Aspiration of blood from the jugular vein during intracarotid drug infusion in monkeys

Implications for extracorporeal drug removal

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Circulation of blood in the ipsilateral jugular vein through an extracorporeal circuit for drug removal during intracarotid chemotherapy has recently been reported to decrease the systemic drug exposure. The reduced systemic exposure achieved by the use of this technique should permit a several-fold increase of the intracarotid dose of chemotherapy without increasing systemic toxicity. To determine the influence of the rate of blood removal from the jugular vein on the fraction of the blood flowing through the ipsilateral internal carotid artery (ICA) collected for extracorporeal drug removal, the authors aspirated blood from the jugular bulb into an extracorporeal circuit at varying rates during a constant infusion of the indicator dye, indocyanine green (ICG), into the ICA of rhesus monkeys. The fraction of the ipsilateral carotid blood channeled into the extracorporeal circuit increased linearly with the rate of aspiration of jugular blood. This suggests that the absence of valves in the intracranial venous system should permit increasing fractions of drug removal during intracarotid infusion by increasing the rate of collection of venous blood from the ipsilateral jugular bulb. The measurement of ICG concentrations in a similar manner in patients undergoing isolated perfusion may prove to be a clinically useful method for estimating the maximum safe dose in high-dose intra-arterial chemotherapy.

KEY WORDS • chemotherapy • brain-tumor therapy • internal carotid artery • indocyanine green • jugular vein • drug removal

INTRACAROTID infusion of antineoplastic agents for the treatment of brain tumors has been performed for over two decades. Pharmacokinetic analyses have established that certain drug and local blood flow characteristics determine whether intra-arterial delivery substantially increases drug exposure of the perfused organ compared to the intravenous administration of the same dose. The intra-arterial administration of drugs that are rapidly cleared from the body allows increased tumor exposures compared to an equivalent dose injected intravenously, or decreased systemic exposure and equivalent tumor exposures at decreased doses. We have recently studied the effect of removal of blood from the jugular bulb for extracorporeal hemoperfusion during intracarotid administration of BCNU (1,3-bis(2-chloroethyl)-1-nitrosourea) in monkeys and humans (EH Oldfield, et al., in preparation). By channeling the jugular blood through an extracorporeal circuit for drug removal and then back to the general circulation, systemic drug exposure was reduced two- to eightfold. Theoretical analysis of this technique suggests that the fraction of infused blood which is channeled into the extracorporeal circuit is a major determinant of the pharmacokinetic advantage.

In this study, an indicator dye was infused into the internal carotid artery (ICA) of rhesus monkeys during aspiration of blood from the ipsilateral jugular bulb at different rates. The purpose of the study was to determine the relationship between the rate at which blood is pumped from the jugular vein and the fraction of the ipsilateral carotid blood that is collected for extracorporeal circulation.
Jugular blood removal during ICA infusion

Materials and Methods

Three healthy adult rhesus monkeys weighing 7.0 to 10.2 kg were studied. Following induction of anesthesia with 10 mg/kg of intramuscular ketamine (Vetalar), light anesthesia was maintained with intravenous sodium pentobarbital. A No. 9 French Silastic catheter was placed transfemorally in the jugular bulb for channeling the jugular blood through an extracorporeal circuit. A No. 3.5 French catheter was placed transfemorally in the ICA for infusion of indocyanine green (ICG).* The blood was returned to the animal via a No. 9 French catheter placed in the left femoral vein. Systemic venous sampling was performed from the sural vein.

Indocyanine green, a synthetic dye, has been widely used to study hepatic blood flow and cardiac output in both animals and humans. A 0.5 mg/ml solution was prepared by dissolving 24 to 48 mg ICG in 5 to 10 ml sterile aqueous solvent. This was diluted with sodium phosphate-buffered 0.9% saline to pH 7.2. To achieve a stable plasma ICG concentration, each monkey received 2 mg intravenously immediately prior to a continuous intracarotid infusion of 345 µg/min. The jugular venous catheter was connected to an extracorporeal circuit containing a roller pump, † and blood was pumped from the jugular bulb and returned to the left femoral vein at flow rates of 10 to 60 ml/min. The pump rate was varied by 10 ml/min at 6-minute intervals. In the first monkey, a vacuum developed in the line when the flow rate reached 40 ml/min. It is assumed that this rate constituted the maximum rate achievable with that animal. In the second animal, the pump rate was increased from 10 to 60 ml/min at 6-minute intervals. The rate was then returned to 10 ml/min. In the third animal, the pump rate was gradually increased to 50 ml/min and then decreased by 10 ml/min every 6 minutes until it reached 10 ml/min. In all animals, blood samples were collected at 2- and 6-minute intervals from the pump inlet and sural vein, respectively, for measurement of plasma ICG levels.

Plasma ICG concentrations were measured as follows: 500-µl aliquots of plasma were obtained after centrifugation of the samples for 5 to 10 minutes at 2500 rpm. They were then diluted with 2.0 ml of 5% bovine serum albumin (BSA) prepared by dissolving BSA in sodium phosphate-buffered 0.9% saline. The samples were analyzed spectrophotometrically at 797 nm. The standard was 1 ml of monkey plasma in 5 ml of 5% BSA solution.

Results

Increasing the rate of aspiration from the jugular bulb during constant intracarotid infusion of ICG solution proportionately increased the fraction of the carotid blood receiving the infusate which was collected for extracorporeal circulation (Fig. 1).

The fraction of blood flowing through the ipsilateral ICA which was collected for extracorporeal circulation \( f \) was calculated by the equation:

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f = \frac{Q (1 - H)}{I} (C_1 - C_2),
\]

where \( Q \) is the blood flow to the pump; \( H \) is the hematocrit; \( C_1 \) is the pump inlet concentration of ICG; \( C_2 \) is the systemic concentration; and \( I \) is the ICG infusion rate. \( C_1 \) was calculated by averaging plasma ICG concentrations at the pump inlet at a particular pump rate \( Q \). \( C_2 \) was calculated by averaging systemic ICG concentrations obtained immediately before and at the end of each flow rate interval. The difference between \( C_1 \) and \( C_2 \) ranged from 6.5 to 19.8 mg/ml. The hematocrit, which was determined before and after each experiment, diminished during the period of extracorporeal circulation and blood sampling, but did not fall below 0.37. It was assumed to decrease linearly during the experiment.

The fraction of the ipsilateral ICA blood collected...
for extracorporeal circulation (f) increased linearly with blood flow to the pump (Fig. 2). The fractions collected at the same pump rates varied considerably in different animals. This phenomenon has been observed in humans (EH Oldfield, et al., in preparation), and may be the result of anatomic variations in the venous sinuses or differences in individual total brain blood flow. The fraction of the ipsilateral carotid blood collected ranged from 0.123 at the lower pump rates to 0.965 at the higher rates. No hysteresis was evident (Fig. 2). Fractions of ipsilateral carotid blood removed at 10 ml/min at the beginning and end of the second study are in close agreement (0.123 and 0.125, respectively).

Discussion

In spite of surgery, radiation therapy, and intravenous chemotherapy, the median survival time of patients with malignant gliomas is about 1 year after diagnosis, with an incremental survival attributable to chemotherapy of only 4 to 6 weeks. Attempts to increase the efficacy of chemotherapy include the clinical introduction of new agents, increased doses of drugs with proven activity, administration of drugs into the carotid artery ipsilateral to the tumor, intra-arterial delivery following disruption of the blood-brain barrier, or some combination of these alternatives.

Intracarotid artery administration of drugs with high total body clearance, such as BCNU, increases tumor exposure compared to the same dose delivered intravenously. However, intracarotid therapy has not yet been shown to significantly increase the median duration of survival. It may be possible to improve responses with the chemotherapeutic agents currently available if increased tumor exposures can be achieved by increasing the intracarotid dose. The dose-limiting factor for many of the agents currently in use is systemic toxicity. Therefore, systemic drug exposure must be decreased before increased doses can be safely used. One way of accomplishing this is to remove blood from the ipsilateral jugular bulb during intracarotid infusion of the chemotherapeutic agent and to circulate this blood through an extracorporeal circuit for drug removal before it returns to the systemic circulation. This allows dose escalation based on brain tissue tolerance rather than systemic toxicity. To safely begin dose escalation, it is necessary to quantify the fraction of carotid blood into which the drug is infused that can be channeled into an extracorporeal circuit for drug removal. This study demonstrates the use of ICG for this purpose in monkeys.

The difference between the concentration of ICG in the systemic circulation and at the pump inlet was relatively constant and not strongly affected by blood flow to the pump. This observation is consistent with removal from a relatively well mixed cerebral venous circulation.

Most of the blood containing ICG was removed by pumping it from the jugular bulb faster than the normal rate of unilateral internal jugular flow. This agrees with previous studies of BCNU removal from the jugular blood of monkeys during ICA infusion. Additionally, clinical studies in four patients demonstrated a 46% to 87% reduction in systemic exposure to BCNU when jugular blood was pumped through an external circuit containing an adsorption column at 300 ml/min (EH Oldfield, et al., in preparation).

The tolerable rate of aspiration of blood from the jugular bulb is unclear. The monkeys reported here and in our previous studies tolerated a removal rate of jugular blood as rapid as 60 ml/min, a rate approximating the total cerebral blood flow. In spite of these high rates of withdrawal, no neurological deficit occurred.

The results of this study suggest that during intracarotid chemotherapy the fraction of the infused blood that can be recovered from the ipsilateral jugular vein for potential drug removal is linearly related to the rate of blood removal from the jugular system until rates approaching total cerebral blood flow are reached. They also suggest that similar ICG measurement during patient treatment may prove to be a useful technique for estimating the fraction of carotid blood that can be pumped from the jugular bulb. Application of this technique to patients immediately before high-dose intracarotid chemotherapy combined with extracorporeal removal could be used for dose adjustment to guard against excessive systemic drug exposure and potential toxicity.

References

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