Title: ACCURACY AND EFFICACY OF A PHARMACOKINETIC MODEL-DRIVEN DEVICE TO INFUSE FENTANYL FOR ANESTHESIA DURING GENERAL SURGERY

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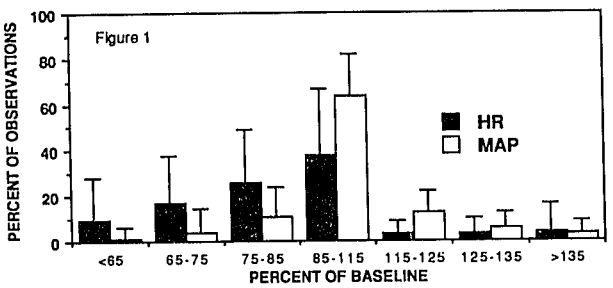
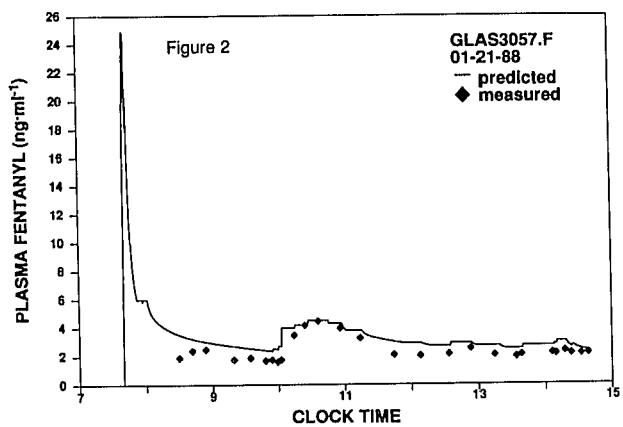
INTRODUCTION. Administration of intravenous anesthetic agents is traditionally based on dosage, utilizing either intermittent boluses, continuous infusions, or a combination of both. In contrast, inhalational anesthetics are administered to a partial pressure, which is assumed to be at a concentration in equilibrium with the plasma. In an attempt to deliver intravenous anesthetics in a similar manner (i.e., to a desired plasma concentration), pharmacokinetic model-based infusion devices have been developed.[1,2] This study evaluated both the efficacy of general anesthesia provided using a pharmacokinetic model-driven device to administer fentanyl and the accuracy with which the device could predict plasma fentanyl concentrations.

METHODS. Following IRB approval and written informed consent, 25 patients were enrolled in the study. They were premedicated with diazepam 10 mg p.o. approximately 90 min prior to operation. A cannula for blood sampling was inserted into the anticubital vein opposite that used for drug infusion. N_2O 70% in oxygen was administered 2 min prior to fentanyl infusion and was continued until after skin closure. Fentanyl was then administered by a computerized pharmacokinetic model-driven drug delivery device programmed with mean kinetic parameters for fentanyl.[3] This instrument uses a real-time pharmacokinetic simulation to infuse the agent at rates optimized to theoretically maintain the drug plasma concentrations (setpoints) specified by the anesthesiologist. The setpoint fentanyl levels for induction were 15-25 ng·ml^{-1}, intubation 6-10 ng·ml^{-1}, and skin incision 3-6 ng·ml^{-1}. The dose of fentanyl required to achieve loss of eyelash reflex was recorded. Muscle relaxation was obtained with vecuronium utilizing doses that maintained at least 2 twitches of a train-of-four. Blood pressures and heart rate (HR) were recorded every minute for the first 10 min following induction and every 3 min thereafter using an automated noninvasive blood pressure device. Following skin incision, the setpoint was reduced 0.2-0.5 ng·ml^{-1} every 15-20 min until a sign of inadequate anesthesia was present (15% increase in HR or systolic blood pressure over baseline, movement, or signs of autonomic discharge). When this occurred, the setpoint was increased in 0.5-1.0 ng·ml^{-1} steps until the response was ablated. Blood samples for subsequent radioimmunoassay of their fentanyl content were taken at 5 min prior to any decrease in setpoint, whenever the patient had signs of inadequate anesthesia, and at set stimuli occurring during anesthesia. Neuromuscular blockade was antagonized at the end of surgery. The times from N_2O off until spontaneous ventilation and orientation to place, person, and birth date were recorded. The incidence of nausea and vomiting and the need for additional analgesics during the first postoperative hour was noted in 18 of the patients. To assess the accuracy of the predicted versus measured fentanyl plasma levels, the bias, the precision, and the mean absolute prediction error (APE) were computed[2] for the samples from each patient, and from these the group means were calculated. Hemodynamic data were compared to baseline values, which were calculated as the mean of 3 readings taken the day prior to surgery, the morning of surgery, and just prior to induction, and were expressed as a percent change. A frequency histogram was constructed for each patient and the group means calculated. Values are reported as mean±SD.

RESULTS. There were 16 male and 9 female patients 36±8 years of age, weighing 78±18 kg. All underwent major orthopedic (n=23) or gynecological (n=2) procedures with a duration of 4.5±2.1 hr. The induction dose of fentanyl was 12.1±3.1 μg·kg^{-1} and the total dose was 30±16 μg·kg^{-1}. Average HR and mean arterial blood pressure (MAP) data are shown in figure 1. Times from N_2O off to spontaneous ventilation and orientation were 2.2±2.4 and 5.4±4.1 min, respectively. Naloxone was used to restore adequate spontaneous ventilation in 3/25 patients (12%), 7/18 patients (39%) had nausea or vomiting, and 15/18 patients (83%) required no analgesics during the first postoperative hour. Predictive accuracy was calculated using 409 plasma samples, with 16±6 samples/patient. Average bias was -0.11 ng·ml^{-1} (-13%) and its mean SD (the precision) was 0.84 ng·ml^{-1} (25%). APE was 0.95±0.52 ng·ml^{-1} (29± 18%). Figure 2 shows predicted and assayed drug levels in a typical patient.

DISCUSSION. Administration of fentanyl according to plasma concentration (ng·ml^{-1}) rather than dose (μg·kg^{-1}) was a satisfactory technique for the induction and maintenance of anesthesia in the presence of N_2O 70% for procedures of 1-8 hr. The 29% APE can be attributed primarily to intersubject pharmacokinetic variability, and was the same as that seen in a similar study with alfentanil.[2] The pharmacokinetic model-driven device used in this study was sufficiently accurate for efficacious clinical use.





References: 1) Alvis et al.: Computer-assisted continuous infusion of fentanyl during cardiac anesthesia: comparison with a manual method. Anesthesiology 63:41-49, 1985; 2) Ausems et al.: An evaluation of the accuracy of pharmacokinetic data for the computer assisted infusion of alfentanil. Br J Anaesth 57:1217-1225, 1985; 3) McClain DA, Hug CC: Intravenous fentanyl kinetics. Clin Pharm Ther 28:106-114, 1980