Title : Pharmacokinetics of a continuous infusion of alfentanil for coronary artery surgery

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Introduction. In an endeavour to optimize a continuous infusion of alfentanil as sole anesthetic agent for coronary artery surgery (CAS), a pharmacokinetic model was used to rapidly achieve a predetermined plateau alfentanil plasma concentration. This model uses a fast priming infusion and a subsequent maintenance infusion both based on the drugs, pharmacokinetic parameters to rapidly achieve steady state plasma concentration.[1] The present study was designed to validate this method of continuous infusion in respect to predicted maximal and plateau plasma concentrations vs measured concentration and to evaluate the steadiness of the plateau phase as well as calculating the clearance precardiopulmonary bypass (CPB). In addition the hemodynamic stability provided during surgery by the alfentanil plateau concentration achieved was examined.

Methods. After approval of the study by the Committee of Medical Ethics and informed patient consent, eight patients, aged between 47 and 65 years with NYHA angina classification II or III and with no hepatic or renal disease were premedicated with lorazepam 0,08 $mg.kg^{-1}$ given orally two hours before arrival in the OR. Beta-adrenergic blockers, nitrates and slow channel blockers were continued to the time of surgery; patients taking any other medication apart from these anti-anginal drugs were excluded from the study. In the OR baseline hemodynamic parameters were recorded and a control alfentanil blood sample was taken. A priming infusion of alfentanil was started at 18.97 $mcg.kg^{-1}.min^{-1}$ and continued for 20 min when an arterial blood sample was drawn to measure peak plasma concentration; then a maintenance infusion rate of 3.5 $mcg.kg^{-1}.min^{-1}$ was commenced.[1] These infusion rates were aimed at achieving a steady state alfentanil plasma concentration of 1000 $ng.ml^{-1}$ before CPB. This concentration was considered necessary to provide hemodynamic stability before CPB and was based on another study which used a continuous alfentanil infusion a sole anesthetic agent during CAS.[2] The Pharmacokinetic parameters used to calculate these rates were: a clearance of 3.5 $ml.kg^{-1}.min^{-1}$ and an elimination half-life of 68 min. These values were obtained before CPB in a previous study in patients undergoing CAS and given a single bolus of alfentanil for anesthetic induction.[3] Arterial blood samples for plasma alfentanil determination were taken every 5 min until CPB which followed at least 50 min after starting the maintenance infusion.

Results. The predicted maximal alfentanil concentration was 1660 $ng.ml^{-1}$. The measured mean peak concentration was 1764 $\pm$ 313 $ng.ml^{-1}$ (mean + SD) which was not significantly different from the predicted. The steady state plasma concentration before CPB was 1300 + 263 $ng.ml^{-1}$ which was significantly different from the predicted at the 5% level. Linear regression on the log plasma concentrations vs time from five minutes after the peak plasma concentration and until the start of CPB did not show a slope significantly different from zero thus it was considered that a steady state had been achieved and the mean plasma concentration in each patient was used to calculate clearance. The clearance in this study (calculated by dividing the mean steady state plasma concentration into the maintenance infusion rate) was 1.5 + 0.4 $ml^{-1}.min^{-1}$. None of the patients showed any significant change in hemodynamic parameters in response to anesthetic manipulation or to surgical stimuli.

Discussion. The results of this study indicate that the clearance of alfentanil before CPB in patients undergoing CAS and receiving a continuous infusion are different from those receiving a bolus dose of alfentanil. The mean measured plasma steady state concentration was 30% higher than the expected concentration (1000 $ng.ml^{-1}$). This suggests that the clearance value used in the pharmacokinetic calculation of the infusion rate was too high. Subsequent calculation of the clearance in our patients confirmed that the clearance was half of that which had been found in a previous alfentanil bolus study done in patients before CPB.[3] The implication of these findings are: (1) the pharmacokinetics before CPB of a rapid continuous infusion of alfentanil are different from those of a bolus in patients undergoing CAS, (2) a mean steady state plasma alfentanil concentration of 1300 $ng.ml^{-1}$ provided hemodynamic stability during surgical stimulation before CPB, (3) a two stage method of continuous infusion (rapid priming and maintenance) appears promising in optimizing alfentanil infusion techniques.

References

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