

Paraquat vitamin C 가 plasma total antioxidant capacity

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=Abstract=

Effect of vitamin C on plasma total antioxidant status(TAS) in patients with paraquat intoxication

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Background : This study was undertaken to evaluate the effect of plasma concentration of vitamin C is on the plasma total antioxidant status(TAS) in patients with paraquat intoxication.

Methods : As a preliminary research for this study, we measured plasma vitamin C levels, uric acid, TAS, and bilirubin from 100 healthy Koreans aged between 25-55 years. Various concentrations of vitamin C were constructed in vitro with normal pooled plasma between 1mg/dl and 100 mg/dL and TAS was measured. Both vitamin C concentrations and TAS were measured from the blood samples, taken at 0.5, 1, 2, 3, 5, 7, 9 hours after a bolus injection of vitamin C(50 mg/kg) from 7 volunteers who had been recruited from medical students at our hospital. Various amounts of vitamin C were given to 10 patients with paraquat intoxication for 5 consecutive days in the morning : first day ; 100 mg single dose, second day; 500 mg single dose, third day ; 1,000 mg single dose, fourth day : 3,000 mg single dose, and fifth day ; 3,000 mg three times every 8 hours.

Results : The mean value of TAS and vitamin C measured in 100 healthy Korean adults was 2.22 ± 0.16 mmol/L and 0.48 ± 0.10 mg/dL. Age and sex do not influence these levels($p > 0.05$, data are not presented). A direct correlation was observed between TAS and vitamin C concentrations of 1 mg/dL and 100 mg/dL both in vivo and vitro. As the vitamin C concentration was increased gradually 5 consecutive days, the TAS values increased in the same way as follows : first day(vitamin C 100 mg) 2.26 ± 0.98 mmol/L, second day(vitamin C 500 mg) 2.76 ± 0.78 mmol/L, third day(vitamin C 1,000 mg) 2.81 ± 0.68 mmol/L, fourth day(vitamin C 3,000 mg) 3.18 mmol/L. On the fifth day when 3,000 mg of vitamin C was given by bolus intravenous injection 3 times(every 8 hours for a day), the TAS values measured one hour after the injection was 3.58 ± 0.37 mmol/L.

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Conclusion : When vitamin C is used as a free radical scavenger, the loading dose and maintenance dose should be around 2278 mg intravenous bolus and 146 mg/hour. High doses of vitamin C are effective and safe for patients with acute paraquat intoxication.(Korean J Med 58:666-674, 2000)

Key Words : Paraquat; Free radical scavengers; Ascorbic acid; Pulmonary fibrosis

500 . Paraquat
 ROS
 (Reactive oxygen species : ROS) . ROS paraquat
 (antioxi- Paraquat vitamin C antioxidant
 dant) (oxidative damage) 33- 36)
 , supero- (basal antioxidant status : BAS)
 xide dismutase, catalase, glutation peroxidase 가
 vitamin A, vitamin C, vitamin E, glutathione, .
 bilirubin, urate 1). vitamin C (pharma-
 ROS cokinetics) (therapeutic
 2, 3), 4), window)
 5), 6, 7), 8), 9, 10),
 3, 11), 1), postischemic reoxygenation 1)
 12),
 13) melatonin¹⁴⁾, alpha- toco- 28 76
 pherol¹⁵⁾, urate⁸⁾, dexamethasone¹⁶⁾, butylated hydroxy- 50 (30 , 20) 7
 toluene¹⁷⁾, vitamin B¹⁸⁾, aminoacids(sulfhydryl group)¹⁹⁾, 4 , paraquat
 vitamin C^{20- 27)} . vitamin C 가 10 (5 5)
 가 vitamin C
 (Handok pharmaceuticals Co.,
 Paraquat (1,1' - dimethyl- 4,4' - bipyridium dichloride) Seoul, Korea, Under license of Hoechst AG. Frankfurt,
 가 Germany). Vitamin C
 (photosynthesis) ROS가
 , 50 , X-ray, , SGOT/SGPT, ,
 28- 32). vitamin C TAS
 . Vitamin
 가 , , ,
 가 가 1 ,
 가 200 50% 가
 Vitamin C (pharmacokinetics)

Table 1. Baseline characteristics of the study subjects

Parameters	Medical Students	Paraquat Intoxication	Healthy Pt Participants
Male/Female(n)	4/3	5/5	30/20
Age(years)	23.2±0.5	45.7±13.4	47.4±16.7
Height(cm)	169.8±3.5	165.7±3.8	165.3±7.2
Weight(kg)	60.2±3.5	60.0±2.8	60.1±1.5
Blood chemistry			
Total protein(mg/dL)	7.6±0.6	7.5±0.8	7.8±0.4
Albumin(mg/dL)	4.4±0.2	3.2±0.3	4.6±0.2
Fasting glucose(mg/dL)	95±2.6	101±4.7	93.9±6.4
Bilirubin total(mg/dL)	0.7±0.3	1.5±0.8	1.0±0.4
BUN(mg/dL)	15.4±2.4	13.7±3.8	14.5±2.8
Creatinine(mg/dL)	0.7±0.2	1.2±0.6	0.9±0.6
Uric acid(mg/dl)	5.4±1.3	5.6±1.5	5.5±1.1
Cholesterol total(mg/dL)	175.7±22.0	165.0±22.3	171.1±26.4
Triglyceride(mg/dL)	101.1±23.4	95.6±31.2	97.8±36.9
Vitamin C(mg/dL)			0.48±0.10

Datas are presented as mean ± SD

7 . creatinine, FBS, urate Table 1 .

4

1. Vitamin C

Photometric method

ascorbic acid가 Cu²⁺ dehydroascorbic acid

2,4- dinitrophenylhydrazine (bis- hydrazone) .

0.5 mL metaphosphoric acid 2

5) Vitamin C 가 TAS mL vortex 2,500 x g 10

1.2 mL DTCS(thiorea solution 5mL, copper sulfate solution 5 mL, 2,4- dinitrophenylhydrazine 100 mL) 0.4 mL 가 . 37 3

12 mol/L sulfuric acid 2 mL 가 520 nm

21.2±5.4

vitamin C TAS

36 Kit(ABTS^R · Randox Lab. Ltd., UK)

(wash out period) . Vitamin C Hitachi^R 7150(Hitachi Ltd. Tokyo)

(total antioxidant status) .

vitamin C vitamin (free radical) ABTS[2,2'- aminoacid TAS vitamin Azino- di- (3-ethylbenzthiazolline sulphonate)]

, BUN peroxidase (metmyoglobin) H₂O₂

8 : Paraquat vitamin C 가 plasma total antioxidant capacity

ABTS + 2.00] . Vitamin C

600 nm Vitamin C vitamin C

가 distribution volume(32.0 L)

3. Vitamin C 가 TAS

In vitro In vivo vitamin C

TAS . In vitro

5 normal pooled plasma

vitamin C 가 1 mg/dL 100 mg/dL

vitamin C TAS

In vivo 7 basal

level vitamin C 50 mg/kg

(2,500-3,000 mg) 0.5, 1, 2, 3, 5, 7, 9

vitamin C TAS

Vitamin C

4. Paraquat Vitamin C 가

TAS

Paraquat 10

가 4

vitamin C 100 mg, 2 500 mg, 3

1,000 mg, 4 3,000 mg

TAS . 5 3,000 mg

8 1

3 TAS . Vitamin C

, , , 4

CBC, liver function test, urinalysis, arterial blood gas analysis 1 .

5.

data mean ± SD . Paraquat

vitamin C data

paired t-test . Vitamin C

TAS (basal

levels: 2.22±0.16 mmole/L) two standard deviation

(0.16×2 mmole/L) 가 vitamin C

(In vivo) vitamin C TAS

{[TAS(mmole/L)=0.078xvit.C(mg/dL)

1. vitamin C TAS

50 vitamin C

0.48±0.01 mg/dL, TAS 2.22±0.16 mmole/L

(p>0.05).

2. Vitamin C 가 TAS

In vitro : Normal pooled plasma vitamin C 가

1 mg/dL 100 mg/dL

TAS vitamin C TAS

{[TAS(mmole/L)=0.036 × vit.C(mg/dL)

+2.32], R-squared : 0.976, p=0.0001, Figure 1}.

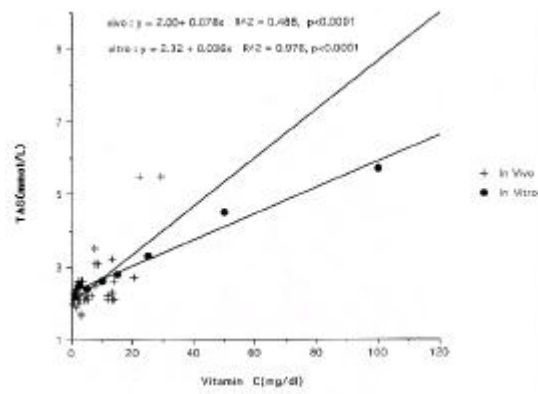


Figure 1. Relationship between TAS and vitamin C concentrations of 1mg/dL and 100 mg/dL both in vivo and vitro. Note there is a direct correlation in vitro {[TAS (mmole/L)=0.036 × vit.C(mg/dL)+2.32], R-squared : 0.976, p=0.0001} and in vivo {[TAS (mmole/L)=0.078 × vit.C(mg/dL)+2.00], R-squared : 0.488, p=0.0001}.

In vivo : Vitamin C 50 mg/kg 0.5, 1, 2, 3, 5, 7, 9

vitamin C TAS

가 {[TAS(mmole/L)=0.078 × vit.C(mg/dL)

+2.00], R-squared : 0.488, p=0.0001, Figure 1}.

3. Vitamin C (pharmacokinetics)

Vitamin C distribution

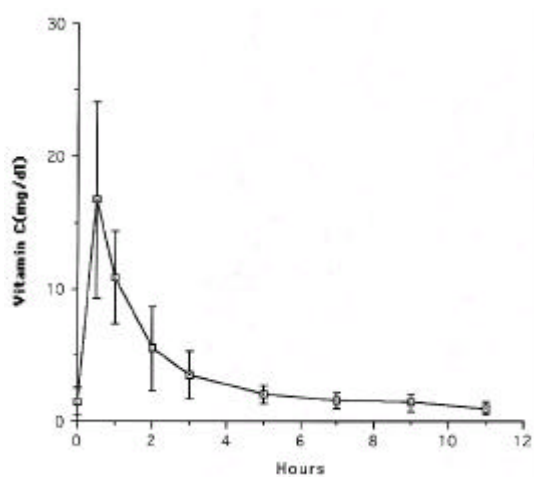


Figure 2. Vitamin C pharmacokinetics : The pharmacokinetic data obtained from 10 volunteers after 3,000mg of vitamin C injection intravenously : Distribution volume : 32.0 ± 14.4 L, AUC(area under curve) : 36.4 ± 11.3 mg.hour/dL, plasma clearance 2.13 ± 1.36 L /hour, Half life($T_{1/2}$) : 10.2 ± 7.8 hour, C_{max} (maximum concentration) : 17.1 ± 7.1 mg/dL, T_{max} 0.64 ± 0.24 hour.

volume 32.0 ± 14.4 L, AUC(area under curve) : 36.4 ± 11.3 mg.hour/dL, plasma clearance 2.13 ± 1.36 L/hour, ($T_{1/2}$) : 10.2 ± 7.8 hour, C_{max} (maximum concentration) : 17.1 ± 7.1 mg/dL, T_{max} 0.64 ± 0.24 hour (Figure 2).

4. Paraquat Vitamin C 가 TAS
 Paraquat 10
 가
 vitamin C 100 mg, 2 500 mg, 3
 1,000 mg, 4 3,000 mg
 TAS 2.21 mmol/L, 2.26
 mmol/L, 2.76 mmol/L, 2.81 mmol/L, 3.18 mmol/L
 vitamin C 가 TAS가 가 .
 vitamin C 3,000 mg 8
 1 TAS 3.58
 ± 0.37 mmol/L (Figure 3).

Table 2. Change of clinical datas before and after vitamin C injection in patients with paraquat intoxication

Parameters	Basal levels	After Vita. C Infusion*	p - value
Systolic BP(mmHg)	120.4 ± 7.3	122.3 ± 6.5	>0.05
Diastolic BP(mmHg)	80.4 ± 5.2	80.3 ± 3.4	>0.05
Respiratory Rate(/min.)	17.3 ± 2.4	18.2 ± 12.1	>0.05
Body Temperature()	36.8 ± 0.2	36.7 ± 0.2	>0.05
CBC			
WBC count(mm ³)	9,000 ± 564	8,500 ± 347	+
Hemoglobin(g/dL)	14.3 ± 1.3	14.7 ± 1.2	>0.05
Hematocrit(%)	39.5 ± 5.2	39.4 ± 7.8	>0.05
Liver function test			
SGOT (IU)	27.0 ± 3.8	22.0 ± 2.7	++
SGPT (IU)	18.7 ± 3.7	17.7 ± 3.6	>0.05
Urinalysis			
RBC(HPF)	(2/ 10)	(2/ 10)	>0.05
WBC(HPF)	(1/ 10)	(1/ 10)	>0.05
Proteinuria [†]	(1/ 10)	(1/ 10)	>0.05
Arterial blood gas analysis			
PaO ² (mmHg)	99.5 ± 3.4	87.3 ± 7.1	+++
PaCO ² (mmHg)	35.5 ± 2.1	38.4 ± 3.2	+

* After the sampling for the basal level, the amount of vitamin C had increased every day from 100 mg to 9,000 mg/day(for details, see the text). Blood samples were drawn at the next day of last vitamin C injection.

† Only one case showed one plus proteinuria before and after vitamin C injection.

+ ; $p < 0.05$, ++ ; $p < 0.01$, +++ ; $p < 0.001$

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가 , 14.4 L . 2,176 mg(32 x 69
 . WBC, SGOT, PaO₂
 PaCO₂ 가 (Table 2). vitamin C 10.2 . 2
 500 mg
 1,000 mg/ 10 paraquat
 vitamin C 가 가 . 8 2,000-3,000 mg vitamin C
 vitamin C antioxidant
 (aerobic metabolism)가 therapeutic window
 ROS 가
 ROS (defence mechanism) vitamin C
¹⁾ 가 paraquat ROS 1 mg/dL 100 mg/dL TAS
 ROS 가 vitamin C 100 mg/dL
 antioxidant 가 가 32g vitamin C(32 x 1,000 mg/L)
 antioxidant vitamin C (100- 200
 uric acid, protein thiol, ascorbic acid, α-tocopherol mg)
^{2, 3)} vitamin C(ascorbic Vitamin C , ,
 acid) antioxidant 가 , oxalate
 Vitamin C antioxidant vitamin C
 (anticarcinogenic) , folate, amine, glucose, iron, 3,000 mg 3 (9 g)
 cyclic nucleotide, cholesterol, 가
^{20, 21)} 가 WBC,
 interferon, carnitine SGOT, PaO₂ 가
 . Fujimoto vitamin C가 paraquat WBC, SGOT 가
 paraquat WBC SGOT가
²²⁾ , PaO₂ 가 vitamin C
 vitamin C paraquat
 [Food and
 Nutrition Board of National Academy of Siences, (high
 U.S.A.] 1989 60 mg perpermance computerized tomography) ground
 100- 200 mg glass appearance , ,
²³⁾ Vitamin C 가 Vitamin C PaO₂
 TAS가 가 TAS 가 vitamin C paraquat Kang
 (basal levels: 2.22±0.16 mmole/L) two standard metal ion 가 ³³⁾
 deviation(0.16 x 2 mmole/L)가 가 vitamin C
 vitamin C 가 6.9 mg/dL vitamin C
 (Figure 2). Vitamin C distribution volume 32.0± vitamin

C TAS (therapeutic window) ,
 , , , arterial blood gas .
 analysis : In vitro in vivo vitamin C
 TAS . In vitro
 . paraquat , 5 normal pooled
 vitamin C plasma vitamin C 가 1 mg/dL 100 mg/dL
 paraquat , vitamin C TAS
 . Vitamin C . In vivo 7
 paraquat basal level vitamin C 50
 mg/kg 2,500-3,000 mg) 0.5, 1, 2, 3, 5,
 7, 9 vitamin C TAS
 Vitamin C
 paraquat 2,000-3,000 mg 3 (pharmacokinetics) .
 . 10 Paraquat 10
 가 가 vitamin C 100 mg, 2 500 mg, 3
 , 1,000 mg, 4 3,000 mg
 vitamin C TAS . 5 3,000mg 8
 TAS 가 1 3
 TAS . Vitamin C
 , , , 4 ABC, liver
 function test, urinalysis, arterial blood gas analysis
 paraquat 1 .
 ROS 가 가³²⁾ paraquat : 50
 vitamin C 가 TAS BAS 2.22±0.16 mmole/L ,
 가 가 (p>0.05). Normal pooled plasma
 vitamin C 가 1 mg/dL 100 mg/dL
 (critical condition) 가 TAS vitamin C
 paraquat total antio-
 xidant status vitamin C TAS
 36 mg/kg 2 In vivo : Vitamin C 50 mg/kg 0.5, 1, 2, 3,
 5, 7, 9
 vitamin C TAS
 TAS가 paraquat 가 {[TAS(mmole/L)=0.078 × vit.C(mg/dL)+
 2.00], R-squared : 0.488, p=0.0001}.
 가 Vitamin C , distribution
 volume 32.0±14.4 L, AUC(area under curve) : 36.4±
 11 3 mg.hour/dL, plasma clearance 2.13±1.36 L/hour,
 (T 1/2) : 10.2±7.8 hour, Cmax (maximum con-
 TAS : Paraquat Vitamin C 가 centration) : 17.1±7.1 mg/dL, Tmax 0.64±0.24 hour
 (pharmacokinetics) Vitamin C . Paraquat 10

8 : Paraquat vitamin C 가 plasma total antioxidant capacity
 가
 vitamin C 100 mg, 2 500 mg,
 3 1,000 mg, 4 3,000 mg
 TAS 2.21 mmol/L,
 2.26 mmol/L, 2.76 mmol/L, 2.81 mmol/L, 3.18 mmol/L
 vitamin C 가 TAS가 가
 vitamin C 3,000 mg 8
 1 TAS
 3.58 ± 0.37 mmol/L
 , , CBC, liver function test, urinalysis, arterial
 blood gas analysis 가 , ,
 500 mg
 1,000 mg/ 10
 vitamin C (9,000 mg/day)가 가
 : Paraquat total antioxidant
 status vitamin C
 36 mg/kg 2
 vitamin C
 TAS가 paraquat
 가 가

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