Carotid artery mixing with diastole-phased pulsed drug infusion

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Focal injury to the brain or retina is a frequent complication of drug delivery to the internal carotid artery (ICA) and may be due to poor mixing of the drug with blood at the infusion site. Rhesus monkeys were studied to determine whether phased drug delivery during diastole from a modified pulsatile angiographic injector would improve drug mixing in vivo. A radiolabeled flow tracer, carbon-14-iodoantipyrine (14C-IAP), was injected into the ICA of three monkeys in 80-msec pulses, each ending at least 50 msec before the end of local diastole. Local isotope concentration in the brain was determined by quantitative autoradiography. The ratio of highest to lowest concentration was 1.86 ± 0.26 (mean ± standard deviation) in the frontoparietal cortex, 1.65 ± 0.42 in the frontoparietal white matter, 1.89 ± 0.28 in the temporal cortex, and 1.39 ± 0.17 in the basal ganglia. These results were similar to recordings in three control animals that received intravenous 14C-IAP to demonstrate complete drug mixing (1.37 ± 0.12, 1.41 ± 0.11, 1.70 ± 0.08, 1.22 ± 0.24, respectively), and contrasted to findings in five animals which received continuous intracarotid infusions to demonstrate standard ICA drug delivery (4.54 ± 2.07, 2.94 ± 1.45, 5.43 ± 3.57, 3.60 ± 2.90, respectively). Pulsed intra-arterial infusion during diastole provides a technically simple method for improving intravascular drug mixing, and results in drug delivery to tissue capillaries that is proportional to blood flow.

KEY WORDS: chemotherapy · 14C-iodoantipyrine · brain neoplasm · drug delivery · rhesus monkey

ALTHOUGH increased clinical efficacy over intravenous infusion has not been shown in a controlled prospective manner, the intracarotid infusion of certain drugs for treatment of gliomas offers several pharmacokinetic advantages. In patients and animals, the most common complication following infusions in the infraophthalmic and supraophthalmic segments of the internal carotid artery (ICA) is focal injury of the retina or brain. One possible cause of these injuries is poor mixing of the drug with blood at the infusion site. This can result in intra-arterial streaming of the infusate, which causes drug delivery to the tissue that is not proportional to blood flow, and can produce delivery of toxic concentrations of drug to some tissue regions and suboptimal delivery to others. In addition, heterogeneous drug delivery to different tumor regions may limit the treatment response.

In vitro investigations of drug streaming in a polystyrene model of human intracranial carotid vessels have shown that a phased, pulsatile infusion during the slow blood flow phase of local diastole provides excellent mixing of injectate with blood. In this study, we confirm and extend these observations in vivo by studying the distribution of a blood flow reference tracer, carbon-14-labeled iodoantipyrine (14C-IAP), in the brains of rhesus monkeys following pulsed intra-arterial administration with a diastole-phased, pulsatile infusion (DPPI) pump.

Materials and Methods

Three groups of animals were studied. Group 1 consisted of three adult rhesus monkeys which received intracarotid infusions of 14C-IAP from a DPPI pump.*

control group received intravenous bolus injections of 14C-IAP followed by sacrifice and rapid brain removal.

The brain was cut axially in 20-μm sections using a Bright microtome. After rapid drying, the sections were exposed to single-coated Kodak SB-5 x-ray film along with previously calibrated 14C-methyl methacrylate standards. The autoradiograms were analyzed by computerized scanning microdensitometry. The 14C-methyl methacrylate standards were used to generate a curve of radioactivity (nanocuries/gram) versus optical density; optical density measurements of the tissue section images were then converted by the computer to nanocuries/gram.

Four regions of brain perfused by the middle cerebral artery were analyzed in each monkey: the frontoparietal cortex, frontoparietal white matter, temporal cortex, and basal ganglia. The digitized image was visually assessed on a color monitor and measurements of the highest and lowest areas of radioactivity were made in at least three different brain sections for each anatomical area in each monkey. Each measurement represented a mean value (nanocuries/gram) in a 1 mm × 1 mm × 20-μm region of interest. A delivery ratio was calculated and is defined as the highest area of radioactivity divided by the lowest area of radioactivity within a particular brain region. The mean delivery ratio and its standard deviation were calculated for each anatomical area in each group, and the Kruskal-Wallis test of independent samples (animals) used to analyze the data. The data for monkeys in Group 1 (with pulsed intra-arterial DPPI pump administration) were compared with data for animals in Group 2 (with continuous intracarotid infusions) and Group 3 (with intravenous bolus delivery).

**Results**

In the three monkeys that received ICA infusions with the DPPI pump (Group 1), the ratio of highest to lowest concentration was 1.86 ± 0.26 (mean ± standard deviation) in the frontoparietal cortex, 1.65 ± 0.42 in the frontoparietal white matter, 1.89 ± 0.28 in the temporal cortex, and 1.39 ± 0.17 in the basal ganglia. In the monkeys that received continuous intracarotid infusions (Group 2), the delivery ratios were 4.54 ± 2.07, 2.94 ± 1.45, 5.43 ± 3.57, and 3.60 ± 2.90, respectively. In the control monkeys that received intravenous infusion (Group 3), the delivery ratios were 1.37 ± 0.12, 1.41 ± 0.11, 1.70 ± 0.08, and 1.22 ± 0.24, respectively. These data are shown graphically in Fig. 2 and by representative quantitative autoradiograms in Fig. 3.

In all four anatomical areas, the delivery ratios of the three animals that received intracarotid infusions with...
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**Table 1**

<table>
<thead>
<tr>
<th>Group</th>
<th>Drug Delivery Route</th>
<th>Amount of Isotope (µCi)</th>
<th>Duration of Infusion (sec)</th>
<th>Rate of Infusion (cc/min)</th>
<th>Volume of Infusion (µl)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>IC</td>
<td>200</td>
<td>45</td>
<td>0.4</td>
<td>200</td>
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<tr>
<td>1</td>
<td>IC</td>
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<td>IC</td>
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<td>2</td>
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<td>3</td>
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* This table includes data from Blacklock, et al. IC = intracarotid; IV = intravenous.

The rationale for administering chemotherapeutic drugs intra-arterially has been described elsewhere. 6, 7 One advantage is that increased tissue levels during the initial pass through target organ capillaries can be obtained by intra-arterial drug administration in comparison to intravenous administration, although this initial advantage is reduced by subsequent recirculation of drug through the tissue or tumor vessels. A second advantage is that extraction and retention (or elimination) of drug during the initial pass through the target organ reduces the amount of recirculating drug and can thereby reduce systemic toxicity. 7, 8 A third advantage is that to obtain an equal tumor response might require a lower intracarotid than intravenous dose. A lower dose to the ICA would result in lower systemic toxicity. This was demonstrated by experiments carried out by Bullard, et al., 3 in which equal therapeutic responses were obtained in one group of brain tumor-bearing animals that received intravenously 13.3 mg/kg of 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) as in a second group that received one-quarter of this dose via the ICA.

Apart from the 1% major morbidity 13 associated with carotid artery catheterization, the major disadvantage of ICA drug infusion is focal toxicity in the brain and retina. This was described by DeWys and Fowler 1 and Omoljola, et al., 14 after ICA injection of BCNU in dogs. Clinical reports of brain and retinal toxicity include those of Kapp, et al., 11 who found focal cerebral necrosis and blindness after intracarotid delivery of BCNU, and of Greenberg, et al., 10 who reported that seven of 36 patients who received intracarotid administration of BCNU developed hypodense lesions (consistent with focal injury) as demonstrated by computerized tomography. A possible cause of these focal injuries is intr-
vascular streaming due to poor mixing of the infusate with blood, which results in excessive drug delivery to some regions of the brain and retina. Lutz, et al., demonstrated this infusate streaming in a polystyrene model of the human intracranial carotid artery and its branches, and Blacklock, et al., extended this finding in rhesus monkeys with autoradiographic studies. Although streaming could be eliminated with fast retrograde infusion, it is impractical and potentially dangerous to maintain these high rates of flow in patients with a catheter in an intraophthalmic or suprachiasmatic intracarotid position.

We sought to develop a clinically applicable system that would eliminate infusate streaming. The practical requirements included a high injection velocity to achieve mixing and a low, clinically acceptable injection volume. These criteria are met by the modified angiographic injector, which uses a diastole-phased pulsatile infusion technique. During the period of lowest local blood flow, a precise off-on-off pulse is generated at a predetermined point in the cardiac cycle. The controllable parameters include the interval after the R-wave when the pulse injection begins, the average and the pulse infusion rates, the pulse duration, and the number of cardiac cycles between each pulse. This technique was used by Shook, et al., to eliminate streaming in vitro.

We extended this approach to rhesus monkeys and demonstrated that a DPPI pump can be used to infuse small volumes of fluid into the carotid artery over an extended period of time. We demonstrated reduction in streaming with the DPPI method in the four anatomical areas studied, to the extent that there was no difference from intravenous delivery in a control group in three of the four areas, and a minimal difference in the fourth. Regional (ICA) infusion of chemotherapeutic drugs by diastole-phased pulsatile injection should reduce the heterogeneity of drug delivery to tumor, which may decrease tumor response in those zones receiving less drug. If our animal findings are confirmed in patients, intracarotid drug delivery with a DPPI pump should reduce the major central nervous system complication of therapy and may result in more effective adjuvant treatment of malignant gliomas.

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References


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