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Research paper

Significance of water solubility in the gastrointestinal absorption of *trans*-bis(*n*-valerato)(1*R*,2*R*-cyclohexanediamine)(oxalato)platinum(IV), an orally active antitumor platinum complex, and its analogs

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***Trans*-bis(*n*-valerato)(1*R*,2*R*-cyclohexanediamine)(oxalato)-platinum(IV) (C5-OHP) is an orally active platinum complex we prepared. The gastrointestinal absorption of C5-OHP was examined in rats and compared with those of C5-OHP analogs which have a general formula of *trans*-bis(*n*-$OCOC_nH_{2n+1}$)(1*R*,2*R*-cyclohexanediamine)(oxalato)platinum (IV) as well as C5-OHP. The complexes did not show significant differences in pharmacokinetic behavior after i.v. injection. Plasma platinum level after a single oral administration at a dose was higher for a complex with higher water solubility. The intestinal absorption rate measured by an *in situ* recirculating perfusion technique was higher for a complex with higher lipophilicity. These results indicate that the water solubility is a more dominant factor than the lipophilicity in the gastrointestinal absorption of the complexes. Then, the effects of surfactants and α-cyclodextrin (α-CD) on the solubility of C5-OHP was studied. Among the agents tested, α-CD showed the highest effect in increasing the solubility. Administration of C5-OHP together with α-CD gave approximately three times higher plasma platinum levels than administration of C5-OHP alone. Water solubility was found to be a dominant factor in the gastrointestinal absorption of C5-OHP and its analogs. [© 1998 Rapid Science Ltd.]**

Key words: Antitumor platinum complex, gastrointestinal absorption, oral agent, oxaliplatin derivatives, rat, water solubility.

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Introduction

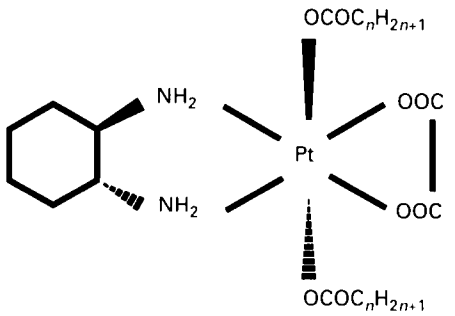
Platinum complexes are now a well-established class of cancer chemotherapy agents. While cisplatin [*cis*-diamminedichloroplatinum(II)] and carboplatin [diammine(1,1-cyclobutanedicarboxylato)platinum(II)] have been successfully used in the treatment of human malignancies, their clinical usefulness has been limited by undesirable side effects such as nephrotoxicity, emesis and myelosuppression.[1–3] Thus, much effort has been devoted to develop second-generation antitumor platinum complexes with greater activity and/or less toxicity.[4,5]

The platinum agents developed have been administered by parenteral ways including the i.v. long-term infusion, intra-arterial and i.p. injection. Recently, much attention has been paid for the quality of life (QOL) of cancer patients. Taking into consideration the ease of administration, treatment of patients who cannot be treated systemically, and the possibility to treat terminal patients and outpatients at hospices and homes, oral agents would be a class of platinum complexes of the next generation and development of such complexes could be a significant advantage in progressing QOL.

The first complexes found to be orally antitumor active are the ammine/amine platinum(IV) dicarboxylate class of platinum complexes including JM216 [*trans*,*cis*,*cis*-bis(acetato)ammine(cyclohexylamine)dichloroplatinum(IV)].[6] Among the complexes of this class, JM216 was chosen for full clinical development.[7–9] It has undergone phase I clinical trial[10,11] and is now undergoing phase II trial.

On the other hand, oxaliplatin [(1*R*,2*R*-cyclohexanediamine)(oxalato)platinum(II), *l*-OHP] developed by Kidani *et al.*[12] has proceeded beyond clinical trials to be licensed as a new cancer chemotherapy drug in France in 1996 on the basis of its prominent antitumor activity and toxicity profile.[13-17] It has been found to lack cross-resistance to cisplatin in several tumor models.[14,18,19] Our idea is that if an *l*-OHP-derivative which is absorbable in the gastrointestinal (GI) tract and serves as a prodrug of *l*-OHP could be prepared, it would become a new orally active platinum complex with similar biological features to those of *l*-OHP. Thus, a number of *l*-OHP-derivatives of a general formula *trans*-bis(*n*-$OCOC_nH_{2n+1}$)(1*R*,2*R*-cyclohexanediamine)(oxalato) platinum(IV) were synthesized, being designated as C2-OHP (n=1), C3-OHP (n=2), C4-OHP (n=3), C5-OHP (n=4), C6-OHP (n=5), C7-OHP (n=6) and C8-OHP (n=7). C5-OHP, the most active one in the screening test among these derivatives, was found to be orally active against i.p. mouse leukemia L1210.[20] C5-OHP was considered to be a prime candidate for an oral agent.

It is necessary to optimize the dose and administration schedule of C5-OHP for further development. To this end, it is important to clarify the factors influencing the GI absorption of C5-OHP. However, little is known about factors involved in GI absorption of oral platinum complexes, even about what physiochemical property plays an important part in the GI absorption. Thus, the authors examined the plasma platinum level of C5-OHP after a single oral administration in comparison with those of C5-OHP analogs in order to get further insight into the factors involved in the GI absorption of C5-OHP. This paper describes the significance of water solubility in the GI absorption of C5-OHP and its analogs. Structural formulas of *l*-OHP derivatives used in this study are shown in Figure 1.



	Complex
n=1	C2-OHP
n=2	C3-OHP
n=4	C5-OHP
n=5	C6-OHP

Figure 1. Structural formulas of C5-OHP and its analogs used in this study.

Materials and methods

Chemicals

C5-OHP analogs used in this study were C2-OHP, C3-OHP and C6-OHP. These complexes and C5-OHP were synthesized according to the method described in our preceding paper.[20] The complexes synthesized were identified by elemental analysis. Platinum contents in the complexes were determined by a colorimetric method.[21] Other chemicals of reagent grade or better were commercially obtained and used as received.

Animal

Male Wistar rats purchased from Japan SLC (Hamamatsu, Japan) were raised for at least 1 week before experiments. Rats, 8–9 weeks of age and weighing 230–270 g, were fasted but allowed free access to water for approximately 20 h prior to experiments. All animal experiments were carried out in accordance with the Guidelines for the Care and Use of Laboratory Animals in Takara-machi Campus of Kanazawa University.

In vivo GI absorption study after a single oral administration

Rats were treated under light anesthesia with ether. Prior to administration of the complexes, a rat was incised in the cervix so that the jugular vein was bared. The rat was given a complex in aqueous solution or suspension by oral gavage (5 ml/kg volume of sterile water as vehicle). Blood was collected at intervals from the jugular vein into a heparinized syringe. A blood

sample was immediately transferred into a 0.5 ml test tube and centrifuged at 12000 r.p.m. for 2 min at 4 C to obtain plasma. Plasma samples were stored at −20 C until platinum concentration analysis. Plasma platinum concentrations were determined by graphite furnace atomic absorption spectrophotometry after nitric acid-hydrogen peroxide digestion.[22] Area under the plasma platinum concentration-time curve (AUC) was calculated up to 24 h by the trapezoid rule and designated as $AUC_{0-24\ h}$.

Pharmacokinetic behavior of plasma platinum after a single i.v. injection

The complexes were dissolved freshly at a concentration of 0.5 μmol/ml in isotonic phosphate-buffered saline (PBS, NaCl 8.0 g/KCl 0.2 g/Na_2HPO_4 1.15 g/KH_2PO_4 0.2 g in 1 l). Rats were treated under light anesthesia with ether. A rat was incised at two places of the cervix so that the right and left jugular veins were bared. A complex was injected into the left jugular vein at a dose of 1 μmol/kg. Blood was collected at intervals from the right jugular vein into a heparinized syringe. The procedures of sample treatment and platinum analysis were the same as above.

In situ intestinal absorption study by the recirculating perfusion technique

The procedure was similar to that described by Karino *et al.*[23] Complex solutions were prepared freshly with PBS to contain 50 μM complex and 0.32 mg/ml inulin. Rats were anesthetized by i.p. injection of sodium pentobarbital (32 mg/kg). After midline incision, a 20 cm loop of the jejunum (5 cm away from the ligament of Treitz) was prepared by cannulation of silicon tubing (3 mm i.d., 5 mm o.d.). Contents in the jejunum loop were washed out through the cannulas with PBS warmed at 37 C until the outflow became clear (approximately 50 ml). Then, the proximal one of the two cannulas was connected to the outlet of the peristaltic pump (model SJ-1211; ATTO, Tokyo, Japan) and the solution left in the lumen was expelled with air. Thereafter, the recirculating perfusion of each complex solution (10 ml) prewarmed at 37 C in the reservoir was started through the cannulas at a flow rate of 5 ml/min. The complex solution in the reservoir was stirred and kept at 37 C during the experiment. After 10 min lag time, each 100 μl aliquot of the complex solution in the reservoir was withdrawn at 15 min intervals. A 50 μl aliquot of the withdrawn sample was immediately subjected to HPLC to determine the complex concentration. Another aliquot was used for determination of the inulin concentration by a colorimetric method.[24] Changes in volume of the recirculating complex solution were corrected by inulin concentration since inulin is a high molecular compound and therefore non-absorbable in the lumen. Any decrease of the rat body temperature was prevented by the heating lamp.

Water solubility

The solubilities of C5-OHP and C6-OHP were measured in several aqueous solutions that included water, 1% Tween 80, 50 mM sodium laurylsulfate (SDS), 50 mM sodium cholate and 50 mM α-cyclodextrin (α-CD) solutions. To 1 ml of a solution was added 25 mg of a complex. The resulting solution was stirred vigorously at 50 C for 5 h and then at room temperature (about 20 C) for 2 h. The undissolved complex was filtered off with a membrane filter (pore size 0.45 μm). The platinum concentration in filtrate was determined by the colorimetric method.[21]

HPLC

The complexes were chromatographed on a Shimpack ODS-H column (4.6 mm i.d. × 25 cm, 40 C) (Shimadzu, Kyoto, Japan) with methanol/50 mM phosphate buffer (pH 4.5) eluent (1 ml/min) and spectrophotometrically detected at 210 nm. Methanol concentrations (v/v%) in eluents were as follows: 10% for C2-OHP, 25% for C3-OHP, 50% for C5-OHP and 60% for C6-OHP.

Statistical analysis

Student's *t*-test was used for the statistical analysis, whereby a value $p<0.05$ was considered to be significant.

Results

Plasma platinum concentration after a single oral administration

Plasma platinum concentrations of C2-OHP, C3-OHP, C5-OHP and C6-OHP following a single oral administration were compared in male Wistar rats. Figure 2 shows the time-courses of plasma platinum concentra-

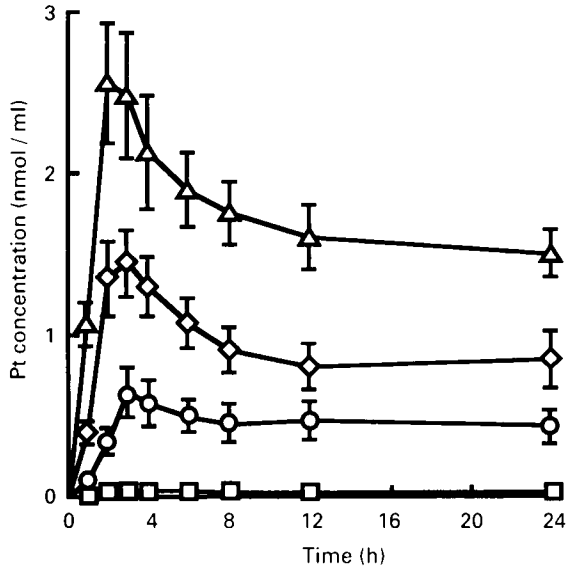


Figure 2. Time courses of plasma platinum concentrations of C2-OHP (△), C3-OHP (◇), C5-OHP (○) and C6-OHP (□) in rats given a single oral dose of 50 μmol/kg. Each point represents the mean ± SD (n=3).

Table 1. Pharmacokinetic parameters of C2-OHP, C3-OHP, C5-OHP and C6-OHP following a single oral administration in rats

Complex	T_{max} (h)	C_{max} (nmol/ml)	$AUC_{0-24\,h}$ (nmol·h/ml)
C2-OHP	2	2.56 ± 0.37[a]	40.2 ± 5.3[a]
C3-OHP	3	1.45 ± 0.20[a]	21.5 ± 3.5[a]
C5-OHP	3	0.65 ± 0.16	10.7 ± 2.5
C6-OHP	3–8	0.03 ± 0.01[a]	0.5 ± 0.2[a]

Values are expressed as the mean ± SD (n=3).
Dose: 50 μmol/kg.
[a]Significantly different from C5-OHP (p<0.01).

tions at a dose of 50 μmol/kg, and Table 1 lists the highest platinum concentration in plasma (C_{max}), the time of the highest platinum concentration in plasma (t_{max}) and $AUC_{0-24\,h}$ value of each complex. While the t_{max} value seemed to increase in the order C2-OHP < C3-OHP ≤ C5-OHP ≤ C6-OHP, there was no definitive difference among them. C_{max} and $AUC_{0-24\,h}$ values increased in the order C6-OHP < C5-OHP < C3-OHP < C2-OHP. This order is the same as the increasing order of water solubility and reverse of that of lipophilicity. C_{max} and $AUC_{0-24\,h}$ values of C2-OHP were approximately three times larger than those of C5-OHP. Plasma platinum levels of C6-OHP were outstandingly low.

In order to evaluate the extents of the complexes absorbed in the GI tract using C_{max} and $AUC_{0-24\,h}$ values, it is necessary to know the pharmacokinetic behaviors of the complexes in the systemic circulation. Figure 3 shows time-courses of plasma platinum concentrations of the complexes after a single i.v. injection at a dose of 2 μmol/kg. The complexes showed almost the same time-courses of plasma platinum concentrations. The plasma platinum levels of the complexes declined in a biexponential fashion and a significant difference was not observed in pharmacokinetic parameters including the disappearing rate constant, AUC, total clearance and apparent volume of distribution. The complexes did not show any significant difference in the pharmacokinetic behaviors in the systemic circulation, indicating that the plasma platinum levels after oral administration reflect the extent of the complexes absorbed in the GI tract.

In situ intestinal absorption study by the recirculating perfusion technique

The intestinal absorption of the complexes was examined *in situ* by means of the recirculating perfusion technique. Concentrations of the complexes in recirculating solutions decreased with time and their semi-logarithmic plots as a function of time gave straight lines as shown in Figure 4. The complexes were absorbed in the first-order kinetics on complex concentration and the absorption rate was higher for a complex with higher lipophilicity. The intestinal

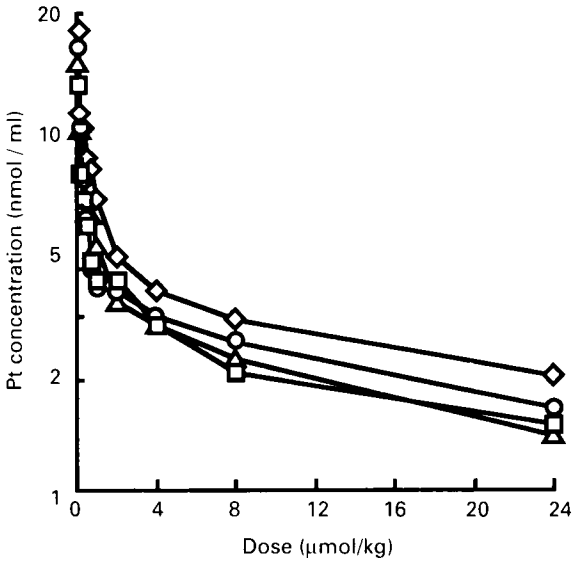


Figure 3. Time courses of plasma platinum concentrations of C2-OHP (△), C3-OHP (◇), C5-OHP (○) and C6-OHP (□) in rats given a single i.v. dose of 5 mmol/kg. Each point represents the mean ± SD (n=3).

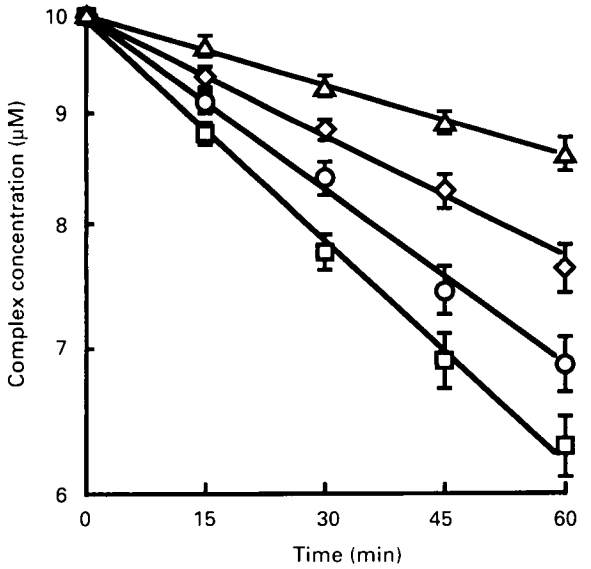


Figure 4. *In situ* intestinal absorption of C2-OHP (△), C3-OHP (◇), C5-OHP (○) and C6-OHP (□) in rats. Each point represents the mean ± SD (n=3).

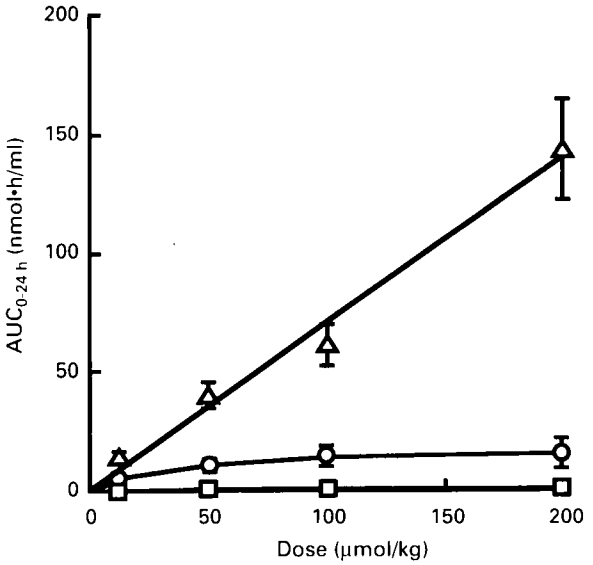


Figure 5. Dose-relationship of $AUC_{0-24\ h}$ values of C2-OHP (△), C5-OHP (○) and C6-OHP (□) following a single oral administration in rats. Each point represents mean ± SD (n=3).

absorption of the complexes was found to be dependent on the lipophilicity under the condition that the effect of the water solubility was eliminated.

Plasma platinum levels at various doses

Next, plasma platinum levels of C2-OHP, C5-OHP and C6-OHP were examined at various doses. Figure 5 shows $AUC_{0-24\ h}$ values of the complexes over a dose range of 20–200 μmol/kg. The $AUC_{0-24\ h}$ value was the largest on C2-OHP and the smallest on C6-OHP at any doses. The $AUC_{0-24\ h}$ value of C2-OHP increased almost proportionally with an increase of dose up to 200 μmol/kg. The $AUC_{0-24\ h}$ value of C5-OHP increased but less than proportionally with dose escalation up to 100 μmol/kg. The $AUC_{0-24\ h}$ value of C5-OHP at 200 μmol/kg was almost the same as that at 100 μmol/kg. Increase in the $AUC_{0-24\ h}$ value with dose elevation was not observed with C6-OHP. These results show that water solubility plays an important role in the GI absorption of the complexes.

Increase in plasma platinum levels of C5-OHP and C6-OHP by increasing the water solubilities

The results described above suggest that the extent of a complex absorbed in the GI tract would increase by increasing solubility in the GI tract. Agents which increase the water solubilities of C5-OHP and C6-OHP were investigated. Table 2 lists the solubilities of C5-OHP and C6-OHP in aqueous solutions of Tween 80, SDS, sodium cholate and α-CD, which are commonly used in preparing aqueous solutions of drugs with poor water solubilities. The solubilities of C5-OHP and C6-OHP increased in all the solutions and were the highest in the α-CD solution. The solubilities of C5-OHP and C6-OHP in the α-CD solution were approximately four and 19 times higher than those in water, respectively.

Then, C5-OHP and C6-OHP were dissolved in water together with α-CD to give concentrations of 10 mM for the complexes and 50 mM for α-CD. The resulting solutions were immediately given to rats by oral

Table 2. Solubilities of C5-OHP and C6-OHP in various solutions

Solution	Solubility (mM)	
	C5-OHP	C6-OHP
Water	6.4 ± 0.3	1.0 ± 0.1
5% Tween 80	13.6 ± 0.5[a]	1.4 ± 0.1[a]
5% SDS	12.1 ± 0.4[a]	1.6 ± 0.1[a]
5% cholate	10.3 ± 0.4[a]	1.3 ± 0.1[a]
5% α-CD	27.8 ± 1.1[a]	18.1 ± 0.7[a]

Values are expressed as the mean ± SD (n=3).
[a]Significantly different from water (p<0.01).

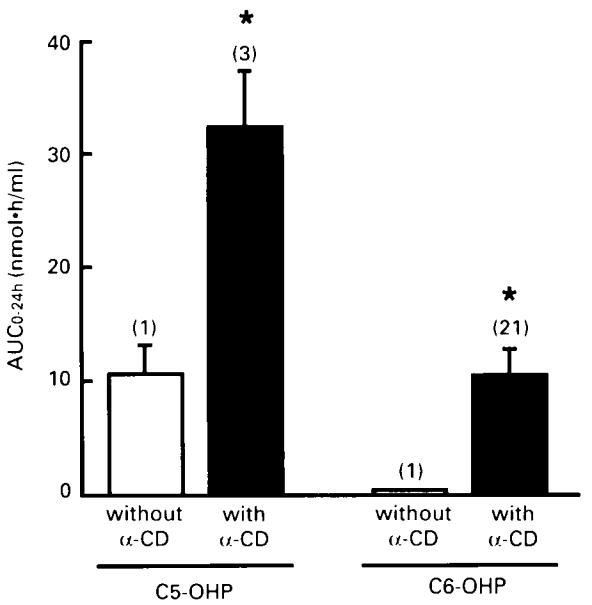


Figure 6. $AUC_{0-24\,h}$ values of C5-OHP and C6-OHP following a single oral administration with and without α-CD in rats. Each column represents the mean ± SD (n=3). *Significantly different from administration without α-CD ($p<0.01$).

gavage. Doses were consequently 50 μmol/kg for the complexes and 250 μmol/kg for α-CD. Figure 6 shows $AUC_{0-24\,h}$ values of C5-OHP and C6-OHP when C5-OHP and C6-OHP were administered with and without α-CD. Values in parentheses represent the relative values of $AUC_{0-24\,h}$ on respective complexes. When C5-OHP and C6-OHP were administered together with α-CD, their $AUC_{0-24\,h}$ values significantly increased, and were approximately three and 25 times larger than those without α-CD, respectively. It was proved that increasing solubilities of C5-OHP and C6-OHP in the GI tract brought about an increase in the extents of the complexes absorbed.

Discussion

In general a drug with higher lipophilicity is more permeable through the cell membrane and accordingly absorbed more efficiently in the GI tract. One of our aims with which we designed the formula of *l*-OHP derivatives including C5-OHP is to prepare lipophilic complexes.[20] On the other hand, JM216, a lipophilic complex, showed non-linear GI absorption in preclinical[26] and phase I studies.[11] In these studies AUC after a single oral administration of JM216 increased less than proportionally to dose and reached a plateau with dose escalation. While this phenomenon was presumed to be due to low water solubility of JM216, it is still unclear what factor is responsible. There has been no study to compare the susceptibilities of the ammine/amine platinum(IV) dicarboxylate complexes to the GI absorption and accordingly what factor is important in the GI absorption has been unknown. Thus, the authors compared plasma platinum levels of C5-OHP and its analogs in rats given a single oral dose to clarify what physiochemical property is significant in the GI absorption.

With C5-OHP and its analogs used in this study, lipophilicity increases in the order C2-OHP < C3-OHP < C5-OHP < C6-OHP and water solubility increases in the reverse order.[20] Although the authors expected that a complex with higher lipophilicity was more susceptible to GI absorption, C_{max} and $AUC_{0-24\,h}$ values were greater for a complex with higher water solubility as shown in Figure 2 and Table 1. Time-course of plasma platinum level of a drug given orally is governed by not only the GI absorption step but also many disposition processes such as biliary and urinary excretion and distribution to tissues. If the complexes are mutually different in pharmacokinetic behavior in the systemic circulation, there is the possibility that C_{max} and $AUC_{0-24\,h}$ values do not reflect the extents of the complexes absorbed in the GI tract. As can be seen in Figure 3, the complexes did not show any significant difference in the time-courses of plasma platinum concentration and pharmacokinetic parameters calculated from plasma data after a single i.v. injection. It is appropriate to consider that C_{max} and $AUC_{0-24\,h}$ values reflect extents of the complexes absorbed in the GI tract.

The plasma platinum levels of C5-OHP and its analogs after oral and i.v. administration suggested the importance of the water solubility in the GI absorption. The *in situ* recirculating perfusion technique was adopted to examine the intestinal absorption of the complexes under the condition that the effect of water solubility was eliminated. As can be seen in Figure 4, the *in situ* intestinal absorption, in other words, penetration through the gut cell membranes was more rapid for a complex with higher lipophilicity, indicating that the water solubility profoundly participates in the GI absorption of the complexes after oral administration. Further, as shown in Figure 5, C5-OHP and C6-OHP showed a non-linear GI absorption as reported with JM216, while C2-OHP showed a proportional increase in the $AUC_{0-24\,h}$ value with dose escalation. All the results discussed above indicate that the water solubility is a dominant factor in the GI absorption of the complex after oral administration. Water solubility of JM216, 0.92 mM,[25] is lower than that of C5-OHP and C6-OHP, 6.8 and 1 mM,

respectively.[20] The results in this study indicate that the non-linear GI absorption of JM216 is also due to low water solubility.

It would be reasonable to consider that the increase in the water solubilities of C5-OHP and C6-OHP elicit an increase in the extents of the complexes absorbed in the GI tract after oral administration. As shown in Figure 7, C5-OHP and C6-OHP showed significantly increased $AUC_{0\text{-}24\ h}$ values when they were orally administered together with α-CD which significantly increased the water solubilities of C5-OHP and C6-OHP. This result confirmed the significance of water solubility in the GI absorption of C5-OHP and its analogs after oral administration, and presented a way to increase the extents of the complexes absorbed. CDs are well known to form inclusion complexes with a number of compounds. Any increase in water solubilities of C5-OHP and C6-OHP in the presence of α-CD is considered to result from the formation of inclusion complexes. On the basis of studies on inclusion complexes of α-, β- and γ-CD,[27] α-CD is considered to form the inclusion complexes with C5-OHP and C6-OHP through axial carboxylate ligands. In fact, the saturated concentration of C5-OHP in 5% (51.4 mM) α-CD solution is 27.8 mM as listed in Table 2 and, therefore, the molar ratio of α-CD against C5-OHP is approximately 2. The GI absorption of JM216 could be facilitated by increasing solubility of JM216 in the GI tract. JM216 has axial acetate ligands. α-CD would be available for an increase in solubility of JM216 in the GI tract.

Conclusion

The authors revealed that water solubility is a dominant factor in the GI absorption of C5-OHP, an orally antitumor active platinum complex, and its analogs after oral administration. An increase in solubility of C5-OHP in the GI tract leads to an increase in the extent of C5-OHP absorbed, providing useful knowledge for optimizing the dose and administration schedule of C5-OHP. α-CD is considered to be an adequate agent to increase the solubility of C5-OHP in the GI tract.

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