Summary

• In ongoing studies we observed significant retention of cationic formulations after intraarterial (IA) delivery when injections are made during transient cerebral hypoperfusion (TCH).

• Mitoxantrone (MTO) is an antineoplastic drug which also carries a net positive charge.

• IA pulsed injection of drugs during TCH offers several advantages to regional drug delivery. That could apply to MTO delivery.

• We assessed the delivery of MTO in healthy Sprague Dawley rats after the disruption of the BBB and having observed significant uptake after IA-TCH delivery, we then determined the effectiveness of IA-TCH delivery in the delivery of drugs to C-6 tumor bearing animals.

• We observed that effective delivery of MTO is feasible to brain tumors by the TCH method.

Introduction

• Mitoxantrone (MTO) is an antineoplastic drug that is locally effective for glioma treatment, IA MTO is used for treating peripheral malignancies.

• Although simulations and experimental data show a significant improvement in intraarterial (IA) drug delivery with the reduction of cerebral blood flow, we had failed to observe any such improvement in IA MTO deposition in rabbits.

• Subsequent studies revealed that the uptake of MTO was a function of blood brain barrier (BBB) permeability and that hyperosmotic BBB disruption was unreliable in rabbits.

• Since the BBB is impaired around brain tumors, we re-evaluated IA mitoxantrone delivery in C6 glioma bearing Sprague Dawley rats.

Methods

• Preliminary dose response studies with IA-TCH (IA injection during transient cerebral hypoperfusion) drug delivery were conducted on healthy rats with hyperosmotic BBB disruption with intracarotid mannitol.

• Using diffuse reflectance spectroscopy (DRS) we determined the brain tissue concentrations of MTO after injection of 0.1, 0.25, 0.5 and 1 mg of MTO, intravenously (IV), IA and with IA-TCH.

• Surgical preparation and technical details of the DRS method are available in our earlier publications (4, 7).

• Next, we injected healthy rats with 1 million C6 cells that resulted in significant tumor development after 1 week.

• We then evaluated 0.5 mg IA-TCH MTO delivery in the tumor bearing hemisphere and contralateral brain.

• Six tumor bearing rats were sacrificed 5 min after injection and 6 were sacrificed 4 hrs after injection after letting the animals recover form anesthesia.

Results

• The experiments show that it is feasible to deliver MTO to C6 glioma implants by IA-TCH assisted drug delivery. BBB impairment due to tumor infiltration is sufficient to permit tumor tissue uptake.

• Furthermore, it is possible that the cationic nature of MTO also improves its uptake after IA injections, as we have recently reported with liposomes (7).

• Experiments are now underway to assess impact of IA TCH MTO delivery on tumor size, histology and survival.

Acknowledgment: NIH R01(s): CA 127500 and CA 136843 (S.J.).