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Pharmacokinetic Investigation on a Novel Antitumour Platinum Compound in Rabbit Plasma by Inductively Coupled Plasma Mass Spectrometry After Intravenous Administration

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The purpose of this study was to investigate a novel platinum anticancer compound named as SM54111 [cis-3, 5-diisopropylsalylic cyclohexanodiaminoplatinum (II)], which is under development as a new drug candidate, on its pharmacokinetics in plasma after intravenous administration to rabbits at concentration of 2.5, 5.0, and 9.0 mg/kg. The concentration of SM54111 in plasma expressed as Pt was determined utilizing ICP-MS method, and the method was thoroughly validated. The data were analyzed with 3P97 pharmacokinetic software to find the parameters. The results showed that the linear range lay at the 1 ~1000 ng/mL level, and the LOD and LOQ were 0.4 ng/mL and 1 ng/mL, respectively. It proved that this new drug candidate underwent disposition in rabbit plasma by a two-compartment open model at the three doses above, and the main pharmacokinetic parameters were obtained as the initial concentrations of three doses (C_0) were 8.68 0.80, 20.04 1.92, and 28.88 2.32 mg/L, respectively; the areas under concentration-time profile from time 0 to 72 h ($AUC_{0\sim t}$) were 90.0 13.0, 251.3 45.3, and 396.9 61.1 mg*h/L, respectively; the terminal elimination half-life times ($t_{1/2\beta}$) 29.1 4.8, 35.2 7.5, and 29.4 2.8 h, respectively; and the total clearances (CL_{tot}) were 0.026 0.004, 0.019 0.002, and 0.022 0.004 L/h, respectively. First order rate pharmacokinetics were observed for SM54111 with the doses used, and it showed a long retention and slow elimination in vivo, There showed no prolongation of the $t_{1/2\beta}$ with larger dose, and the CLs of the three doses were proximate. It is reasonable to surmise that SM54111 follows first order rate pharmacokinetics, and no saturation was detected at concentrations from 2.5 to 9.0 mg/kg. This result suggested that SM54111 experienced an amiable procedure in vivo and was worthy of the further development.

Keywords SM54111; pharmacokinetics; platinumcomplex; anticancer; ICP-MS

INTRODUCTION

Platinum compounds are an important class of anticancer drugs, which are widely used in the chemotherapy of lung, cervical, testicular, head and neck, bladder, and ovarian cancers. Cisplatin (cis-diamminedichloroplatinum (II)) was the initial platinum chemotherapeutic derivative, whose impact on the development of platinum anticancer agents still remains. Much effort has been dedicated to seek new platinum-based anticancer agents, with the hope of finding ones superior to cisplatin or its analogues, such as carboplatin (cis-diammine1,

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1–cyclobutanedicarboxylato–platinum (II)) (Bernard, 1989). Up until now several compounds have been universally or had been regionally approved for clinical use, the former involving cisplatin and carboplatin, and the latter oxaliplatin (cyclohexane-1, 2–diamine–ethanedioato (2-)–platinum (II)) (Luo & Wyrick, 1999), nedaplatin (cis–diammine–glycolatoplatinum (II)) (Alberts & Fanta, 1997), and lobaplatin ((1, 2–cyclobutane-dimethanamine–hydroxypropanoato–platinum (II)) (Guchelaar & Uges, 1992). Meanwhile, more than three thousand different platinum derivatives have undergone preclinical trials, among which 30 or so underwent, more or less, successful phase II clinical trials, with more than half of them being rejected for their serious toxicity or lack of efficacy. Encouragingly, the anticancer mechanism of platinum (II) is well understood, as is its toxicity and drug resistance mechanism. Recent researches have indicated that Pt-DNA adduct formation can be as high as for every 1×10^5 bases, that is, around 10,000 platinum atoms per cell (Yamad, et al. 2005), and the ultimate event of the anti-cancer function lies in apoptosis, under the control of a number of genes as p53 and the bcl-2 gene family (Smith et al., 2003).

It is reported that remaining its 1, 2-diamminocyclohexane (DACH) group the platinum complex can overcome the drug resistance (Kelland, 2000). Uehara et al. (2005) verified that altering the structure of the leaving group of platinum complexes to be more stabile influenced the tissue and intracellular distribution of the platinum complexes and improved the drug's toxicity profile. These results suggested that the greater lipophilic nature of Pt (II) complexes enabled the circumvention of cisplatin-resistance because of decreased Pt accumulation. These results also suggested that a suitable leaving group could improve the stability, even more ideally than hydrophilic or lipophilic characteristics, which influenced the distribution intercelluarlly (Wong, 1999).

Currently, two compounds are currently in human trials, L-NDDP (Draqovich et al., 2003) and TRK-710 (Saito & Manabe, 1995). Such platinum complexes as cis-conformation, amimo carriers, and divalue-platinum are available in clinic exclusively. Accordingly we designed and synthesized a novel platinum complex, with a DACH as its ligand moiety to avoid the drug resistance, and diisopropyl salylic acid as its leaving group, named as SM54111, to improve its lipophilic propriety expecting to decrease its nephrotoxicity. The chemical structure (MW 529) could refer to Figure 1.

This new chemical entity showed promising anticancer efficacy and less toxicity compared with carboplatin. Its LD_{50} is 230.9 mg/kg, much higher than that of carboplatin 150.0 mg/gk in mice inoculated with non-small cell lung cancer NCI-H460 cell line, and its ID_{50} is half of that of carboplatin, as well as 1/50 in A549 cell line, 1/10 in 3AO, 1/5 in BGC-823, DU145, and MDA-MB-231, respectively (Yu, 2006). Thus it could be recognized as a potential candidate for further development.

It has been well known that the pharmacokinetic characteristics of the compound plays a significant role in new drug development, giving useful information for dosage form design and affecting the clinic therapeutic efficacy. Therefore, the aim of this work was to investigate the pharmacokinetic parameters in rabbits with exposure to SM54111 to obtain preliminary information about the pharmacokinetic characteristics. This study was performed with ICP-MS method, which detected the Pt concentration specifically to characterize the content of SM54111, after a single intravenous administration of 3 doses.

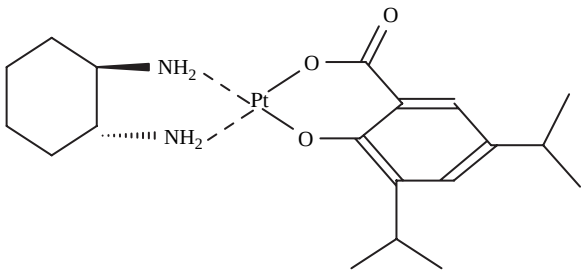

FIGURE 1. Chemical structure of SM54111.

MATERIALS AND METHODS

Materials

SM54111 (Patent No: 200510010663) was synthesized in our laboratory, characterized and determined with element analysis, UV, IR, NMR, and MS, and the accordance with the structure given was demonstrated. It was dissolved with 60% 1, 3-glycol before administration, while the remainders of the dosing solution were stored at 4°C until analysis. Platinum (Pt), rhodium (Rh), indium (In), and boron (B) standard solutions were supplied by the National Centre of Standard Metals (Ministry of Metallurgy, Beijing, China), diluted in succession with solutions assigned before detection freshly. 68% (w/w) HNO_3 (ultra pure grade) and 30% (w/w) H_2O_2 were purchased from Beijing Chemical Factory (Beijing, China). Distilled, deionized water was prepared with a Milli-Q Academic system (Millipore, USA).

Animal Studies

The rabbits were offered by the Centre of Experimental Animals (Medicine School of Beijing University, Beijing, China). The entire experiment was performed in accordance with the Regulations of the Animal Ethical Committee of Shenyang Pharmaceutical University. 15 rabbits (2.7 ± 0.3 kg) were randomly divided into 3 groups and were fastened 12 h prior to administration of the drug tested with free access to water. The rabbits were then injected with the drug solution through a marginal ear vein with 2.5, 5.0, and 9.0 mg/kg body weight, correspondingly. A blood sample (about 0.6 mL) was collected from the marginal ear vein of the other ear into a heparinized tube at 0, 0.16, 0.33, 0.5, 1, 2, 3, 5, 8, 12, 24, 48, 72, 96, and 144 h following drug administration, respectively. All

blood samples were centrifuged at 11000 × g for 10 min after standing 15 min, and the plasma was transferred into each clean tube and stored at −20ºC till ICP-MS analysis.

ICP-MSSassay

The sample treatment was optimized as following: An aliquot of 100 μL plasma was correspondingly put into each numbered glass vessel, added concentrated HNO_3 3 mL, laid then on a heating block to digest for 1 h at 180ºC, cooled, added H_2O_2 0.6 mL, heated again till thorough clarification. The acid was driven away till 0.3 ~ 0.5 mL residue, which was diluted with 3 % HNO_3 solution and metered volume 10 mL as analytes.

All experiments were carried out on the X series ICP-MS (Thermo electron corporation, USA), which was equipped with Fassel torch, standard cooled (8ºC) impact bead spray chamber, and concentric Meinhard nebulizer. PlamaLab software was adopted for instrument control, data acquisition, and analysis. The instrumental and operating condition was optimized with the commentated tune solution.

The major isotopes of platinum and rhodium were monitored at m/z 195 and 103, respectively, and rhodium as internal standard. The radio frequency forward power was set at 1.2 kW. Argon flow rates of the plasma and auxiliary gas were 15 and 1.0 L/min, respectively, and were controlled by mass flow controller. The nebulizer gas flow rate was 0.88 L/min. Ion lens parameters were optimized across the mass range 8–238 atomic mass units (amu). Data were acquired at an amu of 195 with one mass unit resolution, 50 sweeps per reading, 10 ms dwell time, and three replicates per measurement. The detection modes for both isotopes were set at peak jumping. The typical operating condition of ICP-MS is listed in Table 1.

Quantization was based on the mean (n = 3) count of platinum against a calibration curve by linear regression analysis, which was profiled with a series of standard platinum solutions of different concentration, in order, 0, 1, 5, 10, and 50 ng/mL. As acquired, the line equation was y = 1.0034 × −0.2603, r = 0.9999. The limit of detection (LOD) of Pt was 10 pg/mL by calculating three times the standard deviation of 3 blanks.

TABLE 1
Typical Operating Conditions for ICP-MS

Parameter	Value
ICP Radio frequency (RF) power	1200 W
Plasma gas flow rate	15 L/min
Auxiliary gas flow rate	1.0 L/min
Nebulizer gas flow rate	0.80 L/min
Sample uptake rate	0.5 mL/min
Spray chamber	cyclonic
Sample cone	Ni (1.0mm)
Skimmer cone	Ni (0.6mm)
Detection mode	Peak jumping
Dwell time	10ms

Statistics and Pharmacokinetic Analysis

Analysis was performed with the computer program Microsoft Excel X, including statistical calculations of standard deviations (SD), relative standard deviation (RSD), and *T*-test, whereas the pharmacokinetic analyses were processed with the program 3P97 Pharmacokinetics Software (Chinese Society of Mathematical Pharmacology).

RESULTS AND DISCUSSION

ICP-MS Method Validation

Evaluation of the assay was performed with a six-point calibration curve over the SM54111 concentration range 1 ~ 1000 ng/mL. The slope rate and intercept of the calibration graphs were calculated by weighted least squares linear regression. The standard curves (n = 4) was y = 0.0319 × −0.0012, r = 0.9996, with recovery 78 ~ 112%. The lower limit of detection (LOD) was 0.4 ng/mL, and the lower limit of quantification (LOQ) was 1.0 ng/mL. The average recoveries at concentration of 1, 10, and 1000 ng/mL were 90.8, 97.0, and 94.6%, respectively (Table 2). The precision of intra-day and inter-day was investigated by assay of samples at 1, 10, and 1000 ng/mL, respectively. The intra- and inter-day RSDs laid at the range of 1.3 ~ 5.1% and 3.9 ~ 7.8%, respectively (Table 3).

The stability of the method and some samples under various storage conditions also was investigated. The results proved that under all conditions below, standing at room temperature, frozen-thawed from −20ºC to room temperature by 5 cycles and stored at −20ºC for 26 d, the samples remained stable (Table 4).

It has been widely reported that ICP-MS is an advanced analytic method for determination of precious and microelements, such as Pt, Ga, Pd, Cd, Cr, Mn, Co, Ni, As, Se, and so forth. (Miles et al., 2007; Morrison et al., 2000; Wang et al., 2000), with high accuracy, precision, stability, and good linear range. It can be used in bio-sample analysis for the compounds containing microelements. The method established in this paper also showed the advantages above. Untill now most investigations on anticancer platinum complexes have employed ICP-MS as their analytical methods (Beauchemin, 2004).

TABLE 2
Recovery ($M \pm SD$, n = 6) of SM54111 in Rabbit Plasma

Concentration Prepared (ng/mL)	Recovery (%)	RSD (%)
1.000	90.8 ± 3.5	3.9
10.00	97.0 ± 5.9	6.1
1000	94.6 ± 7.4	7.8

TABLE 3
The Precision of Intra- and Inter-Day in Rabbit Plasma ($M \pm SD$, $n = 6$)

Concentration Prepared (ngmL)	Intra-Day		Inter–Day	
	Concentration Measured (ng/mL)	RSD (%)	Concentration Measured (ng/mL)	RSD (%)
1.000	0.918	5.1	0.908	3.9
10.00	9.73	1.4	9.70	6.1
1000	918	1.3	946	7.8

TABLE 4
Bias of the Same Samples of Stability Experiment Under Different Conditions

Conditions	Room Temperature	Frozen-Thawed 5 Circles	–20ºC for 60 Days
Bias	0.9%	2.8%	2.4%

The total platinum, instead of the parent compound, was detected, and the former characterized inexactly the pharmacological function. Some researchers, however, have proved that the concentration of the parent platinum complex related to its active metabolites, which mainly stand monoqueous and biqueous aminoplatin (II), stemmed from hydrolysis and the concentration of these metabolites, in turn, showed correlation to the total platinum quality, if only with a comparable plasma protein concentration (Bernard, 2002). Therefore, detection of the total platinum by ICP-MS may, after all, be accepted as applying to the pharmacokinetic convey on the platinum complexes in vivo (Welink, 1999).

Pharmacokinetic Parameters

The validated method was established to determine the plasma concentrations of SM54111 in rabbits after single i.v. administration at 3 doses, and to find out its pharmacokinetic parameters. The result showed that the plasma concentration-time curve of SM54111 fitted to a two-compartment open model at the 3 doses used (Figure 2). For 3 doses, 2.5, 5.0, and 9.0 mg/kg, the initial concentrations (C_0) were 8.68 ± 0.80, 20.04 ± 1.92, and 28.88 ± 2.32 mg/L, respectively. The area under concentration-time profile from time 0 to 144 h ($AUC_{0\sim t}$) were 90.0 ± 13.0, 251.3 ± 45.3, and 396.9 ± 61.1 h/L, and the terminal elimination half-life time ($t_{1/2\beta}$) were 29.1 ± 4.8, 35.2 ± 7.5, and 29.4 ± 2.8 h, respectively. The areas under concentration-time profile from time 0 to infinity ($AUC_{0\sim\infty}$), distribution half-lives ($t_{1/2\alpha}$), mean retention times (MRT), total clearance rates (CL_{tot}), and the distribution values (Vd) were produced and are presented in Table 5.

After intravenous administration, there showed a linear increase in C_0 ratio to dose ($\gamma = 0.960$), the same as for the $AUC_{0\sim72}$ ($\gamma = 0.976$) and $AUC_{0\sim\infty}$($\gamma = 0.964$). There showed no prolongation of the $t_{1/2\beta}$ with larger dose, and the CLs of the 3 doses were proximate. It is reasonable to surmise that SM54111 follows first order rate pharmacokinetics, and no saturation was detected at doses from 2.5 to 9.0 mg/kg.

There was much research focused on the anticancer effect of experimental animals in vivo of many platinum complexes (Farrell & Quy, 1990; Han et al, 2003; Ho & Au-Yeung, 2003; Hoeschele et al., 1994), but fewer research focused on their

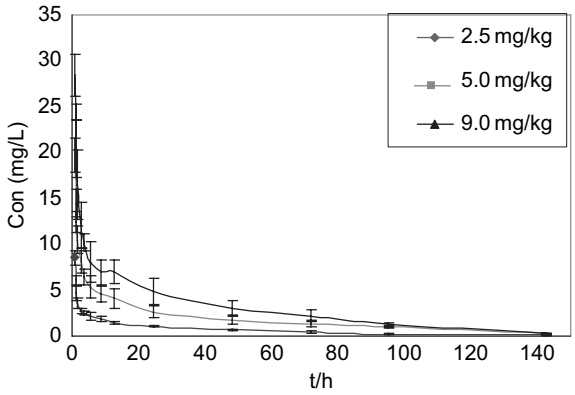

FIGURE 2. The concentration-time curve of SM54111 in rabbit plasma after i.v. administration of 3 doses (2.5, 5.0, and 9.0 mg/kg).

TABLE 5
Pharmacokinetic Parameters of SM54111 after Intravenous Administration of 2.5, 5.0, and 9.0 mg/kg in Rabbits ($n = 5$)

Dose (mg/kg)	2.50	5.0	9.0
C_0 (mg/L)	8.68 ± 0.80	20.04 ± 1.92	28.88 ± 2.32
$AUC_{0\sim t}$ (mg h/L)	94.0 ± 12.9	251.3 ± 45.3	396.9 ± 61.1
$AUC_{0\sim\infty}$ (mg h/L)	98.8 ± 14.6	272.4 ± 40.1	414.0 ± 64.6
$t_{1/2\,\beta}$(h)	29.1 ± 4.8	35.2 ± 7.5	29.4 ± 2.8
$MRT_{0\sim t}$ (h)	34.5 ± 4.9	39.5 ± 2.7	37.1 ± 3.5
CLtot (L/h)	0.026 ± 0.004	0.019 ± 0.002	0.022 ± 0.004
Vd (L)	0.285 ± 0.047	0.307 ± 0.081	0.294 ± 0.017

pharmacokinetics (Kim et al., 1996; Kizu et al., 1993). The parameters presented by these few studies focused on various aspects, making it inconvenient to compare with each other totally. Referring to Kizu et al., cisplatin and oxaliplatin showed biexponential pharmacokinetical profiles in rabbit plasma, such is the same case in SM54111. And SM 54111 had similar distribution volume (0.3 ± 0.04) to oxaliplatin (0.5 ± 0.05) in rabbit plasma. After all, it is prudent to deduce that the pharmacokinetic property of SM54111 is consistent with that of oxaliplatin, similar with cisplatin, but distinguishable with carboplatin (O'Dwyer, 2000).

The result proved that SM54111 underwent a long retention in rabbit plasma, expressed as Pt, and a slow elimination according to the huge distribution value, which was much larger than the rabbit's blood volume. The main mechanism is that Pt^{2+} in the compound has a tight combination with biosubstances such as thiol peptides and amino acids, apart from bases, nucleoside, and DNA. Specifically, the more the anticancer platinum complex dissociated to produce Pt^{2+}, the more combinations occurred. For example, while cisplatin dissociated in vivo more easily than carboplatin, the excretion rate of the former of ~36% in urine during the first 5 days was lower than the later of ~86% (Bernard Desoize, 2002). Admittedly, there might be other considerations to be demonstrated, such as the liposolubility or the coefficient of oil-water partition, and steric structure of the platinum complexes,and so forth (Kim et al., 1996; Motofumi et al., 1994; Shimakura et al., 2002). These results offered important insight for procedures in vivo, such as pharmacological mechanism, toxicity, and indications, thus it would be helpful to further develop this.

Indeed, pharmacokinetic investigation on a new drug candidate is a necessary preclinical and/or clinical process during drug development, which enables an understanding of the disposition of the drug in vivo, and a consideration of the pros and cons of the drug, so as to decide what kind of dosage form could be favorable, and so forth (Lv et al., 2006; Meibohm, 2002). Pharmacological experiments have indicated that SM54111 has high antitumor activity with much low effective dose compared with other compounds, such as carboplatin, oxaliplatin, and others. Doses of 2.5 mg/kg used in the pharmacokinetic study were calculated according to the pharmacological dose by the method of body surface area (BSA), and no perceivable adverse reactions and toxicity were observed till 9.0 mg/kg. Therefore, it can be understood that SM54111 cannot easily lead to disposition and toxicosis of Pt in vivo after clinical administration.

CONCLUSION

This study employed an ICP-MS method, which detected Pt concentration with high sensitivity, excellent selectivity, and reliability to investigate the pharmacokinetics in rabbit plasma on SM54111, a novel anticancer platinum complex, which was under research and development as a promising drug candidate. The results showed a long retention and slow elimination in vivo. There showed no prolongation of the $t_{1/2\beta}$ with large dose, and the CLs of the 3 doses were proximate. It is reasonable to surmise that SM54111 follows first order rate pharmacokinetics, and no saturation was detected at concentrations from 2.5 to 9.0 mg/kg. It suggested that SM54111 experienced an amiable procedure in vivo and is worthy of the further development.

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