

- Reduce inflammation -> less pain
  - Before surgery starts
    - Steriods: dexamethasone 10 mg or higher dose
    - NSIAD’s: diclofenac 150 mg
  - Reduce edema -> less pain
    - Keep patient dry, give fluids only if pulse pressure variation increases.

- Use local wound infiltration with bupivacaine

- Sedatives?
Reduce opioid side effects

- Reduce tolerance and hyperalgesia
  - Low dose ketamine 10 mg before opioid
  - or 50 mg/10 h

- Reduce PONV
  - Droperidol,
  - Dexamethasone,
  - Ondansetron
  - Empty stomach before extubation
VAS scores are better with a lower morphine consumption post operative

- Randomised study in 40 lap RNY patients
- Patients got OFA or Opioids per-op only
- Same post op additive drugs: paracetamol and diclofenac
- Morphine pump PCIA: VAS score at PAZA and Ward first day

2013 R. Wouters; J. P. Mulier
- Observational study in 400 lap RNY patients
- Patients got OFA or OA per-op and post-operative
- Same post-op additive drugs: paracetamol and diclofenac
- Morphine (or piritramide) as required

Qo40 Questions that are significant different OFA versus OA

* Chi square p < 0.05
Observational study in 2318 consecutive lap RNY patients (2012 - 2013)

- Patients got OFA, OA or OSA per-op and post operative
- Analgetics according to the prescribing anesthesiologists (NSAIDs, paracetamol and opioids)
- Total Morphine (or morphine analogue) for day of surgery

10 000 lap RNY in Bruges on Thursday 30 April 2015
2004 -> 2015

<table>
<thead>
<tr>
<th></th>
<th>OA</th>
<th>OFA</th>
<th>OSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013 - 2014</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no complications</td>
<td>994</td>
<td>1124</td>
<td>118</td>
</tr>
<tr>
<td>complications</td>
<td>39</td>
<td>35</td>
<td>8</td>
</tr>
<tr>
<td>% complications</td>
<td>3.8%</td>
<td>3.0%</td>
<td>6.4%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>OA</th>
<th>OFA</th>
<th>OSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>anesthesia related</td>
<td>3</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>bleeding</td>
<td>9</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>cardiac</td>
<td>8</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>infection (non pulm)</td>
<td>3</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Unurable pain, vomiting</td>
<td>8</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>respiratory</td>
<td>7</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>surgical</td>
<td>1</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>other</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>total</td>
<td>39</td>
<td>35</td>
<td>8</td>
</tr>
<tr>
<td>after bar surgery</td>
<td>7</td>
<td>14</td>
<td>1</td>
</tr>
</tbody>
</table>

Number of lap RNY 2013 2014

Average total morphine first day

mg Morphine or analogue
Key points to remember

- Lean body weight is the optimal scalar for i.v. Opioids
  - Remifentanil is easier to dose but faster tolerance

- Loading dose followed by maintenance of short acting
  - Avoid high plasma levels post operative

- Why do you use opioids peri operative?
  - Low dose as analgesia, only effective when awake
  - Medium dose in balanced anesthesia
  - High dose to get full sympathicolysis

- Use an additive to reduce opioids per operative
  - Dexmedetomidine or lidocaine or Magnesium or Ketamine

- Use an additive to reduce opioids post operative
  - Clonidine and ketamine and Procaine

- Multimodal with all additives to work total opioid free
  - Become ESPCOP member and follow next ESPCOP meeting in Bruges
Following the advice in using less peri-operative opioids in morbidly obese patients, it has now become time to discuss "from low-opioid to opioid free" anaesthesia (OFA).

Why, how and when do we use low-opioid or opioid free anaesthesia combined with post-operative multimodal analgesia in morbidly obese patients?