Investigation of the cerebral pharmacokinetics of the fluorine(18) labeled anesthetics isoflurane and halothane utilizing PET

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Authentic labelled ($\sp{18}$F) Halothane (CF$\sb3$CHClBr) and ($\sp{18}$F) Isoflurane (CF$\sb3$CHClOCF$\sb2$H) were synthesized. Overall, thirteen compounds were labelled via a novel, facile isotopic ($\sp{18}$F$\sp-$) fluoride for ($\sp{19}$F$\sp-$) fluoride exchange reaction. The positron emitting fluoroether and fluoroalkyl compounds synthesized comprised ten inhalation anesthetics spanning a tenfold range in potency and three structurally related non-anesthetics. All the agents possessed a similar molecular framework and were composed of a trifluoromethyl group $({\bf CF\sb3})$ adjoining a carbon atom bonded to both and acidic α-hydrogen (H) and at least one halogen or some other strong electron withdrawing group (X), $\Longrightarrow$ ${\bf CF\sb3CHXR}.$

The postulated reaction mechanism calls for the formation of an intermediate carbanion, formed after the loss of the acidic α-proton to a base (carbonate). Carbanion stabilization is attributed to the electron delocalizing effects of fluorine hyperconjugation. A qualitative correlation was found between each compounds ability to undergo deuterium exchange (with the α-proton) in a scaled up reaction and the degree of isotopic fluoride exchange that occured during the radiochemistry.

The anesthetics that were labeled include Isoflurane-CF$\sb3$CHClOCF$\sb2$H (97% radiochemical purity, 99% radiochemical yield), Halothane-CF$\sb3$CHBrCl (98%, 95%), Sevoflurane-CF$\sb3$CHCF3OCFH$\sb2$ (98%, 98%), Desflurane-CF$\sb3$CHFOCF$\sb2$H (90, 99) Fluroxene-CF3CH2OCH=CH2 (98%, 25%), CF$\sb3$CHClCF$\sb3$ (99%, 90%), CF$\sb3$C$\sb2$Cl (95%, 98%), CF$\sb3$CH$\sb2$I (95%, 95%) and CF$\sb3$CH$\sb2$Br (95%, 18%). All compounds that showed evidence of a deuterium for proton exchange were found to undergo (F-18) F$\sp-$ for (F-19) F$\sp-$ exchange.

The cerebral pharmacokinetics of labelled Isoflurane, Halothane and Desflurane were monitored with Positron Emission Tomography. Both of the agents, Isoflurane and Desflurane, were effectively modelled as inert diffusible tracers. However, a third rate constant was necessary in the case of Halothane, which may be necessary to account for the known metabolism of this drug. No evidence was uncovered for long term binding ($\sim$45 minutes) of these agents to brain tissue. A simple "pharmacological weighting" of the PET data did reveal an avid uptake into basal ganglia and thalamus. The high concentration of anesthetics into the gray matter nuclei does not support the idea that lipid solubility is the sole driving force in the biodistribution of these agents. The inhalation anesthetics may undergo low affinity binding to specific proteins in brain tissue. (Abstract shortened with permission of author.)