Reduced Systemic Drug Exposure by Combining Intraarterial cis-Diamminedichloroplatinum(II) with Hemodialysis of Regional Venous Drainage

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ABSTRACT

During cancer chemotherapy toxicity to normal tissues often limits the tolerable dose. To increase drug delivery to tumor while maintaining tolerable systemic exposure, regional treatments, such as intraarterial drug delivery, have been used. Despite intraarterial delivery, systemic toxicity often remains the dose-limiting sensitivity. If systemic drug exposure could be reduced after intraarterial infusion, the intraarterial dose could be increased, which should increase the therapeutic response. We compared the pharmacokinetic advantage after cisplatin infusion into the internal carotid artery to that obtained after infusing cisplatin into the internal carotid artery during extracorporeal removal of cisplatin from the jugular blood by hemodialysis.

Four patients with malignant gliomas received intracarotid cisplatin, 100 mg/m² over 60 min, every 4 weeks. During one treatment, while cisplatin was infused into the internal carotid artery, the jugular blood was dialyzed extracorporeally at 300 ml/min and returned to the inferior vena cava.

Seventy to 96% of the free platinum that entered the dialyzer was removed. By aspirating blood from the jugular vein at 300 ml/min, 30–79% of the ipsilateral carotid blood was collected for extracorporeal circulation. Hemodialysis of the cerebral venous drainage during intracarotid infusion reduced the systemic exposure to cisplatin by 51–61% when compared to the exposure from internal carotid artery infusion without hemodialysis. The pharmacokinetic advantage (brain/body exposure ratio) was increased from 3 to 5/1 during internal carotid artery infusion alone to as much as 15/1 during treatment combining intracarotid infusion with hemodialysis of the jugular blood.

Systemic toxicity now limits the dose of cisplatin that can be administered safely. Increased tumor exposure without increased systemic toxicity may be possible with the technique described and greater doses of cisplatin. Assuming no associated local toxicities, the results of the current study indicate that the dose of intracarotid cisplatin can be increased while maintaining tolerable systemic exposure.

INTRODUCTION

A basic tenet of cancer chemotherapy is that tumor response should increase with increased drug exposure. Extensive laboratory and clinical evidence supports this dictum. However, contemporary anticancer drugs have a narrow therapeutic index and toxicity to normal tissues frequently limits the amount of drug which can be safely administered in a single dose, the interval between treatments, and the cumulative dose. To increase drug delivery to tumor while maintaining tolerable systemic exposure, regional infusions, such as intrathecal, i.p., or intraarterial delivery, have been used.

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Glioblastoma multiforme, the most common primary brain tumor, causes morbidity and mortality by local growth. After treatment with surgery and radiation therapy 90% of malignant gliomas of the cerebral hemispheres regrow within 2 cm of the original tumor margin (1). Over 90% of malignant gliomas occur in the frontal, temporal, or parietal lobes and are perfused by blood from the internal carotid artery (2). The tendency for local growth and isolated blood supply suggest that many cerebral gliomas may be responsive to treatment by intraarterial infusion of suitable drugs. Preliminary results from several centers indicate that the rate of tumor response is increased after intracarotid infusion (3–6). Improved survival compared to the limited response which occurs with i.v. chemotherapy with currently available agents has not yet been demonstrated in a properly designed study.

Cisplatin has clinical activity against many human cancers (7). However, cisplatin causes severe nausea and vomiting, peripheral neuropathy, ototoxicity, myelosuppression, and renal toxicity, which often limit the tolerable dose (7–12). To increase delivery of cisplatin to tumor without increasing exposure to normal tissues, intraarterial administration has been used (3, 13–15). Initial clinical studies using intraarterial cisplatin have been reported to increase response rates in patients with melanomas, soft tissue sarcomas, colon carcinomas, and primary and secondary malignant tumors of the brain (3, 13–15). Despite increased drug delivery after intraarterial administration, systemic toxicity, not toxicity to the tissues containing the neoplasms, is often dose limiting (3).

We sought to diminish the systemic exposure to cisplatin after intracarotid infusion by removing the cisplatin from the blood after one pass through the brain, before the blood carrying a high concentration of cisplatin reached sensitive normal tissues. The molecular size of cisplatin is similar to that of creatinine, which suggested the hemodialysis would remove it from circulating whole blood. We compared the systemic exposure and toxicity after intracarotid infusion of cisplatin to those after intracarotid infusion during extracorporeal hemodialysis of the jugular blood in four patients with malignant gliomas.

MATERIALS AND METHODS

In Vitro Experiment. We initially established the capability of a dialyzer to remove cisplatin from circulating whole blood in vitro and compared the extraction of cisplatin to that of creatinine, a molecule of similar size. Heparin (10,000 units) was added to 1,000 ml of whole blood which was pumped at 300 ml/min through a circuit containing a hollow fiber dialyzer (CF-model 1500, Travenol, Chicago, IL) while cisplatin was infused at 1.03 mg/min into the dialyzer inflow line. Paired samples for measurement of plasma total and ultrafilterable platinum and creatinine were obtained at 2-min intervals from the blood entering and leaving the dialyzer.

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Subjects. Patients eligible for entry into the study had histologically confirmed malignant gliomas, an independent performance status, and normal function of the bone marrow (WBC > 3,500/mm³, platelets > 150,000/mm³) and kidneys (serum creatinine < 1.5 mg/dl, creatinine clearance > 60 ml/min). Four patients (15–59 years old; 3 males and 1 female) with regrowth of malignant cerebral gliomas after surgery and radiation therapy received internal carotid artery infusions of cisplatin. All subjects participated in the study after informed consent was obtained as required by a NIH institutional review board (Protocol 84N78).

Procedure. All patients were hospitalized for treatment. A central catheter was placed in the right atrium the evening before treatments. Aspirin, 300 mg, was given orally the evening before and at 7 a.m. the day of the procedure. The patients received dazepam, 5.0 mg i.v., and droperidol, 5.0 mg i.m. 60 min before beginning the procedure. Transfemoral catheterization of the internal carotid artery ipsilateral to the tumor was performed. Digital subtraction arteriography was performed to ensure that the tumor was perfused by the internal carotid artery and to evaluate the configuration of the carotid siphon and the symmetry of the transverse cerebral venous sinuses and the internal jugular veins.

Cisplatin, 100 mg/m², was dissolved in 900 ml 0.9% saline containing 200 units of heparin sulphate and infused through a 0.22-μm filter (3) into the internal carotid artery over 60 min with an infusion pump. The cisplatin dose was preceded by an i.v. bolus injection of 12.5 g of mannitol, and was followed by a 6-h i.v. infusion of mannitol at 10 g/h. Intravenous hydration with 5% dextrose in 0.45% saline was started 14 h before chemotherapy. It was infused at 165 ml/h until 2 h before the cisplatin infusion, when the rate was increased to 250 ml/h. The latter rate was maintained until 6 h following the cisplatin treatment. To control nausea and vomiting metoclopramide, 2 mg/kg, was given i.v. 30 min before infusing cisplatin then and every 2–3 h as needed. Patients received 2 to 4 treatments at intervals of 4 weeks.

During one of the treatments the jugular blood was channeled extracorporeally for cisplatin removal by hemodialysis. A 10-French thin-walled Teflon catheter with multiple large side holes was introduced transfemorally in the left groin and its tip was positioned in the bulb of the internal jugular vein ipsilateral to the tumor. Venous blood was aspirated at 300 ml/min and pumped through a hemodialysis circuit for cisplatin removal and then returned to the inferior vena cava through a catheter in the right femoral vein (Fig. 1). Aspiration began at 50 ml/min and was increased in increments of 50 ml/min at 1–3-min intervals. Cisplatin infusion began after the final rate of 300 ml/min was achieved. Hemodialysis was continued for 30 min after completion of the cisplatin infusion. The hemodialysis circuit contained two hollow fiber dialyzers (CF-model 1500; Travenol) connected in series. The dialysate flow rate was 590 ml/min. The blood lines and associated instrumentation are shown in Fig. 1.

During treatments the patients received 5000 units of heparin sulfate i.v. During treatments with hemodialysis, 1500 units/h were also infused into the inflow line of the dialyzers. In two patients, additional heparin was administered to maintain an activated clotting time of greater than 3 min. At the completion of the procedure the blood within the extracorporeal system was reinfused and protamine sulfate, 50 mg, was administered i.v.

During each patient's treatment with hemodialysis and one treatment without hemodialysis, blood samples were obtained from the right atrium at frequent intervals for platinum measurement. During the treatments with dialysis, samples were also obtained at frequent intervals during hemodialysis from the inflow and outflow lines of the dialyzers and from the effluent dialysate. Blood samples were collected in heparinized tubes and centrifuged at 1000 g for 10 min, after which the plasma was removed. Protein-free ultrafiltrates were prepared by centrifuging 2–3 ml of the remaining plasma in Centriflo CF50A membranes (Amicon Corp., Lexington, MA) at 1000 g for 20 min. Aliquots of each plasma specimen and its corresponding protein-free ultrafiltrate were stored at −20°C until the time of assay. Plasma and plasma ultrafiltrates were analyzed for platinum by flameless atomic absorption spectrophotometry, employing the same instrumentation and methodology as reported previously (16).

Complete blood counts, platelet counts, serum osmolality, prothrombin time, partial thromboplastin time, serum urea nitrogen, creatinine, and magnesium were obtained the day before the treatment, at 6, 24, and 48 h, and weekly for 4 weeks following each cisplatin infusion. Audiological and ophthalmological evaluations were performed before each treatment and 4–6 weeks after the last treatment.

Mathematical Methods. Drug exposures were calculated by determining the AUC² by the trapezoidal method with extrapolation to infinity using a terminal platinum half-life determined from the slope of the disappearance of cisplatin for each treatment. Since the active fraction of cisplatin is that drug which is not bound to plasma proteins (17, 18), calculations used the PtPUF concentration, unless stated.

As an internal check, we used two separate methods to calculate the fraction of PtPUF entering dialysis which was removed. The first method used the AUCs of PtPUF in blood from the hemodialysis inlet and outlet (AUCin – AUCout/AUCin). The second method used the difference in the means of PtPUF concentration which entered and left the dialyzers at 10–30 min ([mean PtPUF in – mean PtPUF out]/mean PtPUF in).

The brain/body exposure ratio for each patient during the combined treatment was also calculated using two different methods. The first method calculated brain exposure assuming an internal carotid artery blood flow of 300 ml/min (19) and the systemic exposure as described above. The second method calculated the ratio of brain/body exposure by the formula:

\[
\frac{AUC_{\text{brain}}}{AUC_{\text{body}}} = \frac{1 + EQ_a + Cl_{\text{in}}}{Q} - \frac{1 - fE}{Q}
\]

where \(E\) is the fraction of drug removed from the blood flowing through the dialyzers, \(Q\) is the internal carotid artery plasma flow rate (assumed to be 300 ml/min × (1 – hematocrit)), \(f\) is the fraction of blood into which the cisplatin is infused that is collected for extracorporeal circulation, \(Q_a\) is the plasma flow through the dialyzers from the rest of the body (i.e., plasma flowing through the hemodialysis circuit in addition to the internal carotid artery blood flow which received the cisplatin infusion) and \(Cl_{\text{in}}\) is the cisplatin clearance by the body (dose of cisplatin)/AUC PtPUF (20).

RESULTS

In Vitro. The single dialyzer removed 71% of the PtPUF and 67% of the creatinine from whole blood passing through it at 300 ml/min. Values for plasma PtPUF in the inflow to the dialyzer were 4.21–5.48 μg/ml, while those leaving the dialyzer were 1.14–1.68 μg/ml.

2 The abbreviations used are: AUC, area under the curve of concentration versus time; BCNU, 1,3-bis(2-chloroethyl)-1-nitrosourea; PtPUF, plasma ultrafilterable platinum.
**In Vivo.** In all patients the tumor was perfused by the internal carotid artery. The cerebral venous blood drained into the transverse sinuses and internal jugular veins symmetrically in three patients and totally to the side opposite the tumor in one patient, who had a hypoplastic ipsilateral transverse and sigmoid sinus (patient 3). In this latter patient blood for hemodialysis was diverted extracorporeally from the jugular vein contralateral to the infused internal carotid artery.

Hemodialysis of the jugular blood during internal carotid artery infusion reduced systemic PtPUF exposure, increased total body PtPUF clearance, increased the brain/body exposure ratio, and resulted in lower peak plasma PtPUF levels when compared to internal carotid artery infusion alone (Table 1). The combined treatment reduced systemic exposure to PtPUF by 51–61% (Fig. 2, Table 1). After completion of the cisplatin infusion, ultrafilterable platinum disappeared in a monoeXponential manner. The terminal plasma half-life for PtPUF was $31 \pm 3$ min after internal carotid artery infusion alone compared to $23 \pm 3$ min after the combined treatment. Peak systemic plasma PtPUF concentrations were reduced by 40–70% by hemodialysis. Intracarotid infusion combined with hemodialysis of the jugular venous drainage markedly increased brain exposure to PtPUF compared to the exposure of the remainder of the body (Table 2). After i.v. administration the brain and systemic exposures would be identical. Assuming internal carotid artery flow of 300 ml/min, the ratio of brain PtPUF exposure to systemic PtPUF exposure was increased from 3.2–4.7 to 1 following internal carotid artery infusion alone to 5.2–8.1 to 1 following the combined treatment. Calculations based on an independent pharmacokinetic analysis of AUCbrain/AUCbody during the combined treatment, using the previously cited formula (20), resulted in brain-to-systemic cisplatin exposure ratios of 4.6–14.7 to 1. Thus, the pharmacokinetic advantage, derived from the two different methods of calculation, is in general agreement.

Our calculations indicate that 0.30–0.79 of the internal carotid artery blood into which the drug was infused was collected for extracorporeal hemodialysis (Table 3). Calculations of the effectiveness of removal of free cisplatin by the two hollow fiber dialyzers in vivo by (a) material balance from dialysis using the AUCs of PtPUF entering and leaving the dialyzers and (b) from the mean concentrations of PtPUF entering and leaving the dialyzers at 10, 20, and 30 min demonstrate, with very close agreement, that hemodialysis removed 76–93% of the PtPUF entering the dialyzers (Table 3). The fraction of the administered dose which was removed by the dialyzers can be checked independently by comparing (a) the systemic AUC values from Table 1 with and without hemodialysis, (b) the amount of the injected dose which appears in the dialysate, (c) the mass balance of the dialysis inlet and outlet measurements with the injected dose, and (d) the concentration of protein-bound platinum at 180 min, since almost all the circulating cisplatin is irreversibly bound to plasma proteins by 120 min after comple-

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**Table 1** **Systemic pharmacokinetics of ultrafilterable platinum**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Infusiona</th>
<th>$t_1/2$ (min)</th>
<th>$C_{L\infty}$ (ml/min)</th>
<th>Peak Pt (µg/ml)</th>
<th>AUC body (µg min/ml)</th>
<th>Reduction AUC bodyb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>ica</td>
<td>33</td>
<td>427</td>
<td>3.25</td>
<td>274</td>
<td>52%</td>
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<tr>
<td></td>
<td>ica+</td>
<td>32</td>
<td>892</td>
<td>1.95</td>
<td>131</td>
<td>52%</td>
</tr>
<tr>
<td>Patient 2</td>
<td>ica</td>
<td>30</td>
<td>515</td>
<td>2.62</td>
<td>236</td>
<td>61%</td>
</tr>
<tr>
<td></td>
<td>ica+</td>
<td>20</td>
<td>1292</td>
<td>1.32</td>
<td>92</td>
<td>61%</td>
</tr>
<tr>
<td>Patient 3</td>
<td>ica</td>
<td>23</td>
<td>455</td>
<td>3.91</td>
<td>247</td>
<td>51%</td>
</tr>
<tr>
<td></td>
<td>ica+</td>
<td>18</td>
<td>948</td>
<td>2.18</td>
<td>122</td>
<td>51%</td>
</tr>
<tr>
<td>Patient 4</td>
<td>ica</td>
<td>38</td>
<td>602</td>
<td>3.44</td>
<td>210</td>
<td>58%</td>
</tr>
<tr>
<td></td>
<td>ica+</td>
<td>23</td>
<td>1409</td>
<td>1.04</td>
<td>88</td>
<td>58%</td>
</tr>
</tbody>
</table>

Mean ± SE

<table>
<thead>
<tr>
<th>Patient</th>
<th>Infusiona</th>
<th>$t_1/2$ (min)</th>
<th>$C_{L\infty}$ (ml/min)</th>
<th>Peak Pt (µg/ml)</th>
<th>AUC body (µg min/ml)</th>
<th>Reduction AUC bodyb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>ica</td>
<td>31 ± 3</td>
<td>499 ± 39</td>
<td>3.31 ± 0.27</td>
<td>242 ± 13</td>
<td>55.5 ± 2.4%</td>
</tr>
<tr>
<td></td>
<td>ica+</td>
<td>23 ± 3</td>
<td>1135 ± 127</td>
<td>1.62 ± 0.27</td>
<td>108 ± 11</td>
<td>55.5 ± 2.4%</td>
</tr>
</tbody>
</table>

a icA, internal carotid artery.

b $t_{1/2}$, terminal plasma half-life of ultrafilterable platinum from systemic circulation.

c $C_{L\infty}$, clearance rate of ultrafilterable platinum from systemic circulation.

d AUC of ultrafilterable platinum in systemic circulation.

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**Fig. 2.** Plasma concentrations of ultrafilterable platinum in four patients during the two types of treatment. Systemic PtPUF concentrations after beginning intracarotid cisplatin infusion during treatments in which intracarotid infusion was combined with extracorporeal hemodialysis of the jugular blood (O) are compared with levels during intracarotid delivery of the same dose without hemodialysis ( ). The systemic exposure, the AUC, was reduced 51–61% by the combined treatment.
treatment in which hemodialysis was combined with intracarotid infusion. One patient developed maculopathy, central scotoma, and reduction in visual acuity in the eye ipsilateral to the side of the infusions after the third cisplatin infusion. One patient, who had a large tumor in the temporal lobe, developed diminished level of consciousness and a dilated pupil ipsilateral to the tumor 6 h following internal carotid artery infusion combined with hemodialysis. The deficit reversed with a single dose of i.v. mannitol. There was no change in the level of circulating platelets, WBCs, hematocrit or hemoglobin, blood urea nitrogen, serum creatine, or creatinine clearance following the treatments.

**DISCUSSION**

Pharmacokinetic analyses have established that, if the perfused region does not eliminate a significant amount of drug, the pharmacokinetic advantage, $R_A$, of intraarterial infusion compared to i.v. administration is a function only of the total body clearance, $C_{lb}$, of the drug infused and the blood (or plasma) flow perfusing the region of interest, $Q$ [i.e., $R_A = 1 + C_{lb}/Q$ (21–23)]. Thus, for a specific artery the pharmacokinetic advantage of intraarterial delivery can be increased by selection of a drug with a high $C_{lb}$ or by the application of techniques which increase $C_{lb}$ of a drug being used. The $C_{lb}$ can be increased by removing drug from circulating blood. Since during intraarterial infusion, drug for potential removal is most concentrated after a single passage through the tissue harboring the tumor, drug removal from the venous drainage of the infused region should be more efficient. Analysis of the pharmacokinetics of drug removal from the venous blood draining the infused region during intraarterial infusion demonstrates that the pharmacokinetic advantage of this technique is a function of (a) the effectiveness of drug extraction by the removal process and (b) the fraction of the blood that receives the infusate which can be collected from drug removal (20).

We previously demonstrated in rhesus monkeys that brain exposure 18–87-fold greater than systemic exposure could be achieved by combining intracarotid carmustine (BCNU) infusion with drug removal from the ipsilateral jugular blood by extracorporeal hemoperfusion (24). Subsequently, in patients with malignant gliomas a pharmacokinetic advantage (brain/body exposure ratio) of 21–55 to 1 was obtained when BCNU was infused into the internal carotid artery while blood from the jugular vein was pumped extracorporeally through a hemoperfusion cartridge for BCNU removal (25). However, focal brain toxicity curtailed our plans to increase the dose of intracarotid BCNU in patients.

Cisplatin has several characteristics that make it attractive for use in a similar manner. Cisplatin reacts with and inhibits the replication of cellular DNA by interstrand cross-linking of adjacent guanine bases (26), and since it is a cell cycle-nonspecific agent, it is suitable for intraarterial delivery. It has been demonstrated to have clinical activity both as a single agent and in combination with other drugs and has radically changed the prognosis of some malignant tumors (10). It is cleared from the plasma rapidly by irreversible binding to plasma and tissue proteins and by renal excretion (18, 27, 28). It is a potent antineoplastic agent, with steep dose-response relationships against many solid tumors *in vitro* (29, 30) and *in vivo* (9–11). In addition, it penetrates the normal blood-brain barrier slowly (31), which allows greater delivery to tumor than to the surrounding normal brain (32).

A dose-response relationship *in vivo* with cisplatin has re-

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**Table 2 Pharmacokinetic advantage of intracarotid cisplatin with and without hemodialysis of jugular blood**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Mean</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>± SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose removed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reduction $AUC_{body}$</td>
<td>Percent</td>
<td>52</td>
<td>61</td>
<td>51</td>
<td>58</td>
<td>56 ± 2</td>
</tr>
<tr>
<td>$AUC_{dialyzer}$</td>
<td>Percent</td>
<td>60</td>
<td>68</td>
<td>65</td>
<td>75</td>
<td>67 ± 3</td>
</tr>
<tr>
<td>Dialyzer ($AUC_{dialyzer} / AUC_{body} – 1$)</td>
<td>Percent</td>
<td>47</td>
<td>41</td>
<td>37</td>
<td>83</td>
<td>47 ± 6</td>
</tr>
<tr>
<td>Protein-bound Pt at 180 min with and without hemodialysis</td>
<td>Percent</td>
<td>38</td>
<td>57</td>
<td>81</td>
<td>78</td>
<td>63 ± 20</td>
</tr>
</tbody>
</table>

**Table 3 Pharmacokinetics of hemodialysis circuit**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Units</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fraction of carotid flow channeled into dialyzers</td>
<td>0.30</td>
<td>0.47</td>
<td>0.32</td>
<td>0.79</td>
<td></td>
</tr>
<tr>
<td>Plasma flow to dialyzers contributed by infused carotid</td>
<td>ml/min</td>
<td>63</td>
<td>93</td>
<td>57</td>
<td>158</td>
</tr>
<tr>
<td>Plasma flow to dialyzers from systemic circulation</td>
<td>ml/min</td>
<td>149</td>
<td>106</td>
<td>124</td>
<td>42</td>
</tr>
<tr>
<td>$AUC_{PptuF}$ into dialyzers</td>
<td>µg-min/ml</td>
<td>139</td>
<td>211</td>
<td>179</td>
<td>311</td>
</tr>
<tr>
<td>$AUC_{PptuF}$ leaving dialyzers</td>
<td>µg-min/ml</td>
<td>33</td>
<td>18</td>
<td>28</td>
<td>30</td>
</tr>
<tr>
<td>Fraction of $PptuF$ entering dialyzers which was removed</td>
<td>0.76</td>
<td>0.91</td>
<td>0.84</td>
<td>0.90</td>
<td></td>
</tr>
<tr>
<td>$AUC_{body}$/AUC$_{dialyzer}$</td>
<td>0.78</td>
<td>0.92</td>
<td>0.87</td>
<td>0.93</td>
<td></td>
</tr>
<tr>
<td>Concentration in – concentration out at 10–30 min</td>
<td>0.78</td>
<td>0.91</td>
<td>0.84</td>
<td>0.90</td>
<td></td>
</tr>
</tbody>
</table>

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Fig. 3. Concentrations of total, protein-bound, and filterable platinum in the peripheral plasma of patient 4 during treatment with intracarotid cisplatin alone (A) and with intracarotid cisplatin during extracorporeal hemodialysis of the jugular blood (B). By 180 min after the cisplatin infusion almost all the free platinum ($P_{ptuF}$) had disappeared.

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cently been evaluated in patients, and there is evidence that higher doses are more effective (9–11). The duration of response and survival in patients with bronchogenic lung cancer were prolonged approximately 2-fold with 120 mg/m² compared to 60 mg/m² (9). After combination chemotherapy which included high-dose cisplatin at 200 mg/m² a complete response was reported in 15 of 17 patients with previously untreated, nonsemionomatous testicular cancer which had produced advanced bulky lung and abdominal disease (10). Partial responses occurred in three of six patients whose tumor had been resistant to conventional doses of cisplatin (10).

Although the therapeutic response to cisplatin is enhanced by increasing the dose, the incidence and severity of attendant toxicities, such as ototoxicity, vomiting, and peripheral neuropathy are increased (9–11). Early clinical trials with cisplatin demonstrated nephrotoxicity to be the dose-limiting toxicity. Renal damage, due to tubular necrosis of the proximal and distal convoluted tubules, was dose related, occasionally irreversible (8), and occurred in as many as 1/4 to 1/3 of patients treated with 50–75 mg/m² of cisplatin. Although this complication is now greatly reduced by intensive hydration with saline solutions, cumulative nephrotoxicity still results from repeated exposure to cisplatin and many physicians do not exceed a total cisplatin dose of 600 mg/m², even if a therapeutic gain may be expected with continued treatment (33). Although saline-induced diuresis mitigates the nephrotoxicity of cisplatin, other drug toxicities become dose limiting. Nausea and vomiting are almost universal, begin within 1–2 h after administration, and last 24–48 h, despite the use of metoclopramide. Neurotoxicity, which includes high frequency hearing loss, polyneuropathy, and retinopathy, seems to be dose related and cumulative (9–12). Myelosuppression is severe in patients who receive 200 mg/m² of cisplatin a single course of treatment (10, 11).

If systemic toxicity could be reduced by decreasing the systemic exposure after internal carotid artery infusion, the intracarotid dose could be increased until the exposure causing a dose-limiting toxicity is reached. Before administering doses with potentially lethal systemic complications, the pharmacokinetics of the combination of intracarotid infusion and the drug extraction technique had to be determined, which was the purpose of this study.

The level of total platinum in the serum does not accurately reflect the level of active drug present. The irreversible binding of the drug to protein retains a considerable amount of drug in the plasma compartment as an inactive protein-platinum complex (18, 27, 28) (Fig. 3). Only the free-circulating platinum species (which include intact cisplatin) appear to have cytotoxicity (17, 18). Flameless atomic absorption spectrophotometry and centrifugal ultrafiltration procedures permit measurements of the free (filterable) drug and protein-bound (nonfilterable) fractions (16–18). In the current study by 180 min after beginning the infusion almost all of the circulating platinum was in fractions (16–18). In the current study by 180 min after beginning the infusion almost all of the circulating platinum was in the protein-bound, inactive form (Fig. 3). The rate constant for the biotransformation of cisplatin to fixed metabolite in plasma, determined by dividing the bound platinum concentration at 180 min by the area under the filterable platinum curve, was 0.0082 ± 0.0009 min⁻¹ (mean ± 1 SE). It has also been determined from in vitro incubation studies to be 0.0074 min⁻¹ (34, 35).

Plasma disappearance of ultrafilterable platinum after treatments with and without hemodialysis is well described by a single exponential. The terminal plasma half-life during the treatments without hemodialysis, 31 ± 3 min (mean ± SE), was in accordance with those previously reported for cisplatin fol-

lowing a bolus i.v., infusion (18, 27, 28, 36). The t₁/₂ value was 23 ± 3 min following the combined treatment. The C₁₀, 499 ± 39 ml/min, of P₅₅₆ was increased to 1135 ± 127 ml/min by the combined treatment. Of the filterable platinum which entered the dialyzer, 76–93% was removed. Otoxicity was not observed after the combined treatments. Retinopathy should be prevented by using current techniques to place the catheter tip distal to the origin of the opthalmic artery (25, 37).

By channeling the blood extracorporeally for cisplatin removal the body's exposure to free platinum was reduced by 51–61%. This suggests that, if cerebral toxicity is not dose limiting, a 2–3-fold increase in dose would have been possible while maintaining systemic exposures at the levels occurring after internal carotid artery infusion alone. Such a dose increase would expose intracerebral tumors to about 10 times the exposure achieved by i.v. injection of the current dose.

The pharmacokinetic advantage obtained in the patients treated in this study can be further increased by increasing the rate of aspiration of blood from the jugular bulb for extracorporeal circulation, if the effectiveness of drug removal by hemodialysis can be preserved at higher rates. This is feasible because the walls of the jugular bulb are fixed to the surrounding bone and fibrous dural attachments, which should permit aspiration of blood at high rates without collapsing on the catheter tip. The fraction of the internal carotid artery blood flow which is collected for extracorporal circulation in rhesus monkeys is linearly related to the rate at which the blood is pumped from the jugular bulb (38). At higher rates of aspiration almost all of the indocyanine green which is injected into the internal carotid artery can be channeled extracorporeally. In the current study 30–79% of the blood flowing in the ipsilateral internal carotid artery was collected for extracorporal circulation. These results, and those of our previous studies (24, 25, 38), suggest that the midline, freely communicating sinuses of the intracranial venous system permit diversion of most of the cerebral venous drainage to one side and enable extracorporeal circulation of most of a drug infused unilaterally by aspiration from a single jugular bulb.

We have described hemodialysis of the jugular drainage during intracarotid infusion of chemotherapy. This technique and the related pharmacokinetic principles can also be applied to other drugs and other organs, either for tumor therapy or for other diseases in which the pharmacological dose is limited to one which is ineffective because of systemic toxicity and in which arterial drug delivery and collection of venous blood for drug removal can be performed.

We have now treated three patients with doses of intracarotid cisplatin of 200 mg/m² infused over 60 min during hemodialysis of the jugular blood. Although no systemic toxicity occurred, two patients suffered focal brain toxicity with irreversible hemiplegia and all had ipsilateral retinal damage and blindness. Dose escalation of intracarotid cisplatin using the technique described should be done cautiously.

REFERENCES

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INTRAARTERIAL CISPLATIN WITH VENOUS HEMODIALYSIS


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