Study synopsis

EudraCT number: 2011-003648-31

ClinicalTrials.gov number: NCT01490268

Title: Pharmacokinetic-pharmacodynamic modeling of the postoperative pain sensation during Patient-Controlled Analgesia with Target-Controlled Infusion of hydromorphone, taking into account the interaction with intraoperatively administered sufentanil for elective cardiac surgery

Principal investigator: Prof. Dr. med. Christian Jeleazcov, Department of Anesthesiology, University Hospital Erlangen, Germany

Trial centre: Department of Anesthesiology, University Hospital Erlangen, Germany

Study design: Prospective, single-blinded, randomized, single-centre, two-arm with parallel assignment

Study type: Interventional (Clinical Trial)

Phase of development: Phase 4

Actual Enrollment: 50 participants

Primary purpose: Treatment

Study start date: 17. November 2011

Study completion date: 10. September 2012

Study population: Adult patients undergoing elective cardiac surgery involving thoracotomy and subsequent stay in the intensive care unit

Inclusion criteria:

- Male and female subjects aged 30 - 80 years
- American Society of Anesthesiologists (ASA) physical status classification of 3 or less
- Left ventricular ejection fraction of at least 40%
- Ability to understand the nature of Patient-Controlled Analgesia and other study-specific procedures

Exclusion Criteria:

- Pregnant or nursing females
- Body mass index > 30 kg/m^2
- Allergy to opioid drugs
- Use of MAO inhibitors in the last 14 days
- Use of nonsteroidal anti-inflammatory drugs
- Pain therapy with opioids 14 days before the start of the study
- Chronic inflammatory disease or chronic obstructive lung disease
- Chronic alcoholism or drug addiction in medical history
- Severe obstructive or restrictive pulmonal disorders in medical history
- Severe hepatic and renal disorders in medical history,
- Hypothyroidism, pancreatitis in medical history

- Medical history of diabetes mellitus, renal, neurological, or psychiatric disease

Arms and interventions:

Arm 1: Sufentanil low titration

Interventions: Intraoperatively: Target Controlled Infusion with 0.4 ng/ml sufentanil, Postoperatively: Patient-Controlled Analgesia with Target-Controlled Infusion of Hydromorphone

Arm 2: Sufentanil high titration

Interventions: Intraoperatively: Target Controlled Infusion with 0.8 ng/ml sufentanil, Postoperatively: Patient-Controlled Analgesia with Target-Controlled Infusion of Hydromorphone

Objectives:

Primary objective:

- Development of a Target-Controlled Infusion model for Patient-Controlled Analgesia (TCI-PCA) with hydromorphone

Secondary objectives:

- Development of a pharmacokinetic model for hydromorphone
- Development of a pharmacodynamic model for the analgesic effect of hydromorphone
- Modelling of the pharmacodynamic interaction between sufentanil and hydromorphone
- Assessment of safety and tolerability of postoperative pain therapy with hydromorphone using TCI-PCA

Outcome measures:

Primary outcome measures:

- Plasma concentrations of sufentanil and hydromorphone: 28 arterial blood samples, taken during the study period of 48 hours postoperatively for characterizing the pharmacokinetics
- Numerical Rating Scale (NRS) for clinical pain: 11 assessments of patient's pain sensation using NRS during TCI-PCA with hydromorphone 8 hours after extubation for characterizing the analgesic effect

Secondary Outcome Measures:

- Cumulative dose of hydromorphone during TCI-PCA for characterizing the analgesic requirement
- Modified Observer's Assessment of Alertness/Sedation (MOAA/S) Scale: 11 assessments of the MOAA/S score during TCI-PCA with hydromorphone over 8 hours after extubation for characterizing the sedation level
- Hemodynamics and respiration during TCI-PCA with hydromorphone
- Adverse events during postoperative pain therapy with TCI-PCA of hydromorphone

Endpoints:

Primary endpoints:

- Estimates of pharmacokinetic model parameters (clearances, volumes of distribution) of hydromorphone
- Time course and distribution of NRS values
- Estimates of pharmacodynamic model parameters (half-maximum effect site concentration EC_{50}) of hydromorphone

Secondary endpoints:

- Time course of MOAA/S scores
- Mean arterial blood pressure, heart rate, peripheral arterial oxygen saturation, respiration rate
- Incidence and severity of adverse events

Statistical methods

Data are presented as median with range or as mean ± SD. Differences between the two sufentanil groups were identified using the Mann–Whitney test. Pharmacokinetic/-pharmacodynamic modeling was performed by nonlinear mixed effect modeling with mammillary multi-compartment models for the plasma concentrations of hydromorphone and an ordinal logistic regression model for the pain rating.

Results

From 174 patients assessed for eligibility, 50 patients were enrolled and randomized. One patient was excluded during anesthesia because the operation was prolonged unexpectedly. From the remaining 49 patients (36 males, 13 females) 26 and 23 patients received a TCI of sufentanil with target concentrations of 0.4 and 0.8 ng/ml, respectively.

Pharmacokinetics

Data from 49 patients were used for pharmacokinetic modeling. A three-compartment model best described the pharmacokinetics of hydromorphone. All clearances and volumes were linearly scaled with body weight. Elimination clearance and central volume of distribution decreased with age. The final estimates of the model parameters for the typical adult (67 years, 70 kg) were: CL1=1.01 l/min, V1=3.35 l, CL2=1.47 l/min, V2=13.9 l, CL3=1.41 l/min and V3=145 l.

Pharmacodynamics

Pharmacodynamic analysis could be performed in 43 patients. The hydromorphone dose during TCI-PCA was 0.26 (0.07 – 0.93) mg/h. The median value of the hydromorphone concentration during TCI-PCA was 2.8 (0.8 – 7.0) ng/ml in group 1 and 1.6 (0.9 – 8.9) ng/ml in group 2 (p=0.31). The NRS score under deep inspiration was below 5 in 83% of the ratings. The EC_{50} of hydromorphone for NRS≤4 was 4.1 (0.6 - 12.8) ng/ml. A concomitant sufentanil concentration of 0.1 ng/ml reduced the median EC_{50} of hydromorphone by 3.3 ng/ml. The MOAAS score increased to a median value of 5 (alert) within the first 30 min after extubation and remained at this value until the end of the observation period.

Hemodynamics and respiration

During TCI-PCA, mean arterial blood pressure was 77 ± 10 mmHg, heart rate was 91 ± 12 bpm, peripheral arterial oxygen saturation was 98.0 ± 1.9%, and respiratory frequency was 14.0 ± 2.2 min^{-1}

Safety and adverse events

No rescue medications were required during the study phase. No serious adverse advents were reported. Nausea was observed in 30%, vomiting in 9%, respiratory insufficiency in 7%, and shivering in 14% of the patients. Adverse events were rated as mild (62%) or moderate (38%), and were resolved without sequelae within the active study phase.

Conclusion

The developed pharmacokinetic/-dynamic model based on arterial plasma concentrations of postoperative hydromorphone and residual intraoperative sufentanil adequately described the measured plasma concentrations and the observed probabilities of pain levels. This model should therefore be suitable for TCI-PCA with hydromorphone for postoperative pain therapy. TCI-PCA with hydromorphone offered satisfactory pain relief after cardiac surgery with thoracotomy. Whereas the frequency of respiratory adverse events during TCI-PCA was comparable to values reported for PCA, the observed mean rates of nausea and vomiting were lower than values described in the literature.