

## **Cover page**

### **Official title:**

Modelling propofol pharmacokinetics and pharmacodynamics during an intravenous anaesthesia guided by the bispectral index (BIS)

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# Study protocol and statistical analysis plan

## Anaesthetic protocol

### *Preoperative evaluation*

- Assessment of past medical history, allergies and current medications;
- Physical exam (vital signals, weight, height) and airway assessment with Mallampati score, dentition, range of neck motion and thyromental distance;
- Laboratory tests confirmation when necessary;
- Frailty quantitative clinical evaluation – Clinical Frailty Scale;
- Single-frequency bioelectrical impedance analysis;
- Presentation and discussion of informed consent elements;
- Participant information leaflet delivery.

### *Anaesthetic technique*

- Intra-operative monitoring: continuous pulse oximetry, electrocardiography, invasive blood pressure, neuromuscular blockade (*train-of-four* pattern) and bilateral BIS (BIS VISTA™ Bilateral Monitoring System, Covidien, Colorado, US);
- Remifentanyl effect-site concentration set at 3 ng/mL (Minto's model), using a target controlled infusion device (Orchestra® Base Primea – Fresenius Kabi) and arterial line placement;
- Induction of general anaesthesia: remifentanyl effect-site concentration set at 3 ng/mL, rocuronium 0.6 mg/kg and propofol at 2000 mg/h until LOC, defined by “loss of eye-lash reflex” and “loss of response to name calling”;
- At LOC, propofol infusion rate will be adjusted to 6 mL/kg/h and orotracheal intubation will be accomplished when TOF count 0-1 and BIS 40-60;
- Time to LOC in seconds and total dose of propofol in mg will be recorded;
- Maintenance of general anaesthesia: remifentanyl effect-site target will be adjusted by 0,5 ng/mL changes according to physiologic parameters, propofol will be altered by 5 mg/mL changes targeting the BIS values between 40 and 60 and rocuronium 0.1 mg/kg in order to maintain TOF count  $\leq 2$ ;

- Maintenance fluid requirements follow estimated by the 4-2-1 rule: 4 mL/kg/h for the first 10 kg, 2 mL/kg/h for the second 10 kg and 1 mL/kg/h for every kg above 20 kg;
- Parameters of mechanical ventilation: volume-controlled mode, tidal volume 6-8 mL/kg, PEEP (positive end-expiratory pressure) 5 mmHg and FiO<sub>2</sub> 40-50%;
- Thirty min before the end of surgery intravenous paracetamol 1000 mg, parecoxibe 40 mg and tramadol 100 mg will be administered;
- Postoperative nausea and vomiting prophylaxis with dexamethasone 4 mg in the beginning of surgery and ondansetron 4 mg thirty min before the end of surgery;
- At the end of surgery, propofol and remifentanyl infusions will be discontinued and neostigmine 2.5 mg and atropine 1 mg or sugammadex 2 mg/kg will be administered to reversal neuromuscular blockade;
- Extubation will be performed after an adequate reversal of neuromuscular blockade (TOF ratio  $\geq$  90%) considering consciousness recovery and respiratory mechanics adequacy;
- Arterial blood samples will be obtained after arterial line placement, immediately after LOC, immediately before surgery and after every 20-30 min during propofol infusion. After stopping propofol infusion, arterial blood samples will be acquired every 10 min until recovery of consciousness. The maximum blood sample per patient will be 20 mL;
- Total dose of propofol and total dose of remifentanyl, total time of propofol and remifentanyl infusion and the time until consciousness recovery after propofol discontinuation will be recorded.

#### *Post-operative evaluation*

- Application of modified Brice protocol in the recovery room and in the first 24-48 h after the surgery.

\*With respect to patients submitted to an orthopaedic surgery, the anaesthetic protocol will be slightly different considering the standard practice in the hospital. When indicated, a peripheral nerve block will be executed and the opioid of choice will be fentanyl instead of remifentanyl. When possible, a laryngeal mask airway will be used.

### **Quantification of serum propofol concentration**

The quantification of propofol in plasma will be performed using gas chromatography/ion trap-mass spectrometry (GC/IT-MS).

Arterial blood samples are collected into serum tubes and centrifuged at 4000 rpm for 5 min in order to obtain plasma. Serum is preserved at -80 °C until analysis.

Extraction procedure is performed by the addition of 50 µL of thymol (0.01 mg/mL) and 1mL of ultra-pure water to a 0.5 mL aliquot of serum and to the propofol calibration standards. To each processed sample 0.5 mL of borate buffer (pH=9) is added and mixed by inversion for 5 min. Then, 300 µL of chloroform:ethylacetate (70:30 v:v) is added and also mixed by inversion for 20 min. After a 10 min centrifugation, 2 µL of the organic phase is injected into the GC/IT-MS injector.

The identification of propofol in each sample is performed in the same chromatographic conditions, by comparative analysis between the retention times of pure compounds with the compounds in the injected samples. Blank samples are obtained from propofol-free plasma, which were requested to the Clinical Haematology Service of CHP. All the plasma donors received both written and oral information regarding the study and they signed informed consent.

### **Statistical analysis:PKPD Modeling Analysis**

A conventional 3-compartment, first-order elimination, PK model will be used to fit propofol data. Parameter estimates will be obtained using a nonlinear mixed effects model with the program NONMEM.