

## Influence of aging on the perioperative dosage of methadone

### Introduction

Increasingly, elderly patients undergo anesthesia and surgery. There are multiple factors that affect the dosage of anesthetic drugs in this age group, such as the normal aging process, age-related morbidity and polypharmacy, commonly observed in the elderly patient (1). The older adult presents pharmacodynamic and pharmacokinetic changes associated with alterations in absorption, distribution, metabolism, and excretion, which commonly translate into an increase in the potency of the drugs, so significant dose reductions may be required(1-5).

Opioids are non-steroidal analgesic drugs widely used in the management of intra and postoperative pain. Numerous studies have described important changes in the pharmacokinetics and pharmacodynamics of these drugs in the elderly population (3,6,7). Morphine clearance, for example, is reduced by 50% in the elderly compared to the young adult, which may prolong the action of this drug in the first group (6). The potency of fentanyl or remifentanil increases progressively with age, requiring substantially lower concentrations in the elderly compared to a young adult to obtain the same effect (3,8).

Methadone is considered a first-line opioid in the treatment of chronic pain due to numerous advantages compared to other opioids (9). Methadone does not generate active metabolites after its liver biotransformation (10), it has a long half-life that translates into a prolonged effect and simple dosing schedules (10), it has antihyperalgesic and antiallodynic properties that give it great effectiveness in the relief of neuropathic pain (11). Despite these advantages, the use of methadone in the surgical population is comparatively less than other opioids such as morphine or fentanyl. Although the general recommendation for the use of opioids in the elderly is to decrease the doses, the great inter-individual variability characteristic of elderly patients and the greater susceptibility to adverse effects in this population, make anesthetic dosing challenging and requires a new approach, to establish more precise dosages in terms of effectiveness and safety. However, to date there are no pharmacokinetic or pharmacodynamic studies that allow standardizing a dose adjustment of methadone in the elderly patient.

### Research Question:

What is the influence of age, on intraoperative methadone dosing, in adult patients undergoing laparoscopic abdominal surgery under general anesthesia?

### General objective:

Generate a population pharmacokinetic and pharmacodynamic model, that allows the generation of reference dosage schedules for intraoperative use of methadone, according to the age of the patient.

### Specific objectives:

- 1) Characterize the changes in methadone volumes and clearance, attributable to age in the adult population.
- 2) Characterize the changes in methadone potency, attributable to age in the adult population.
- 3) Design intraoperative methadone dosing schedules, according to the age of the patient.

### Materials & Methods

This study is a controlled, randomized, double-blind study.

- Inclusion criteria: Age> 18 years, ASA I, II or III, Laparoscopic Abdominal Surgery
- Exclusion Criteria: BMI> 35, opioid use up to 5 days prior to surgery, acute liver failure or chronic liver disease Child C, kidney insufficiency with creatinine clearance estimated by Cockcroft-Gault formula <60 ml / min.

### Recruitment

Recruitment will be carried out by the Research team of the Anesthesiology Division, by daily review of the surgical table and the application of inclusion and exclusion criteria. On the day of hospital admission, patients will be explained what the study consists of and they will proceed to sign the informed consent if they agree to participate in it.

### **Distribution by random groups**

Patients who agree to participate will be randomized into four groups according to the dose of intravenous methadone to be received during anesthetic induction. Group P (placebo), Group M1 (0.05 mg / kg), Group M2 (0.1 mg / kg), and Group M3 (0.2 mg / kg). The random sequence will be generated on a research laboratory computer and will be stored in an encrypted file. This information will be known exclusively by a member of the research team present during the surgery, who will hand over preparing the corresponding medicine in a 20 cc syringe and hand it over to the treating anesthesiologist.

### **Anesthesia**

General anesthesia will be administered in a standard way including frontal electroencephalogram with BIS. The only opioids that patients will receive will be remifentanil and methadone in doses defined according to the corresponding group. Methadone will be administered once the patient is intubated and has hemodynamic stability.

### **Postoperative**

Upon admission to the recovery unit, the patient is given a PCA pump for intravenous administration of morphine. In the first two hours after admission to the recovery unit, the patient will be evaluated every 30 minutes and subsequently these evaluations will be carried out just before taking the blood samples for measurement of plasma methadone. Patient evaluations will be compiled by the research assistant in charge who will be blind to the methadone doses administered.

### **Blood Sampling**

Five venous blood samples will be taken from each patient, for plasma methadone analysis. Patients will be randomly divided into two groups of sampling times: Group 1 at 0.05, 0.75, 1.5, 6, 18 hours after drug administration and Group 2 at 0.25, 1, 3, 12 and 24 hours. Blood samples will be collected in heparin tubes and centrifuged at the UC-Christus Health Network Central Laboratory to be plasma separated and labeled. The extracted serum will be placed in cryo tubes that will be stored at 20 ° C until analysis. Methadone samples will be analyzed using a high performance liquid chromatography (HPLC) spectrofluorometric method at the UC Faculty of Chemistry. The lower limits of quantification (LLOQ) will be determined. Those responsible for the sample collection process, and the coordination for the centrifugation process and transportation to the San Joaquín Campus will be the research nurse and the research fellow.

Once obtained, the blood samples will be sent to the Central Laboratory of the UC-Christus Health Network to be separated in plasma and then they will be sent to the laboratory of the Faculty of Chemistry in San Joaquín, where they will be processed for the specified measurements. Later they will be eliminated according to the corresponding protocol of the laboratory.

### **Data collection**

The data obtained will be collected in a form within the REDCAP computer system, to subsequently generate an encrypted database, maintaining the confidentiality of the recruited patients. The study will be prospectively registered at [clinicaltrials.gov](https://clinicaltrials.gov).

### **Pharmacokinetic analysis**

One, two and three compartment linear models will be used to fit the methadone plasma concentration data over time. Models will be parameterized in terms of elimination clearance, inter-compartment distribution clearance, central volume, and peripheral distribution volumes, as appropriate. Estimates of population parameters (clearance and volumes) will be obtained using nonlinear mixed effects models (NONMEM VII, Icon Development Solutions, Ellicot City, MD, USA).

### **Pharmacodynamic analysis**

The use of rescue morphine in the PACU will be used as a measure to relate the methadone dose (mg / kg) with the analgesic efficacy using an EMAX model. The data will be modeled using NONMEM VII. A proportional term will be used for variability between subjects. Additive and proportional terms will be used to characterize the unknown residual variability. The convergence criterion will be three significant digits.

### **Analysis of covariables**

The parameter values will be standardized for a body weight of 70 kg using an allometric model.

$$P(i) = P(std) \times \left( \frac{Weight(i)}{Weight(std)} \right)^{EXP}$$

Where  $P_i$  is the individual's parameter, weight ( $i$ ) is the individual's weight and  $P_{std}$  is the parameter in an individual with a standard weight of 70 kg. This standardization allows a better comparison of parameters in populations of different sizes. The exponent of EXP will be assumed to be 0.75 for the clarifications and 1 for the distribution volumes.

### **Pharmacodynamic analysis**

The use of rescue morphine in the PACU will be used as a measure to relate the methadone dose (mg / kg) with the analgesic efficacy using an EMAX model.

$$Morphine\ Rescue\ Dose\ (mg/kg) = SO \times \frac{Dose\ (mg/kg) \times Emax}{Dose\ (mg/kg) \times ED50}$$

$SO$  is the required morphine rescue without the use of methadone, EMAX is the maximum required morphine rescue dose and ED50 is the methadone dose that reaches half of this maximum morphine rescue dose. The data was modeled using NONMEM VII. A proportional term was used for variability between subjects. Additive and proportional terms were used to characterize the unknown residual variability. The convergence criterion was three significant digits.

### **Model fit quality**

The Bootstrap methods, incorporated within the NONMEM program, will provide a means of evaluating the uncertainty of the parameters (13). A total of 1000 repetitions will be used to estimate the confidence intervals of the parameters. A Visual Predictive Verification (VPC) (14), a modeling tool that estimates concentration prediction intervals and graphically superimposes these intervals on concentrations observed after a standardized dose, will be used to assess how well the model predicts the distribution of observed methadone concentrations. The VPC simulation will be performed using 1000 subjects with characteristics similar to the patients studied.

### **Sample size**

Sample size calculations were estimated using a simulation-based approach and previous work with similar methodology. We estimate that approximately 50 patients (5-6 samples per patient) are required to detect the effect of age, assuming a 20% proportional decrease in elimination clearance, with 80% potency. To achieve an adequate representation of all age groups, a number of 60 patients will be required, distributed among 20 patients between 18 and 40 years, 20 patients between 41 and 65 years and 20 patients > 65 years. The PharmPow package used for these calculations is available at <http://cran.r-project.org/web/packages/PharmPow/PharmPow.pdf>.

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