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Pharmacokinetic Study of Cerebrospinal Fluid Penetration of cis-Diamminedichloroplatinum (II)

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Summary. *The ability of cis-DDP and several analogs to enter the CSF was investigated in rhesus monkeys that had subcutaneoulsy implanted Ommaya reservoirs connected to catheters in each monkey's fourth ventricle. Plasma and CSF samples were analyzed for platinum content by atomic absorption spectroscopy. Plasma platinum curves were biphasic with a very slowly declining terminal phase. CSF platinum curves rose to maximum concentrations 30–40 min after an IV bolus injection and declined mono-exponentially ($T_{1/2}$ = 60 min) without displaying a detectable slow terminal phase. cis-DDP given as an IV bolus of 1.5 mg/kg or 3.0 mg/kg produced peak CSF concentrations of 0.35 and 0.78 μM platinum. The ratio of CSF platinum:plasma platinum never exceeded 0.04. When cis-DDP at 3.0 mg/kg was given as a 2- or 7-h infusion, the peak CSF concentrations were 0.28 and 0.17 μM platinum, respectively. The total CSF exposure, measured as concentration × time, was the same for bolus and for 2- and 7-h infusions. Studies with analogs showed that neither malonato 1,2-diaminocyclohexane platinum (II) nor 4-carboxyphthalato 1,2-diaminocyclohexane platinum (II) had better CSF penetrance than cis-DDP. Sulfato 1,2-diaminocyclohexane platinum (II) could not be detected in the CSF. The ratio of CSF platinum:plasma platinum was never greater than 0.02–0.03 for any of the analogs.*

Introduction

A considerable body of information has developed on the biochemistry, metabolism, distribution and toxicity of the antineoplastic agent cis-diamminedichloroplatinum (II) (cis-DDP). The preclinical animal data revealed multiple toxicities, including renal and hematopoetic effects, but did not reveal evidence of neurotoxicity [4, 11]. The lack of CNS toxicity in animals correlated well with early reports of low levels of platinum in brain tissue samples after cis-DDP treatment [5, 7]. However, with increasing clinical experience, DDP-induced peripheral neuropathy has become a well-described entity [3] and there have been reports of possible cis-DDP related seizures [12]. In addition, there is animal model evidence that cis-DDP may interact synergistically with radiation in the treatment of brain tumors [2]. Because of these observations, the present studies were undertaken in an attempt at better definition of the entry of cis-DDP into the CSF.

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Methods

Animals. Adult male rhesus monkeys were obtained from the NIH primate center. Each animal was kept in a separate cage and fed Purina Monkey Chow and water. Monkey weights ranged between 3 and 8 kg.

Sampling. CSF sampling and intraventricular drug injection was performed in a previously described subhuman primate model, in which a silicone Pudenz catheter was surgically placed through the foramen of Magendie into the fourth ventricle and attached to an Ommaya CSF reservoir subcutaneously implanted in the occipital region [13]. This animal model permits repetitive sterile access to ventricular CSF fluid over extended periods and under physiological conditions without compromise of the blood-brain barrier [13, 14]. All samplings were performed on conscious monkeys sitting in primate chairs. Prior to each sampling, the Ommaya reservoir was pumped four times to mix reservoir and ventricular fluid thoroughly and 150–200 μl CSF was obtained for each sample. Blood samples were obtained from an IV catheter inserted prior to the start of the experiment. Studies utilized single animals except where noted.

Test Agents. All drugs were obtained from the Division of Cancer Treatment, NCI.

A) cis-Diamminedichloroplatinum (II), NSC # 119875, was obtained as sterile vials of 10 mg cis-DDP, 100 mg mannitol, and 90 mg NaCl. Prior to infusion, 10 ml sterile water was added to each vial; B) Malonato 1,2-diaminocyclohexane platinum (II), NSC # 224964; C) Sulfato 1,2-diaminocyclohexaneplatinum (II),

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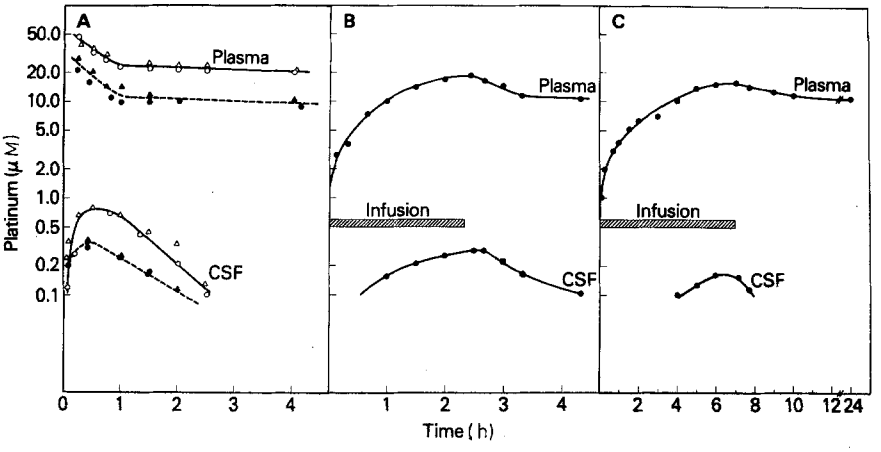

Fig. 1A–C. Plasma and CSF concentrations of platinum after **A** IV bolus injection of cis-DDP, 1.5 mg/kg (●, ▲) and 3.0 mg/kg (○, △) to rhesus monkeys. Two monkeys were studied, one designated by triangles the other by circles; **B** a 2.25-h IV infusion of cis-DDP at a rate of $1.3\ mg \cdot kg^{-1} \cdot h^{-1}$; **C** a 7-h IV infusion of cis-DDP at a rate of $0.43\ mg \cdot kg^{-1} \cdot h^{-1}$

NSC # 250427; D) 4-Carboxyphthalato 1,2-diaminocyclohexane-platinum (II), NSC # 271674.

All solutions except the cis-DDP were filtered through Millipore 0.22-μm filters prior to infusion.

Drug Analysis. The levels of platinum in monkey serum and CSF were determined by flameless atomic absorption spectroscopy [6]. Samples of serum or CSF were heated slowly to 2,700° C in a Perkin-Elmer HGA-2000 graphite furnace and the absorbance of the atomized platinum was measured at 265.7 nm against a deuterium reference beam. The maximum sample size that could be analyzed was 30 μl. The limit of sensitivity was 5×10^{-7} *M* in serum and 1×10^{-7} *M* in CSF. The improved sensitivity achieved in CSF was possible because of the low concentration of protein in the sample. Platinum absorbance values were interpreted by comparison with standard absorbance values obtained with hexachloroplatinic acid. This method directly measures elemental platinum.

Results

cis-DDP IV Bolus

Figure 1A shows the plasma and CSF concentrations of platinum achieved in two monkeys after injection of 1.5 mg cis-DDP/kg and 3.0 mg cis-DDP/kg. The plasma concentrations of platinum declined in a biphasic pattern, which could be fit with a bi-exponential function of the form $Ae^{-\gamma t} + Be^{-\beta t}$. The Marquardt-Sevenberg curve-fitting method was used to obtain values for γ and β: $\gamma = 2.71 \pm 1.14 \cdot h^{-1}$ and $\beta = 0.018 \pm 0.008 \cdot h^{-1}$. The platinum concentrations in the CSF were also fit to a bi-exponential expression, with the form $Ae^{-\beta t} - Be^{-\gamma t}$, and the values obtained were $\gamma = 6.5 \pm 2.5 \cdot h^{-1}$ and $\beta = 0.81 \pm 0.07 \cdot h^{-1}$. The corresponding terminal half-lives were: plasma, 38.5 h; and CSF, 51 min. Peak CSF platinum values were reached 20–40 min after the injection of the IV dose and, from the peak, the platinum concentration fell mono-exponentially. The platinum concentration achieved in the CSF was linearly related to dose, with a peak CSF value after the 1.5 mg/kg dose of 0.35 μ*M* and a peak after the 3.0 mg/kg dose of 0.78 μ*M*. The CSF:plasma ratio at the time of the peak CSF value was 0.02–0.03. By 2.5 h post-injection, CSF platinum concentration had fallen below the limit of detection.

cis-DDP IV Infusion

The plasma and CSF concentrations achieved with 2.25- and 7-h infusions are shown in Fig. 1B and C. Both infusions delivered a total dose of 3.0 mg cis-DDP/kg, providing infusion rates of 1.3 and $0.43\ mg \cdot kg^{-1} \cdot h^{-1}$. The CSF reached peak concentrations at, or just after, the end of the infusions. Peak CSF platinum values were never as high with infusions as with bolus administration: bolus, 0.78 μ*M*; 2-h infusion, 0.28 μ*M*; and 7-h infusion,

Table 1. Area under concentration × time curve for cis-DDP in CSF

Dose cis-DDP mg/kg (μmole/kg)	Mode of administration	Peak CSF concentration μ*M* platinum	CSF exposure C × T (m*M* · min)
1.5 (5.1)	Bolus	0.35	6.4
3.0 (10.2)	Bolus	0.78	13.6
3.0 (10.2)	2.25-h infusion	0.28	10.8
3.0 (10.2)	7-h infusion	0.17	13.0

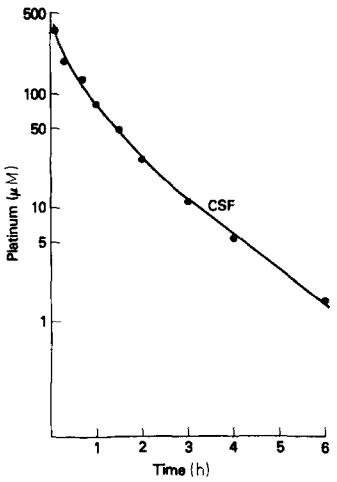

Fig. 2. Platinum concentrations found in CSF ventricular fluid after 0.5 mg cis-DDP was administered intraventricularly through an Ommaya reservoir

0.17 μ*M*. The CSF curves in Fig. 1 were transformed onto linear graph paper and then extrapolated to zero platinum to permit estimation of the area under the curves. The results are shown in Table 1. Although the peak CSF concentrations varied depending on the length of the infusion, the total exposure as measured by area under curve remained relatively constant.

cis-DDP Intraventricular Bolus

After cis-DDP (0.5 mg) was given intraventricularly, Fig. 2, the CSF platinum values were found to drop rapidly and biphasically: an initial phase ($T_{1/2}$ of 17 min) was associated with a volume of distribution of 5 ml, and the slower phase ($T_{1/2}$ of 60 min) was associated with a volume of 17–18 ml. The initial rapid half-life probably reflects distribution into total CSF, while the slower half-life probably reflects the actual clearance of platinum from the CSF. The maximum ventricular concentration was 450-fold higher than the maximum achieved with IV administration at 3.0 mg/kg. The monkey who received the intraventricular injection died suddenly 48 h after the injection.

cis-DDP Analogs

Several cis-DDP analogs were examined to ensure that the CSF findings with cis-DDP were reasonably representative of the entire class of platinum co-ordination compounds and not highly unique to the parent drug. The analogs were selected on the basis of potential clinical interest [10]. The three analogs were administered by IV bolus: malonato (3 mg/kg), sulfato (3 mg/kg), carboxyphthalato (5 mg/kg).

All three analogs showed the biphasic plasma decay curve typical of cis-DDP, with a rapid early phase and a prolonged terminal phase. None of the analogs achieved CSF concentrations greater than those achieved with cis-DDP. The malonato compound achieved CSF concentrations very similar to those recorded with cis-DDP, while the sulfato compound was undetectable in the CSF. The concentrations of the carboxyphthalato compound were measurable, but considerably lower than that achieved with cis-DDP. For all platinum compounds, entrance to the CSF was poor and the maximum ratio of CSF to plasma platinum was never greater than 0.04.

Discussion

After cis-DDP was administered intravenously to rhesus monkeys, platinum clearly entered the CSF. Not surprisingly, the platinum concentrations achieved in the CSF were much lower than the corresponding plasma concentrations; the CSF:plasma ratio never rose higher than 0.03–0.04. cis-DDP is poorly soluble in organic solvents and its low lipid solubility predicted poor entrance into the CNS [9]. After an IV bolus injection of cis-DDP, the platinum concentration in the CSF rose rapidly and then declined rapidly and mono-exponentially with a $T_{1/2}$ of 1 h. While the CSF platinum fell rapidly, the serum platinum concentration remained nearly constant with a $T_{1/2}$ of many hours.

These pharmacokinetic differences possibly reflect differences in the composition of serum and CSF. It has been shown that within a few hours of cis-DDP injection, nearly all the platinum found in the serum is bound to serum protein [1, 7]. Serum has high concentrations of protein while normal CSF has concentrations of protein 100-fold lower. Since CSF has little protein, protein-bound platinum is not present in a sufficient concentration to produce a detectable slow terminal phase. In addition, since protein-bound drugs cross into the CSF very poorly [4], the platinum that appears in the CSF represents penetration of only the free (non-protein-bound) platinum. Patton et al. have shown that in man non-protein-bound serum platinum declines with a terminal half-life of about 30–40 min [8], and therefore, free platinum (capable of entry into the CSF) is present in the serum for only a few hours after intravenous administration.

The dose of cis-DDP administered to the monkeys were set at the maximum nontoxic dose

(3 mg/kg) and did produce some renal toxicity. However, even at the maximal dose, the CSF platinum concentration achieved (0.1–1.0 μM) was probably too low to have appreciable cytotoxicity [15]. An alternative route of administration, the intraventricular route, led to cytotoxic concentrations of cis-DDP, but the subsequent death of the treated monkey suggests that unacceptable risks may be associated with intraventricular cis-DDP. These studies suggest that cis-DDP and many of its analogs are unlikely to be effective in the treatment of malignant disease sheltered by an intact blood-brain barrier.

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