The Effect of Cisplatin on Kidney Uptake of Technetium-99m-MDP in Rats

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Objective: The following experiments were performed to study the effect of cisplatin on the uptake of ^{99m}Tc-MDP in kidneys. There is renal accumulation of ^{99m}Tc-MDP bone imaging agents in patients treated with cisplatin.

Methods: Donryu rats weighing 150–160 g were administered 0.8 mg/kg of cisplatin intravenously for 7 days. On the day following the cisplatin injections and on the 37th day, we obtained ^{99m}Tc-MDP clearance from the blood and it showed two components: a fast and a slow component.

Results: On both the first and 37th days, the fast component of the cisplatin-treated group was identical to the control rats. On the contrary, the slow component of the cisplatin-treated group and control rats was 393.6 ± 116.4 min and 85.2 ± 19.9 min, ($p < 0.001$), respectively. On the 37th day, the slow components in both groups were not significantly different. Technetium-99m-MDP bone scanning was performed on the first, 15th and 37th days following cisplatin administration. The scintigram on the first day showed high uptake ^{99m}Tc-MDP in kidneys, bones and liver. On the 15th day, relatively high uptake in kidneys was observed. However, on the 37th day, ^{99m}Tc-MDP uptake of the kidneys returned to normal. The binding rate of ^{99m}Tc-MDP and ^{99m}Tc-MDP with cisplatin were 99.4 ± 0.6% and 79.0 ± 4.6%, respectively.

Conclusion: This study suggested that high renal uptake of ^{99m}Tc-MDP following administration of cisplatin was mainly due to delayed excretion of the radiopharmaceutical by binding with cisplatin.

Key Words: technetium-99m-MDP; hot kidneys; cisplatin; binding rate; bone scintigraphy

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Many kinds of phosphate compounds are used for bone imaging: tripolyphosphate by Subramanian (*1*), polyphosphate (*2*), pyrophosphate (*3*), hydroxy-ethylidene-disodium-phosphonate (*4*), and ethane-hydroxy-diphosphonate (*5*). However, methylene-diphosphonate (MDP) (*6*) and hydroxy-methylene-diphosphonate (HMDP) (*7*) are the main choices in recent years. They are easily prepared from $^{99m}TcO_4^-$ and phosphate compounds for intravenous injection, have fast plasma and tissue clearance, and distribute throughout the whole skeletal system. Therefore, they are widely used to diagnose, follow-up and determine the effect of the treatment on diseases, such as the early stage of metastasis, osteomyelitis, inflammation of joints, location of a fracture and others. Cis-diaminedichloroplatinum (cisplatin), a chemotherapeutic agent used for carcinoma, is frequently prescribed for the following cancers: lung, esophagus, head and neck, urinary tract, gynecological, neuroblastoma and others (*8*). When bone imaging was performed, following a treatment with cisplatin, the diffuse distribution throughout the whole-body and abnormal renal uptake were observed. This study was performed to clarify the mechanism of these abnormal accumulations by investigating the plasma clearance time, the bone images and the labeling efficiency of a compound. We used rats for this study to illustrate the influence of cisplatin on bone uptake and the bonding state of the compound.

MATERIALS AND METHODS

The following experiments were performed with ^{99m}Tc-MDP: technetium-99m-MDP plasma clearance, bone imaging, and technetium-99m-MDP labeling efficiency.

Technetium-99m-MDP Plasma Clearance

Twenty Donryu rats (weight 150–160 g) were used. Ten rats were used for a cisplatin study group and the other 10 were used for a control group. The amount of cisplatin administered was 0.8 mg/kg which was equivalent to human clinical use, reduced to the rat's weight. Cisplatin was administered once a day for 7 consecutive days. For the control group, the same amount of normal saline was given. Cisplatin and normal saline were injected intravenously through the rat's tail. On the first day after the end of the cisplatin administration, ^{99m}Tc-MDP

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(11.1 MBq) was injected through tail veins, and then 0.2-ml samples of blood were taken by cardiopuncture immediately, 0.5, 1.0, 2.5, 3.0, 4.0 and 5.0 hr. The activity was counted in a well counter, and adjusted by the decay factor. Then plasma clearance $T_{1/2}$ was calculated, and compared between the study and control groups. These 20 Donryu rats were kept without any further treatment for another 37 days. On the 37th day, ^{99m}Tc-MDP was injected as before, and then the same amount of blood was drawn for the measurement of plasma clearance to investigate the influence of cisplatin withdrawal.

Bone imaging

Cisplatin (0.8 mg/kg) was injected into the 10 Donryu rats for 7 days consecutively, and bone imaging with ^{99m}Tc-MDP was performed on the first, 15th and 37th days following the cisplatin administration. Three- to 4-hr delayed images were obtained with fixed counts (600 k cts) following the injection of ^{99m}Tc-MDP (37–74 MBq) in the lateral tail vein, and ^{99m}Tc-MDP uptake in the bones and kidneys were examined on scintigrams. In addition, on the first and 37th days following the cisplatin administration, the ^{99m}Tc-MDP uptake ratio in the following regions of interest (ROIs) were compared: lumbar spine, kidney and background (BG). The gamma camera (ZLC 7500, Shimazu Manufacture, Inc., Japan) used for this study was fitted with a low-energy high-resolution collimator, and the spatial resolution measurement of a ^{99m}Tc source was 3.7 mm full-width-at-half-maximum.

Technetium-99m-MDP Labeling Efficiency

Labeling efficiency was investigated for radiochemical purity 30 min after labeling ^{99m}Tc-MDP alone, and ^{99m}Tc-MDP with 100 mg cisplatin. The second elution of $^{99m}TcO_4^-$ from the generator was mixed with MDP in order to avoid radiochemical impurities. The labeling efficiency was accomplished by paper chromatography with filter paper (No. 51 Toyo, Japan) as strips, and 85% methanol as solvent. An origin was 5 cm from the end of the strips. After the application of ^{99m}Tc-MDP at the origin, the strips were dried in air, placed in developing tanks and the chromatography was carried out for 4 hr. The strips were completely dried in air again, and cut at intervals of 5 mm. The ratio between the labeled and free technetium was obtained by counting the radioactivity of each piece of the filter paper strips placed in the wells of an automatic gamma counter.

RESULTS

Plasma Clearance

Figure 1 shows the representative measurements of the plasma clearance on the first day following the 7 days consecutive cisplatin administration. Two different components were found in clearance curves. The first component was a sharp negative slope, and the second component was a slow negative slope. The $T_{1/2}$ of the control group on the first day was: 15 min for the first component and 72 min for the second component. The $T_{1/2}$ of the study group was 19.5 min and 525 min, respectively. The study group exhibited the prolonged time on the second component when compared with the control group. Table 1 shows the average of components of the $T_{1/2}$ for the study and control groups on the first and 37th day. The averages of the first component on the first and 37th day were 22.8 ± 5.0 min (on both days) for the control group, and 32.8 ± 11.8 min, and 28.8 ± 3.5 min for the study groups, respectively. There was no significant difference between the groups. The average of $T_{1/2}$ of the second component was 85.2 ± 19.9 min for the control group on the first and 37th day. The second component for the study group on the 1st day was 393.6 ± 116.4 min, and the clearance time prolongation was very significant. However, the second component for the study group on the 37th day was 96.0 ± 32.4 min, and there was no significant difference from the control group.

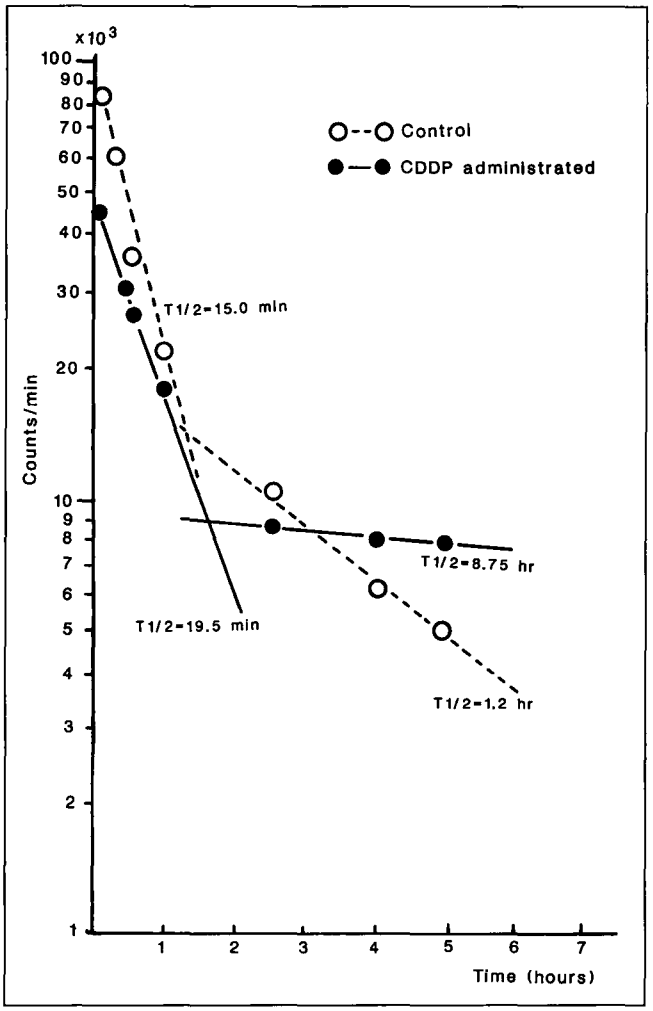

FIGURE 1. Plasma clearance on the first day following cisplatin in a control and a study rat.

Bone Imaging

Figure 2 shows the progression of the bone images. Figure 2 A shows a 4-hr delayed image with ^{99m}Tc-MDP (37 MBq) on the first day following the cisplatin administration. The high renal uptake is obvious, so-called "hot kidneys." The count ratios from the ROIs from these images were: kidney to bone

TABLE 1
Blood Clearance $T_{1/2}$ of Technetium-99m-MDP

	First component $T_{1/2}$ Mean ± s.d. in min		Second component $T_{1/2}$ Mean ± s.d. in min	
	Control n = 10	CDDP administered n = 10	Control n = 10	CDDP administered n = 10
1 day	22.8 ± 5.0	32.8 ± 11.8	85.2 ± 19.9*	393.6 ± 116.4*
37 days	22.8 ± 5.0	28.8 ± 3.5	85.2 ± 19.9*	96.0 ± 32.4

*$p < 0.001$

= 0.73 and bone to background = 2.30. Unusual uptake in the liver was recognized also.

Figure 2 (B) is the 4-hr delayed image following the injection of ^{99m}Tc-MDP (47 MBq) on the 15th day. Renal uptake was moderate and liver uptake was no longer apparent. Background uptake was still high. No significant renal uptake was identified on the 3-hr delayed image following ^{99m}Tc-MDP (47 MBq) on the 37th day, and the image was a normal bone image (Figure 2C). The count ratios were: kidney to bone = 0.38 and bone to background = 5.32.

Labeling Efficiency

Table 2 shows the result of the paper chromatography. The labeling efficiency 30 min after the preparation was 99.4% ± 0.56% for ^{99m}Tc-MDP alone, and 79.0 ± 4.58% for the mixture of ^{99m}Tc-MDP and cisplatin. The labeling efficiency was significantly decreased ($p < 0.001$) when ^{99m}Tc-MDP was mixed with cisplatin.

DISCUSSION

There are many clinical observations regarding hot kidneys caused by cisplatin. Although no definite descriptions of mechanisms are known, high renal uptake of ^{99m}Tc-MDP is the result of the inverse relationship between decreased renal function caused by the toxicity of cisplatin (*9*). No reports concerning operating mechanisms based on experiments were found. Cisplatin in blood is rapidly taken up by tissues, and its $T_{1/2}$ of concentration in blood shows two components. With mice, the first component of plasma clearance is 0.08 hr, and the second component is 19.8 hr (*10*). With rats, the first component is 9.7 min, and the second component is 35.7 hr (*11*). When cisplatin is injected into a person, it is reported that the first component is 25–49 min, and the second component is 58–73 hr (*12*). The concentration in organs, depending upon the species, varies somewhat. Kidneys always show high uptake. The liver, spleen, lungs, ovaries, uteri and tissues show relatively high accumulation. The excretion of cisplatin is mainly through kidneys. It is known that a large amount is excreted at the beginning and the remainder is excreted gradually for a long period of time (*12*).

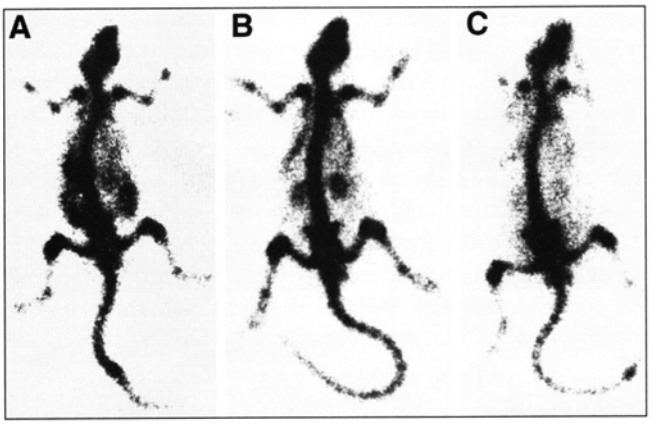

FIGURE 2. Technetium-99m-MDP bone images acquired following cisplatin. (A) Bone image acquired on the first day following cisplatin; there is a high level of renal uptake resulting in hot kidneys. (B) Bone image acquired on the 15th day following cisplatin with moderate renal uptake. (C) Bone image acquired on the 37th day, with no significant renal uptake.

In this study, we found hot kidneys in the early days following the cisplatin administration. By the 15th day, the renal uptake had decreased to moderate. By the 37th day, bone images had normalized without any abnormal uptake in the kidneys. These findings indicate that the primary factor in the relationship between cisplatin and high renal uptake is the time between cisplatin administration and bone imaging. This result agreed with the results of clinical observation described by Igari, et al. (*13*).

Among the rats in the control group, the ^{99m}Tc-MDP plasma clearance was 22.8 ± 5.0 min for the the first component, and 85.2 ± 19.9 min for the second component. On the first day, the study group exhibited about a four times prolonged plasma clearance on the second component when compared with the control group. However, on the 37th day, both groups did not show any significant differences. This indicates

TABLE 2
Percent Radiochemical Purity of Technetium-99m-MDP with and without Cisplatin

	^{99m}Tc-MDP (n = 5) Mean ± s.d.	^{99m}Tc-MDP + CDDP (n = 5) Mean ± s.d.
% Binding	99.4 ± 0.6*	79.0 ± 4.6*

*$p < 0.001$

that the first component of the plasma clearance is mainly related to the drug distribution in the body and the second component is related to the excretion from the body (*14*). Therefore, as the result of the bone image findings and the plasma clearance, we have concluded that: (a) the renal disorder caused by cisplatin is temporary and reversible, and (b) the high cisplatin concentration in the blood and kidneys has changed ^{99m}Tc-MDP's bonding condition into another which is not easily excreted through kidneys.

Technetium-99m-MDP has a stable (about 99%) labeling efficiency for at least 4 hr after preparation (*15*). Our study has shown ^{99m}Tc-MDP labeling efficiency decreased to about 80% by adding cisplatin. This decreased labeling efficiency is the possible result of ^{99m}Tc-MDP unbonding caused by cisplatin, a chelate compound, which made the chelate bonding of ^{99m}Tc-MDP unstable. One mechanism for this phenomenon is that the valence of technetium transformed resulting in a decreased labeling efficiency. Free technetium, which excretes slowly through kidneys, has formed and accumulated in the kidneys (*16*). Also, there is the possibility of colloidal formation of phosphate compounds. This statement is based on the liver uptake finding on the bone scintigraphy on the first day (*17*).

Yamada (*18*) investigated the renal disorder caused by cisplatin on renal scintigraphy. He injected cisplatin (1.8 mg/kg/day) into the abdominal cavities of rats, and investigated the renal uptake rate of ^{99m}Tc-dimercaptosuccinic acid (DMSA) by scintigraphy and measured the creatinine clearance. He reported the DMSA renal uptake slowly decreased following 7 days of cisplatin administration, and it recovered slowly toward the 15th day. DMSA was taken up by the tubular cells of renal cortex and showed the dysfunction of the renal cortex. On the other hand, cisplatin is known to cause disorders to the tubular cells about 4 days following cisplatin administration (*19*).

Our study has shown hot kidneys are frequently seen following cisplatin administration. This finding decreased gradually with time. The appearance of the hot kidneys with ^{99m}Tc-MDP may be a different phenomenon of renal uptake. The study of ^{99m}Tc-DMSA uptake rate by scintigraphy seems to be detecting renal dysfunction.

CONCLUSION

When the study and the control groups were compared, the study group revealed prolonged ^{99m}Tc-MDP plasma clearance. The second component of clearance $T_{1/2}$ of the study group demonstrated a four-fold prolongation in clearance. Four-hr delayed bone scintigraphy performed on the first day following the 7 consecutive days of cisplatin administration exhibited abnormal accumulation in the kidneys. However, the bone scintigraphy done on the 37th day following the cisplatin administration displayed a bone image without any abnormal accumulation of ^{99m}Tc MDP in the kidneys. The ^{99m}Tc-MDP labeling efficiency was decreased in the presence of cisplatin. This indicates the renal uptake caused by cisplatin, the decreased ^{99m}Tc-MDP labeling efficiency and possible colloidal formation should be considered when cisplatin has been administered.

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REFERENCES

1. Subramanian G, McAfee JG. A new complex of ^{99m}Tc for skeletal imaging. *Radiology* 1971;99:192–196.
2. Subramanian G, McAfee JG, Bell EG, et al. Technetium-99m-labeled polyphosphate as a skeletal imaging agent. *Radiology* 1972;102:701–704.
3. Baker JP. Technetium-99m-pyrophosphate-A new bone-seeking nuclide. *J Nucl Med Technol* 1973;1:24–26.
4. Castronovo FP Jr., Callahan RJ. New bone scanning agent: ^{99m}Tc-labeled 1-hydroxy-ethylidene-1,1-disodium phosphonate. *J Nucl Med* 1972;13:823–827.
5. Yano Y, Mcrae J, Van Dyke DC, et al. Technetium-99m-labeled stannous ethane-1-hydroxy-1,1-disphosphonate: a new bone scanning agent. *J Nucl Med* 1973;14:73–78.
6. Subramanian G, McAfee JG, Blair RJ, et al. Technetium-99m-methylene diphosphonate—A superior agent for skeletal imaging: comparison with other technetium complexes. *J Nucl Med* 1975;16:744–755.
7. Hayasaka K, Arakawa K, Sugie H, et al. An experience with ^{99m}Tc-hydroxy methylene diphosphonate ^{99m}Tc-HMDP as a new bone scanning agent. *Radioisotopes* 1984;33:714–716 (in Japanese).
8. Yokoyama M. Cisplatin. *Antibiotics and chemotherapy*. 1987;11:1839–1849 (in Japanese).
9. Sakatoku H, Kawai K, Kamiya H, et al. Studies on adequate intervals of cisplatin administration to ameliorate cisplatin-induced nephrotoxicity. *Jpn J Cancer Chemother* 1986;13:239–246 (in Japanese).
10. Litterst CL, LeRoy AF, Guarino AM. Disposition and distribution of platinum following parenteral administration of cis-dichlorodiammineplatinum (II) to animals. *Cancer Treat Rep* 1979;63:1485–1492.
11. DeConti RC, Toftness BR, Lange RC, et al. Clinical and pharmacological studies with cis-diaminedichloroplatinum (II). *Cancer Res* 1973;33:1310–1315.
12. Inagaki J, Kimura K. Cisplatin. *Saishin-Igaku*. 1986;41:497–502 (in Japanese).
13. Igari H, Yamada K, Fuziwara T, et al. Renal accumulation of ^{99m}Tc-labeled bone imaging in patients treated with cisplatin. *Nippon Act Radiol* 1989;49:1017–1024 (in Japanese).
14. Takada K, Asada S. *Drug Dynamics*. Hirokawa Book Concern: 1979 (in Japanese).
15. Ogata Y, Terui T, Sato T. Investigation of the quality control for ^{99m}Tc-binding chemical compounds. *Tohoku J Nucl Med Technol* 1989;1:105–122 (in Japanese).
16. Nakahara S. *Biochemistry and chemistry complex. Antibiotics and chemistry*. Nanei-Do: 1967;79:3–35 (in Japanese).
17. Eckelman WC, Reba RC, Kubota H, et al. ^{99m}Tc-pyrophosphate for bone imaging. *J Nucl Med* 1974;15:279–283.
18. Yamada M. Assessment of ^{99m}Tc-DMSA renography and uptake compared with creatinine clearance in rats with drug-induced nephrotoxicity-II. cisplatin-induced nephrotoxicity. *Japanese J Nucl Med* 1991;28:347–354 (in Japanese).
19. Yoshimine K. Experimental study of nephrotoxicity after administration of cis-diaminedichloroplatinum (II). *Nishi-Nippon Urology* 1983;45:511–525 (in Japanese).