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Pharmacokinetic Modeling of Cisplatin Disposition in Children and Adolescents with Cancer*

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Summary. *A flow-limited physiologic pharmacokinetic model using volume terms, flow rates, distribution ratios, metabolic rate constants, and clearance terms restricted to physiologic or measured values was used to simulate the disposition of cisplatin in children and adolescents. Physiologic model simulations of parent cisplatin and total platinum serum concentrations were not statistically different from concentrations of these platinum species measured in 14 patients. A simplified first-order multicompartment operational model was also developed, and produced comparable simulations of parent cisplatin disposition but less accurate simulations of total platinum serum concentrations. These data provide further clarification of cisplatin disposition in humans and provide the basis for previously observed changes in the renal clearance of total platinum.*

Introduction

cis-Diamminedichloroplatinum (CDDP, cisplatin) is an antineoplastic drug with established activity for several pediatric [11] and adult [12] malignancies. In a previous paper [5], we have described the serum disposition and renal clearance of total platinum in children receiving cisplatin. Serum concentrations of total platinum declined in a biphasic manner following a 6-h IV infusion, with $t_{1/2}\,\alpha$ and $t_{1/2}\,\beta$ of 0.42 ± 0.10 h and 44.4 ± 8.23 h, respectively. Renal clearance of total platinum changed during the 48-h interval following the IV dose, declining from 36.4 ± 12.8 ml/min/m^2 in the 0–3 h interval to a constant value of 2–4 ml/min/m^2 beginning 6 h after the dose. Using the ultrafiltration-atomic absorption spectrophotometric procedure of Bannister et al. [1] to measure serum concentrations of the parent drug (cisplatin) [8], we also observed that serum concentrations of this platinum species declined rapidly to undetectable levels, with a $t_{1/2}$ of 1.3 ± 0.4 h.

The purpose of this paper is to describe the development of two pharmacokinetic models (a physiologic flow-limited model and a first-order multicompartment operational model) that simulate the disposition of cisplatin in humans.

Methods

Physiologic Pharmacokinetic Model

Model Development. The flow-limited physiologic pharmacokinetic model of Bischoff and Dedrick [3], which has been modified to describe cisplatin disposition in dogs [8], served as the framework for model development. The basic model structure is shown in Fig. 1. Volumes, flow rates, distribution ratios, rate constants, and clearance terms were restricted to physiologic or measured values, and were derived as follows.

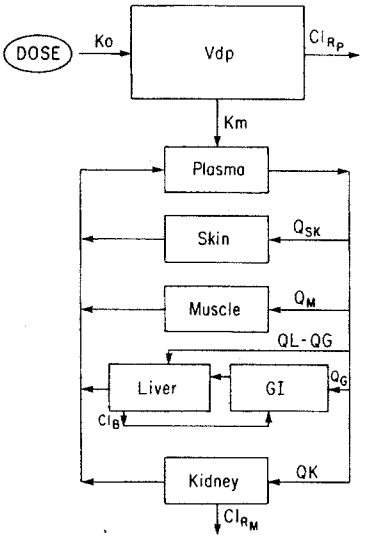

Fig. 1. Scheme of the modified physiologic flow-limited pharmacokinetic model for the simulation of *cis*-diamminedichloroplatinum disposition

Volume Terms. The volumes of serum, kidney, liver, gastrointestinal (GI) tract, and skin were scaled to patient weights according to the previously derived [2] equations shown in the *Appendix*. The volume of muscle was adjusted to patient weight throughout childhood and adolescence [9]. A value of 25% of body weight (kg) was used for patients 1–8 years of age, 33% for patients 9–15, and 40% for patients 16–20 years of age [9]. The volume of distribution for the parent compound (Vd_p) was calculated from the standard equation [13]:

$$Vd_p = \frac{K_0}{K_e} \cdot \frac{(1 - e^{-K_e t'})}{Cp_0},$$

where K_0 is the zero-order drug infusion rate, K_e is the measured elimination rate constant for parent platinum, t' is the duration of infusion, and Cp_0 is the parent platinum serum concentration at the end of the infusion. Clinical pharmaco-

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kinetic studies conducted to determine these parameters were described in an earlier paper [5]. Thus,

$$Vd_p = \frac{250\ \mu g/min/m^2}{0.009\ min^{-1}} \cdot \frac{(0.961)}{1.8\ \mu g/ml} = 14{,}833\ ml/m^2.$$

Flow Rates. Plasma flow to the various model compartments was scaled to patient weight or body surface area using the equations shown in *Appendix I*, which were derived from previously published data [2].

Tissue-Plasma Distribution Ratios. The tissue-plasma distribution ratios (R) of total platinum for all tissues except muscle were assumed to be the same as those previously reported by LeRoy et al. [8] from canine experiments. Since the data of LeRoy indicated that a muscle-plasma ratio of 0.7 overestimates muscle concentrations during and shortly after drug administration a smaller value of 0.4, calculated from published data [8], was used for our model.

Metabolic Rate Constants. The previously reported [8] first-order rate constant for nonenzymatic transformation of CDDP in aqueous media at 37° C (K_m = 0.006 min^{-1}) was used to describe the conversion of parent drug to the aquation products (metabolites).

Clearance Terms. The renal clearance of cisplatin metabolites (Clr_m) was calculated as previously described [5], using fractionated urine collections obtained from 3 to 48 h following the cisplatin dose. Renal clearance of total platinum during this time interval ranged from 1.0 to 6.2 ml/min/m^2 and was assumed to represent renal clearance of metabolites since free platinum (parent) serum concentrations were undetectable (< 5% of total platinum) after 3 h. A value of 4.0 ml/min/m^2 was used for model simulations.

Renal clearance of parent CDDP ($Clrp$) was calculated using the equation:

$$Clr_p = Vd_p \times Kr_p.$$

$Kr_p = Ke - Km$, where Kr_p equals the first-order renal elimination rate constant, Ke equals the first-order elimination rate constant calculated from the slope of free platinum serum concentrations[5] (0.0089 min^{-1}), and Km equals the first-order metabolic rate constant previously described (0.006 min^{-1}). Thus,

$$Kr_p = 0.0089 - 0.006 = 0.0029\ min^{-1}.$$

Calculating renal clearance of parent drug as $Clr_p = Vd_p \times Kr_p$, using the previously calculated Vd_p:

$$Clr_p = 14{,}833\ ml/m^2 \times 0.0029\ min^{-1} = 43\ ml/min/m^2.$$

Biliary clearance (Cl_{bm}) for cisplatin metabolites was assumed to be 0.0035 ml/min/kg, as previously calculated by LeRoy et al. [8] in canine experiments. Complete GI reabsorption of platinum was assumed, since previous studies have documented biliary excretion and the presence of platinum in the upper part of the intestine [4, 13] but have failed to detect platinum in fecal samples [14].

Mathematical Equations for Model Simulations. A set of differential equations (*Appendix*) describing the mass-balance of each model compartment was used to simulate the concentration of drug in each compartment as a function of time. These differential equations were simultaneously solved by a numerical method using the Runge-Kutta [10] algorithm.

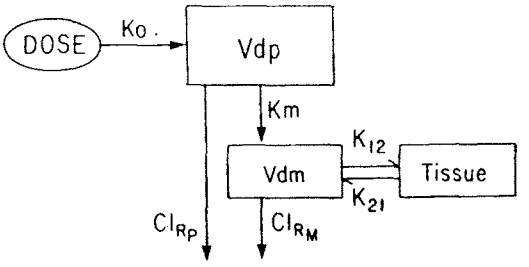

Fig. 2. Scheme of first-order multicompartment operational model for the simulation of *cis*-diamminedichloroplatinum disposition

Multicompartment Operational Model. Since the physiologic model contains several tissue compartments which cannot be readily assessed from clinical samples, a simplified first-order multicompartment pharmacokinetic model was designed to simulate cisplatin disposition. The model, shown in Fig. 2, combines all tissues into one compartment and utilizes intercompartment distribution rate constants (K_{12}, K_{21}) derived from previously reported data [6] by subtracting the concentrations of parent drug at early time points and fitting the resulting curve to a two-compartment model. The values for these constants were K_{12} = 0.003 min^{-1} and K_{21} = 0.00165 min^{-1}. The volume terms for parent cisplatin (Vd_p), the first-order rate constant for nonenzymatic metabolism of cisplatin (Km) and the clearance terms for parent cisplatin (Clr_p) and platinum metabolites (Clr_m) are the same as those described above for the physiologic model. The volume of the metabolite compartment (Vd_m) is an apparent volume, derived from the concentration of total platinum at 15 min following the end of the infusion. This value was determined to be 8,454 ml/m^2. A series of three differential equations (*Appendix*) was solved simultaneously to simulate the concentrations of parent cisplatin and total platinum.

Statistical Analysis. To assess the accuracy of simulations by either model, the mean, standard error, and 95% confidence limits of measured serum concentrations at each time point were calculated and compared with simulated data. When the simulated values fell within the 95% confidence limits of the measured data, the two were considered statistically equivalent.

Results

The physiologic model simulations of total platinum and unchanged cisplatin concentrations are shown in Fig. 3. The mean (± SE) serum concentrations of 14 patients given 90 mg cisplatin/m^2 as a 6-h IV infusion are shown for comparison. Demographic characteristics of these patients have been described in detail in a previous paper [5]. As shown, the physiologic model accurately simulates serum concentrations of both parent cisplatin and total platinum through at least 48 h post-infusion. Model simulations of both parent cisplatin and total platinum were within the 95% confidence limits of the measured concentrations at all time points (Fig. 5), thus indicating that model simulations were not statistically differ-

ent from measured data. The serum half-life derived from the terminal slope of the total platinum simulation is 44.2 h, which is in agreement with measured values (44.4 ± 8.2 h). Renal clearances of total platinum simulated by the model were comparable to renal clearances previously measured in children and adolescents [5]. This supports our previous hypothesis that decreasing renal clearance of total platinum during the 48 h post-infusion period is a result of two independent first-order clearance rates for parent cisplatin and metabolites, and not a result of changing renal function, urine flow, or total platinum concentration.

As shown in Figs. 4 and 5, simulations obtained with the simplified multicompartment operational model were accurate for parent cisplatin but were less accurate for total platinum serum concentrations, when compared to the physiologic model. At one time point (1 h) the simulated concentration exceeded the 95% confidence limits of the measured data, while the simulation fell within these limits at all other time points. Thus, the overall accuracy of the simplified model is lower than that of the physiologic model. Moreover, this model does not allow simulation of cisplatin disposition in individual extravascular tissues and cannot be used to predict alterations in cisplatin disposition induced by changes in selected physiologic variables (i.e., biliary obstruction, decreased muscle mass, etc.).

These data provide further clarification of the disposition of cisplatin in children and adolescents. However, further investigations are needed to precisely define the accuracy of tissue compartment simulations produced by either pharmacokinetic model. Moreover, the clinical significance of the rapid decline in serum concentrations of parent drug is unknown, since the contributions of the parent drug and the various platinum metabolites to cisplatin's therapeutic effects and/or toxicity are currently unclear. Previous cell culture studies [7] demonstrating that the protein-bound fraction is inactive and that only the free-circulating platinum species has cytotoxic activity, coupled with the pharmacokinetic data described herein, suggest a potential rationale for the long-term continuous infusion or regional administration of cisplatin.

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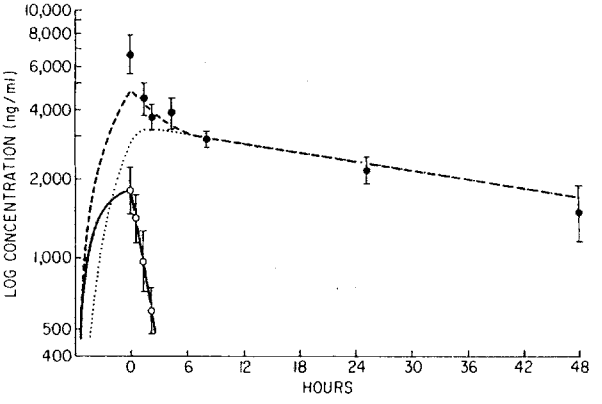

Fig. 3. Physiologic pharmacokinetic model simulations of parent cisplatin (———), cisplatin metabolites (. . . . . .), and total platinum (– – –) serum concentrations following a 6-h IV infusion of cisplatin 90 mg/m^2. Serum concentrations (mean ± SE) of parent (free) cisplatin (○) and total platinum (●) measured in 14 patients given 90 mg cisplatin/m^2 as a 6-h infusion are shown for comparison

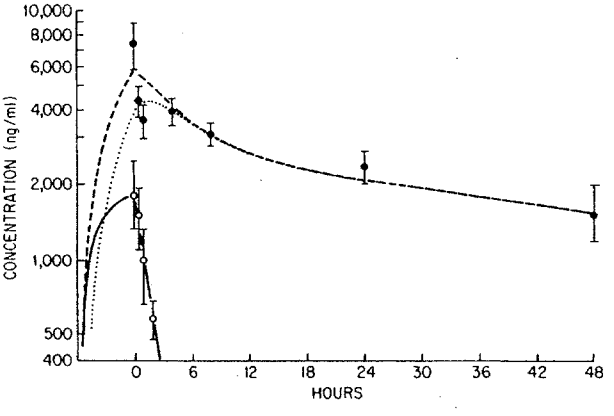

Fig. 4. First multicompartment operational model simulations of cisplatin disposition. Serum concentrations (mean ± SD) measured in 14 patients are shown for comparison. See Fig. 3 for symbol key

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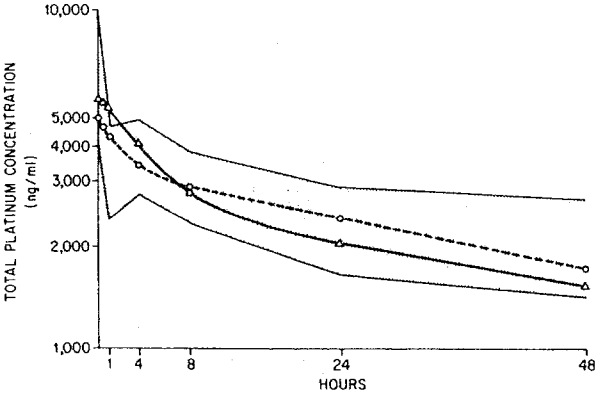

Fig. 5. Simulations of total platinum serum concentrations by the physiologic (– – –) and operational (———) pharmacokinetic model, versus the 95% confidence limit of the measured serum concentrations (*shaded area*)

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Appendix

Differential Equations for Physiologic Model

Parent Cisplatin:

$$\text{Plasma: } \frac{dCp_p}{dt} = \frac{K_0(t) - (Clr_p \cdot Cp_p) - (K_m \cdot Vd_p \cdot CP_p)}{Vd_p}.$$

Cisplatin Metabolites:

$$\text{Plasma: } \frac{dCp_m}{dt} = \frac{K_m \cdot Vd_p \cdot Cp_p + Q_l \cdot \frac{C_l}{R_l} + Q_k \cdot \frac{C_k}{R_k} + Q_m \cdot \frac{C_m}{R_m} + Q_{sk} \cdot \frac{C_{sk}}{R_{sk}} - (Q_l + Q_k + Q_m + Q_{sk}) \cdot Cp_m}{V_p}$$

$$\text{Kidney: } \frac{dC_k}{dt} = \frac{Q_k \cdot \left(Cp_m - \frac{C_k}{R_k}\right) - Clr_m \cdot \frac{C_k}{R_k}}{V_k}$$

$$\text{Liver: } \frac{dC_l}{dt} = \frac{(Q_l - Q_{gi})\left(Cp_m - \frac{C_l}{R_l}\right) + Q_g \cdot \left(\frac{C_g}{R_g} - \frac{C_l}{R_l}\right) - Cl_b \cdot \frac{C_l}{R_l}}{V_l}$$

$$\text{GI: } \frac{dC_g}{dt} = \frac{Q_{gi} \cdot \left(Cp_m - \frac{C_g}{R_g}\right) + Cl_b \cdot \frac{C_l}{R_l}}{V_{gi}}$$

$$\text{Skin: } \frac{dC_{sk}}{dt} = \frac{Q_{sk} \cdot \left(Cp_m - \frac{C_{sk}}{R_{sk}}\right)}{V_{sk}}$$

$$\text{Muscle: } \frac{dC_m}{dt} = \frac{Q_m \cdot \left(Cp_m - \frac{C_m}{R_m}\right)}{V_m}$$

Where:

Tissue-plasma distribution ratios equal

Kidney: $R_k = 8$
Liver: $R_l = 6$
GI: $R_g = 1$
Skin: $R_{sk} = 3.5$
Muscle: $R_m = 0.4$

and,

K_0 = zero-order infusion rate
t = time
Clr_p = renal clearance of parent cisplatin
Clr_m = renal clearance of cisplatin metabolites
Cl_b = biliary clearance of metabolites
Vd_p = apparent distribution volume of parent cisplatin.

Differential equations for operational model

Parent Cisplatin

$$\text{Plasma: } \frac{dCp_p}{dt} = \frac{K_0(t) - (K_m \cdot Vd_p \cdot Cp_p) - Clr_p \cdot Cp_p}{Vd_p}$$

Cisplatin Metabolites

$$\text{Plasma: } \frac{dCp_m}{dt} = \frac{K_m \cdot Vd_p \cdot Cp_p + K_{21} \cdot At - K_{12} \cdot Cp_m \cdot Vp_m - Clr_m \cdot Cp_m}{V_p}$$

$$\text{Tissue: } \frac{dAt}{dt} = (K_{12} \cdot Cp_m \cdot Vp_m) - (K_{21} \cdot At)$$

Where: At = amount of drug in tissue
K_{12}, K_{21} = intercompartment distribution rate constants

Volumes equal

Plasma: $V_p = 44 \cdot Wt^{0.99}$
Kidney: $V_k = 7.5 \cdot Wt^{0.85}$
Liver: $V_l = 34 \cdot Wt^{0.87}$
GI: $V_g = 49 \cdot Wt^{0.94}$
Skin: $V_{sk} = 1640 \cdot BSA$ (m^2)
Muscle: V_m = (see text)

and

Organ plasma flow equals

Kidney: $Q_k = 24.5 \cdot Wt^{0.792}$
Liver: $Q_l = 29.96 \cdot Wt^{0.767}$
GI: $Q_g = 0.82 \cdot Q_l$
Skin: $Q_{sk} = 32.8 \cdot BSA$ (m^2)
Muscle: $Q_m = 18.17 \cdot Wt^{0.738}$.