TITLE: A PHARMACOKINETIC MODEL CHARACTERIZING ANTIPYRINE DISPOSITION FROM THE MOMENT OF ITS ADMINISTRATION

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The onset of anesthesia occurs during the initial distribution of I.V. induction agents. Traditional pharmacokinetic models are usually based on data collected after initial drug distribution. This study examines a model which includes antipyrine (a lipid-soluble tracer drug) concentration-time data both before and after intravascular mixing, for detailed characterization of such a drug's disposition from the moment of its injection.
METHODS: Five dogs (25-34 kg) were anesthetized with 2% halothane, and catheters were placed in the pulmonary and femoral arteries. Antipyrine, 25 mg, and indocyanine green (ICG), 5 mg, were administered rapidly into the right atrium. A computer-controlled roller pump facilitated arterial blood collection every 3 sec for the first 2 min and every 15 sec for the next 4 min. Subsequent blood samples were collected less frequently up to 6 hrs. Plasma antipyrine concentration-time data were analyzed with the SAAM30 pharmacokinetic modelling program. The multicompartmental model included time-delay functions to account for the time of appearance of drug in the sampling compartment, and for recirculation.
RESULTS: Measurable concentrations of antipyrine first appeared at a mean of 0.22 min after its administration, a time interval modelled by inclusion of a delay function between the administration and sampling sites. The decreasing concentrations following the initial peak were interrupted by a lesser recirculation peak, and this was modelled by adding a second time delay of 0.10 min associated with a peripheral volume. Similar time delays were derived for ICG. When antipyrine concentration-time data obtained in the first 2 min were ignored, the central volumes and time delays of this complex model were easily replaced with an equivalent, single, initial distribution volume. The remainder of the concentration-time curve was characterized by addition of two further peripheral compartments, without time-delays. The V_C of this model differed from that of ICG by a volume identical to the estimated extravascular lung water. The estimated steady state distribution volume was consistent with those expected for total body water.
DISCUSSION: Abundant early data necessitated a more complex model than the traditional one, with dissection of the central volume into several parts and inclusion of time-delays. Estimated variables of this model of data reflect or may directly measure anatomic/physiologic states. When combined with both marker compounds, the new model will facilitate investigation of factors influencing initial distribution of drugs which are administered intravenously for rapid onset of effect.

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TITLE: CP50 FOR SUFENTANIL

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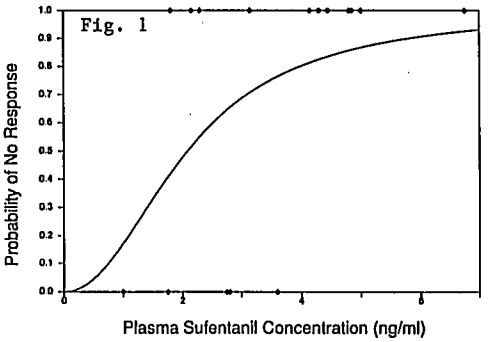
Cp50 provides an index of anesthetic potency for intavenous drugs. Opiates display hysteresis of onset and offset of effect which varies between different drugs[1]. Thus it is important that the Cp50 is established when plasma-brain concentrations are constant and in equilibrium. Pharmacokinetic model-driven drug delivery systems enable a steady plasma drug concentration to be obtained and maintained so that hysteresis is accounted for. With the aid of a pharmacokinetic model-driven infusion device (CACI) we determined the CP50 for sufentanil as the concentration of drug in plasma sufficient to prevent a somatic response to skin incision (MAC equivalent).

Sixteen volunteer patients 18 to 55 years were entered into the study after obtaining informed consent and IRB approval. All were ASA 1 or 2 undergoing either orthopedic or gynecological surgery. Patients with a history of chronic narcotic or alcohol use were excluded. Patients were allocated to various predicted plasma sufentanil levels between 1-7 ng/ml. All patients were unpremedicated. An intravenous catheter for drug infusion and a radial arterial catheter for blood sampling were placed. Patients received 65 mcg/kg of curare and then breathed 70% N2O in oxygen via mask for 4 minutes. Patients were then induced with sufentanil via CACI until loss of lid reflex was noted. Succinylcholine 1.5 mg/kg was given to facilitate intubation and during laryngoscopy the trachea was anesthetized with topical lidocaine. Immediately following loss of lid reflex the predetermined plasma level of sufentanil was entered into CACI. This concentration once achieved was held constant for a minimum of 10 minutes and until surgical incision. Blood samples for sufentanil were taken prior to skin incision and 1 minute post skin incision. At skin incision patients were monitored for a somatic response.

All pre and post-incision samples were within ± 30% of each other and therefore were all included in the calculation of Cp50 using logistic regression analysis. The CP50 for sufentanil was 2.08±0.62 ng/ml (fig. 1). Using the same model we[2] previously reported the Cp50 for fentanyl was 3.84±0.44 ng/ml and likewise Ausems et al[3] have reported the Cp50 for alfentanil as 241±16ng/ml. Thus the relative potencies of sufentanil to fentanyl to alfentanil are 1:1.8:116. Defining the relative potencies of these opioids will enable a true comparison of there pharmacodynamic effects.



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