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Influence of intensive care treatment on the protein binding of sufentanil and hydromorphone during pain therapy in postoperative cardiac surgery patients

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Editor's key points

- The authors studied if changes in physiological covariables could be linked to the changes in protein binding of sufentanil and hydromorphone during intensive care pain therapy.
- Sufentanil protein binding was significantly dependent on changes in the total drug concentration and volume balance.
- Hydromorphone protein binding was nearly constant throughout the study period and no significant covariate effects were found.

Background. Our objective was to evaluate the effect of intensive care treatment on the protein binding of sufentanil and hydromorphone in cardiac surgery patients during postoperative analgesia using a target-controlled infusion (TCI) and patient-controlled analgesia (PCA).

Methods. Fifty adult patients were enrolled in this prospective randomized study; of which, 49 completed the study (age range 40–81 yr). Sufentanil was administered as an analgesic intraoperatively, and hydromorphone was dosed after operation with TCI and PCA until 8 a.m. on the first postoperative day. Arterial plasma samples were collected for drug and protein concentration measurements up to 24 h after cardiac surgery. Corresponding patient data were collected from the electronic patient data system. After explorative data analysis with principal component analysis, multivariate regression analysis and non-linear mixed effects modelling was used to study the effect of treatment on protein binding.

Results. Data of 35 patients were analysed. The median protein binding of sufentanil and hydromorphone was 88.4% (IQ range 85.7–90.5%) and 11.6% (IQ range 9.5–14.3%), respectively. Free fraction of sufentanil increased towards the end of the study period, whereas hydromorphone free fraction remained nearly constant. The total sufentanil concentration and volume balance were identified as significant covariates for the protein binding of sufentanil. For the protein binding of hydromorphone, no significant covariate effects were found.

Conclusions. Sufentanil protein binding was significantly dependent on changes in the total drug concentration and volume balance addressing the importance of adequate dosing and fluid-guided therapy. Hydromorphone protein binding was nearly constant throughout the study period.

Clinical trial registration. EudraCT 2011-003648-31 and ClinicalTrials.gov: NCT01490268.

Keywords: analgesics, opioids; intensive care; pain management; pharmacokinetics; protein binding

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Pain therapy of critically ill patients is complex and challenging due to the acute dysfunction of organs and several pre-existing illnesses. These conditions might influence the pharmacokinetic properties of a drug and predispose the critically ill to adverse drug reactions on the one hand and failure of the pain therapy on the other. Since pain therapy is usually given with i.v. drug administration, changes in drug disposition are of particular interest during intensive care.

Sufentanil and hydromorphone are opioid analgesics currently widely used in clinical anaesthesia and postoperative analgesia. Sufentanil is highly bound to plasma proteins with a protein binding of more than 90%,[1 2] thus the effects of protein binding on the pharmacokinetics of sufentanil are of importance as has been pointed out previously.[3–5] Contradictory findings for protein binding for hydromorphone in humans have been published previously.[6–8] Effects of protein binding

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on the pharmacokinetics of hydromorphone might partly explain the large interindividual variability in the drug concentrations after hydromorphone administration.[9–11]

Previous literature demonstrates that factors affecting protein binding may cause changes in unbound drug concentrations.[3 4 9] Such changes may be expected to be clinically significant for drugs that are used i.v., are heavily bound to the plasma proteins, and which have a high hepatic extraction ratio.[4 5] Several opioid analgesics, such as fentanyl and sufentanil, belong to this group,[1 2 12] and significant changes in unbound opioid concentrations have been reported during perioperative pain therapy.[13 14] However, the effect of intensive care on the pharmacokinetic properties of opioids used in postoperative pain therapy is not thoroughly studied.

We studied the pharmacokinetics and pharmacodynamics of sufentanil and hydromorphone during postoperative pain therapy in the intensive care unit (ICU) after cardiac surgery. During this study, we also gathered data to investigate the effect of intensive care treatment on the protein binding of sufentanil and hydromorphone as judged by the ratio between free and total plasma concentrations. We evaluated the importance of several biomarkers and biometric parameters on the protein binding during the intensive care treatment using multivariate regression analysis and hypothesized that patient characteristics and changes in physiological variables could be linked to the changes in protein binding of sufentanil and hydromorphone during intensive care pain therapy.

Methods

The study was performed in accordance with the guidelines for Good Clinical Practice and Ethical Principles for Medical Research Involving Human Subjects outlined in the Declaration of Helsinki, and adopted in October 2000 by the World Medical Association. The study was approved by the Institutional Review Board (Ethikkommission der Medizinischen Fakultät der Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany) and it was registered to the EudraCT (Number: 2011-003648-31) and ClinicalTrials.gov (Identifier: NCT01490268) databases. CONSORT guidelines[15] were followed and the study was clinically monitored by the Center for Clinical Studies (CCS) Erlangen.

Clinical protocol

This is a secondary analysis of a previously published study.[16]

After receiving written informed consent, 50 adult patients undergoing cardiac surgery involving thoracotomy were enrolled. Inclusion and exclusion criteria are stated in the ClinicalTrials.gov-database registration and have been published recently.[16]

The study was of prospective, single-blinded, randomized, single-centre design with two parallel arms and was conducted in the University Hospital of Erlangen, Germany. Details of the clinical study protocol, drug dosing, and data management are described previously in detail.[16] Shortly, after a premedication with 7.5 mg midazolam p.o. (Dormicum®, Roche Pharma, Grenzach-Wyhlen, Germany), anaesthesia was induced and maintained with target-controlled infusions (TCI) of propofol (Disoprivan® 2%, AstraZeneca, Wedel, Germany) and sufentanil (Sufenta®, Janssen-Cilag, Neuss, Germany). Intubation was facilitated with cisatracurium 0.15 mg kg^{-1} (Nimbex®, Glaxo SmithKline, Munich, Germany). Propofol was administered as TCI using the pharmacokinetic model of Marsh and colleagues[17] targeting plasma concentrations between 2.5 and 4 $\mu g\ ml^{-1}$. Sufentanil was administered as TCI using the pharmacokinetic model of Gepts and colleagues.[18] The patients were randomized into two treatment groups with target sufentanil plasma concentrations of 0.4 (Group 1) or 0.8 ng ml^{-1} (Group 2). These target concentrations were kept constant throughout the anaesthesia after induction of anaesthesia. After the end of the surgery, the patients were transferred to the ICU where the sufentanil infusion was discontinued while the propofol infusion was continued for a further 2–3 h until weaning from mechanical ventilation with an infusion rate of 2.5 mg $kg^{-1}\ h^{-1}$. Patients were considered ready for extubation, when they were alert, breathed spontaneously with pressure support of 7 cm H_2O, PEEP 5 cm H_2O, $Sa_{O_2} \geq 90\%$, $F_{I_{O_2}} < 40\%$, and $f/TV < 105$.

Hydromorphone dosing

Throughout the study period on the ICU, hydromorphone (Palladon® inject, Mundipharma GmbH, Limburg, Germany, consisting of hydromorphone-HCl, 1 mg corresponding to 0.89 mg hydromorphone free base) was administered using three different dosing regimens: TCI, TCI as patient-controlled analgesia (TCI–PCA), and patient-controlled analgesia (PCA) as described previously in detail.[16]

Haemodynamic monitoring and vasoactive therapy

During the three study-phases, the patients were treated and monitored on the ICU according to normal ICU protocols. Arterial pressure, oxygen saturation, and heart rate were measured continuously (Siemens SL 9000 XL Patient Monitor, Siemens Medical Systems, Solna, Sweden). Parameter values were stored to the electronical database.

Vasoactive drugs were infused goal-directed depending on clinical demand to maintain mean arterial pressure of 70–90 mm Hg. Dobutamine, norepinephrine, and glycerylnitrate infusions were routinely used. If the vasoactive control was insufficient, epinephrine was administered instead of dobutamine. Laboratory data were determined regularly by blood gas analysis (ABL800 FLEX analyzer, Radiometer Medical ApS, Brønshøj, Denmark) and the results were collected from the ICU documents.

Blood sampling and concentration analysis

Arterial blood samples (4–7 ml each) were drawn. The sampling scheme has been previously described in detail.[16] The samples were kept on ice and plasma was separated within 15 min and stored at 70°C until analysis. Sufentanil and hydromorphone plasma concentrations were determined using validated liquid chromatography-tandem mass spectrometric