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Monitoring Local Disposition Kinetics of Carboplatin *in Vivo* after Subcutaneous Injection in Rats by Means of ^{195}Pt NMR

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The anticancer drug carboplatin has been monitored in rats during treatment by means of *in vivo* ^{195}Pt NMR spectroscopy at 2.0 T. The purpose of the study was to assess local disposition kinetics in intact tissue following subcutaneous injection of a platinum-containing drug. Serial ^{195}Pt NMR measurements have been carried out in four animals after administration of carboplatin solutions with doses ranging from 37.1 to 59.4 mg per kg body weight. A surface coil of 2 cm diameter tuned to 18.3 MHz was placed over the injection site (back of the neck of the animals). To optimize measurement parameters of the single-pulse-acquire sequence and to determine chemical shifts and the detection threshold, *in vitro* ^{195}Pt NMR experiments have been performed on model solutions of potassium tetrachloroplatinate(II), carboplatin, and cisplatin with different solvents such as H_2O, DMSO, and DMF. Resonances of $PtCl_4^{2-}$, carboplatin, cisplatin, and *cis*-$[Pt(NH_2)Cl(DMSO)]^+$ were observed at chemical shift positions $\delta = -1623$ ppm, -1705 ppm, -2060 ppm (cisplatin in DMSO), and -3120 ppm, respectively, relative to the reference signal of Na_2PtCl_6 at $\delta = 0$ ppm. A spin–lattice relaxation time of carboplatin of $T_1 = (0.103 \pm 0.02)$ s was measured. The threshold for NMR detection of platinum-containing compounds estimated from the *in vitro* experiments was 10 μmol (corresponding to $\sim$4.8 mM). *In vivo* ^{195}Pt NMR spectra obtained in four rats after administration of carboplatin showed a broad resonance at $\delta = -(1715 \pm 8)$ ppm. The signal-to-noise ratio of this peak (starting 2 min after the injection) was $\sim$9:1 for a measurement time of 6 min (T_R= 13 ms, 28672 transients). The elimination rate constant of local disposition of carboplatin was $k_{el} = 0.017$ (0.008–0.025) min^{-1} (median and range).

INTRODUCTION

In vivo NMR has been performed with a variety of nuclei, particularly with ^{1}H, ^{13}C, and ^{31}P present in endogenous metabolites. Rare nuclei with physiological concentrations below the detection limit of *in vivo* NMR could be observed in tissue after exogenous administration of the free atom (hyperpolarized noble gases ^{3}He (*1*) and ^{129}Xe (*2*)) or of biologically active compounds that carry the magnetic nucleus (^{7}Li (*3, 4*), ^{19}F (*5, 6*)).

Another potential nucleus for *in vivo* NMR following exogenous administration is platinum, which has an NMR-detectable isotope of relatively high natural abundance (^{195}Pt). Its presence in some antineoplastic agents such as carboplatin (diammine[1,1-cyclobutandicarboxylato(2−)-*O,O′*]platinum(II)) and cisplatin (*cis*-diammine-dichloroplatinum(II)) (Fig. 1) suggests a potential for drug monitoring *in vivo* by ^{195}Pt NMR spectroscopy.

The properties of ^{195}Pt relevant for its detection with NMR are as follows: nuclear spin 1/2, gyromagnetic ratio $\gamma_{195Pt} = 5.768 \times 10^7$ (sT)$^{-1}$ (Larmor frequency 18.30 MHz at $B_0 = 2$ T), maximum nuclear Overhauser effect (NOE) factor in extreme narrowing $\eta = \gamma_{1H}/2\gamma_{195Pt} = 2.32$, chemical shift range $\sim$5000 ppm, natural abundance 33.8%, relative sensitivity 0.00994 (^{1}H: 1.00), absolute sensitivity 0.00336.

The direct observation of platinum-195 NMR signals was first reported in 1951 by Proctor and Yu for an aqueous solution of H_2PtCl_6 (*7*). A large number of ^{195}Pt NMR studies on solutions followed (reviews, see Refs. *8, 9, 10*). For example, investigations of the interaction of cisplatin with single- and double-stranded DNA *in vitro* by means of ^{195}Pt NMR (*11*) showed stable intrastrand crosslinks with the N^7-position of purine bases producing an unwinding of DNA by 13 to 23 degrees (as detected by means of 2D ^{1}H NMR and gel electrophoresis (*12, 13*)). Proton decoupling suppressed the strong scalar spin–spin interaction of the ^{195}Pt nuclei with bound ammine protons and was successfully employed in studies of the hydrolysis of platinum complexes (*14, 15*).

Since 1965, platinum-containing compounds have been known to possess antineoplastic activity (*16*), especially cisplatin and carboplatin, a second-generation drug, which have been applied in chemotherapy since 1971 and 1981, respectively. Both drugs have been shown to be effective in the treatment of a variety of malignant tumors in man, including non-small-cell lung cancer, head and neck cancer, and testicular and ovarian cancer (*17*). The antineoplastic effects of these drugs are attributed to Pt-DNA adducts that are capable of blocking replication and transcription of DNA (*11, 18*).

^{195}Pt NMR has been used to study iproplatin metabolites in the urine (*19*) of patients, but, to our knowledge, has not been applied *in vivo* so far. The aim of the present study was to explore the feasibility of ^{195}Pt NMR spectroscopy for monitoring *in vivo* the disposition kinetics of a subcutaneously

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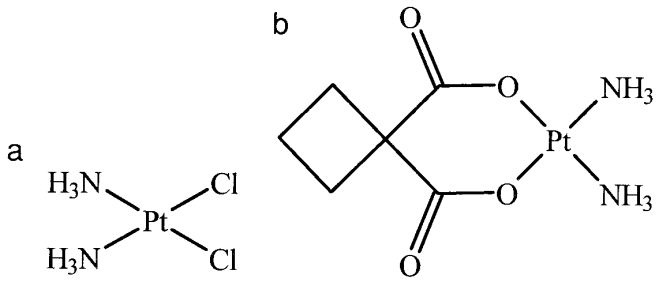

FIG. 1. Chemical structures of (a) cisplatin (*cis*-diamminedichloroplatinum(II)) and (b) carboplatin (diammine[1,1-cyclobutandicarboxylato(2-)-*O,O′*]platinum(II)).

administered platinum-containing drug at the injection site and to assess the potential of the method for biopharmaceutical purposes. The demonstration of a possible clinical relevance of ^{195}Pt NMR was not the aim of this investigation. The experiments were performed as part of a broader study where the purpose is to develop controlled-release preparations of cytostatic agents for local application.

MATERIALS AND METHODS

Animals and Treatment

Male Wistar rats (body weight [b.w.]: 499–732 g; age: 19–29 weeks) were anesthetized with O_2/N_2O (60:40, v/v) containing initially 2% (volume) halothane which was gradually reduced to 0.7% within 90 min (relatively heavy animals were used in order to allow the application of high absolute doses and thereby enhance the chance of detecting *in vivo* signals). Carboplatin, 29–42 mM in isotonic saline, was administered by subcutaneous injection within 15 s; the injection volume was 2.1 ml in all cases. Individual doses ranged from 37 to 59 mg/(kg b.w.) (Table 1). The injection site was in the center line of the back of the neck, immediately cranial of the scapulae. The solutions for injection were prepared less than 24 h before the experiments and stored at 4–7°C.

The animal experiments were performed in compliance with the laws of the FRG relating to the conduct of animal experimentation.

Platinum NMR Spectroscopy

^{195}Pt NMR experiments were performed at $B_0 = 2.0$ T in a 31-cm diameter horizontal-bore spectrometer (SIS 85/310; Varian, Palo Alto, CA). A homebuilt 2-cm diameter circular surface coil (tunable to ^{1}H and ^{195}Pt Larmor frequency) was used in all experiments. An external sample (commercial 5-mm diameter NMR tube, volume 0.5 ml) of K_2PtCl_4 dissolved in 1 M HCl served as platinum chemical shift reference (chemical shift $\delta = -1623$ ppm vs sodium hexachloroplatinate(IV), Na_2PtCl_6, resonating at $\delta = 0$ ppm). The solution was also used for calibration of the spectrometer prior to the *in vivo* ^{195}Pt NMR experiments. For the measurements with model solutions, the reference tube was placed in the center of the sample solution.

The platinum spin–lattice relaxation time T_1 was measured with the aperiodic pulse saturation (APS) sequence which is insensitive to B_1-field inhomogeneity. For driving the spin system into saturation, APS uses a train of RF pulses with decreasing interpulse delays applied at time t prior to the readout pulse. The resulting NMR signal intensity is $I(t) = I_0 \times \sin \alpha_2 \times [1-(1-\cos \alpha_1) \times \exp(-t/T_1)]$, where α_1 is the effective flip angle of the saturating pulse train, α_2 the flip angle of the readout pulse, and I_0 the signal of the equilibrium magnetization. The delay t was varied from 0.05 to 0.80 s in steps of 0.05 s. T_1 was determined by least-squares fit of $I(t)$ to the observed signal-time profile.

In the *in vivo* ^{195}Pt NMR experiments the rats were placed on a support with the surface coil positioned on the back of the neck of the animals on top of the injection site. After shimming on the tissue ^{1}H water resonance (resulting linewidth $\Delta\nu_{1/2}(^1\text{H}) \cong 30-40$ Hz [full width at half maximum]), a series of ^{195}Pt NMR spectra was acquired.

Individual transients of 1024 (1K) complex data points were accumulated over an 80-kHz spectral window using a 10-μs excitation pulse and an acquisition time of 4 ms. The delay between RF pulse and data collection was 20 μs, and repetition time T_R was 13 ms (*11*). All FIDs were zero filled to 2K data points and multiplied by an exponential function for line broadening ($\tau^{-1} = 1$ kHz) prior to Fourier transformation and phase correction. After baseline correction the Fourier spectra were analyzed by means of a least-squares fit routine assuming Lorentzian lineshapes of the resonances.

To enhance ^{195}Pt NMR signal-to-noise ratio (S/N) for the kinetic analysis of animal experiments, spectra were added resulting in a temporal resolution of 6 min (28672 transients). Half-lives ($t_{1/2}$) of the administered drug in the examined tissue region were estimated by extended least-squares fit (*20*) of a monoexponential function to the integrated peak areas, whereby the midpoints of the measuring time interval for each spectrum were taken as measurement times.

TABLE 1
Data of Examined Animals, Administered Doses, and Elimination Constants of Carboplatin

Rat no.	Body weight (kg)	Dose[a] (mg/(kg b.w.))	Rate constant[b] (k_{el}/min^{-1})	C. V.[c]
1	0.528	59.4	0.025	6%
2	0.611	44.5	0.019	10%
3	0.732	37.1	0.008	13%
4	0.499	44.5	0.015	25%

[a] LD_{50} for 500-g rats at intravenous administration: 85.0 mg carboplatin per kg b.w.
[b] $k_{el} = 1n2/t_{1/2}$.
[c] Coefficient of variation of the estimates.

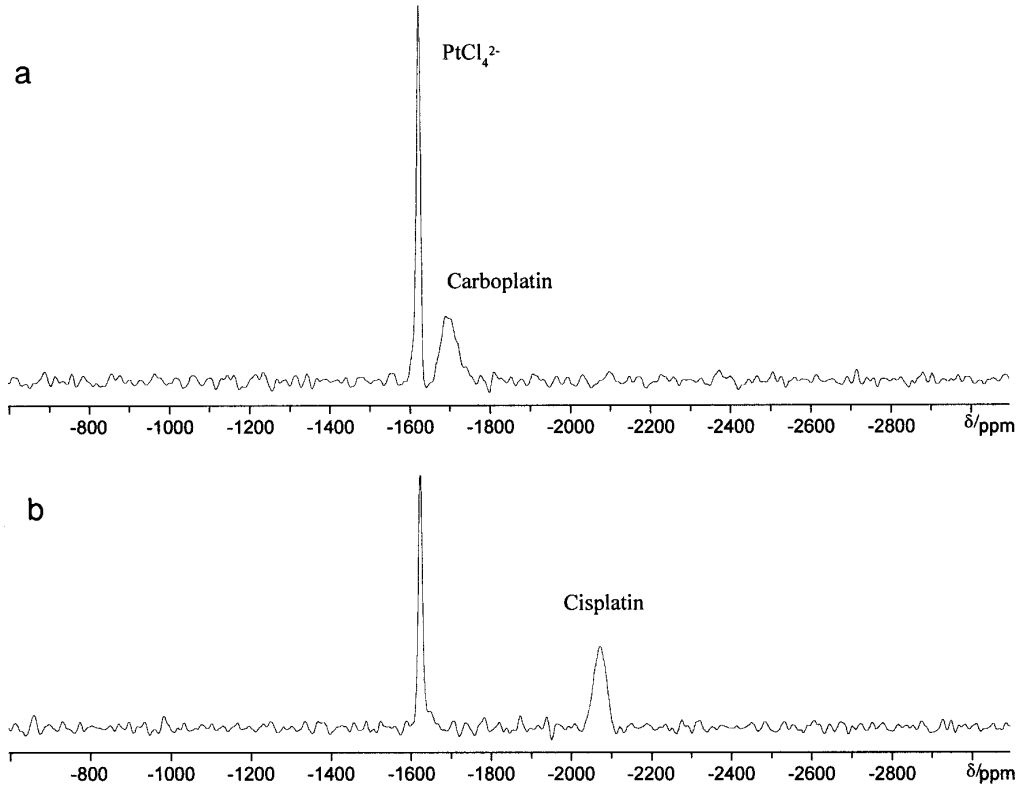

FIG. 2. ^{195}Pt NMR spectra of model solutions of (a) carboplatin (40 μmol; solvent: H_2O) and (b) cisplatin (40 μmol; solvent: DMF). Platinum resonances with $S/N \cong 10$ are found at chemical shift positions $\delta = -1705$ ppm (a) and $\delta = -2080$ ppm (b) and $\delta = -1623$ ppm ($PtCl_4^{2-}$) relative to the reference signal of $PtCl_6^{2-}$ at $\delta = 0$ ppm. Experimental parameters: $T_R = 13$ ms, measurement time = 30 min, $B_0 = 2.0$ T.

Model Solutions

14.8 mg carboplatin (purchased from Sigma-Aldrich Chemie GmbH, FRG) was dissolved in 0.5 ml H_2O by intense stirring giving a concentration $c = 80$ mM (amount of substance $A = 40$ μmol). Hydrolysis of carboplatin was not observed during the experiments. Stable carboplatin solutions were only obtained in the absence of Cl^- (chloride ions were found to trigger the transformation of carboplatin to cisplatin (*21*, *22*)). This solution was successively diluted with H_2O to estimate the minimum drug concentration that can be detected with our equipment.

Because of the poor solubility of cisplatin in aqueous solution (maximum concentration $c_{max} \cong 16$ mM), dimethylsulfoxide (DMSO) and *N*,*N*-dimethylformamide (DMF) were used to predissolve the cisplatin complex (*15*). Only fresh cisplatin/DMSO solutions could be used for the NMR measurements, because of efficient ligand exchange Cl → DMSO (*15*). DMF is advantageous over DMSO in that the weakly coordinated DMF ligand is easily replaced when water is added. (*Note:* DMF is suspected to be carcinogenic.) To measure the solvolysis kinetics of cisplatin in DMSO, a solution of 45 mg of the compound in 1 ml DMSO was prepared yielding a cisplatin concentration of $c = 150$ mM ($A = 150$ μmol) and was measured at room temperature (23°C) over a period of 9 h.

RESULTS

^{195}Pt NMR spectra of carboplatin and cisplatin model solutions are shown in Figs. 2 and 3. Broad resonances of linewidths $\Delta\nu_{1/2}(^{195}\text{Pt}) \cong 1$ kHz are found at chemical shift positions $\delta = -1705$ ppm (carboplatin, Fig. 2a), $\delta = -2060$ ppm (cisplatin/DMSO, Fig. 3) and $\delta = -2080$ ppm (cisplatin/DMF, Fig. 2b) relative to the external reference signal of $PtCl_4^{2-}$ at -1623 ppm ($\Delta\nu_{1/2}(^{195}\text{Pt}) = 170$ Hz) according to Ref. (*14*). A list of ^{195}Pt NMR chemical shifts observed in this study is given in Table 2 along with data reported in the literature.

^{195}Pt NMR $S/N \cong 10$ was obtained in a measurement time of 30 min. After comparison with the NMR intensity of the dilution series of known platinum concentrations, the detection threshold (requiring $S/N \cong 3$ in a measurement time of 10 min) was estimated to be 10 μmol. Taking into account the sensitive volume of the surface coil of about 2 cm^3 the minimum concentration of the platinum-containing compound that can be detected with our equipment is approximately $c_{min} \cong 4.8$ mM.

The APS experiment on the model solution yielded a ^{195}Pt spin–lattice relaxation time for carboplatin of $T_1 = (0.103 \pm 0.02)$ s at 2.0 T and room temperature (23°C).

Ligand exchange was observed in cisplatin solutions with

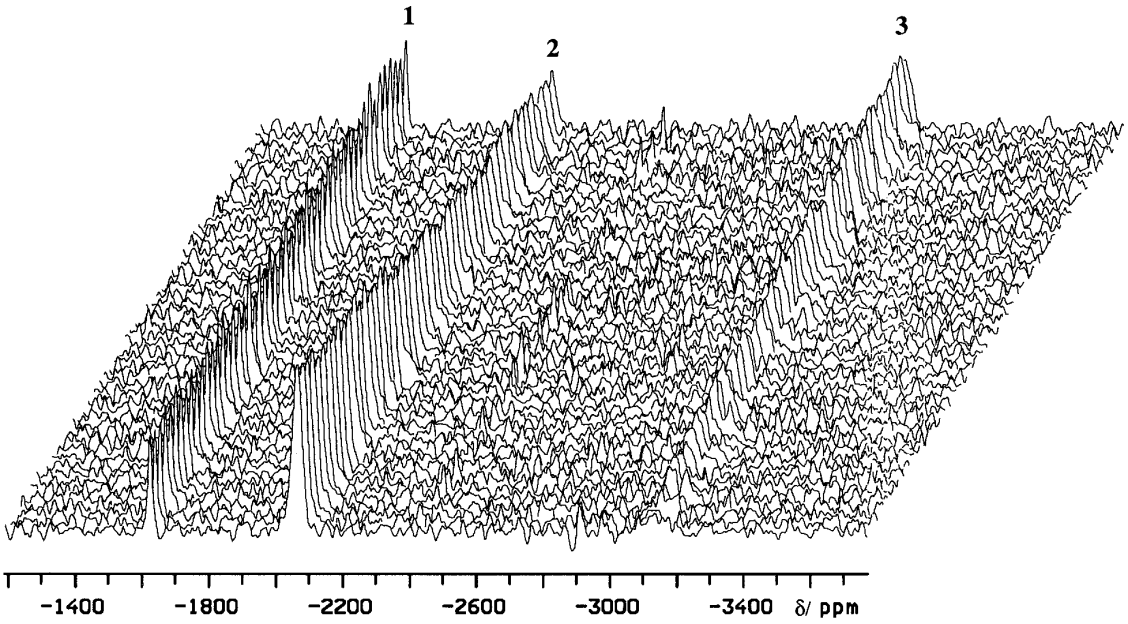

FIG. 3. Series of 6-min ^{195}Pt NMR spectra obtained during solvolysis (9 h, 23°C) of 150 μmol cisplatin in 1 ml DMSO. Every second spectrum is shown. Resonances are found at chemical shift positions $\delta = -1623$ ppm (1, $PtCl_4^{2-}$, chemical shift reference), $\delta = -2060$ ppm (2, cisplatin) and $\delta = -3120$ ppm (3, *cis*-$[Pt(NH_3)_2Cl(DMSO)]^+$).

DMSO as solvent over a period of 9 h after preparation (Fig. 3). In addition to the ^{195}Pt NMR signal at $\delta = -2060$ ppm, another resonance appeared at $\delta = -3120$ ppm which was assigned to *cis*-$[Pt(NH_2)Cl(DMSO)]^+$ according to Ref. (*15*). Signals indicative of further ligand exchange products were not observed.

With an injection volume of 2.1 ml, the maximum quantity of cisplatin in aqueous solution (≈32 μmol) is too small for kinetic NMR measurements with our equipment. Moreover, this amount of the drug would exceed the LD_{50} reported for intravenous administration in rats of 6.2 mg/(kg b.w.) (*23*) or 8.0 mg/(kg b.w.) (*24*), corresponding to 3.1 mg (10 μmol) and 4.0 mg (13 μmol), respectively, for a 500-g rat. In contrast, 170 μmol of carboplatin can be dissolved in 2.1 ml of water, and the reported LD_{50} in rats with intravenous administration is 85 mg/(kg b.w.) (*25*), corresponding to 110 μmol for a 500-g rat, which is expected to provide sufficient sensitivity for kinetic measurements.

Therefore, only carboplatin has been used in the animal experiments in this study. The resulting 6-min *in vivo* ^{195}Pt NMR spectra showed a broad unresolved resonance ($\Delta\nu_{1/2}$ (^{195}Pt) = 1.5 kHz), assigned to carboplatin, at chemical shift position $\delta = -1715 \pm 8$ ppm (Fig. 4) relative to the line of the external chemical shift reference ($PtCl_4^{2-}$) at $\delta = -1623$ ppm ($\Delta\nu_{1/2}$(^{195}Pt) = 130 Hz). The reference signal was measured before the beginning of the *in vivo* experiment.

Figure 4 shows a series of *in vivo* ^{195}Pt NMR spectra with 6-min temporal resolution obtained after subcutaneous injection of aqueous carboplatin solution in rat 1 (dose: 84 μmol). A decrease of *S*/*N* from 9 to 3 of the carboplatin resonance was

TABLE 2
Chemical Shifts of Platinum Complexes

Compound		Chemical shift δ (ppm)[a]	Reference
Tetrachloroplatinate(II)	$PtCl_4^{2-}$	−1623	−1623 (*11*)
Monoaquatrichloroplatinate(II)	$PtCl_3(H_2O)^-$	−1182	−1185 (*14*)
Cisplatin	*cis*-$[Pt(NH_3)_2Cl_2]$	−2060 (in DMSO)	−2097 (*15*)
		−2080 (in DMF)	−2104 (*8*)
	cis-$[Pt(NH_3)_2Cl(DMSO)]^+$	−3120 (in DMSO)	−3147 (*15*)
Carboplatin	$Pt(NH_3)_2(C_6H_6O_4)$	−1715 ± 8 (*in vivo*)[b]	—
		−1705 (model solution)	

[a] Chemical shift vs $PtCl_6^{2-}$ ($\delta = 0$ ppm).
[b] Error owing to B_0-inhomogeneity.

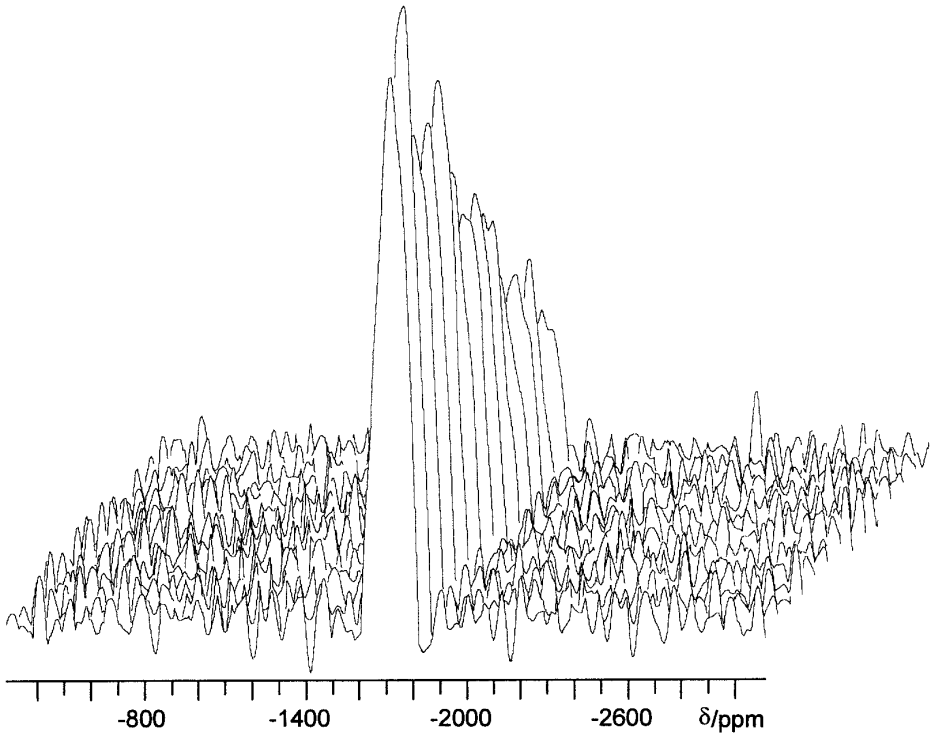

FIG. 4. Series of 6-min *in vivo* ^{195}Pt NMR spectra detected at the injection site in rat 1 during the first 78 min after subcutaneous administration of 84 μmol carboplatin.

observed during 78 min after infusion. After 90 min the carboplatin concentration in the tissue was below the NMR-detectable level. Figure 5 shows the carboplatin *in vivo* ^{195}Pt NMR signal intensity vs time after the beginning of the injection in rat 1. Estimated amounts of the drug in the tissue are also given.

Drug disposition from the injection site was satisfactorily described by a monoexponential function in all animals. The estimated elimination rate constants k_{el} of local drug disposition are given in Table 1 along with the coefficients of variation of the estimates. The half-lives $t_{1/2}$ of local drug disposition ranged from 29 to 85 min.

One animal (rat 1, receiving 59.4 mg carboplatin per kg b.w.) showed transient clinical signs of anemia about 1 week

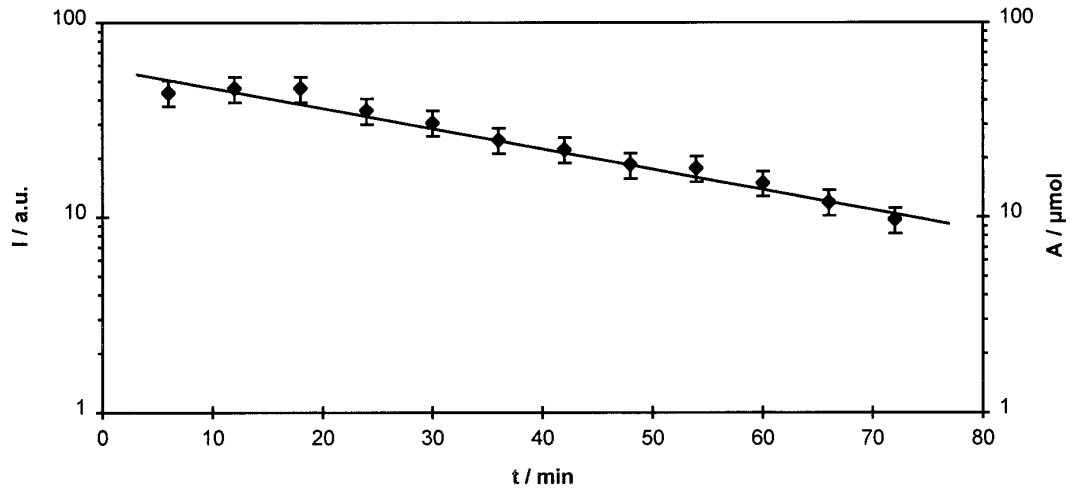

FIG. 5. Time course of *in vivo* ^{195}Pt NMR signal intensities of carboplatin from spectra in Fig. 4. Estimated amounts (A/μmol) of carboplatin in the tissue are plotted as a function of time after administration. Errors were calculated with line fit routine.

after treatment, whereas two more animals (rats 2 and 3) showed no clinical symptoms of toxicity within five weeks after treatment (animal 4 was sacrificed one day after treatment for inspection of the subcutaneous injection site).

DISCUSSION

The ability of ^{195}Pt NMR spectroscopy to follow the local disposition kinetics of a platinum-containing compound in intact tissue (mainly muscle) after subcutaneous injection has been demonstrated. Determining carboplatin disposition kinetics at the injection site will be helpful in optimizing controlled-release preparations for local administration, such as liposome-encapsulated carboplatin. Release kinetics measured *in vitro* can be compared to the disposition kinetics *in vivo* in order to obtain information on the stability of controlled-release drug preparations in a physiological environment and to assess the predictive value of the *in vitro* measurements.

The method is limited by the amount of carboplatin in the tissue region examined. The ^{195}Pt NMR experiment allows detection of 10–15 μmol (3.7–5.7 mg, corresponding to a concentration of 4.8–7.1 mM within the sensitive volume of the surface coil) carboplatin *in vivo*, corresponding to 3.3–5.0 μmol ^{195}Pt. Cisplatin could not be used for *in vivo* ^{195}Pt NMR in this study owing to its higher toxicity, which limits the applicable dose in a 500-g rat to a maximum of about 13 μmol.

Kinetic measurements in rats were possible by using relatively heavy animals and applying doses in the range of 50–100% of the reported highest tolerable intraperitoneal dose of 60 mg/(kg b.w.) (*23*). Carboplatin plasma concentrations in man after an intravenous infusion of 400 mg/(m^2 body surface) over 30 or 60 min range between 10 and 100 μM for about 3 h (*26, 27*). Thus, no attempt to measure carboplatin tissue concentrations by ^{195}Pt NMR in man after systemic administration of a therapeutic dose appears justified unless the detection volume is 1 liter or more, at the sensitivity that has been achieved in this study. However, ^{195}Pt NMR could possibly be useful even with the presently attained sensitivity in monitoring drug concentrations at the application site in ovarian cancer patients treated with intraperitoneal carboplatin.

The reasons for the large interindividual variation of disposition constants (Table 1) are not clear. The subcutaneous location of the injection cannula was verified by careful palpation in each case. One might speculate about different sensitivity to the narcotics and hence different blood perfusion at the injection site, or about disruption of microvessels by the large injection volume as possible explanations for the variation of local kinetics. Even the pressure of the surface coil on the skin directly surrounding the bulging injection site might influence the distribution of the injected fluid volume.

One of the main problems affecting ^{195}Pt NMR of cisplatin and carboplatin is the broad resonances (linewidth ~1.5 kHz) owing to strong scalar spin–spin couplings of the ^{195}Pt nucleus with ^{1}H and directly bound ^{14}N. To improve the sensitivity of the experiment, broadband proton decoupling is required to suppress the scalar ^{195}Pt–^{1}H couplings. Using this technique, *S/N* of *in vivo* ^{195}Pt NMR is expected to increase significantly. However, the interaction of the ^{195}Pt with the spin-1 nucleus ^{14}N of the ammine group is unaffected in this experiment. To reduce these couplings, labeling with ^{15}N (spin 1/2) and ^{1}H decoupling have been employed in studies of the various solvolysis products of cisplatin in DMSO (*15*).

At present, it is difficult to predict the extent of sensitivity enhancement of the cisplatin and carboplatin resonances attainable by ^{195}Pt–{^{1}H} NOE and ^{1}H decoupling, because of unknown limitations of the experiment. The NOE factor could be 2, but intensity enhancement of the dipolar coupled spin system will decrease when competing relaxation pathways are present or when longer repetition times are used to include the pulse train needed for gated/inverse gated broadband decoupling. Likewise, a quantitative comparison of ^{195}Pt NMR vs NMR with isotopically labeled drugs can only be obtained from the experiment.

Relaxation via chemical-shift anisotropy can produce significant line broadening of NMR resonances. This mechanism is field dependent, that is, the corresponding relaxation rate increases proportional to B_0^2 with higher field strength. However, chemical-shift anisotropy is probably insignificant for the broadening of the ^{195}Pt resonances of cisplatin and carboplatin as suggested by linewidths of ~1 kHz of cisplatin observed at 11.7 T without proton decoupling (*11*).

The major limitation of natural abundance ^{195}Pt NMR spectroscopy is the low detection threshold, which is approximately $c_{\min} \cong 4.8$ mM with our 2-cm diameter surface coil. In general, *in vivo* NMR spectroscopy requires concentrations of at least 1 mM to measure the isotopes ^{1}H and ^{31}P in natural abundance and ^{13}C after enrichment (*28*). An increase of ^{195}Pt *S/N* to enable the detection of concentrations of 1 mM must be the aim of further experiments.

Alternative methods to ^{195}Pt NMR are therefore ^{1}H or proton-detected ^{13}C NMR using ^{1}H–^{13}C polarization transfer. Detection of carboplatin by means of ^{1}H NMR, as demonstrated in measurements of human urine (*29*), should also be possible *in vivo*, similar to *in vivo* ^{1}H NMR measurements of iproplatin in mice by selective multiple quantum coherence transfer (*30*). However, after separation of the cyclobutane-1,1-dicarboxylic acid ligand, the remaining Pt complex cannot be detected anymore by means of ^{1}H NMR or ^{13}C NMR (*21*). Reactions in the axial position of the central platinum atom cannot be observed, either.

The absolute sensitivity ($\sim\frac{3}{4}\gamma^3 \times$ natural abundance) of ^{195}Pt NMR is significantly higher than that of natural abundance ^{13}C NMR (0.00336 vs 0.000176). With ^{13}C enrichment, *in vivo* ^{13}C NMR spectroscopy after intraperitoneal injection of drugs is possible at doses of ~400 mg/(kg b.w.) (*31*). Labeling is also possible with platinum. ^{195}Pt NMR spectroscopy with platinum-195-enriched cisplatin has been successfully applied to study reaction pathways with single-stranded DNA (*11*).

Using radiopharmaceuticals that are labeled with metastable platinum (^{195m}Pt), the measurable concentrations are expected to be about 100 times lower than the platinum levels detectable with natural abundance ^{195}Pt NMR (*32*). In animal experiments, it is possible after tissue resection to localize ^{195m}Pt-containing compounds with a spatial resolution even at the cellular level (*33*). However, the radiotracer technique measures the entire ^{195m}Pt pool in the tissue and cannot distinguish among the administered drug and the various platinum-containing compounds that are formed from the precursor. The chemical specificity, promoted by the large chemical shift range of ^{195}Pt, is a particular advantage of NMR.

Direct comparison of different spectroscopic techniques is often very difficult. The choice of a specific method depends on the purpose of the study. The direct NMR detection of the ^{195}Pt nucleus in platinum-containing compounds and their metabolic intermediates could be a useful extension of the applications of NMR to noninvasive drug monitoring.

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