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Optical Detection of Blood Brain Barrier Disruption with Indocyanine Green

Mei Wang, M.P.H., Jane Y. Zhang, B.S., Irving J. Bigio, Ph.D., Shailendra Joshi, M.D.
Anesthesiology, Columbia University, New York, New York

Introduction: Optical pharmacokinetics (OP) is a form of diffuse reflectance spectrometry that permits real time measurements of tissue drug concentrations. Such a method of tissue drug concentration measurement is well suited to assess rapid changes in tissue drug concentrations after intraarterial delivery. While investigating the kinetics of intraarterial drugs we observed that even mechanized injection of mannitol needed to disrupt the blood brain barrier (BBB), resulted in considerable difference in site specific disruption of BBB as detected by Evan's Blue staining. The aim of this experiment was to assess if OP measurements could detect the osmotic disruption of the BBB.

Methods: After approval by the IACUC, the experiments were conducted on New Zealand white rabbits. For the experiment the animals were anesthetized with intramuscular ketamine and thereafter the anesthesia was maintained with intravenous infusion of propofol (10-20 mg/kg/hr) with mechancial ventilation. Surgical preparation included, venous, femoral arterial and selective internal carotid arterial cannulations. The skull was carefully milled to the inner table. The laser Doppler and the OP probes were placed to measure cerebral blood flow and drug concentration measurements. The experimental protocol involved two injection of Indocyanine green (ICG) (1.25 mg IV) 30 minutes apart. BBB was intact during the first injection but was disrupted in the second. BBB disruption was achieved with intracarotid injection of 25% mannitol 8 ml over 40 seconds.

Results: The study was conducted on eight New Zealand white rabbits. Hemodynamic parameters remained stable during ICG injections with or without the osmotic disruption of the BBB. Osmotic disruption of the BBB increased tissue ICG concentrations. Although the peak ICG concentrations were similar, the area under the curve, and the concentration of ICG at 30 minutes was increased after osmotic disruption, see Fig. 1.

Conclusions: Preliminary analysis of our data suggests that it is feasible to detect the disruption of the blood brain barrier by the OP techniques. The disruption of BBB results in a significant increase in concentrations of ICG. Such measurements might help us better assess methods of intraarterial drug delivery, Fig. 2.[figure1]

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Figure 1