Drug streaming during intra-arterial chemotherapy

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Treatment of brain tumors by intra-arterial (IA) chemotherapy is occasionally complicated by sites of focal toxicity in the brain and retina. A possible cause of focal toxicity is non-uniform drug delivery due to intravascular drug streaming. To investigate this phenomenon in vivo, the authors examined the distribution of drug delivery after internal carotid artery (ICA) infusion in rhesus monkeys. Carbon-14 (14C)-labeled iodoantipyrine was delivered into the ICA of eight monkeys at slow infusion rates (1% to 2% of ICA flow) or at fast infusion rates (20% of ICA flow) combined with additional techniques to promote mixing with ICA blood. Two monkeys received intravenous (IV) 14C-antipyrine. Uniformity of delivery was assessed by comparing high-to-low ratios of isotope concentration in four brain regions evaluated by quantitative autoradiography.

There was striking non-uniformity of drug delivery in the slow IA infusion group, with as much as 13-fold differences in drug concentration in anatomically contiguous areas. The values of high-to-low concentration ratios (mean ± standard deviation) in individual autoradiographic planes were: 1) frontoparietal cortex: slow IA infusion 4.54 ± 2.07, fast IA infusion 1.71 ± 0.31, IV infusion 1.30 ± 0.174; 2) frontoparietal white matter: slow IA infusion 2.94 ± 1.45, fast IA infusion 1.59 ± 0.41, IV infusion 1.34 ± 0.21; 3) temporal cortex: slow IA infusion 5.43 ± 3.57, fast IA infusion 1.69 ± 0.24, IV infusion 1.67 ± 0.25; 4) basal ganglia: slow IA infusion 3.6 ± 2.9, fast IA infusion 1.18 ± 0.10, IV infusion 1.09 ± 0.04. Differences between concentration ratios after slow IA and fast IA infusion are significant (p < 0.01); those between fast IA and IV infusion are not significant.

Intra-arterial drug administration at infusion rates analogous to those currently used clinically results in drug streaming with markedly heterogeneous drug deposition in the perfused hemisphere. This may cause suboptimal drug levels in the tumor, and toxic levels at sites within the perfused hemisphere. This effect can be abrogated by techniques that eliminate drug streaming.

**KEY WORDS** - chemotherapy - intra-arterial drug delivery - 14C-iodoantipyrine - brain tumor - monkey

Intra-arterial administration of antineoplastic agents is being studied in several centers for the treatment of malignant gliomas, metastatic tumors, and primary lymphomas in the brain. Although various techniques, including changes in solvents, drug filtration, blood-brain barrier disruption, supraophthalmic infusion, and hemoperfusion or hemodialysis of regional venous blood, are being used to enhance effective drug delivery and avoid toxic side effects, focal toxicity in the perfused region remains a problem.16-18,20,21,26-28,31 The most frequently reported local toxicity is retinal damage after infusion of BCNU (1,3-bis(2-chloroethyl)-1-nitrosourea) or cisplatin into the infraophthalmic segment of the internal carotid artery (ICA).14,16,18,20,24,35 Focal sites of cerebral toxicity and patchy hemorrhagic infarction with arteriolar necrosis have been observed in animal studies and clinical trials.13,14,18,29 We have recently recognized delayed development of focal brain injury at sites distant from glial tumors in patients who received intracarotid BCNU therapy.

A possible cause of focal tissue damage is non-uniform drug delivery. Variable drug distribution in the brain during intracarotid infusion could result in toxic levels in some regions and subtumoricidal levels in others. We have examined factors that govern mixing
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<table>
<thead>
<tr>
<th>Infusion Rate</th>
<th>Monkey No.</th>
<th>Volume Infused</th>
<th>Infusion Period</th>
<th>Infusion Rate Rate</th>
<th>% of ICA†</th>
<th>Needle Direction</th>
</tr>
</thead>
<tbody>
<tr>
<td>slow</td>
<td>S1</td>
<td>0.2 ml</td>
<td>30 sec</td>
<td>0.4 ml/min</td>
<td>2%</td>
<td>antegrade</td>
</tr>
<tr>
<td>slow</td>
<td>S2</td>
<td>0.2 ml</td>
<td>30 sec</td>
<td>0.4 ml/min</td>
<td>2%</td>
<td>antegrade</td>
</tr>
<tr>
<td>slow</td>
<td>S3</td>
<td>0.2 ml</td>
<td>30 sec</td>
<td>0.4 ml/min</td>
<td>2%</td>
<td>antegrade</td>
</tr>
<tr>
<td>slow</td>
<td>S4</td>
<td>0.2 ml</td>
<td>30 sec</td>
<td>0.4 ml/min</td>
<td>2%</td>
<td>antegrade</td>
</tr>
<tr>
<td>slow</td>
<td>S5</td>
<td>0.2 ml</td>
<td>30 sec</td>
<td>0.4 ml/min</td>
<td>2%</td>
<td>antegrade</td>
</tr>
<tr>
<td>fast</td>
<td>N1</td>
<td>2.0 ml</td>
<td>30 sec</td>
<td>4.0 ml/min</td>
<td>20%</td>
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<tr>
<td>fast</td>
<td>N2</td>
<td>2.0 ml</td>
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<td>4.0 ml/min</td>
<td>20%</td>
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</tr>
</tbody>
</table>

* All infusions contained 100 μCi 14C-iodoantipyrine dissolved in saline. All infusions were unilateral except for one (in Monkey S3), which was bilateral and simultaneous.
† Infusion rate expressed as the percent of blood flow in one internal carotid artery (ICA); namely, 20 ml/min.

When a miscible fluid is infused via catheters into an in vitro model of the human ICA carrying a pulsatile receiving fluid. The in vitro results indicate that mixing is enhanced as the infusion rate is increased relative to the flow rate of the receiving fluid. At low infusion rates, the solution issues from the catheter tip as a thin stream which remains stable for distances of several centimeters and exits in variable concentrations into arterial branches. At higher infusion rates, the infused jet is unstable and mixes more uniformly with the receiving fluid near the site of infusion. This provides a more uniform distribution of the infused solution in subsequent downstream branches of the model.

To investigate this phenomenon in vivo, we assessed the cerebral distribution of carbon-14-labeled iodoantipyrine (14C-IAP) infused into the cervical segment of the ICA of rhesus monkeys. The distribution of 14C-IAP in the brain following a slow infusion (1% to 2% of estimated ICA blood flow) was compared with that following rapid infusion (20% of estimated ICA blood flow). The results from these two groups were also compared to the distribution of 14C-antipyrine (14C-AP) delivered to two rhesus monkeys as intravenous infusions. These studies are reported here.

Materials and Methods

Eight adult rhesus monkeys (each weighing 5.5 to 7.2 kg) were anesthetized with ketamine and thiopental and maintained with endotracheal halothane, nitrous oxide, and oxygen. The cervical segment of the carotid artery was exposed and the external carotid artery was ligated. Each infused artery received 100 μCi of 14C-IAP dissolved in saline. All intracarotid infusions were made by direct arterial puncture with a No. 30 needle connected by tubing to a syringe infusion pump* for continuous flow. Five monkeys received infusions in the direction of blood flow, four at a rate of 0.4 ml/min and one at 0.2 ml/min. One monkey received simultaneous bilateral infusions. These animals comprised the "slow intra-arterial infusion group." Three monkeys received infusions at a rate of 4.0 ml/min into the common carotid artery below the origin of the ligated external carotid artery. These infusions were directed against the blood flow and are referred to as the "fast intra-arterial infusion group." Two rhesus monkeys received 60-second intravenous infusions of 14C-AP while in a quiet conscious state as part of a previous study. They comprise the "intravenous group." Table 1 summarizes the intra-arterial infusion data. Four monkeys in the intra-arterial infusion groups underwent transfemoral cerebral angiography under ketamine anesthesia the day before intra-arterial infusion to assess the intracranial arterial anatomy.

Following intra-arterial infusion, the anesthetized animals were decapitated and the entire head was immersed in liquid Freon for at least 20 minutes. The time elapsed from the conclusion of isotope infusion to immersion of the heads in Freon did not exceed 30 seconds. Specimens were stored at −85°C. Each specimen was mounted on a large planchette in carboxymethylcellulose, 6% in water, by partial immersion in isopentane cooled to −85°C. Specimens were sectioned horizontally at 20-μ thickness on a sledge microtome. A section was retained for autoradiography at intervals of 3 mm. Photographs were taken of the embedded specimens at each interval for anatomic correlation with the autoradiographs. The retained slices were freeze-dried, mounted on Brainbridge board, and placed in x-ray cassettes on single-coated x-ray film† for 7 days. Each film was developed with 14C-methylmethacrylate standards, previously calibrated to reference 20-μ thick brain sections of known radioactivity.

To convert the x-ray film images to radioactivity

* Syringe infusion pump manufactured by Harvard Apparatus Co., Inc., Millis, Massachusetts.
† Sledge 2258 PMV cryomicrotome manufactured by LKB Instruments, Stockholm, Sweden.
‡ X-ray film, SB-5, manufactured by Eastman Kodak, Rochester, New York.
§ Methylmethacrylate standards obtained from Amersham Corp., Arlington Heights, Illinois.

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(nCi/gm), the optical densities of the images produced by the $^{14}$C standards were measured, and a standard curve that related optical density to tissue radioactivity was generated for each film. Measurements of optical density within 200 × 200-µm elements of the autoradiographic images on the x-ray film were made using a computerized scanning microdensitometer. The optical density data were stored in a computer and could be converted to radioactivity using the standard curve and displayed on a video monitor with an image array processor.* Each digitized image was visually evaluated, and measurements of the highest and lowest values of isotope activity were made in four anatomically defined regions. The value of an individual measurement is the mean radioactivity (nCi/gm) of 100 points in a 2-mm × 2-mm × 20-µm volume of tissue. The regions from which these measurements were derived were: 1) cortical ribbon of frontoparietal cortex perfused by the middle cerebral artery (MCA); 2) cortical ribbon of temporal cortex perfused by the MCA; 3) white matter in the frontoparietal area perfused by the MCA; and 4) basal ganglia (caudate and/or putamen). Radioactivity was measured only in areas that were clearly perfused by the MCA; watershed zones and areas served by arteries other than the MCA were avoided.

Areas with the highest and lowest values of radioactivity in each of the four anatomic regions of each section were used to calculate a delivery ratio, as follows: highest isotope concentration (nCi/gm)/lowest isotope concentration (nCi/gm) = delivery ratio. This ratio expresses the multiple of the difference between the highest and lowest values of isotope activity measured within the defined region in each section of the infused hemisphere. The magnitude of the delivery ratio in a given section indicates the variability of isotope distribution during infusion. A delivery ratio of 1 denotes uniform isotope delivery in the region evaluated; a ratio of 2 indicates a twofold difference between the values of the highest and lowest isotope activity in the tissue region. Comparisons of the uniformity of isotope delivery among the fast intra-arterial infusion, the slow intra-arterial infusion, and the intravenous infusion groups were made using the calculated ratios from each anatomic region. A delivery ratio greater than 2 was considered as indicating a degree of non-uniformity that would be clinically important; based on this, the delivery ratios among the infusion groups were analyzed by the chi-square method.

**Results**

Cerebral angiography in four monkeys receiving intra-arterial infusions demonstrated patency of the circle of Willis with bilateral filling of the carotid and basilar systems. Azygous A$_2$ and pericallosal segments of the anterior cerebral artery system were noted in each animal. This arterial anatomy is consistent with previous studies in rhesus monkeys.*

The deposition of isotope in the infused hemisphere after slow intra-arterial infusion was markedly heterogeneous, with delivery ratios as high as 13.9:1 (Fig. 2). In the four anatomic regions evaluated, the mean values (± standard deviation) of these delivery ratios in the slow infusion group were: 4.54 ± 2.07 in the frontoparietal cortex; 2.94 ± 1.45 in the frontoparietal white matter; 5.43 ± 3.57 in the temporal cortex; and 3.6 ± 2.9 in the basal ganglia. Several brain areas exhibited greater than 10-fold differences in drug delivery.

Animals that received intra-arterial infusions designed to promote drug mixing (fast intra-arterial group) had more uniform drug deposition in the perfused hemisphere (Fig. 2). The means (± standard deviation) of the delivery ratios were less than 2 in all four anatomic regions (1.71 ± 0.31 in the frontoparietal cortex; 1.59 ± 0.41 in the frontoparietal white matter; 1.69 ± 0.24 in the temporal cortex; and 1.18 ± 0.10 in the basal ganglia). The range of delivery ratios was limited, and there were no examples of extreme degrees of non-uniform drug delivery. The highest delivery ratio measured was 2.2:1 in this group.

The brains of the monkeys that received intravenous $^{14}$C-AP showed a more uniform isotope deposition than either of the intra-arterial infusion groups (Fig. 2). The means (± standard deviation) of the delivery ratios were less than 2 in the four anatomic regions (1.30 ± 0.174 in the frontoparietal cortex; 1.34 ± 0.21 in the frontoparietal white matter; 1.67 ± 0.25 in the temporal cortex; and 1.09 ± 0.04 in the basal ganglia). The differences in each anatomic region between the fast and slow intra-arterial and the intravenous infusion groups are clearly shown in Fig. 2.

The differences observed in the delivery ratio concentrations between the fast and the slow intra-arterial

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* Video monitor, Model 8025, manufactured by Aydin Controls, Fort Washington, Pennsylvania.

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Infusion groups were significant in the frontoparietal cortex (p < 0.0005), the temporal cortex (p < 0.0005), the basal ganglia (p < 0.0005), and the frontoparietal white matter (p = 0.01). The differences between the fast intra-arterial infusion group and the intravenous infusion group were not significant.

The images in Fig. 3 demonstrate 14C-IAP deposition in the brains of animals in the slow intra-arterial infusion group (a, b, and c) and in animals in the fast intra-arterial infusion group (d, e, and f) at comparable levels. The color bar that accompanies the reconstructed images can be used to estimate the tissue radioactivity, and thus drug delivery, in the areas shown for each animal. The white area in the anterior putamen in Fig. 3b has a tissue radioactivity value exceeding 8000 nCi/gm, which was measured by extrapolation of the standard curve for that autoradiographic image. It is apparent from the representative images in Fig. 3 that differences in drug delivery can vary widely within small areas of the same anatomic structure, with sharp delineation of areas of high and low isotope deposition following slow intra-arterial infusion.

Discussion

Instances of focal cerebral toxicity following intracarotid infusion of BCNU have been well documented. Similarly, the sporadic occurrence of ocular toxicity following infraophthalmic infusion of BCNU has been reported.14,15,17,30,34,35 Kapp, et al.,18 reported two patients with brain toxicity following intracarotid BCNU infusion. One patient had areas of focal necrosis in the infused hemisphere at autopsy. Another patient developed multiple separate areas of hypodensity on CT scanning after one infusion of 250 mg/sq m. In the series of Greenberg, et al.,14 seven of 36 patients who received intracarotid BCNU developed focal areas of decreased attenuation on CT scanning in the subcortex of the infused hemisphere. This is similar to our experience with intracarotid BCNU in humans, in whom stereotaxic biopsy revealed necrotic tissue in areas of focal tissue damage separate from the tumor site. These experiences with intra-arterial infusions in humans suggest the possibility that intravascular streaming during intra-arterial drug administration causes a variable distribution of drug delivery to account for the observed toxicity.

Drug streaming in the intracranial circulation after slow intra-arterial infusion was demonstrated qualitatively in 1949, when McDonald and Potter25 used Evans blue dye to examine blood flow in the basilar artery of the rabbit. After ligation of both axillary arteries, they infused Evans blue into one axillary artery while filming the flow in the basilar artery. They noted: “Analysis of a cinematographic film taken at 24 frames/second showed no evidence of eddying or mixing even at the point where the two streams meet. Normally the line between dye and blood appeared as if it had been drawn with a straight edge down the center of the artery from the angle made by the fusing walls of the vertebral arteries. The two streams were seen to supply the blood flowing into the branches arising from the respective sides of the basilar.”25 A similar streaming in converging

![Diagram](image-url)

**Fig. 2.** The range and mean values (crossbar) of the delivery ratios for each infusion group are displayed. Individual delivery ratios are indicated in the slow intra-arterial (I.A.) infusion group. The degree of non-uniformity of drug delivery is indicated by the magnitude of the ratio of highest to lowest isotope concentration in each section (drug delivery ratio). I.V. = intravenous; N = number of autoradiographic sections evaluated in each group displayed.
arteries is likely in our study. In most of the experimental animals reported here, the isotope entering the azygous A2 and pericallosal segments of the anterior cerebral artery was deposited in the frontal pole on the side of infusion. In one experiment with fast intra-arterial infusion, the isotope was delivered in higher concentration to the contralateral frontal pole (Fig. 3f). This suggests that a stream of isotope formed at the fusion of the A1 segments crossed to the opposite side of the single A2 segment in this animal. This observation emphasizes the fact that sites of concentrated drug deposition due to streaming are unpredictable and may be influenced by local blood flow patterns.

In 1952, French, et al., reported the effects of intracarotid delivery of nitrogen mustard to cats and monkeys. Histological examination of the animals that suffered neurological deficits showed areas of patchy neuronal changes alternating with normal-appearing areas. In the animals that survived longer, patchy areas of vessel degeneration, chronic neuronal degeneration, demyelination, and glial proliferation were noted. Omojola, et al., reported focal sites of angionecrosis and infarction in dogs that received intracarotid BCNU. Our studies suggest that the patchy distribution of cerebral toxicity noted by these workers may be due to intravascular drug streaming and a variable pattern of drug delivery following intracarotid infusion.

Selective delivery of certain chemotherapeutic agents to regionally defined areas by intra-arterial infusion may provide a pharmacological advantage over intravenous infusion of the same amount of drug. The pharmacokinetic principles of intra-arterial drug administration have been described in detail.7-9 These analyses assume that the infused drug mixes uniformly with the arterial blood. To assess the pharmacokinetic advantage of intra-arterial delivery, Levin, et al., infused 14C-BCNU for 5 or 20 minutes intravenously or into the carotid artery of squirrel monkeys. Sixty minutes after completion of the infusion they measured the concentration of soluble BCNU products and the radioactivity bound to ribonucleic acid (RNA), deoxyribonucleic acid (DNA), and protein in the frontal, parietal, and temporal lobes. After intracarotid infusion, the soluble BCNU-derived products and radioactivity bound to nucleic acids were 2.4- to 2.7-fold greater than those following intravenous administration. However, some areas of the brain served by the MCA were found to contain four to five times more isotope following intracarotid delivery than after intravenous delivery.23 This difference in radioactivity distribution is consistent with a modest drug-streaming effect.

The average rate of intracarotid infusion of antineoplastic drugs in published clinical series is about 4 ml/min.1,6,10,14,15,53,38-41 Assuming a blood flow of 270 ml/min in the ICA, the delivery rate in these series is 0.6% to 3.7% of ICA blood flow.3,36 Implanted continuous infusion pumps have been used to deliver antineoplastic agents at extremely low rates, ranging from 2.5 to 4.0 ml/24 hrs.12,30 In the present study, we assumed the blood flow in the ICA of the rhesus monkey to be 20 ml/min.5,24,27 The monkeys in the slow intra-arterial infusion group received 14C-IAP at 1% to 2% of the ICA blood flow. Autoradiographic images of brain sections of all the monkeys in this group showed marked variability of isotope deposition in the brain structures analyzed. In contrast, monkeys in the fast intra-arterial infusion group received 14C-IAP at an injection rate equal to 20% of the ICA flow. The animals in this group demonstrated a distribution of isotope that was much more uniform than in the slow intra-arterial group and was similar to that following intravenous infusion.

The technique that we used to calculate the highest to lowest radioactivity ratio probably underestimates the magnitude of variability in drug delivery after slow and fast intra-arterial infusions. The delivery ratios reported in Fig. 2 were calculated from values obtained in single autoradiographic planes. A comparison of highest and lowest isotope activities in different autoradiographic planes of a single region in some of the studies yielded ratios that were higher than those obtained from a single plane. Frequently, however, the highest and lowest isotope concentration in an anatomic region were present in a single plane. These observations imply that drug streaming into a focal area tends to deprive surrounding sites of a proportionate amount of drug.

The differences in the uniformity of isotope delivery between the slow and fast infusion groups provide evidence for drug streaming at low infusion rates in this experimental model. Since complete mixing of 14C-AI-P is assumed during intravenous delivery, the ratios of the intravenous infusion group are attributable to differences in blood flow within the regions evaluated. The mean values and ranges of the isotope delivery ratios of the fast intra-arterial infusion group exceed those of the intravenous group in each region, but these differences are not significant. This suggests that, while the techniques employed to promote uniform drug delivery in the fast intra-arterial infusion group were not entirely effective, the variation in isotope deposition seen in this group approximates the variation in cerebral blood flow within these regions.

Drug mixing in the carotid artery in the fast intra-arterial infusion group was facilitated by: 1) increasing the rate of infusion 10-fold compared to that in the slow infusion group (20-fold greater than the rate in Monkey S3); 2) an infusion velocity increase at the needle tip to 370 cm/sec in the fast infusion group (compared to 37 cm/sec in the slow infusion group); 3) directing the needle tip against the direction of blood flow; and 4) infusing the 14C-IAP into the common carotid artery just proximal to an acutely ligated external carotid artery, thereby exposing the infusate to increased flow disturbance.

Autoradiographic analysis of isotope deposition in
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FIG. 3. Computer-reconstructed autoradiographic images of the brains of monkeys that received intra-arterial infusions of 14C-iodoantipyrine at infusion rates equal to 1% to 2% (a, b, and c) or 20% (d, e, and f) of the estimated blood flow in the internal carotid artery.
the retina was not possible with the sectioning technique employed in this study. However, the sporadic occurrence of variable degrees of ocular toxicity reported in clinical trials of intracarotid BCNU suggests that streaming of concentrated drug into the ophthalmic artery may be a causative factor.

Conclusions

This study demonstrates that the infusion of ¹⁴C-IAP into the cervical segment of the rhesus monkey ICA at infusion rates of 1% and 2% of the ICA blood flow results in a variable deposition of the agent in the ipsilateral hemisphere. An increased infusion rate combined with other techniques to promote mixing of ¹⁴C-IAP with blood at the site of infusion results in more homogeneous isotope deposition, resembling that of intravenous delivery. We believe that the cause of heterogeneous drug deposition observed in this study is drug streaming in the ICA and its branches. Streaming can persist through several orders of bifurcations and results in marked differences in drug concentration in contiguous areas of brain. A variable delivery of antineoplastic agents to the perfused tissue during intraarterial infusion of the magnitude observed in this study may result in subtherapeutic drug levels at sites containing tumor and toxic levels at other sites within the perfused hemisphere. Drug streaming during intraarterial infusion may be the cause of the focal cerebral toxicity currently being observed in patients who have received intracarotid chemotherapy. The results of this study suggest particular caution in using indwelling infusion pumps to deliver antineoplastic agents at extremely low infusion rates.

The principles that govern drug streaming have important implications for the treatment of malignancies in the brain as well as in any organ in which intraarterial infusion of chemotherapeutic agents is used. The efficacy and safety of intraarterial chemotherapy cannot be established until clinical trials are conducted in which intravascular drug streaming has been reliably eliminated.

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