THE METABOLISM OF TITANIUM AND OTHER ELEMENTS IN WISTER RATS*

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ABSTRACT

The concentrations of Ti and Ca, P, K, Fe, Cu and Zn in blood samples were determined by PIXE after a single intravenous and a single oral dosing with titanium- ascorbate (Ti- Vc) in Wister rats. Following the intravenous injection with 50 mg Ti- Vc/kg body weight, the absorption, distribution and clearance in blood could be described by an exponential equation of three terms. After gavaged with 500 mg Ti- Vc/kg body weight, at 1.5 h the content of Ti reached the highest level. The concentration of Ca was increasing with the absorption, distribution and clearance of Ti in blood. The contents of Fe and K were decreasing. And the contents of Cu and Zn were significantly fluctuating. The effect of Ti on animal growth could be explained by the fact that Ti- Vc supplementation could promote the absorption of Ca.

Keywords: PIXE Titanium- ascorbate Pharmacokinetics Dosing Major and trace elements

Ⅰ. INTRODUCTION

Titanium- ascorbate (Ti- Vc) as an additive for animal feed and plant (fruit and crop so on) fertilizer is more widely used in order to obtain more and more better food for human being. A series of experiments show the benefits of 5—30% for agricultural and livestock products can be obtained. The remains of titanium in some food sources will be increased with the wide spread of Ti- Vc. Sequentially, the total intake quantity of titanium will be increased in human body. Effects of Ti- Vc on animal reproduction and pig heart have been observed[1]. According to the criteria of "beneficiality" defined by Pais[2], titanium is one of the beneficial elements. Therefore in animal information of titanium metabolism and its influence on other elements are of interest[3,4]. Proton- induced X- ray emission spectrometry (PIXE) has been used for the determination of titanium and other elements in blood and organs of Wister rats at different time after a single oral and a single intravenous administration.

Ⅱ. MATERIALS AND METHODS

Titanium metabolism was measured in twenty four Wister rats. Three male rats

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(250—300g) were dosed orally with 500 mg/kg body weight using the solution of Ti- Vc 50 mg/ml. The other fifteen male rats (250—300g) were dosed intravenously with 50 mg/kg body weight using the solution of Ti- Vc 10 mg/ml, twelve of them were prepared for organs analysis. The three females were dosed in the same way using the solution of Ti- Vc (10 mg/ml) mixed with $FeSO_4$ (2 mg/ml). Before and after oral or intravenous administration 0.2—0.3 ml of blood in nine rats, three rats for each dosing way, was drawn at different time as shown in figures. The three male rats before treatment were killed and the twelve rats were divided into four groups after intravenous treatment were killed at 8 h, 24 h, 3 d and 7 d. The components of Ti- Vc are 15.2% Ti, 45% Vc and 27.6% Cl.

The X- rays were induced by 2.4 MeV proton beam from Van de Graaff in IHEP, Academia Sinica, a Si(Li) detector with the resolution of 176 eV (FWHM at 5.9 keV) was used and an absorber of 10 mg/cm^2 aluminum with a hole (1 mm diameter) was placed between detector and target in our PIXE system.

The target preparation was that 0.1ml of blood or about 30 mg dried tissues each was taken from a sample into a 3 ml quartz vessel, dried at 60°C, weighted and ashed at a low temperature, then 0.1 ml of nitric (1:1) acid and 60 μ g yttrium, as an internal standard, was added, dropped on a polycarbonate film (5μ m) and dried at room temperature for PIXE. The IAEA's Freeze Animal Blood (A- 13), standard reference material (SRM) was determined by the same procedure. Considering the inhomogenerity of SRM, four samples of IAEA- A- 13 with different weight about 10—30 mg and the standard solutions of Fe, Zn and Cu with various concentrations were determined. The Ti- Vc solution of known concentration was considered as a standard of Ti in order to avoid system errors between different methods. The levels of titanium in feces, urine and most of organs were analyzed by spectrophotometry[7]. Other details on the residue, accumulation and toxicity with organic titanium are given elsewhere[8,9].

III. RESULTS AND DISCUSSION

1. Absorption, distribution and clearance of titanium

In Fig.1 the relation between the average concentration of Ti in three rats and time after intravenous administration was shown. By means of residue method[5] the distribution and clearance of titanium in blood could be described by an exponential equation of three terms. The concentration expression of blood titanium is

$$C = 1.05 \exp(-0.27t) + 0.324 \exp(-0.016t) + 3.10 \exp(-2.45t)$$

The three different components of the curve have been identified with the half- time of 0.28, 2.56 and 43.6 h, respectively. After intravenous dosing, at 11.5 h the distribution of Ti from blood to organs and other tissues was about 95% of the administered Ti, at 196 h about 95% intravenous dose, as calculated by

pharmacokinetics model[6], was cleared from blood. As reported elsewhere[7] after intravenous administration the distribution of titanium in organs at the different time was described in Table 1. The highest concentrations were found in the liver, kidney and lung at 8 h after treatment. The total Ti contents of organs have accounted 90% of dosing at 168 h, these results of measurement were in good coincidence with the value of our estimation and could implicate that Ti possibly in bound state exist in organs or tissues with higher affinity. The relation between the concentration (average value of three rats) of Ti in blood and time after oral dosing was shown in

Table 1

Concentrations(ppm) of Ti in specific organs after a single intravenous administration at different time (wet weight)

Time	Heart	Liver	Spleen	Lung	Kidney	Stomach	Intestine	Testis	Muscle	Brain
	7.85	44.94	3.90	16.07	11.96	1.78	3.01	0.59	4.41	0.16
8 h	(0.87)	(1.04)	(0.69)	(5.76)	(3.75)	(0.57)	(0.43)	(0.0)	(1.42)	(0.0)
	7.63	43.29	8.35	6.60	15.07	1.05	3.64	0.91	4.44	0.93
24 h	(1.89)	(14.34)	(1.32)	(1.87)	(1.70)	(0.36)	(0.53)	(0.06)	(0.81)	(0.15)
	7.54	35.94	12.99	4.66	17.61	2.78	4.19	0.96	4.61	1.31
3 d	(0.59)	(2.90)	(2.12)	(0.40)	(2.49)	(1.05)	(0.20)	(0.22)	(0.45)	(1.04)
	3.20	19.66	25.94	3.88	26.49	6.07	3.68	1.47	5.18	2.01
7 d	(1.60)	(3.20)	(2.08)	(1.05)	(4.02)	(1.50)	(0.43)	(0.72)	(0.27)	(0.67)
Before dosing	<MDL	0.1	0.2	0.1	0.3	0.1	0.1	<MDL	0.1	0.1

Note: The number in brackets is the standard deviation

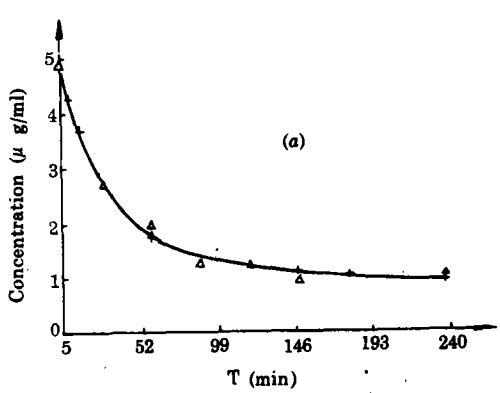

Fig.1*a*. Regression of blood Ti concentration as a function of time after intravenous administration to rats

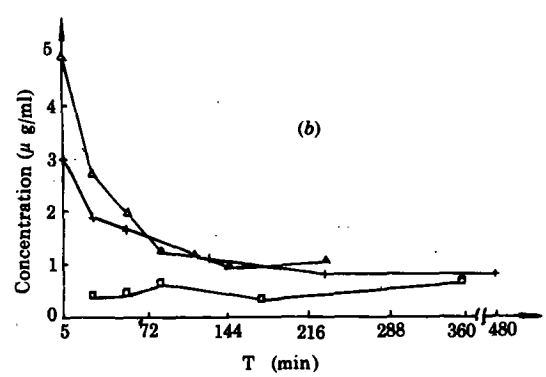

Fig.1*b* Change of concentration of blood Ti with time after administration

□ oral group △ intravenous group (male)

\+ intravenous group (female)

Fig.1*b*. After oral dosing at 1.5 h the content of titanium reached a highest level. Fig.2 illustrated that the accumulate percentage of the excretion from feces after oral dosing was 79—80% of the administered titanium at 72 h and the main part was not from urine, it means that gastrointestinal absorption was low in rats. Both of the

administrations indicated the clearance of Ti from whole body was very slow, because the sampling time and the sensitivity were not optimal, the biological half- life of element Ti in whole body could not be accurately determined in this study.

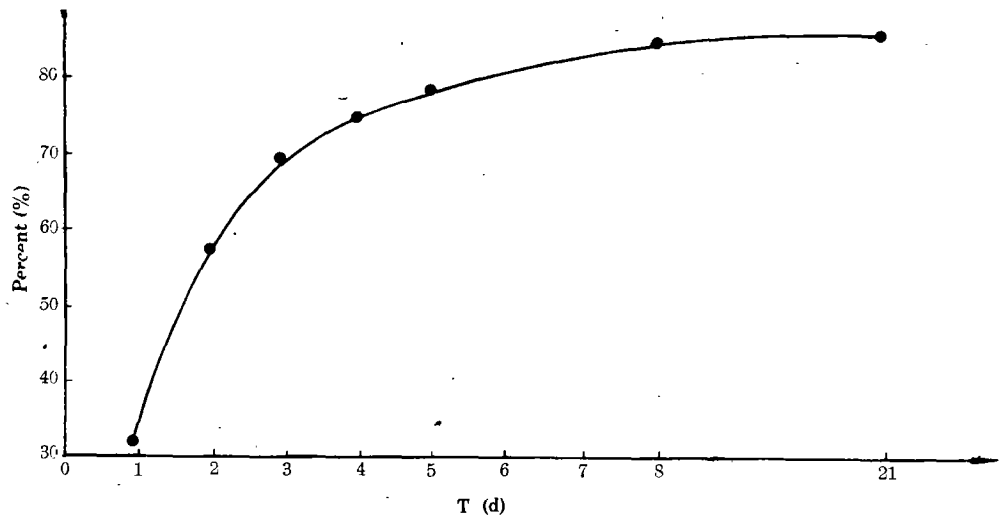

Fig.2 Excretion from feces (accumulate percent) after oral administration to rat

2. Effects of titanium treatment on other elements

The values of Fe, Zn and Cu were obtained by integration of Fe, Zn, Cu and Y characteristic $K\alpha$ X- ray peaks from the calibration curves made by several standards of known Fe, Zn and Cu concentrations with the same quantity of Y in all of the samples. The Fe, Zn and Cu concentrations of biological SRM (IAEA- A- 13) determined by PIXE technique and the certified values give similar average values. The results are shown in Table 2. The Ca and K concentrations of samples were determined by using SRM, due to the fact that the samples are similar to SRM (IAEA- A- 13) in the ratio of K to Ca peak area, the interference of neighbor elements K and Ca could be partly canceled.

Table 2

Fe, Zn and Cu concentrations in standard reference materials IAEA—A—13

Element	Certified	Found ($n=4$)
Fe (mg/g)	2.5 (2.1—2.8)	2.19±0.25
Zn (μ g/g)	13 (12—14)	13.2±2.8
Cu (μ g/g)	4.3 (3.7—4.8)	4.5±2.5

The relations between the contents of other elements (K, Ca, Fe, Cu, Zn, P) in blood after administration and the time were obtained simultaneously with the measuring titanium (Fig.3). The results revealed that the content of calcium in blood

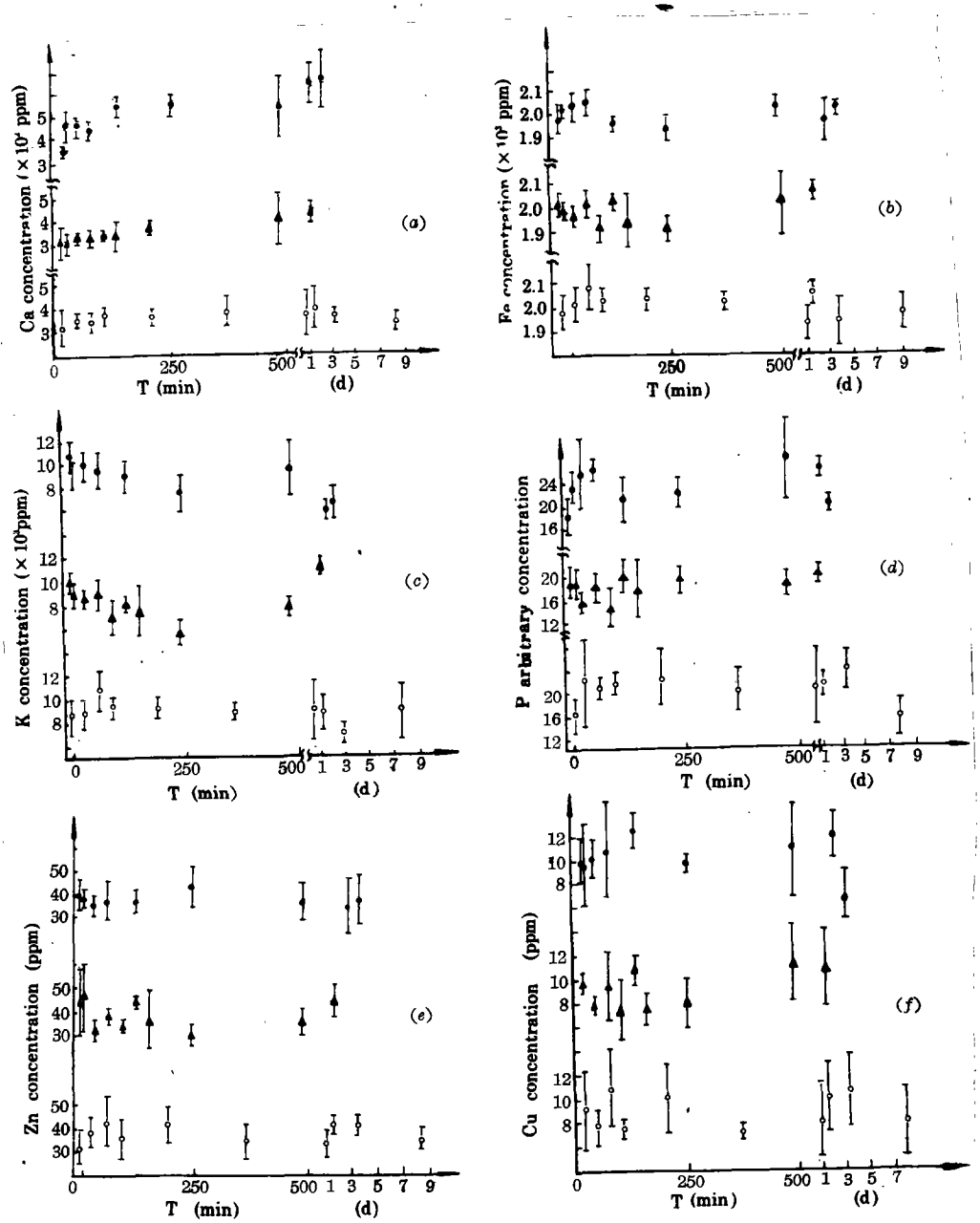

Fig.3 Concentration of other elements at different time after administration with Ti—Vc

O oral group ▲ intravenous group (male) ● intravenous group (female)

Note the bar in Fig.3 is the standard deviation

was obviously increasing (particular in female group) with time; the concentrations of

elements Fe and K were decreasing; and the contents of elements Cu and Zn were significantly fluctuating in both male and female groups. However, all the above changes except for element Ca in female group are smoother and smaller than those in male groups. In the oral group the change of concentration for these elements was less than that of the intravenous group or even not significant.

All of these results implicated that during the absorption, distribution and clearance of Ti after dosing content of other elements could be changed. Our results indicated that probably Ti and Ca are synergetic, and the calcium level in every group was raised more than 20% (Fig.3*a*). The effect of Ti on animal growth could be explained by the fact that Ti– Vc supplementation could promote the absorption of Ca, which is a major element for animal growth. The absorption of Fe might be reduced by the higher absorption of Ca. On the other hand, the reduction of Fe could be attributed to that Ti– Vc is a complex compound, which could increase the clearance of Fe. But the antagonist action between these elements and Ti (or Fe), and the synergetic action between Ca and Ti (or Fe) are very complex and need further investigation.

REFERENCES

[1] I.Pais, Proc. 4th international trace element symposium, Budapest, 1990, p.191.

[2] I.Pais, Proc. 4th international trace element symposium, Budapest, 1990, p.289.

[3] G.Kazantzis, *Environmental Health Prespectrives*, **40** (1981), 143.

[4] L.Friberg et al., Handbook on the toxicology of metals, Vol. II, Elsevier, Amsterdam, 1986.

[5] M.Glbaldi and D.Perrier, Pharmacokinetics, Marcel Dekker Inc., New York, 1975, p.280,

[6] M.Glbaldi and D.Perrier, Pharmacokinetics, Marcel Dekker Inc., New York, 1975, p.89

[7] Wang Min, "The toxicokinetics of titanium– ascorbate in rats", Thesis, Beijing Institute of Labor Hygiene and Occupation Diseases, 1990.

[8] J.L.Li, Proc. Division of Beijing Association Chinese Academy of Preventive Medicine (in Chinese), 1990, p.80.

[9] J.L.Li, Proc. Division of Beijing Association Chinese Academy of Preventive Medicine (in Chinese), 1990, p.85.