Pharmacokinetics of Intra-arterially Administered Pirarubicin in Plasma and Cerebrospinal Fluid of Patients with Glioma

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The present paper investigates the pharmacokinetics of pirarubicin (THP) in the plasma and cerebrospinal fluid (CSF) of two patients with glioma during hyperosmotic disruption of the blood-brain barrier (HODBHB) and intra-arterial combination chemotherapy.

A 42-year-old Japanese man (patient A) with glioblastoma and a 21-year-old Japanese woman (patient B) with astrocytoma received a course of HODBHB and intra-arterial combination chemotherapy with THP, methotrexate, peplomycin, and vindesine. Patient A was initially administered mannitol, followed by the infusion of anticancer drugs into the right internal carotid artery. Patient B was initially administered mannitol, followed by the infusion of anticancer drugs into the right internal carotid artery and, immediately thereafter, into the right vertebral artery. Samples of blood and of CSF in the brain ventricle were obtained. THP concentration was measured by HPLC, and the pharmacokinetic parameters of this drug were estimated in plasma and CSF.

In both patients, the plasma concentration of THP peaked at the end of infusion, then decreased in a bi-exponential decay pattern during the remainder of the treatment period. THP was detectable in CSF beginning 1.0 h after the initiation of infusion, then was slowly eliminated from the ventricle. The maximum CSF concentration of THP was 0.97% of plasma in patient A and 0.89% in patient B. The CSF AUC of THP was 28.4% of plasma in patient A and 13.1% in patient B.

Key words pirarubicin; pharmacokinetics; cerebrospinal fluid; hyperosmotic disruption; intra-arterial combination chemotherapy

Anthracyclines are useful in the treatment of patients with solid tumors, lymphomas, and acute lymphoblastic as well as myelocytic leukemias. Pirarubicin (THP) is a recently developed anthracycline antibiotic with less cardiac toxicity, but comparable efficacy, to that of doxorubicin (DOX). Anthracyclines are usefully administered by the intra-arterial route. The injection of THP into the hepatic artery exhibits a selective and higher uptake into the tumor, accompanied by lower effusion into the plasma than observed with the intravenous injection of the drug. A patient with a glioblastoma who received a combination of cisplatin and THP was reported to show a marked reduction in tumor size on CT examination.

The blood-brain barrier (BBB) can impair the delivery of chemotherapeutic agents, even in the presence of a high systemic blood concentration of drugs. The hyperosmotic disruption of the blood-brain barrier (HODBHB) and the intra-arterial administration of cisplatin and other chemotherapeutic agents has been conducted for patients with brain tumors in an attempt to increase the delivery of drugs to the tumor and surrounding brain tissue.

We selected THP as an anticancer drug for use in HODBHB and intra-arterial combination chemotherapy in patients with glioma. The pharmacokinetics of this and other intra-arterially administered chemotherapeutic agents in the brain ventricles have not been investigated in detail. To clarify the pharmacokinetics of THP, we measured its concentration in plasma and in the cerebrospinal fluid (CSF) of the brain ventricle using an Ommaya’s reservoir in two patients with glioma, following HODBHB and intra-arterial combination chemotherapy.

CASE REPORTS

A 42-year-old Japanese man (53 kg) with glioblastoma (patient A) and a 21-year-old Japanese woman (67 kg) with astrocytoma (patient B), were previously treated by surgical removal of almost the entire tumor and subsequent radiation therapy. They were then administered a course of HODBHB and intra-arterial combination chemotherapy with THP (Therarubicin™, Meiji Seika Kaisha, Tokyo, Japan), peplomycin (Peplo™, Nippon Kayaku, Tokyo, Japan), vindesine (Fiúdesin™, Shionogi, Osaka, Japan), and methotrexate (Methorexate™, Lederle, Tokyo, Japan) after written informed consent was obtained. The anticancer drugs were diluted in distilled water for injection. Patient A received 50 ml of 20% mannitol for 10 min, and was then administered infusions of 70 mg of THP for 30 min, 30 mg of peplomycin for 30 min, 5 mg of vindesine for 30 min, 500 mg of methotrexate for 40 min, and 125 mg of methylprednisolone (Soludrofiltrum™, Upjohn, Tokyo, Japan) for 10 min into the right internal carotid artery. Patient B received 30 ml of 20% mannitol for 5 min, followed by infusions of 40 mg of THP for 15 min, 150 mg of methotrexate for 15 min, 15 mg of peplomycin for 15 min, 2 mg of vindesine for 15 min, and 65 mg of methylprednisolone for 5 min into the right internal carotid artery, followed by the same course of infusion into the right vertebral artery. With each course of treatment, both patients received 15 mg of folic acid (leucovorin: Leucovorin™, Lederle, Tokyo, Japan) orally or intravenously every 6 h for six treatments, beginning 6 h after the administration of methotrexate. MRI examination showed a partial response in both patients, for 4 months in patient A and for 6 months in patient B. No complications were observed during treatment.

MATERIALS AND METHODS

Chemicals THP and daunomycin were kindly supplied

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by Meiji Seika Kaisha, Ltd. (Tokyo, Japan). Methanol and acetonitrile were of HPLC grade. All other chemicals were of analytical grade.

**Sampling** In both patients, an Ommaya's reservoir was inserted into the lateral ventricle to sample the CSF. Samples of plasma and CSF were obtained before treatment and again at 0.5, 1, 1.5, 2, 6, 8, and 24 h after the initiation of treatment in patient A, and before treatment and again at 0.5, 1, 1.5, 2, 4, 8, and 24 h after the initiation of treatment in patient B. Blood samples were drawn into heparinized tubes, centrifuged, and stored at −40°C. CSF samples were frozen immediately and stored at −40°C. Plasma and CSF samples were assayed within 1 week.

**Measurement of THP Concentration** Concentrations of THP in plasma and CSF were measured by the HPLC assay method described by Matsushita et al. and by Ogasawara et al. Briefly, 1.0 ml of plasma or CSF was mixed with 100 ng of daunomycin as an internal standard, and also mixed separately with 0.1 ml of 100 mM NH₄Cl–NH₄OH buffer, pH 9.0, then extracted three times with 2 ml of ethyl acetate and 1-propanol (v/v 9:1) mixture. Following vigorous mixing and centrifugation at 3000 rpm for 10 min, the organic phases were pooled and the solvents were evaporated. The residue was dissolved in 250 µl of methanol, and then 50 µl was injected for HPLC. Quantitative analysis of THP and daunomycin was performed in a liquid chromatograph system (Waters Corp., MA, U.S.A.) consisting of a model 600 E pump, a model 717 plus autosampler, a model 474 variable fluorescence detector, and a model 805 data station. A reversed-phase μ BONDASURF phenyl column (150×3.9 mm i.d.; Waters Corp., MA, U.S.A.) was used for separation of the drugs. The column was eluted with an isocratic mixture of 0.1 M ammonium formate (pH 4.0) and acetonitrile (v/v 7:3) at a flow rate of 1 ml/min. The eluants were monitored for fluorescence at wavelengths of 482 nm for excitation and 550 nm for emission. The lower limit for THP detection was 0.25 ng/ml. Standard curves were linear between 0.25 and 1000 ng/ml. The within- and between-day coefficients of variation were less than 5%.

**Pharmacokinetic Analysis** The pharmacokinetic parameters of THP in plasma were estimated using a modified microcomputer program (MULTI) with a microcomputer, model NEC PC-9801, and a two-compartment model. Values for the area under the time–concentration curve from 0 to 24 h (AUC₀–₂₄) for THP were calculated by the trapezoidal rule.

**RESULTS**

The plasma and CSF concentrations of THP in patients A and B are shown in Figs. 1a and b, respectively. In each patient, the plasma concentration of THP peaked at the end of the infusion of THP, then decreased in a bi-exponential decay pattern during the remainder of the treatment period. The half-lives of THP in the first ($t_{1/2α}$) and second ($t_{1/2β}$) decay phases in plasma according to the two-compartment model and other pharmacokinetic parameters in patients A and B are shown in Table 1.

In patient A, analysis of CSF in the ventricle showed that THP was detectable beginning at 1.0 h after the initiation of infusion. Levels of THP in CSF increased slowly and peaked 24 h after the initiation of infusion. In patient B, THP was detectable in CSF beginning at 0.5 h after the initiation of infusion. CSF levels of THP peaked 0.5 h after the end of the second infusion, then decreased slowly. The half-lives of THP in CSF could not be estimated.

The maximum CSF concentration of THP was 0.97% of plasma in patient A and 0.89% in patient B. The CSF AUC of THP was 28.4% of plasma in patient A and 13.1% in patient B.

![Fig. 1. Plasma and CSF Concentrations of THP after HODBBB and Intra-arterial Combination Chemotherapy in Patients A and B](image)

**Table 1. Maximum Concentrations and Pharmacokinetic Parameters of THP in Plasma and CSF after HODBBB and Intra-arterial Combination Chemotherapy**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Dose (mg)</th>
<th>Infusion time (min)</th>
<th>Cₚ max (ng/ml)</th>
<th>Cₕ max (ng/ml)</th>
<th>AUCₚ₀–₂₄ (ng · h/ml)</th>
<th>AUCₕ₀–₂₄ (ng · h/ml)</th>
<th>$t_{1/2α}$ (h)</th>
<th>$t_{1/2β}$ (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>70</td>
<td>30</td>
<td>483.5</td>
<td>4.67</td>
<td>360.1</td>
<td>102.1</td>
<td>0.105</td>
<td>14.89</td>
</tr>
<tr>
<td>B</td>
<td>80 (40×2)</td>
<td>30 (15×2)</td>
<td>449.8</td>
<td>4.00</td>
<td>450.8</td>
<td>59.1</td>
<td>0.141</td>
<td>10.98</td>
</tr>
</tbody>
</table>

Cₚ max: maximal plasma concentration of THP; Cₕ max: maximal CSF concentration of THP; AUCₚ₀–₂₄: area under the concentration-time curve of plasma from 0 to 24 h; AUCₕ₀–₂₄: area under the concentration-time curve of CSF from 0 to 24 h; $t_{1/2α}$: half-life of THP in plasma of first-phase decay (= $\ln 2/α$); $t_{1/2β}$: half-life of THP in plasma of second-phase decay (= $\ln 2/β$).
DISCUSSION

Anticancer drugs are administered intra-arterially to patients with brain tumors in an attempt to increase the tumor concentration of the drug. Pharmacological studies in normal and tumor-bearing rats and dogs and the extrapolation of clinical data have shown that modification of the BBB increases drug concentrations in the tumor and in those portions of the brain supplied by the infused artery. HODBBB therapy is often used to increase the concentration of anticancer drugs in brain tumors. Clinically, Seike et al. reported that in a patient with glioblastoma treated with a combination of cisplatin and THP, the tumor size decreased more than 80%, as judged by CT examination. Therefore, we selected THP as an anticancer drug for HODBBB and intra-arterial combination chemotherapy in two patients with glioma. In the present cases, we also found THP to be useful in treating glioma.

Several pharmacokinetic studies in humans have shown that THP elimination can be fitted to a three-compartment model. However, due to the very short initial half-life of THP, its plasma decay can sometimes be fitted instead to a two-compartment model. In the present study, we estimated the pharmacokinetic parameters of THP in plasma using a two-compartment model, taking into consideration the sampling points. Our present findings agree with the published values for the plasma half-lives of THP administered intravenously.

The BBB impairs the delivery of anticancer drugs to the brain, even in the presence of a high systemic blood concentration of drugs. However, we previously reported that THP penetrated the BBB after HODBBB and intra-arterial combination chemotherapy. In the present cases, the CSF concentration of THP in the ventricle was substantially lower (>5 ng/ml) than the maximum plasma concentration of THP (<400 ng/ml), but the maximum CSF concentration of THP was higher than the concentration of THP required to inhibit 50% of the growth of cultured L1210 cells (3 ng/ml). The CSF AUC of THP was 28.4% of plasma in patient A and 13.1% in patient B. The primary reason for the high AUC of CSF is assumed to be a longer half-life of THP in the ventricle than in plasma. However, the half-life of THP in the ventricle could not be estimated in the present study because THP in the ventricle was maintained at 24 h. Further studies of the CSF concentration of THP over a longer time are needed.

The present findings suggest that THP administered intra-arterially may be effective in treating glioma, since both of our patients achieved a partial response. HODBBB and intra-arterial administration of combination chemotherapy with THP may represent a useful approach to treating glioma. Further studies of the synergistic effect of combined anticancer drugs during HODBBB and intra-arterial administration of combination chemotherapy are required.

REFERENCES