Quantitative Evaluation of the Effect of Propylene Glycol on BBB Permeability

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Introduction

The blood-brain barrier (BBB) is a system of tissue sites that restrict and regulate molecular movement between the systemic circulation and the central nervous system (CNS). Ischemic stroke is a result of loss of blood supply to the brain tissue resulting from obstruction of a cerebral blood vessel due to a thrombus or an embolus [1]. An important therapeutic intervention method is lysis of the blood clot that is obstructing the blood vessel enabling reperfusion. However, reperfusion carries a significant risk of reperfusion injury, due to the transient opening of the BBB, allowing substances in the blood to enter the brain. One way to reduce the effect of reperfusion injury is by controlling the movement of substances across the BBB i.e., by the use of drugs that block the increased permeability of the BBB. Propylene Glycol (PG), like DimethylSulfoxide, is a pharmaceutical solvent for many poorly soluble drugs that could be an example of a neuroprotective agent with potential BBB blocking properties. A number of laboratory techniques have been proposed in the past to characterize the permeability properties of BBB. However, all these methods are invasive or only suitable for use in animal models. An MRI technique for estimating barrier permeability coefficient, k_i based on the graphical analysis method [2] has been used for testing newer pharmaceutical molecules. This technique involves quantifying temporal distribution of gadolinium-diethylenetriaminepentaacetic acid (Gd-DTPA) in the brain tissue and fitting the data to a tracer kinetic model. The main aims of the study were 1) To establish the BBB blocking property of PG using the ^{14}C sucrose laboratory reference technique. 2) To quantitatively evaluate the effect of PG on BBB permeability coefficient using an MRI technique based on the graphical analysis method and demonstrate the sensitivity of the MRI technique for testing newer investigational drugs.

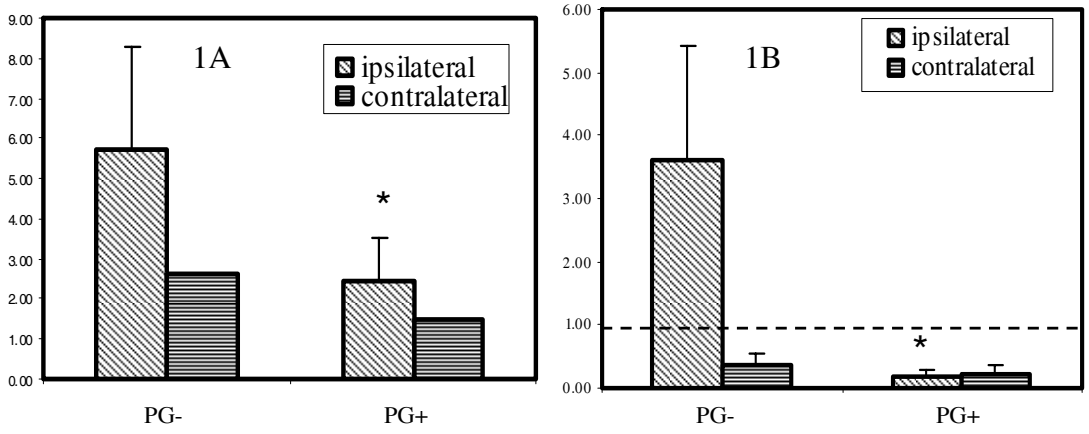
Materials and Methods

Brain uptake of sucrose was measured in treated (PG+) and untreated (PG-) rats using ^{14}C sucrose technique in rat brains (N=10) that had undergone 2 hours of MCAO followed by reperfusion for 3 hours. Another group of rats had MRI performed with PG and/or without PG (N=8). A 4.7T Bruker MR system was used to acquire T2-weighted, DWI images and T2 maps. A rapid T1 mapping protocol was implemented to acquire one pre-Gd-DTPA baseline data set followed by post injection data sets at 3 min intervals for 45 mins. Data were post processed pixel-wise to generate Gd-DTPA concentration and permeability coefficient color maps. Permeability values were estimated from the permeability color maps.

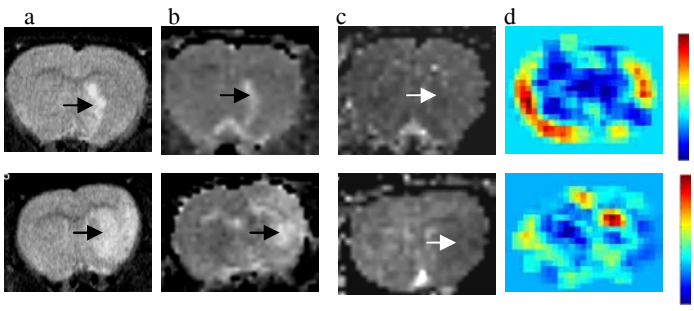
Results & Discussion

Figure 1 A, 1B and 1C summarize the results of the study. Our results show that PG protects the BBB in ischemic stroke and that MRI permeability measurements are sufficiently sensitive to detect small drug effects noninvasively. MRI technique has been shown to be useful for evaluating the BBB blocking effect of propylene glycol in ischemic stroke model of rat brain. The results from the MR experiment agree well with findings from the ^{14}C sucrose technique.

Reference [1] Ewing et al MRM 2003, 50: 283.



1A. Effect of propylene glycol (PG) on the BBB obtained using ^{14}C sucrose technique in ischemic stroke rat brain model. The measure of BBB disruption is the sucrose space (Y-axis), which is the percent ratio of radiolabel sucrose in the brain to that in the blood. The sucrose space on the ischemic side in the control (N=5) untreated brains was 5.74 ± 0.89% while in the PG treated (N=5, dose 7.8g/kg) brains a significant reduction (ANOVA, *p<0.001) to 2.44 ± 0.22% was observed.. [1B] Mean permeability coefficient estimates in PG+ (N=3) and PG- (N=4) rats using the MRI technique. The dashed line represents the upper limit of the range (0-1 x 10^{-3} ml/g-min) of permeability coefficient values in healthy tissue. Treated rats demonstrated a significant reduction in permeability on the ischemic side as compared to the untreated rats (ANOVA, *p<0.05, * indicates significant reduction). No significant difference was observed on the contralateral side between the PG- and PG+ rats. The Y axis error bars represent standard error of mean.



1C. shows (a) T2 weighted (b) T2 maps (c) ADC map (d) color coded permeability coefficient map for propylene glycol treated (PG+, top row) and untreated (PG-, bottom row) rats. The ischemia can be seen as a hyperintense lesion (arrow) on T2 weighted images and T2 maps. Arrows on ADC maps point at ischemic regions with diffusion changes. Color coded permeability maps demonstrate clearly the regions of high and low permeability in PG+ and PG- rats.