Intra-arterial Mitoxantrone Delivery in Rabbits: An Optical Pharmacokinetic Study

Shailendra Joshi, MD*
Roberto Reif, PhD‡
Mei Wang, MS MPH*
Jane Zhang, MS‡
Aysegul Ergin, PhD‡
Jeffery N. Bruce, MD§
Robert L. Fine, MD‖
Irving J. Bigio, PhD‡

*Department of Anesthesiology, College of Physicians and Surgeons of Columbia University, New York, New York; ‡Department of Biomedical Engineering, Boston University, Boston, Massachusetts; §Department of Neurosurgery, College of Physicians and Surgeons of Columbia University, New York, New York; ‖Department of Internal Medicine, Division of Medical Oncology, College of Physicians and Surgeons of Columbia University, New York, New York

Correspondence:
Shailendra Joshi, MD,
Assistant Professor,
Department of Anesthesiology,
P&S P Box 46,
College of Physicians and Surgeons of Columbia University,
630 West 168th Street,
New York, NY 10032.
E-mail: sj121@columbia.edu

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BACKGROUND: Several human studies have demonstrated the feasibility of intra-arterial delivery of mitoxantrone in systemic malignancies. Computational models predict that an intra-arterial bolus injection of mitoxantrone during transient cerebral hypoperfusion will enhance brain tissue drug deposition in comparison with injections during normal blood flow.

OBJECTIVE: To assess whether transient reduction in cerebral blood flow would enhance the delivery of mitoxantrone. This is accomplished by obtaining real-time measurements of mitoxantrone concentrations in brain tissues by using a novel *optical pharmacokinetics technique,* based on reflectance spectroscopy.

METHODS: The blood-brain barrier of anesthetized rabbits was disrupted by intracarotid injection of mannitol (8 mL, 25% over 40 seconds). Thereafter, animals received 3 mg of mitoxantrone injection during normal perfusion (n = 5) or cerebral hypoperfusion that was induced by contralateral arterial occlusion and systemic hypotension (n = 8).

RESULTS: Cerebral hypoperfusion significantly decreased the cerebral blood flow, allowing a longer exposure time of the drug. It was determined that therapeutic concentrations of mitoxantrone were achieved in both groups; however, hypoperfusion did not increase the tissue concentrations of mitoxantrone after 20 minutes.

CONCLUSION: These results demonstrate the effective delivery of mitoxantrone by the intra-arterial route, after blood-brain-barrier disruption, but the predicted benefits of flow reduction for improving intra-arterial deposition of mitoxantrone was not evident.

KEY WORDS: Intracarotid, Mitoxantrone, Optical, Pharmacokinetics

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Computer models of intra-arterial drug delivery suggest that tissue drug deposition is improved when intra-arterial drugs are injected during transient cerebral hypoperfusion (CHP).[1] The availability of small balloon tipped catheters makes it feasible to modulate blood flow in distal regions of the brain.[2] Transient cessation of blood flow, either locally or systemically, is often used during neurosurgical and endovascular interventions while treating potentially life-threatening vascular malformations and brain aneurysms.[3] We therefore hypothesized that intra-arterial bolus injections of mitoxantrone will significantly improve tissue drug deposition. Mitoxantrone, a water-soluble, natural product-derived, non-cell cycle-specific chemotherapeutic drug, normally does not cross the intact blood-brain barrier (BBB). The drug is clinically effective against a range of tumors such as leukemia, colon and breast cancers, and melanomas.[4] Early reports suggest that local mitoxantrone prolongs survival in a rodent glioma tumor model.[5] Intratumoral mitoxantrone has been used to improve survival of patients with recurrent gliomas.[6]

However, the use of mitoxantrone in treating brain tumors is limited by the poor traversement of the BBB. Several studies have demonstrated the feasibility of intra-arterial mitoxantrone delivery for treating human lymphangiosarcoma, melanoma,[7] and breast,[7,8] colorectal,[9] and pancreatic[10] cancers. Thus, methods to improve mitoxantrone delivery to brain tumors, such as

ABBREVIATIONS: BBB, blood-brain barrier; **CHP,** cerebral hypoperfusion; **LD,** laser Doppler; **MTO,** mitoxantrone; **NP,** normal perfusion; **OP,** optical pharmacokinetics

by the intra-arterial route, are of direct clinical interest. The method of "optical pharmacokinetics" (OP) has been recently developed for minimally invasive monitoring of local drug concentrations in tissue.[11,12] The OP method consists of placing a fiberoptic probe at the surface of the tissue to be interrogated, and the measurements are obtained in less than 50 ms. The OP technique has been used to measure tissue concentrations of chemotherapeutic drugs in peripheral tissue and implanted tumors.[13] Similar ability to track brain tissue drug concentrations by optical methods provides a valuable tool to understand intra-arterial drug kinetics.[14] In this project, we used the OP technique to determine whether tissue deposition of mitoxantrone could be augmented by intra-arterial injection during CHP.

METHODS

Animal Preparation

After approval of the investigation protocol by the Institutional Animal Care and Use Committees of both Boston University and Columbia University, studies were conducted on New Zealand White rabbits, 1.5 to 2 kg in weight. Rabbits, like primates, have a clear separation of the internal and external carotid irrigations. The large size of their skull is convenient for placing laser Doppler (LD) or OP probes for cerebral blood flow and drug measurements, respectively. Therefore, rabbits are well-suited for intracarotid drug delivery experiments. After placement of an intravenous line, the animals were anesthetized with 0.2- to 0.5-mL boluses of intravenous 1% propofol (Diprivan, Astra Zeneca, Wilmington, Delaware). Subsequently, through a tracheotomy, the animals were ventilated by Harvard small animal ventilator, to produce an end-tidal CO_2 of 35 $\pm$ 5 mmHg. Anesthesia was maintained with continuous propofol infusion at a rate of 20 to 30 mg/h. The surgical preparation of the animals consisted of cannulation of the femoral and common carotid arteries. The internal carotid artery of the animal was carefully isolated by the use of the retinal discoloration test.[16] The contralateral carotid artery was carefully dissected and secured within a Silastic loop, such that the vessel could be occluded without disturbing the animal in the stereotactic frame.

For the placement of LD and OP probes, the animals were placed prone in a stereotactic frame. The skull was exposed through a midline incision. Electroencephalographic leads were secured to the skull with 1.5-mm stainless steel screws. The skull was gently milled down, such that cerebral arteries could be seen through the inner table. The LD probes were secured in plastic retainers that were glued to the skull. The OP probe was manipulated with a Kite micromanipulator, so that the probe tip was in gentle contact with the thinned skull over the brain. An esophageal temperature probe monitored the core temperature of the animal. The electroencephalogram activity, mean femoral arterial pressure, heart rate, cerebral blood flow (CBF) from the left and right hemispheres, and the ventilatory parameters were recorded by Mac-Lab data (AD Instruments) collection system.

Optical Pharmacokinetics

The OP method is a mode of diffuse reflectance spectroscopy with a specific geometry, which enables the noninvasive real-time measurement of drug concentrations in situ. An abbreviated description of the method is provided here. The OP method determines drug concentrations by measuring the change of the wavelength-dependent total absorption coefficient of the tissue, and can be used for determining the concentrations of drugs that have an optical absorption band within the wavelength range from visible to near-infrared. Our particular instrument was sensitive to wavelengths of a broader range (450-850 nm). An optical fiber probe, comprising separate illumination and collection fibers, is placed in gentle contact with the tissue surface. The diffusely backscattered light samples the underlying tissue (Figure 1). The optical absorption spectrum of mitoxantrone is distinct from that of hemoglobin and of oxyhemoglobin (Figure 2); therefore, it is well suited for tissue concentration measurements by the OP method. The underlying optical-physics concepts for the OP method have been described in detail in earlier publications by Mourant et al,[11] who reported the preclinical measurements of chemotherapeutic drug concentrations in animal models in the peripheral tissues. It was shown that, for an appropriate range of fiber separations, D, between light delivery and collection fibers, the pathlength of the collected photons, L, is insensitive to variations in scattering properties for the range of scattering parameters typically found in tissue. As used in these studies, the fiber separation is 2 mm, and the depth of sensitivity is 2 to 3 mm. The OP device was calibrated with a tissue phantom model by using the light-scattering properties of intralipid (Figure 3). To establish the correlation between measured and dissolved concentration of mitoxantrone, known amounts of mitoxantrone 0.312 μg/mL to 5 μg/mL were dissolved in 1% intralipid fat emulsion. A linear correlation was observed between the measured and dissolved concentrations of mitoxantrone.

Cerebral Hypoperfusion

Bilateral occlusion of carotid arteries is well tolerated in rabbits. Therefore, to significantly decrease the CBF, we used bilateral internal carotid artery occlusion with systemic hypotension by intravenous adenosine (20-30 mg) and esmolol (20-30 mg) to transiently decrease CBF to 10% to 30% of the baseline value. Typically with these doses of the drugs, during CHP the mean arterial pressure decreased from 95 to 100 mmHg to 20 to 30 mmHg. The heart rate decreased from approximately 220 to approximately 125 beats/min. The end-tidal CO_2 decreased from 40 to 50 mmHg to 20 to 30 mmHg.[17,18] Arterial occlusion is released after 2 minutes, such that the heart rate, end-tidal CO_2, mean arterial pressure, and CBF recover rapidly in minutes. Effects of adenosine and esmolol resolve in 5 minutes without any inotropic drugs.[17,18]

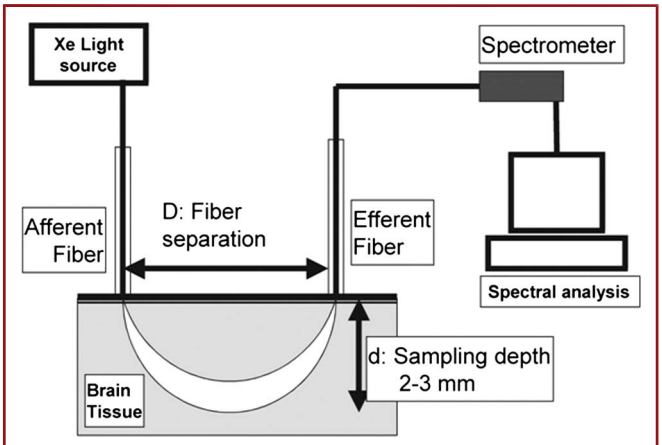

FIGURE 1. *Setup for the diffuse reflectance spectroscopy system.*

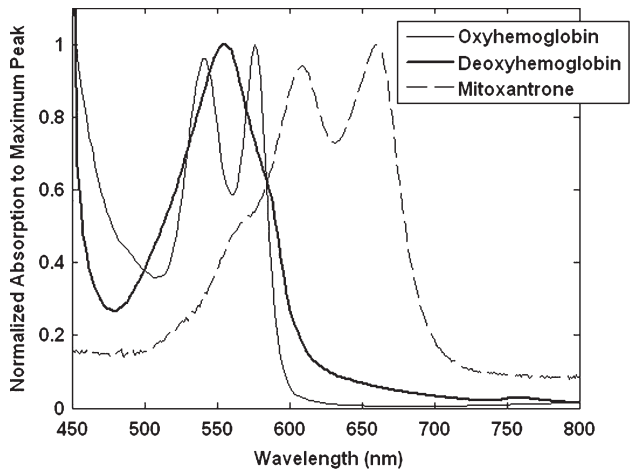

FIGURE 2. *Absorption spectrum for mitoxantrone, deoxyhemoglobin, and oxyhemoglobin normalized to the peak of each spectrum.*

Drug Delivery Protocol

In preliminary studies published earlier, we first determined the need to disrupt the BBB to increase tissue deposition of mitoxatrone (Figure 4).[15] In this publication we are determining whether transient CHP would augment tissue deposition of mitoxantrone. We randomly assigned New Zealand white rabbits, 3 to 4 pounds in weight, to 2 groups that received intra-arterial injections of mitoxantrone (3 mg as 0.1% solution in normal saline injected over 1 minute) with or without CHP. The BBB was disrupted in all animals with an intra-arterial injection of 25% mannitol 8 mL, injected over 40 seconds.[19,20]

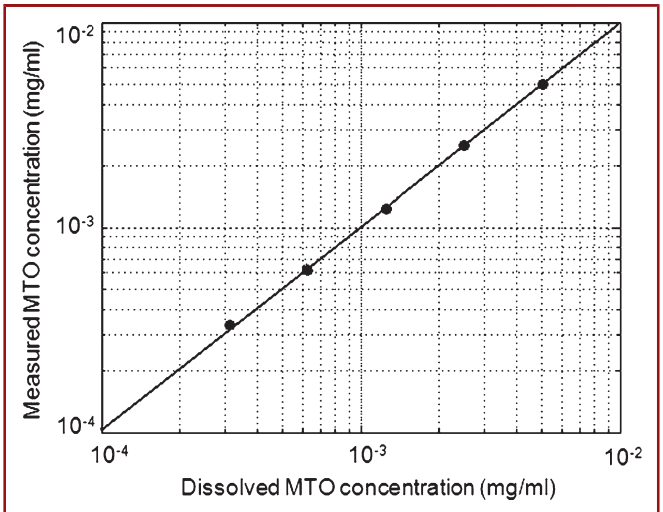

FIGURE 3. *Correlation between measured vs known concentrations of mitoxantrone (MTO) in a tissue phantom consisting of 1% intralipid fat emulsion. The highest concentration tested was 5 μg/mL and the lowest was 0.312 μg/mL. A linear correlation was observed between known and measured concentrations.*

Outcome Data

Mitoxantrone concentration-time curve parameters that were analyzed included the following: (i) baseline concentration, (ii) peak concentration, (iii) area under the concentration time curve, and (iv) final brain tissue concentration at 20 minutes after drug. The hemodynamic data for analysis included the heart rate, mean arterial pressure, ipsilateral cerebral blood flow, core temperature, respiratory rate, and end-tidal carbon dioxide tension. The data were collected in real time but were analyzed at 6 specific time points: (i) baseline, (ii) after intracarotid mannitol injection, (iii) CHP before injection of mitoxantrone, (iv) after injection of mitoxantrone, (v) 5 minutes after the start of drug bolus injection, and (vi) 20 minutes after drug bolus.

Data Analysis

The data were analyzed by factorial and repeated measures ANOVA. For single-factor comparisons, CHP vs normal perfusions (NPs), a P value of .05 was considered significant to compare the 2 groups. The Bonferroni-Dunn test was used to correct for multiple comparisons between 6 different stages of CHP-assisted mitoxantrone delivery; a P value of .003 was considered significant for multiple comparisons.

RESULTS

The study was completed in a total of 13 animals, which were randomly assigned to the CHP (n = 8) and normal perfusion (n = 5) groups. Significant changes in cerebral and systemic hemodynamics occurred during cerebral hypoperfusion. There were statistically significant decreases in heart rate, mean arterial pressure, LD flow, and end-tidal carbon dioxide concentrations during CHP compared with baseline and recovery, as well as the normal perfusion group. The CBF rapidly recovered within 2 minutes after drug injection, corresponding to the release of contralateral internal carotid artery occlusion. The hemodynamic values returned to 10% of the baseline within 5 minutes of drug injection without any pharmacological intervention. Subsequently, the hemodynamic parameters remained stable for the remainder of the experiment (Figure 5, Table). The peak concentrations of mitoxantrone were not affected by CHP 11.16 ± 01.61 vs 11.20 ± 3.18 μg/g tissue, P = .98. The initial peak duration was slightly increased in the CHP group vs normal perfusion (NP) but was not statistically significant, 85 ± 33 vs 56 ± 36 seconds, respectively, P = .17. There was a trend toward an increase in the area under the concentration time curve during CHP vs NP, 928 ± 353 vs 594 ± 306 μg/g per min, P = .11. However, 20 minutes after drug infusion the tissue concentrations were comparable in the CHP vs NP groups, 1.64 ± 0.841 vs 1.80 ± 1.09 μg/g, P = .77 (Figure 6).

DISCUSSION

This study had 2 main outcomes. First, the study demonstrated that it is possible to track local tissue concentrations of drugs in real time by optical means without invading the cranial vault. Second, the concentration of mitoxantrone in the brain tissue achieved by BBB disruption and bolus injection was in the therapeutic range

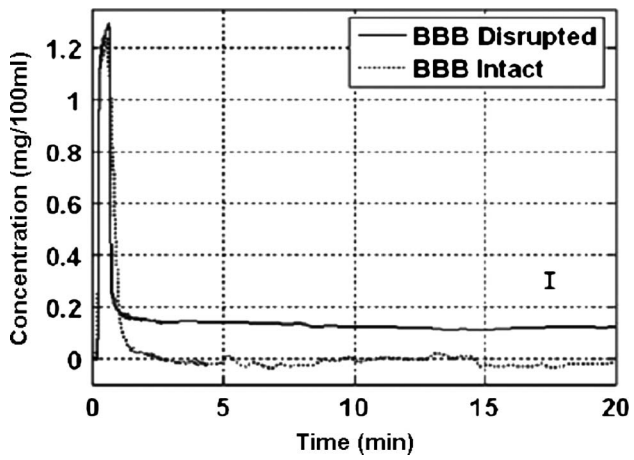

FIGURE 4. *The effect of blood-brain barrier (BBB) disruption on the uptake of brain tissue mitoxantrone as reported in an earlier publication by Reif et al.*[14]

(>50 ng/g tissue),[19] although the concurrent manipulation of blood flow in this animal model did not further augment tissue concentrations of mitoxantrone 20 minutes after injection.

Transient CHP is routinely used during neurological and endovascular surgery when blood flow to the brain is momentarily interrupted to permit surgical interventions such as during the clipping of aneurysms,[20] the deployment of stents,[21] or the treatment of high-flow cerebral arteriovenous malformations.[3,22] The injection of drugs during CHP increases tissue drug deposition in 2 ways. First, it increases the transit time through the cerebral circulation by as much as 50 to 100 times.[23] Second, the rapid injection of drug overwhelms the blood flow, displacing blood and minimizing protein binding, resulting in a significant increase in free-drug concentrations.[24] Whether CHP can improve drug delivery and outcome in tumor models and patients remains to be seen, but the risk benefits of the procedure will have to be assessed against the course of relentless and fatal disease.

The failure to observe an increased tissue deposition of mitoxantrone during CHP is in contrast to our observations with

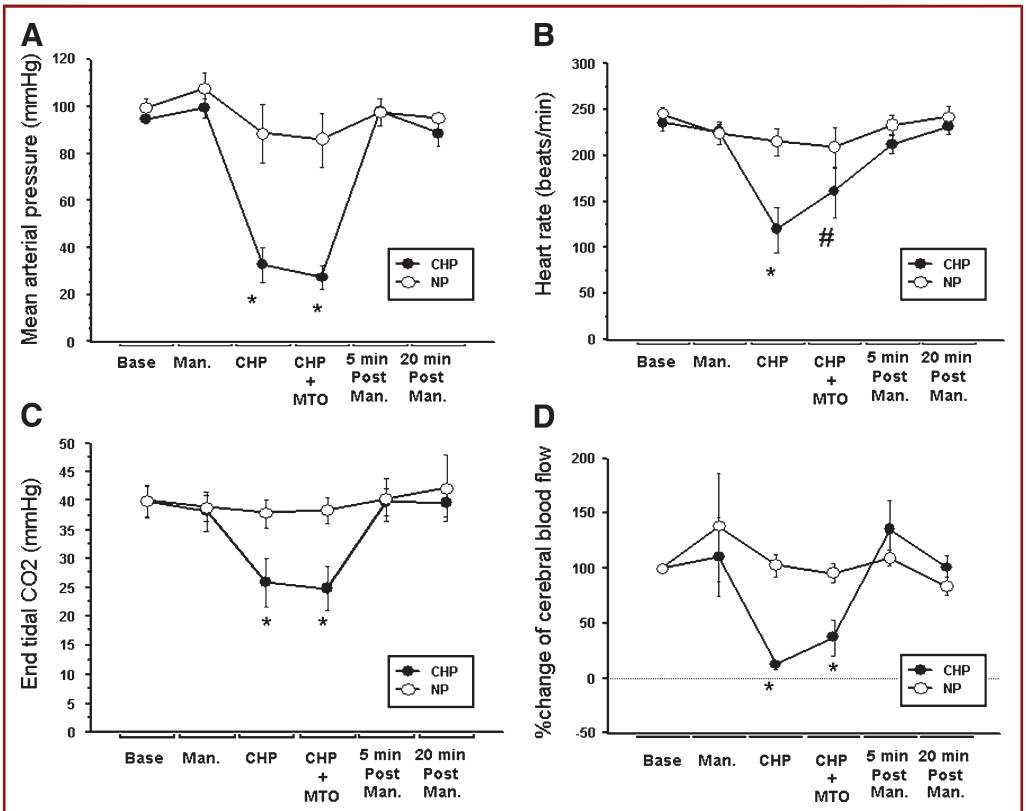

FIGURE 5. *CHP-assisted delivery of mitoxantrone (0.1%*3 mL) Bolus hemodynamic data: Temp and RR, there was no change across and between groups of rabbits normal perfusion (NP = 5, open circles) and cerebral hypoperfusion (CHP = 8, solid circles). Measurements at 6 time points: baseline (BASE), after injection of IC mannitol (MAN.), during CHP before drug (CHP), with mitoxantrone (CHP+MTO), 5 minutes postdrug (5 min. Post Man.), 20 minutes postdrug (20 min Post Man.).* **A**, *mean arterial pressure (mmHg).* **B**, *heart rate (bpm).* **C**, *end-tidal carbon dioxide tension (mmHg).* **D**, *%-Δ cerebral blood flow from baseline. Transient but significant changes in hemodynamic parameters were seen during CHP at the time that intracarotid mitoxantrone was injected. CHP, cerebral hypoperfusion; MTO, mitoxantrone; IC, intracarotid.*

TABLE. Changes in Physiological Parameters During Transient Cerebral Hypoperfusion[a]

		Base	IC Mannitol	CHP	CHP + IC MTO	5 min Post MTO	20 min Post MTO
Temperature, °C	CHP	36.1 ± 1.1	36.2 ±1.1	36.1 ± 1.1	36.1 ± 1.1	36.1 ± 1.1	36.1 ± 1.1
	NP	36.1 ± 1.0	35.1 ± 1.3	36.2 ± 0.8	36.2 ± 0.8	36.2 ± 0.8	36.3 ± 1.1
Respiratory rate, breaths/min	CHP	62 ± 15	62 ± 15	62 ± 15	62 ± 15	62 ± 15	62 ± 15
	NP	64 ± 6	64 ± 6	64 ± 6	64 ± 6	64 ± 6	64 ± 6
Heart rate, beats/min	CHP	235 ± 24	226 ± 23	120 ± 71[bc]	160 ± 75[d]	212 ± 28	231 ± 20
	NP	246 ± 17	226 ± 27	215 ± 32	212 ± 28	234 ± 22	242 ± 26
Mean arterial pressure, mmHg	CHP	95 ± 6	100 ± 12	32 ± 21[bc]	27 ± 14[bd]	98 ± 17	88 ± 16
	NP	99 ± 10	107 ± 16	89 ± 26	86 ± 26	97 ± 4	95 ± 5
End-tidal CO_2, mmHg	CHP	40 ± 7	38 ± 10	26 ± 11[bc]	25 ± 11[bd]	40 ± 7	40 ± 7
	NP	40 ± 6	39 ± 5	38 ± 5	38 ± 5	40 ± 8	42 ± 13
%Δ cerebral blood flow from baseline	CHP	100 ± 0	134 ± 85	13 ± 8[bc]	44 ± 46[bd]	136 ± 74	101 ± 74
	NP	100 ± 0	138 ± 110	104 ± 23	96 ± 19	110 ± 16	84 ± 20

[a]CHP, transient cerebral hypoperfusion (n = 8); NP, normal perfusion (n = 5); IC, intracarotid; MTO, mitoxantrone; IC, intracarotid.
[b]Significant difference between CHP and NP ($P < .05$).
[c]Significant difference between CHP and other stages of the experiment ($P < .003$).
[d]Significant differences between MTO and other stages of the experiment.

other drugs that are lipid soluble. For example, in earlier experiments, electrophysiological effects of intracarotid anesthetics were augmented 5- to 10-fold when injections were made during cerebral hypoperfusion.[17,18] Similarly, tissue concentration of carmustine, 5 minutes after intracarotid drug injection, increased 4- to 7-fold when the drug was injected during CHP compared with a conventional 20-minute intra-arterial infusion with normal blood flow.[25] However, both carmustine and anesthetic

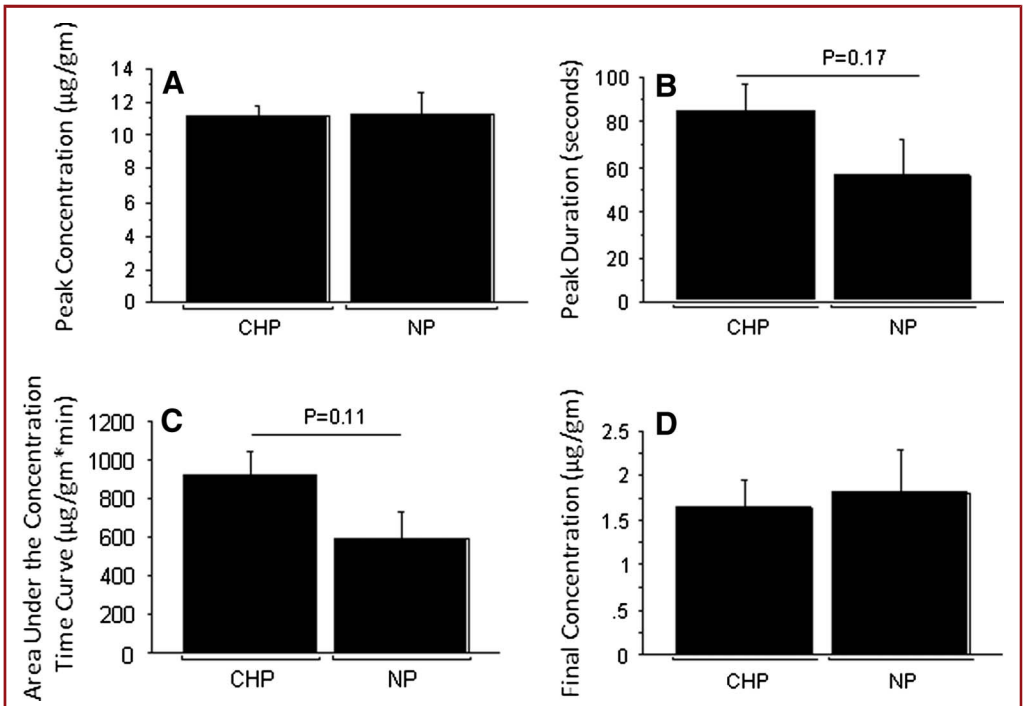

FIGURE 6. *Drug concentration parameters. The peak concentration (µg/g, **A**) and peak duration (s, **B**) was comparable between the cerebral hypoperfusion (CHP, n = 8) and the normal perfusion (NP, n = 5) groups, but the area under the concentration time curve (µg/g*min) showed a trend toward an increase with CHP (**C**). The final concentrations (µg/g, **D**) at the end of 20 minutes were similar in the NP and CHP groups. In animals with breeched BBB, there seems to be no sustained benefit of injecting mitoxantrone during CHP. BBB, blood-brain barrier.*

drugs are highly lipid soluble compared with mitoxantrone. It is possible that, during CHP, highly lipophilic drugs like propofol, pentothal, and carmustine are able to rapidly diffuse through the brain parenchyma, but hydrophilic mitoxantrone does not, thereby limiting its uptake by the tissue (Figure 7). Furthermore, there is evidence to suggest that the capillary area available for the diffusion of lipid-soluble drugs is 100 times greater than that available for the uptake of water-soluble drugs; therefore, the uptake of mitoxantrone might be more restricted in a no- or low-flow state because only a small amount of drug in the capillary will be permitted to diffuse out.[26] Figure 7 depicts a conceptual pharmacokinetics model at the tissue level.

The complex micropharmacokinetics of intra-arterial bolus injections is difficult to investigate (Figure 7). The OP technique that calculates the average concentration of drug within a volume of tissue cannot be used to validate this model. However, the OP method provides the temporal resolution to the understanding of intra-arterial drug kinetics. With bolus intra-arterial injections, the tissue concentrations of drugs change rapidly, and measuring such changes is beyond the time resolution of conventional tissue-sampling techniques, either by undertaking multiple tissue biopsies or with microdialysis, and would also be difficult by imaging techniques. With systemic drug delivery, when concentration parameters in various compartments are stable, arterial blood drug concentrations can be equated to brain drug concentrations by correcting for the blood-to-brain partition ratio. However, to understand bolus kinetics, real-time measurements of drug concentration are required. Although such measurements are feasible by using radioactive drugs and, in some instances, by magnetic resonance imaging, neither of these technologies can be widely used nor used in conventional laboratory settings. Optical measurements, therefore, offer valuable insights into drug delivery to the brain.

The principal limitation with OP is that drugs must have an optical absorption band in the 600- to 950-nm range, preferably one that does not directly coincide with that of hemoglobin and oxyhemoglobin absorption bands. Some anthracycline planar anticancer drugs like mitoxantrone, daunorubicin, and doxorubicin have spectral signatures that easily permit OP measurements of drug concentrations. For other chemotherapeutic agents one possible way to overcome this problem is to tag the molecule with a chromophore, as long as the chromophore does not significantly alter the pharmacology. In some cases, like paclitaxel, tagging is relatively easy without altering its pharmacology, and tagged versions are available commercially. Others, like methotrexate, can be tagged with fluorescein. Another way to overcome this limitation is to develop models of drug delivery that use dyes with known pharmacokinetic properties. Although optical measurements do not compromise the structural integrity of the brain tissue, the technique, even in rabbits, does require shaving the skull. The geometry of the current probe limits its use to a sampling depth of 2 to 3 mm. For clinical use in human research, either the probe geometry will have to be revised or implantable fiberoptic probes will have to be developed. The current technology could be used to understand pharmacokinetics of certain chemotherapeutic drugs when the brain tissue is exposed during surgery.

One of the limitations in the present study is that we used a standard dose of mannitol to disrupt the BBB. Although this

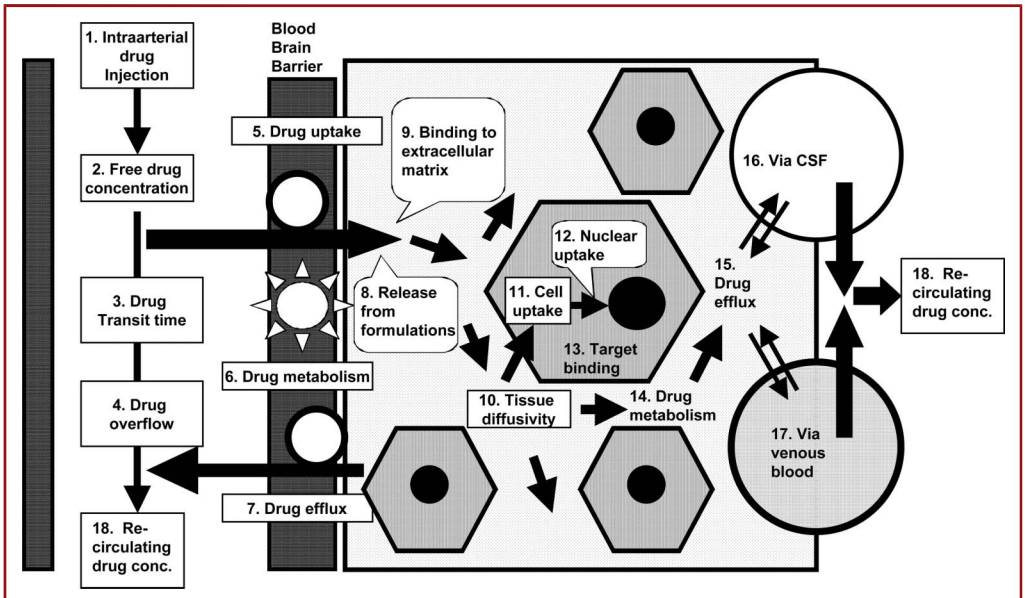

FIGURE 7. *Conceptual micropharmacokinetic events affecting intra-arterial drug delivery. Barriers to drug delivery are not restricted the blood-brain barrier alone. Although diffusion of small lipid-soluble molecules might be unrestricted, most chemotherapeutic drugs face additional hurdles to reach the target site. CSF, cerebrospinal fluid; BBB, blood-brain barrier.*

experimental step was common to both groups, a variable degree of BBB disruption could affect the resulting tissue concentration of drugs. Human data suggest that such variability is less likely to affect carotid injection compared with vertebral artery injection.[27] For the future, the ability of the OP method to track multiple chromophores could enable us to measure concentrations of tracers of BBB disruption such as Evan blue or indocyanine green and thereby normalize tissue mitoxantrone concentrations to that of a tracer that can quantify BBB disruption. Such an approach will be invaluable in the treatment of brain tumors, in experimental or clinical settings, because of the variable degree of BBB disruption around tumor tissue. We are currently undertaking such investigations.

It is feasible to track tissue concentrations of mitoxantrone after intracarotid injection of the drug by the OP method. Significant deposition of mitoxantrone in the brain tissue was evident after bolus injection of the drug following hyperosmotic disruption of the BBB. Contrary to what computer modeling suggests and our own previous observations, CHP does not appear to augment tissue deposition of mitoxantrone after intra-arterial injections. Improvements of intra-arterial drug delivery will require adjuvant strategies, such as the increased lipid solubility of the mitoxatrone, through liposomal formulations to improve intra-arterial drug delivery.

Disclosures

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REFERENCES

1. Dedrick RL. Arterial drug infusion: pharmacokinetic problems and pitfalls. *J Natl Cancer Inst*. 1988;80(2):84-89.
2. Pile-Spellman J, Young WL. Materials and methods for interventional neuroradiology (INR). In: Taveras JM, ed. *Neuroradiology*. 3rd ed. Baltimore, MD: Williams & Wilkins; 1996:1047-1073.
3. Pile-Spellman J, Young WL, Joshi S, et al. Adenosine-induced cardiac pause for endovascular embolization of cerebral arteriovenous malformations: technical case report. *Neurosurgery*. 1999;44(4):881-886; discussion 886-887.
4. Durr FE. Biologic and biochemical effects of mitoxantrone. *Semin Oncol*. 1984;11(3 Suppl 1):3-10.
5. Yemisci M, Bozdag S, Cetin M, et al. Treatment of malignant gliomas with mitoxantrone-loaded poly (lactide-co-glycolide) microspheres. *Neurosurgery*. 2006; 59(6):1296-1302; discussion 1302-1293.
6. Boiardi A, Eoli M, Salmaggi A, et al. Efficacy of intratumoral delivery of mitoxantrone in recurrent malignant glial tumours. *J Neurooncol*. 2001;54(1):39-47.
7. Nitz U, Havenith B, Rost B, Mosny D, Ellerbrok G. [Locoregional intra-arterial chemotherapy of primary incurable local recurrence of breast cancer]. *Geburtshilfe Frauenheilkd*. 1993;53(11):760-767.
8. Gorich J, Tomczak R, Gabelmann A, Wisianowski C, Kramer S. [Intraarterial chemotherapy in cases of breast cancer]. *Radiologe*. 1999;39(9):790-794.
9. Vaglini M, Cascinelli F, Chiti A, et al. Isolated pelvic perfusion for the treatment of unresectable primary or recurrent rectal cancer. *Tumori*. 1996;82(5):459-462.
10. Papachristou E, Link KH, Schoenberg MH. Regional celiac artery infusion in the adjuvant treatment of pancreatic cancer. *Anticancer Res*. 2003;23(2A): 831-834.
11. Mourant JR, Johnson TM, Los G, Bigio IJ. Non-invasive measurement of chemotherapy drug concentrations in tissue: preliminary demonstrations of in vivo measurements. *Physics Med Biol*. 1999;44(5):1397-1417.
12. Bigio IJ, Bown SG. Spectroscopic sensing of cancer and cancer therapy: current status of translational research. *Cancer Biol Ther*. 2004;3(3):259-267.
13. Kanick SC, Eiseman JL, Joseph E, Guo J, Parker RS. Noninvasive and non-destructive optical spectroscopic measurement of motexafin gadolinium in mouse tissues: comparison to high-performance liquid chromatography. *J Photochem Photobiol B*. 2007;88(2-3):90-104.
14. Reif R, Wang M, Joshi S, A'Amar O, Bigio IJ. Optical method for real-time monitoring of drug concentrations facilitates the development of novel methods for drug delivery to brain tissue. *J Biomed Opt*. 2007;12(3):034036.
15. *Deleted in proof.*
16. Joshi S, Wang M, Hartl R. Retinal discoloration test. *J Cereb Blood Flow Metab*. 2004;24(3):305-308.
17. Joshi S, Wang M, Etu JJ, Nishanian EV, Pile-Spellman J. Cerebral blood flow affects dose requirements of intracarotid propofol for electrocerebral silence. *Anesthesiology*. 2006;104(2):290-298, discussion 5A.
18. Joshi S, Wang M, Etu JJ, Pile-Spellman J. Reducing cerebral blood flow increases the duration of electroencephalographic silence by intracarotid thiopental. *Anesth Analg*. 2005;101(3):851-858, table of contents.
19. Green RM, Stewart DJ, Hugenholtz H, Richard MT, Thibault M, Montpetit V. Human central nervous system and plasma pharmacology of mitoxantrone. *J Neurooncol*. 1988;6(1):75-83.
20. Schick U, Dohnert J, Meyer JJ, Vitzthum HE. Effects of temporary clips on somatosensory evoked potentials in aneurysm surgery. *Neurocrit Care*. 2005;2(2):141-149.
21. Plaschke K, Bockler D, Schumacher H, Martin E, Bardenheuer HJ. Adenosine-induced cardiac arrest and EEG changes in patients with thoracic aorta endovascular repair. *Br J Anaesth*. 2006;96(3):310-316.
22. Hashimoto T, Young WL, Aagaard BD, Joshi S, Ostapkovich ND, Pile-Spellman J. Adenosine-induced ventricular asystole to induce transient profound systemic hypotension in patients undergoing endovascular therapy. Dose-response characteristics. *Anesthesiology*. 2000;93(4):998-1001.
23. Wang M, Joshi S. Electrocerebral silence after intracarotid propofol injection is a function of transit time. *Anesth Analg*. 2007;104(6):1498-1503, table of contents.
24. Jones DR, Hall SD, Jackson EK, Branch RA, Wilkinson GR. Brain uptake of benzodiazepines: effects of lipophilicity and plasma protein binding. *J Pharmacol Exp Ther*. 1988;245(3):816-822.
25. Joshi S, Wang M, Etu JJ, et al. Transient cerebral hypoperfusion enhances intraarterial carmustine deposition into brain tissue. *J Neurooncol*. 2008;86:123-132.
26. Muller M, dela Pena A, Derendorf H. Issues in pharmacokinetics and pharmacodynamics of anti-infective agents: distribution in tissue. *Antimicrob Agents Chemother*. 2004;48(5):1441-1453.
27. Zylber-Katz E, Gomori JM, Schwartz A, Lossos A, Bokstein F, Siegal T. Pharmacokinetics of methotrexate in cerebrospinal fluid and serum after osmotic blood-brain barrier disruption in patients with brain lymphoma. *Clin Pharmacol Ther*. 2000;67(6):631-641.

COMMENT

The technique used for optical pharmacokinetic determination is interesting and could be used for many different types of studies. I do question the general concept being tested in this study. Is this type of strategy to increase drug delivery really feasible for general patient use? It is hard to imagine repeated intravenous treatments involving induced patient hypotension. Certainly, risk of stroke or other cardiovascular or neurovascular complications must be considered before this type of therapy would be deemed prudent. This is even less attractive after the negative findings of this study.

Randy L. Jensen
Salt Lake City, Utah