

Paris, France

Euroanaesthesia 2012

The European Anaesthesiology Congress

June 9-12

9AP3-5

Investigation of plasma fentanyl concentrations in patients undergoing mastectomy comparing with simulation

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Background and Goal of Study: We administer fentanyl in general anesthesia predicting concentration with a commercial simulator. However, the precision of simulator wasis not fully understood in clinical settings. We investigated plasma fentanyl concentration in patients undergoing mastectomy.
Materials and Methods: Following Research Ethics Board approval and infromaedinformed consent, women of American Society of Anesthesiologists' class I or II undergoing mastectomy were enrolled. Anesthesia throughout surgery was maintained with sevoflurane and fentanyl after propofol and rocuronium bolus infusion. Anesthesia was titrated subsequently to a bispectral index around 50. A maintenance infusion was administered with 8ml/kg/h of acetate Ringer's solution from anesthesia start to finish of obtaining blood samples. In addition, infusion for blood loss was administered with twice the volume of hydroxylethyl starch 70/0.5. Fentanyl bolus infusion was administered by the attendant anesthesiologist. A blood sample was drawn every 30 minutes during anesthesia. We used Tivatrainer and AnestAssist as a commercial simulator.
Results and Discussion: We measured plasma fentanyl concentrations of 111 samples from seventeen patients who underwent mastectomy. The two simulator, Tivatrainer and AnestAssist, were almost equal in the predicted fentanyl concentration. The plasma fentanyl concentration was significantly correlated with the simulated fentanyl concentration ($r=0.838$, $P< 0.01$). However, the difference between plasma and simulated fentanyl concentration was 0.32±0.6 [-2.7, 2.3]. In addition, 41.1% of all samples had a difference of more than ±0.5 ng/ml. A Bland-Altman plot demonstrated a large variation in the difference between these two values. The mean difference was 0.3 ng/ml (95% CI 0.26-0.50) and the width of the 95% limits of agreement was 1.2 ng/ml. The proportional bias was shown.
Conclusion(s): The predicted data by two simulators was significantly correlated with the plasma fentanyl concentration. However, the difference might have importance in clinical settings that we could not ignore. We might pay attention to the difference in using the simulator in clinical settings.
Acknowledgements: We thank Dr. Matsushita, Dr. Inoue and Dr. Oka, Department of Analytical Chemistry, Kinjo Gakuin University, for the cooperation of measuring plasma fentanyl concentrations.

9AP3-6

Genetic polymorphisms of hepatic organic anion-transporting polypeptide (OATP) 1B1 transporters: no influence on the disposition of fentanyl and midazolam

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Background and Goal of Study: Fentanyl (FENT) and midazolam (MDZ) are routinely administered to patients in anaesthesiology. Plasma levels of both CYP3A4 substrate drugs show a high interindividual variability which might in part be explained by genetic polymorphisms of drug transporters. Hepatic OATP1B1 influx transporters mediate the uptake of a variety of drugs (e.g. statins, bosentan) into hepatocytes. Several genetic variants (single nucleotide polymorphisms) of OATP1B1 are known to affect its transport activity and thereby the disposition of drugs. The aim of this study was to investigate the influence of OATP1B1 polymorphisms on the pharmacokinetics (PK) of FENT and MDZ.
Materials and Methods: This study was approved by the Institutional Review Board of Heidelberg University Hospital. Informed consent was obtained before any study measures were carried out. Only individuals homozygous for the genetic wild type of OATP1B1 (c.388A and c.521T) or for a variant with altered transport activity (c.388G and c.521C) were included in the study. 16 healthy volunteers (22-49 yrs) received MDZ (3 mg p.o.) + FENT (5 µg / kg i.v.), or MDZ + FENT in combination with the known OATP inhibitor rifampicin (RIF, 600 mg p.o.) in a randomized crossover design. Naloxone was used (0.4 mg i.v.) to mitigate the side effects of FENT. Blood was sampled over 24 hours and analyzed by LC-MS/MS. The PK of MDZ was determined by a limited sampling strategy. Non-compartmental models were used for pharmacokinetic calculations.
Results and Discussion: The area under the concentration-time curve (AUC) of FENT was 16.3 ± 8.7 h*nmol/L (mean ± SD) in OATP1B1 wild type individuals (WT) vs. 12.8 ± 1.3 h*nmol/L in individuals with altered OATP1B1 activity (GC polymorphism) (n.s.). Under RIF, FENT AUC was 18.4 ± 7.3 h*nmol/L in WT vs. in GC 16.3 ± 5.2 h*nmol/L (n.s.). FENT clearance was 1345 ± 562 mL/min in WT vs. 1484 ± 287 mL/min in GC (n.s.). Under RIF, FENT clearance was 1061 ± 275 mL/min in WT vs. in GC 1295 ± 558 mL/min (n.s.). MDZ $AUC_{0-\infty}$ in WT was 6.0 ± 2.8 h*ng/mL, and 8.7 ± 5.2 h*ng/mL in GC (n.s.). Under RIF, MDZ $AUC_{0-\infty}$ in WT was 11.0 ± 4.5 h*ng/mL, and in GC 9.8 ± 5.7 h*ng/mL (n.s.). Partial metabolic clearance of MDZ was 1065 ± 390 mL/min in WT vs. 849 ± 451 mL/min in GC (n.s.), and under RIF 646 ± 459 mL/min in WT vs. 745 ± 394 mL/min in GC (n.s.).
Conclusion: Genetic polymorphisms of OATP1B1 do not alter the disposition of intravenously administered fentanyl and oral midazolam.

9AP3-7

Incidence of fentanyl-induced coughing and effect of injection velocity

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Background and Goal of Study: Fentanyl is commonly used as a pre-induction adjunct, but can sometimes elicit cough. The existing literature about the incidence of fentanyl-induced cough (FIC) is extremely diverse and the results of clinical trials are conflicting. The purpose of our study is to investigate the effect of different injection velocity to the intravenous pre-induction dose (2 µg/kg) of fentanyl on the incidence and severity of FIC in Turkish population.
Materials and Methods: Following local ethical approval and written informed consent, 210 ASA I-III, 18-75 year old patients undergoing general anesthesia for elective surgery were enrolled into this randomized placebo controlled study. The exclusion criteria included, a history of bronchial asthma or chronic obstructive lung disease, respiratory tract infection, smoking, and angiotensin converting enzyme inhibitor use. No premedication was used before surgery. Patients received either 2 µg/kg fentanyl injected over 2 sec, 20 sec or same volume saline placebo (NaCl %0.9) injected over 2 sec as group I, II, III respectively. After completion of injections, the onset time and intensity of coughing was observed by a blinded observer for 2 minutes. Severity of coughing was graded based on the number of coughs: mild (1-2), moderate (3-5), severe (>5). Statistical analyses were performed with Chi square and independent sample t tests. $p< 0,05$ was regarded as statistically significant.
Results and Discussion: The mean onset time of coughing was 21±7,71 seconds after injection. Incidences of cough of patients were 11.4%, 8.6%, 0% as group I, II, III respectively.
Conclusion(s): According to our study, the incidence of cough in study participants after 2 µg/kg intravenous fentanyl was in average 10% and take place in the middle of between European and Far East-Asiatic population and most of them were mild in severity.

9AP3-8

Conjunctival administration of remifentanil in rabbits

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Background and Goal of Study: Delivering analgesics via conjunctival application could provide a rapid and convenient pain relief in disaster medicine. We attempted to determine whether conjunctival administration of remifentanil could produce significant effect without side effects.
Materials and Methods: After ethic committee approval, 10 rabbits were administered conjunctivally remifentanil 25 µg/kg. Measured parameters were SpO_2, blood pressure (BP) and heart rate (HR) before administration and in 1 minute intervals and immobilisation time (loss of righting reflex).
The measurements were performed for 20 minutes and naltrexone 0.2 mg i.m. was then administered to antagonise residual psychomotor effects of remifentanil. Conjunctival irritation was measured in 1, 10 and 20 min. after administration of remifentanil according to modified technical standard EN ISO 10993-10. ANOVAs test was used for statistical analysis of hemodynamic parameters.
Results and Discussion: Immobilisation time in nine animals was 159.8±60.6 s, loss of righting reflex was absent in 1 animal. There were no changes in cardiorespiratory parameters (initial, 10 and 20 minutes after administration HR 239.2±27.5, 229.7±58.4 and 274.4±39.9, systolic BP 120.1±25.2 mm Hg, 112.1±15.3 and 125.9±16.1 mm Hg and SpO_2 99.0±0.9, 98.7±1.1 and 98.9±0.7). These results are in contrast to conjunctival administration of sufentanil 5 µg/kg that caused significant decrease of SpO_2 and HR[6]. We can speculate that the reason for stability of cardiorespiratory parameters was due to the stimulation of NMDA receptors caused by remifentanil. There were no