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Reaction kinetics of cisplatin and its monoaquated species with the (potential) renal protecting agents (di)mesna and thiosulfate

Estimation of the effect of protecting agents on the plasma and peritoneal AUCs of CDDP

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Summary. Using simple kinetic modelling, we estimated the effect of nucleophilic (renal) protecting agents (thiosulfate, mesna, diethyldithiocarbamate) on the half-life and the area under the concentration-time curve (AUC) of *cis*-diamminedichloroplatinum(II) (CDDP) in plasma and peritoneum. Our basic assumptions were that (a) under non-protecting conditions, the elimination of intact CDDP from plasma and peritoneum is a first-order process determined by the elimination-rate constant (k), and (b) under conditions of renal protection, the elimination of CDDP is a first-order process determined by $k_{CDDP,P} = k_{CDDP} + k_N.[N]$, with $k_{CDDP,P}$ representing k_{CDDP} under conditions of protection; k_N, the second-order rate constant for direct interaction of the protecting nucleophile (N) and CDDP; and [N], the (steady-state) concentration of N. Half-lives under conditions of protection were $0.693/k_{CDDP,P}$. AUCs were obtained by integration of the first-order equations. The inactivation-indicating parameter was defined as being the ratio of the AUC under protecting conditions to the AUC under non-protecting conditions (R_{inact}). R_{inact} is approximately given by $k_{CDDP}/k_{CDDP,P}$. For renal protection with i.v. thiosulfate (TS, 2 g m^{-2} h), the estimates of R_{inact} were 0.61 in plasma and 0.7 in the peritoneal cavity for i.p. injected CDDP and 0.87 in plasma for i.v. CDDP, indicating inactivation of CDDP under such conditions. Estimates of R_{inact} were 0.84 or 0.96 in plasma and 0.87 in the peritoneal cavity for supposed conditions of renal protection by systemic mesna (4.4 g m^{-2} h), suggesting only minor inactivation of i.p. or i.v. injected CDDP under such conditions. Under reported conditions of protection achieved with 4.4 g m^{-2} h systemic diethyldithiocarbamate (DDTC), R_{inact} was >0.65 or 0.87 in plasma and >0.75 in the peritoneal cavity for i.p. or i.v. injected CDDP, respectively. Thus, DDTC inactivates CDDP to a comparable or lesser extent than does TS.

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Introduction

Nephrotoxicity [9] is the dose-limiting side effect of *cis*-diamminedichloroplatinum(II) (CDDP), which displays antitumor activity against a variety of neoplasms [10–13]. Howell et al. [4] and Pfeifle et al. [7] have demonstrated that thiosulfate (TS) attenuates the nephrotoxicity of both i.v. and i.p. injected CDDP. According to these authors, the protective effect of TS is associated with substantial chemical inactivation of CDDP in the kidneys, where TS is concentrated due to its rapid renal clearance. In plasma the concentration of TS is much lower and, therefore, considerably less inactivation is expected in this compartment. However, under conditions of renal protection with systemic TS (2 g m^{-2} h), the areas under the plasma and peritoneal concentration-time curve (AUC) of i.p. CDDP were substantially reduced [3, 7]. This finding is consistent with the reaction kinetics of CDDP and TS [2].

Recently we analyzed the reaction kinetics of CDDP with TS and the (potential) renal protecting agents mesna (MS) and dimesna (DMS) [5, 6]. The second-order rate constant for direct interaction of the protecting agent with intact CDDP (k_N) appeared to be a valuable kinetic parameter with regard to the effect of the protecting agent on the half-life of CDDP and the extent of inactivation of the latter in plasma.

In this paper we present simple equations based on first-order elimination and k_N for estimation of the effect of (D)MS, TS and diethyldithiocarbamate (DDTC) on the half-life and AUC of CDDP.

Methods

Theoretical approach. Pharmacokinetic studies [3, 4, 7] have revealed that under non-protecting conditions, the elimination of intact CDDP from plasma and from the peritoneal cavity is, in approximation, a first-order process determined by (a) distribution, (b) the reaction of CDDP with low-molecular-weight endogenous nucleophiles (metabolism), (c) protein binding and (d) renal clearance. Loss from the peritoneal cavity is additionally determined by transfer from the peritoneal cavity to plasma. Under non-protecting conditions, endogenous nucleophiles

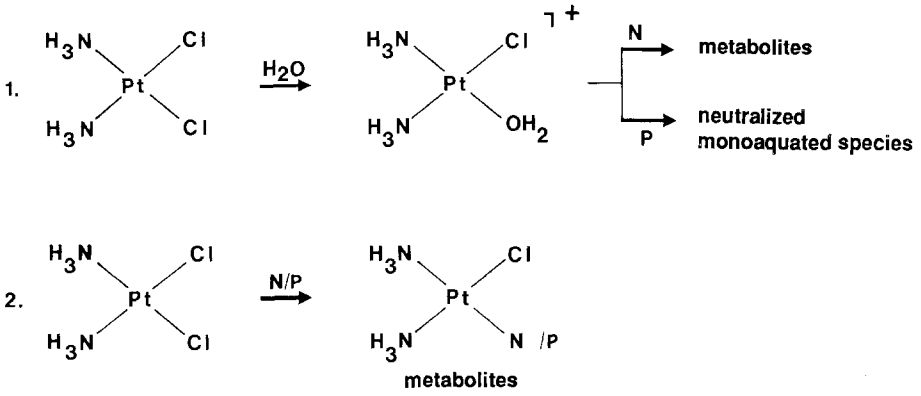

Fig. 1. Reactions of endogenous nucleophiles (*N*) or renal protecting agents (*P*) with CDDP along the parallel pathways of (*1*) the aquation products and (*2*) direct displacement of the chloride ligands in CDDP

react along parallel pathways with (a) the monoaquated species of CDDP, produced in rate-limiting first-order aquation of CDDP; and (b) intact CDDP by direct displacement of its chloro ligands (Fig. 1). Under (renal) protecting conditions, the circulating nucleophilic (renal) protecting agent, N, competes with the endogenous nucleophiles for intact CDDP and its monoaquated species. Consequently, the pattern of metabolites changes. However, reaction of N with the monoaquated species does not result in accelerated inactivation of CDDP, since this production rate is determined by the rate-limiting aquation of the drug. By contrast, direct interaction of N and intact CDDP gives rise to accelerated chemical inactivation.

Under conditions of protection, the first-order elimination rate constant is $k_{CDDP,P} = k_{CDDP}+k_N.[N]$, with k_{CDDP} representing the elimination-rate constant of CDDP under non-protecting conditions; k_N, the second-order rate constant for direct interaction of CDDP and the protecting nucleophile N; and [N], the concentration of this nucleophile in plasma and/or the peritoneal cavity. Based on first-order rate equations and the above concept, simple equations were derived to estimate the effect of N on the half-life ($t_{1/2}$) and the area under the concentration-time curve (AUC) of CDDP.

Effect on the peritoneal AUC of i. p. injected CDDP. The elimination of intact CDDP from the peritoneum is, in approximation, a first-order process [4]:

$$C_t = C_0*e^{-k_{CDDP}t}. \quad (1)$$

The first-order elimination rate constant of CDDP, k_{CDDP}, is 6.7×10^{-3} min^{-1} [3]. Integration over time yields the expression for the area under the concentration-time curve (AUC):

$$AUC = C_0*[1-e^{-k_{CDDP}T}]/k_{CDDP}, \quad (2)$$

with T representing the dwelling time of CDDP in the peritoneal cavity, which is 240 [7] or 360 min [3] in clinical practice.

Under conditions of renal protection by concomitant i. v. infusion of a (renal) protecting agent N, intact CDDP is inactivated in the peritoneum due to direct interaction with N. The extent of this inactivation is determined by k_N and the peritoneal concentration of N ([N]):

$$AUC_P = C_0*[1-e^{-k_{CDDP,P}T}]/k_{CDDP,P}, \quad (3)$$

with $k_{CDDP,P} = k_{CDDP}+k_N.[N]$ and AUC_P representing the peritoneal AUC under conditions of renal protection.

The ratio AUC_P/AUC was used as an inactivation-indicating parameter (R_{inact}). R_{inact} = 1 implies essentially the lack of inactivation of CDDP by N; conversely, R_{inact} = 0 represents complete inactivation of CDDP. Combination of Eqs. 2 and 3 yields $(1-e^{-k_{CDDP,P}T}/\ 1-e^{-k_{CDDP}T}\cong1)$:

$$R_{inact,pf} = k_{CDDP}/k_{CDDP,P}, \quad (4)$$

where $R_{inact,pf}$ denotes R_{inact} in the peritoneal fluid. Thus, R_{inact} is approximated by the quotient of the first-order rate constants k_{CDDP} and $k_{CDDP,P}$. $R_{inact,pf}$ is obtained from Eq. 4. Apart from k, [N] is an essential parameter in the procedure outlined above. However, during instillation of CDDP, [N] rises like the concentration of an infused drug in plasma [3]. Assuming that the peritoneal pharmacokinetic parameters of N are available, the average concentration of N ($[N]_{av}$) during the instillation period T can be obtained from:

$$[N]_{av} = \int_0^T C_{ss}*(1-e^{-kt})dt/T, \quad (5)$$

yielding

$$[N]_{av} = C_{ss}+C_{ss}*(e^{-kT}-1)/kT \quad (6)$$

or approximately ($e^{-kT}\cong0$),

$$[N]_{av} = C_{ss}-C_{ss}/kT, \quad (7)$$

where k denotes the first-order rate constant of N describing the concentration profile of N in the peritoneal cavity and C_{ss} represents the (estimated) steady-state concentration of N in the peritoneum [3].

Effect on the plasma AUC of i. v. injected CDDP. The plasma AUC ($t = 0-t = \infty$) of intact CDDP after i. v. administration is given by:

$$AUC_{pl} = C_0/k_{CDDP}, \quad (8)$$

with k_{CDDP} representing the first-order plasma elimination rate constant of CDDP under non-protecting conditions (2.7×10^{-2} min^{-1}) [3]. Under conditions of renal protection, the plasma AUC of intact CDDP after i. v. administration is determined by (a) elimination from plasma and (b) chemical inactivation due to the direct interaction of CDDP and N:

$$AUC_{P,pl} = C_0/k_{CDDP,P}, \quad (9)$$

with $k_{CDDP,P} = k_{CDDP}+k_N.[N]$. Combination of Eqs. 8 and 9 yields

$$R_{inact,pl} = k_{CDDP}/k_{CDDP,P}. \quad (10)$$

Under conditions of renal protection, i. p. injected CDDP is inactivated by N not only in the peritoneum but also in plasma after its transfer from the peritoneum. Consequently, the resultant inactivation of i. p. injected CDDP in plasma is

$$R_{inact} = R_{inact,pf}*R_{inact,pl}, \quad (11)$$

with $R_{inact,pf} = AUC_{P,pf}/AUC_{pf}$ and $R_{inact,pl} = AUC_{P,pl}/AUC_{pl}$. Eq. 11 is used to estimate the effect of i. p. injected CDDP on the plasma AUC.

Effect of the protecting agent on the half-life of CDDP in plasma and peritoneum. In all instances (N = TS, DMS, DDTC), the half-life of CDDP under conditions of protection ($t_{1/2,P}$) was obtained from $k_{CDDP,P}$ ($t_{1/2,P} = 0.693/k_{CDDP,P}$).

Results

R_{inact} was obtained for TS and MS by applying the derived equations for the reported parameters summarized in Table 1. To afford renal protection, Qazi et al. [8] infused

Table 1. Parameters used to estimate R_{inact} and half-lives under conditions of protection

N	Infusion rate (g m^{-2} h)	k_N (M^{-1} min^{-1})	[N] (M)	
			Peritoneum	Plasma
DMS	4.4[a]	0.26[a]	4 $\times10^{-3}$[b]	5 $\times10^{-3}$[b]
TS	2[c]	2.9[a]	1 $\times10^{-3}$[c]	1.5×10^{-3}[c]
DDTC	4.4[d]	4.4[e]	0.5×10^{-3}[d]	0.8×10^{-3}[d]

[a] See Leeuwenkamp et al. [6]
[b] See Leeuwenkamp et al. [5]. The peritoneal concentration was estimated, assuming that the peritoneal-to-plasma concentration ratio is comparable to that of TS [7]
[c] See Goel et al. [3]
[d] Mean plasma concentration of DDTC during infusion at a rate of 100 mg kg^{-1} h [8] as estimated from Eq. 12. The peritoneal concentration was estimated, assuming that the peritoneal-to-plasma concentration ratio is identical to that of TS [7]
[e] See Bodenner et al. [1]
N, Protecting nucleophile; k_N, second-order rate constant for direct interaction of N and CDDP; [N], steady-state concentration of N

Table 2. Estimates of R_{inact} and half-lives of CDDP under conditions of protection

N	R_{inact}[a]				$t_{1/2}$[b]			
	Plasma		Peritoneum		Plasma		Peritoneum	
	calcd	Lit	calcd	Lit	calcd	Lit	calcd	Lit
–	1	1	1	1	–	26±21[c]	–	104±56[c]
TS	0.61/0.87[d]	0.75[c]	0.7	0.6[c]	22	34±20[c]	72	47±14[c]
MS	0.84/0.96	–	0.87	–	25	–	90	–
DDTC	>0.65/>0.87	–	>0.75	–	23	–	78	–

[a] For estimation of R_{inact} for i.p. injected CDDP in peritoneum and plasma, Eqs. 4 and 11, respectively, were used. R_{inact} for i.v. CDDP in plasma was estimated from Eq. 10
[b] Half-life of CDDP. Half-life under protecting conditions ($t_{1/2,P} = 0.693/k_{CDDP,P}$) was obtained from the estimated elimination-rate constant under conditions of protection $k_{CDDP,P} = k_{CDDP}+k_N.[N]$, with k_{CDDP} representing the elimination-rate constant of CDDP under non-protecting conditions
[c] See Goel et al. [3]
[d] R_{inact} in plasma after i.p./i.v. administration of CDDP, respectively

DDTC for 90 min starting 45 min after the cessation of i.v. CDDP administration. The average DDTC concentration during the infusion period was obtained from Eq. 7. For reasons of simplicity, it was assumed that the DDTC infusion was started at the end of the CDDP infusion and that the effect of DDTC during the post-infusion period was negligible because of its short plasma half-life of 13 min [1, 8]. The first assumption implies that the actual R_{inact} is greater than the estimated value. The calculations were performed using $k_{DDTC} = 4.6\times10^{-2}$ min^{-1} [1].

The estimates of R_{inact} obtained using N = TS, DMS and DDTC are summarized in Table 2. Under conditions of protection by TS, substantial inactivation of intact i.p. injected CDDP takes place in plasma and in the peritoneal cavity. By contrast, protection by MS gives rise to lower inactivation of intact CDDP. Using the schedule of Qazi et al. [8], it was found that $R_{inact,DDTC} > 0.87$. Thus, values for $R_{inact,DDTC}$ and $R_{inact,TS}$ are comparable.

Discussion

The estimates for TS are in fair agreement with experimental data [3, 7]. Because of the high extent of inactivation suggested by R_{inact} and found experimentally [3, 7], a reinvestigation of the effect of TS (2 g m^{-2} h) on the plasma AUC of CDDP using a CDDP-selective analytical procedure is warranted.

Under supposed conditions of (renal) protection by MS [5], the estimated extent of inactivation was considerably lower. From this kinetic point of view, MS would be an attractive renal protecting agent. In contrast to TS, DDTC also protects against the gastrointestinal and myelotoxicity of CDDP [1, 8]. Substantial inactivation of i.p. injected CDDP after i.v. infusion of DDTC is also anticipated (Table 2). However, clinically, DDTC is generally given a few hours after CDDP. Therefore, R_{inact} is appreciably higher in clinical practice. It can thus be concluded that from a kinetic point of view, DDTC is a suitable agent for protection against the (renal) toxicity of i.v. and, possibly, i.p. injected CDDP. However, recent clinical studies have shown that the use of DDTC is hampered by severe neurotoxicity [8].

The area under the concentration-time curve (AUC) is a measure for tumor exposure to the drug. As a consequence, the extent to which the exposure of the tumor to CDDP is reduced by a (renal) protecting agent is given by R_{inact}. This implies that the dose of CDDP must be escalated by a factor of $1/R_{inact}$ to maintain the therapeutic effect. If (nephro)toxicity is adequately suppressed by a (renal) protecting agent, the CDDP dose might be escalated to such an extent ($>1/R_{inact}$) that even a gain in therapeutic effect might be obtained.

It can be concluded that the derived simple equations are versatile tools for estimation of (a) the effect of the nucleophile on the half-life of CDDP and (b) the extent to

which CDDP is inactivated by a nucleophilic (renal) protecting agent. From a kinetic point of view, MS and DDTC would be useful (renal) protecting agents.

References

1. Bodenner DL, Dedon PC, King PC, Borch RF (1986) Effect of diethyldithiocarbamate on *cis*-diamminedichloroplatinum(II)-induced cytotoxicity, DNA cross-linking, and γ-glutamyl transpeptidase inhibition. Cancer Res 46: 2745
2. Elferink F, Van der Vijgh WJF, Klein I, Pinedo HM (1986) Interaction of cisplatin and carboplatin with sodium thiosulfate: reaction rates and protein binding. Clin Chem 32: 641
3. Goel R, Cleary SM, Horton C, Kirmani S, Abramson I, Kelly C, Howell SB (1989) Effect of sodium thiosulfate on the pharmacokinetics and toxicity of cisplatin. J Natl Cancer Inst 81: 1552
4. Howell SB, Pfeifle GE, Wung WE, Olshen RA (1983) Intraperitoneal *cis*-diamminedichloroplatinum with systemic thiosulphate protection. Cancer Res 43: 1426
5. Leeuwenkamp OR, Neijt JP, Van der Vijgh WJF, Pinedo HM (1990) Reaction kinetics of cisplatin and its monoaquated species with the (potential) renal protecting agents (di)mesna and thiosulfate. Clinical implications and alternative mechanism of renal protection. Eur J Clin Oncology (submitted)
6. Leeuwenkamp OR, Van der Vijgh WJF, Neijt JP, Pinedo HM (1990) Reaction kinetics of cisplatin and its monoaquated species with the (potential) renal protecting agents (di)mesna and thiosulfate. Kinetic modelling and relevance of the second-order rate constant. Cancer Res (submitted)
7. Pfeifle GE, Howell SB, Felthouse RD, Woliver TBS, Andrews PA, Markman MP (1985) High-dose cisplatin with sodium thiosulfate protection. J Clin Oncol 3: 237
8. Qazi R, Chang AYC, Borch RF, Montine P, Dedon P, Loughner J, Bennett JM (1988) Phase I clinical and pharmacokinetic study of diethyldithiocarbamate as a chemoprotector from toxic effects of cisplatin. J Natl Cancer Inst 80: 1486
9. Von Hoff DD, Schilsky R, Reichert GM (1979) Toxic effects of *cis*-dichlorodiammineplatinum(II) in man. Cancer Treat Rep 63: 1523
10. Williams SD, Einhorn LH (1980) Cisplatin chemotherapy of testicular cancer. In: Prestayko AW, Crooke ST, Carter SK (eds) Cisplatin: current status and new developments. Academic Press, New York, p 323
11. Williams SD, Donohue JD, Einhorn LH (1979) Advanced bladder cancer: therapy with *cis*-dichlorodiammineplatinum(II), Adriamycin and 5-fluorouracil. Cancer Treat Rep 63: 1573
12. Wittes R, Heller K, Randolph V (1979) *cis*-Dichlorodiammineplatinum(II) based chemotherapy as initial treatment of advanced head and neck cancer. Cancer Treat Rep 63: 1533
13. Young RG, Von Hoff DD, Gormley P (1979) *cis*-Dichlorodiammineplatinum(II) for the treatment of advanced ovarian cancer. Cancer Treat Rep 63: 1539