TITLE: ALFENTANIL PHARMACOKINETIC MODEL APPLIED TO AMBULATORY SURGICAL PATIENTS: DOES A COMPUTERIZED INFUSION IMPROVE PREDICTABILITY?

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INTRODUCTION: Alfentanil, a rapidly distributed synthetic narcotic, is ideally administered by infusion, as opposed to a bolus technique. We have developed a computerized Intravenous Drug Administration (IDA) system for delivering alfentanil by infusion according to a pharmacokinetic model. Maitre et al. established pharmacokinetic model parameters for alfentanil from a retrospective analysis of a diverse patient population[1]. We sought to determine, prospectively, the ability of the computerized IDA system to achieve various alfentanil target concentrations (PTC) in patients undergoing general anesthesia for laparoscopy.

METHODS: Nineteen female patients consented to participate in the study. Midazolam 1-2mg IV was administered for premedication and a 20ga radial arterial cannula was placed for blood sampling. The computerized IDA infused alfentanil according to the pharmacokinetic model to achieve a plasma target concentration of 100ng/ml (PTC_{100}) for ten minutes, 200ng/ml (PTC_{200}) for ten minutes, and 0ng/ml (PTC_0) for the duration of the procedure. Anesthetic technique included sodium thiopental (3-5mg/kg), succinylcholine (100mg), tracheal intubation and mechanical ventilation with 70% N_2O/30% O_2. Arterial blood (2ml) was sampled just prior to, and at one, three, and six minutes following each change in alfentanil plasma target concentration.

Blood samples were immediately centrifuged, frozen, and stored for later analysis. Plasma alfentanil concentration was measured in triplicate using RIA.

The percentage difference (% DIFF) between plasma target measured and concentration was computed at each blood sample point. The bias (mean % DIFF for all patients) at each sample time was calculated. The precision (±1SD of the mean % DIFF for each patient) was determined for the transient (first samples after changes in PTC), PTC_{100}, PTC_{200}, and PTC_0 periods.

RESULTS: The figure shows the average bias for all patients at each sample point. The average bias was -44% ± 26 for the transient blood samples and -26% ± 24 for the steady state blood samples. The average precision was: transient = ±19%, PTC_{100} = ±12%, PTC_{200} = ±12%, and PTC_0= ±7%.

DISCUSSION: The computerized IDA system using Maitre's pharmacokinetic parameters achieved consistently higher alfentanil plasma concentrations than those predicted by the model (ie, negative bias). However, the precision during PTC_{100}, PTC_{200}, and PTC_0 demonstrates that stable alfentanil plasma concentrations can be achieved using an infusion based on this pharmacokinetic model.

The consistent negative bias indicates plasma compartment volume in this population is different from that determined by Maitre. The high degree of precision suggests that the other pharmacokinetic parameters in Maitre's model adequately represent the pharmacokinetic behavior of these patients. In the future, a determination of new parameters for this population by non-linear regression of these data may result in more predictable plasma alfentanil concentrations. The large and variable bias during the transient periods is probably due to inhomogeneous drug distribution in the plasma compartment immediately following rapid administration of alfentanil. The very high concentrations which sometimes result may be responsible for adverse effects of alfentanil such as hypotension and muscular rigidity.

REFERENCES:
1. Maitre, PO, Vozeh S, Heykents J, Thompson DA, Stanski DR: Population pharmacokinetics of alfentanil:The average dose-plasma concentration relationship and interindividual variability in patients. Anesthesiology 66:3-12, 1987.