TITLE: INHIBITION OF HUMAN LIVER ALFENTANIL METABOLISM BY MEDETOMIDINE STEREOISOMERS

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Medetomidine is a new, highly selective α_2 adrenergic agonist with potent anesthetic and analgesic properties (1). Although medetomidine exists as a racemic mixture (DL), anesthetic, analgesic and hemodynamic effects are caused exclusively by the D-stereoisomer, while the L-isomer is essentially without pharmacologic effect (2). Dexmedetomidine (DMED) alone has been shown to decrease potent inhalation anesthetic requirements (3). In addition, DMED completely prevents skeletal muscle rigidity caused by alfentanil (4). Alfentanil undergoes extensive hepatic biotransformation to a number of inactive metabolites. As a substituted imidazole, medetomidine resembles several compounds with known inhibitory effects on hepatic drug metabolism. The purpose of this investigation therefore was to examine the influence of DMED and its optical isomer (LMED) on hepatic microsomal alfentanil metabolism.

Human livers were obtained from kidney donors and microsomes were prepared by ultracentrifugation. Reaction mixtures (37°C,) contained 1 mg/ml microsomal protein, 1 mM NADPH, alfentanil (10-25 μM), and MED (.01-100 μM) in 100 mM potassium phosphate buffer (pH 7.4). Total alfentanil metabolism was determined from the disappearance of parent alfentanil. Microsomes were extracted with alkaline heptane:isoamyl alcohol and opiates analyzed using a gas chromatograph-mass spectrometer.

Alfentanil was rapidly metabolized by human liver microsomes. DMED, present at 0.1 to 100 μM, was found to inhibit alfentanil metabolism. The IC_{50} for DMED inhibition was approximately 1 μM at 10-25 μM alfentanil. LMED also inhibited alfentanil metabolism, although the potency was approximately 1/2-1/10 that of DMED (Figure). Preincubation of DMED with microsomes and an NADPH generating system prior to addition of alfentanil had no effect on inhibition of alfentanil metabolism.

DMED and LMED were potent inhibitors of human liver microsomal alfentanil metabolism. Preincubation experiments with DMED showed this to be a property of the parent drug rather than a metabolite of DMED. DMED has been suggested as a useful anesthetic adjunct or preanesthetic agent because it completely prevents alfentanil-induced skeletal muscle rigidity. The potential of DMED to alter alfentanil metabolism and disposition merits further investigation.

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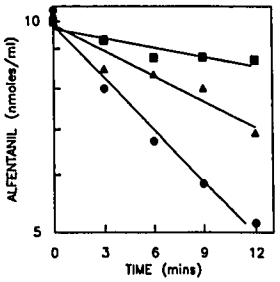

FIGURE: Effect of medetomidine isomers on microsomal alfentanil metabolism. Symbols denote (●) control, (▲) 2 μM LMED, (■) 2 μM DMED. Alfentanil concentrations are plotted on a log scale.

A380

TITLE: THE INTRAVASCULAR DISPOSITION OF INDOCYANINE GREEN (ICG) FROM THE MOMENT OF ITS ADMINISTRATION

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The response to many intravenously administered anesthetic drugs is determined by the plasma drug concentrations vs. time relationship during the first minutes after administration. The process of intravascular mixing is critical to drug distribution at this time but is not well described. This study was designed to develop a model describing the disposition of indocyanine green (ICG), a marker of intravascular space, from the moment of its injection.

METHODS: Five dogs (25-34 kg) were anesthetized with 2% halothane to decrease cardiac output (C.O.). Decreased C.O. prolongs intravascular mixing and accentuates ICG recirculation peaks, facilitating model development. ICG (5 mg) was administered rapidly into the right atrium. A computer-controlled roller pump facilitated collection of femoral arterial blood samples every 3 sec for the first 2 min and every 15 sec for the next 4 min. Subsequent blood samples were collected manually at less frequent intervals until 2 hr after drug administration. Plasma ICG concentrations were measured by HPLC. Pharmacokinetic analysis, with SAAM 30, involved a multiple compartmental model with time delay functions. Blood from serial central blood volumes (CBV) was modelled to recirculate through parallel peripheral volumes. Data obtained before recirculation were also used to calculate classical dye dilution C.O., mean transit time, and CBV.

RESULTS: CBV for the model and classical CBV (mean transit time x C.O.) both averaged 0.71 L. Dye dilution C.O. were 2.45±0.32 L/min, which compared favorably with the sum of intercompartmental clearances from the CBV of 2.52 L/min (population mean). Sixty-six percent of the C.O. flowed through 94% of the peripheral blood volume (the slowly equilibrating volume) while the remaining 34% of C.O. flowed through 6% of the peripheral blood volume (the rapidly equilibrating volume).

DISCUSSION: This new model resembles the parallel channel, lumped-parameter model of the circulation. It gives values comparable to those obtained with the classical dye dilution method and characterizes the later data of the ICG concentration vs. time curve. Application of this intravascular mixing model will allow us to determine the contribution of the circulation to drug distribution. This model will also provide estimates of the distribution of C.O. and blood volumes under various experimental and clinical conditions.