Title : A New Inhalation Anesthetic: Metabolism and Hemodynamics

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Enflurane anesthesia results in excellent cardiac rhythm stability. Methoxyflurane anesthesia is similar in this regard and in addition is associated with post-operative analgesia. Drawbacks include fluoride release from both, with nephrotoxicity definitely established for methoxyflurane, and literature recommendations against use of enflurane when renal compromise is present. In addition, methoxyflurane's low vapor pressure and high rubber solubility results in prolonged induction. We report herein initial studies of a new inhalation anesthetic, chemically difluoromethyl-1, 1-difluoro 2, 2-dichlorethylether* "DEME", which is thus related to both enflurane and methoxyflurane. Vapor pressure at 20°C is 65 mm Hg. Oil/gas solubility is estimated to be 250:1. We performed in vitro metabolic studies in liver microsomes and measured serum fluoride levels in vivo in rats to compare fluoride release with that of enflurane. We also studied the agent in intact dogs to determine MAC and to compare hemodynamic alterations with those of enflurane.

Methods--In vitro Studies: Microsomes were prepared from male Sprague-Dawley rat livers and resuspended in 0.5 M Tris buffer (pH 7.4). Protein and cytochrome P-450 contents were determined. Extent of defluorination was determined by incubating microsomes with the new anesthetic as follows. The reaction flask (10 ml) contained 3 ml liquid with 15 mg microsomal protein, an NADPH-generating system, and 4 µl of the anesthetic. After a 30 minute 37°C incubation, the reaction was terminated by adjusting pH to 5. Inorganic fluoride was measured with an Orion specific ion electrode. Incubation flask atmosphere was either N_2 or O_2.

Methods--In vivo Studies: Rats were exposed to 0.7% of the new agent in 40% O_2 for 2 hours. Blood samples were removed at 0, 2, 4 hours post-exposure and from unexposed animals for the determination of serum fluoride.

Dogs (15-18 kg, N=5) were anesthetized with the agent (intubated with 2.5 mg succinylcholine) in increments, measuring end-tidal anesthetic concentrations with a calibrated infra-red analyser. $PaCO_2$ was held at 38 ± 2 mmHg (SEM); esophageal temperature was held at 36.5 ± 0.2°C (SEM). MAC was determined in standard fashion, using steady (15 min) end-tidal concentration increments and tail-clamp stimuli. Hemodynamic measurements included cardiac output (thermodilution), arterial, pulmonary artery, and right atrial pressures, plus EKG and heart rate, at each steady-state end-tidal concentration. EEG records were also obtained.

Results--In vitro Studies: There appears to be no measurable enzymatic dehalogenation of the new anesthetic. The results did not differ when the investigations were carried out in O_2 or N_2. The presence or absence of the NADPH-generating system did not alter fluoride release. Studies for the presence of acid labile metabolites were negative.

Results--In vivo Studies: Rat serum fluoride levels were not elevated above control levels for 4 hours post-exposure. MAC, determined in dogs in standard fashion, was 0.69 ± .02 (SEM)% V/V. "Initial" hemodynamic measurements were at 0.4% V/V end-tidal concentrations. At 1 MAC, mean arterial pressure had decreased 29% from this value, cardiac output decreased 28% and peripheral vascular resistance decreased 18%. At concentrations higher than 1 MAC, arterial pressure decreased in dose-related fashion (decrease of 57% from that seen at the 0.4% "initial" measurement by 2 MAC). Cardiac rhythm stability was quite striking, without arrhythmias in any animal until concentrations were sufficient to result in MAP < 25 mmHg. Occasional EEG spiking occurred at concentrations greater than 2 MAC.

Conclusions. The in vitro studies indicate that little or no enzymatic fluoride release occurred. The in vivo rat studies support this, and fluoride release by the new agent is thus significantly less than that reported previously for enflurane. Hemodynamic studies indicate the agent to be a direct myocardial depressant and a peripheral vasodilator, similar to halothane and enflurane, with excellent cardiac rhythm stability. Therefore, our initial studies indicate difluoromethyl-1, 1-difluoro 2, 2-dichloroethylether ("DEME") to be similar in hemodynamic effects to enflurane, but with less in vitro fluoride release. Although rate of increase in end-expired tension is slower than that of enflurane, potency is 3 times greater, thus induction probably would not be prolonged. The agent appears sufficiently promising to warrant further study.

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