Bull. Fac. Agr., Saga Univ. No. 80 : 77~83 (1996)

Plasma Concentration-Time Profiles and Pharmacokinetic Analyses of Vitamin C

Toshio KASHIHARA*, Nobuyuki KITAMORI*,** and Akira MURATA
(Laboratory of Biofunctional Chemistry)
Received November 6, 1995

Summary

The changes in the plasma vitamin C level after oral administration of various vitamin C preparations were satisfactorily simulated by a one-compartment model with first-order absorption. The fact that the peak plasma level was seen 3 hours after administration regardless of the dose administered can be explained by the small absorption rate constant estimated. A plot of the ratio of the distribution volume and the fraction of the dose absorbed (V/F ratio) against the dose administered gave a linear relationship, and the extrapolated value of *ca.* 20 L at dose (D) = 0 appears to be a reasonable distribution volume for a water-soluble vitamin. If only the fraction of the dose absorbed decreased as the dose administered increased, its value should be 0.63, 0.50, 0.16, and 0.07 at doses of 500, 1000, 5000, and 12000 mg, respectively. These values were comparable with those obtained on the basis of the urinary excretion of the vitamin.

Key words: vitamin C, plasma level, pharmacokinetics, one-compartment model, simulation

Introduction

The pharmacokinetics of vitamin C have probably been the most comprehensively studied among all the vitamins. Analyses have been performed using one-[1], two-[2], or three-compartment[3] linear pharmacokinetic models. However, no acceptable pharmacokinetic model has yet been derived for plasma vitamin C profile after the administration of vitamin preparations to humans. Kallner *et al.*[3] used a three-compartment model to simulate the plasma vitamin C profile on the basis of plasma radioactivity levels obtained after the administration of ^{14}C labeled vitamin C. However, since the plasma radioactivity is derived from metabolite(s) as well as from the intact compound, their simulation is not suitable for performing a pharmacokinetic analysis of the unchanged form of vitamin C. Determination of the plasma levels of the unchanged compound is essential for pharmacokinetic analysis. The second question is that the basal plasma vitamin C and the plasma vitamin C derived from the vitamin preparation administered cannot be distinguished by ordinary methods. We have proposed that the plasma vitamin C derived from an administered vitamin preparation can be estimated by subtraction of the baseline vitamin C level

* Pharmaceutical Development Laboratories, Takeda Chemical Industries, Ltd., Osaka 532
** Present address: Research Center, Grelan Pharmaceutical Co., Ltd., Hamura 205

from the post-administration level[4].

On the other hand, since vitamin C is considered to be absorbed through a nonpassive, and saturable process, some investigators[5,6] have proposed the use of Michaelis-Menten kinetics for the pharmacokinetic analysis of plasma vitamin C profiles after administration of vitamin preparations.

If Michaelis-Menten kinetics are applicable to the absorption of vitamin C, the time to reach the peak plasma level should prolong with increasing doses. However, many studies have shown that the time to reach the peak plasma level of vitamin C remains almost constant about 3 hours after administration over a wide range of doses and regardless of the dosage form administered. Melethil *et al*[7]. tried to explain this discrepancy by assuming that the absorption time was limited to 3 hours. The presence of an absorption window in the upper small intestine has also been suggested. However, our studies on sustained-release preparations of vitamin C have demonstrated that the peak plasma level is seen 6 to 9 hours after administration[8], and Brenner[9] also reported that the time to reach the peak plasma level was noted 8 hours after administration of sustained-release preparations. Thus, the absorption of vitamin C seems likely to continue for at least 6 to 9 hours. The constant time at which the peak plasma level of vitamin C occurs also cannot be explained by applying Michaelis-Menten kinetics to the metabolism or elimination process.

The purpose of this study was to perform a pharmacokinetic analysis of the results reported by ourselves[8,10] as well other investigators[7,11], and to propose a general outline of the profiles of the plasma vitamin C level on the basis of a linear pharmacokinetic analysis.

Methods

Plasma vitamin C data used for calculation

We have already studied the vitamin C level after oral administration of a single 500-mg dose of vitamin C under unsaturated[10] and saturated conditions[8] in the body pool.

We also used the data reported by Kübler *et al*.[11] and Melethil *et al*.[7]. Kübler *et al*. studied the plasma profiles of vitamin C of 75 subjects who were administered 1.5, 3.0, 6.0, or 12.0 g of vitamin C, and in whom the body pool was saturated with the vitamin. Since they only reported their results in graphical form, we read the plasma levels of the vitamin from their graphs. Melethil *et al*. also reported on the plasma vitamin C levels after administration of 0.5, 1.0, 2.0 g of the vitamin to subjects with a saturated body pool. They also only reported in graphical form, so we again used data read from the graphs.

Analysis of the plasma vitamin C profile

The changes in the plasma levels from the baseline level were used for these calculations. Simulation of the plasma vitamin C profile was performed using the computer program devised by Yamaoka *et al*.[12], which determines the constants in a model equation by the least-squares method to provide a curve which best fits the observed data.

Results and Discussion

The mean plasma levels of vitamin C after a single oral dose of 500 mg under the conditions of unsaturated or saturated body pool reported by ourselves were analyzed. A good simulation curve could be obtained for these data using a one-compartment model with first-order absorption. Figure 1 shows the curves obtained, and the pharmacokinetic parameters derived from them are listed in Table 1. When a two- or three-compartment model was used, no reasonable pharmacokinetic parameters were obtained. In contrast, a one-compartment model fitted our data well under both saturated and unsaturated body pool conditions. Therefore, the pharmacokinetics of plasma vitamin C show little relation to the degree of saturation of the body pool with the vitamin. In fact, the degree of saturation influences only the baseline of the plasma vitamin C level.

A one-compartment model also provided a good fit for Kübler's data[11] and Melethil's data[7]. The curves obtained by simulation are shown in Figures 2 and 3, and the pharmacokinetic parameters derived from the simulation are shown in Table 2. The absorption and elimination rate constants, Ka and Ke, were very similar to each other. In particular, the findings reported by Kübler *et al.*, which contained numerous data points in many subjects, gave the best fit to the model equation. This indicates that the plasma vitamin C profile after the administration of the vitamin preparation is well represented by a one-compartment model.

As shown in Tables 1 and 2, the absorption rate constants were consistently very small. Such a small rate constant suggests that gastrointestinal absorption of vitamin C may involve a carrier protein and require a long time for passage through the intestinal membrane, so that the time to reach the peak plasma level of the vitamin should be 3 hours. A certain fraction of the vitamin C administered may also move into the lower part of the intestinal tract without being absorbed,

Table 1 Pharmacokinetic parameters determined from the simulation of plasma vitamin C profiles after administration of 500 mg of vitamin C

	Unsaturated	Saturated
Ka (h^{-1})	0.36	0.41
Ke (h^{-1})	0.27	0.27
V/F (L)	28	32

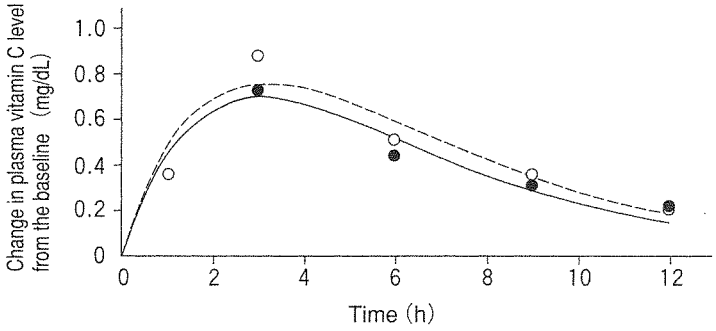

Fig. 1 Typical Simulated Curve for the Change in Plasma Vitamin C Level from the Baseline reported by Murata *et al.* (dose of 500 mg).
●, saturated; ○, unsaturated.

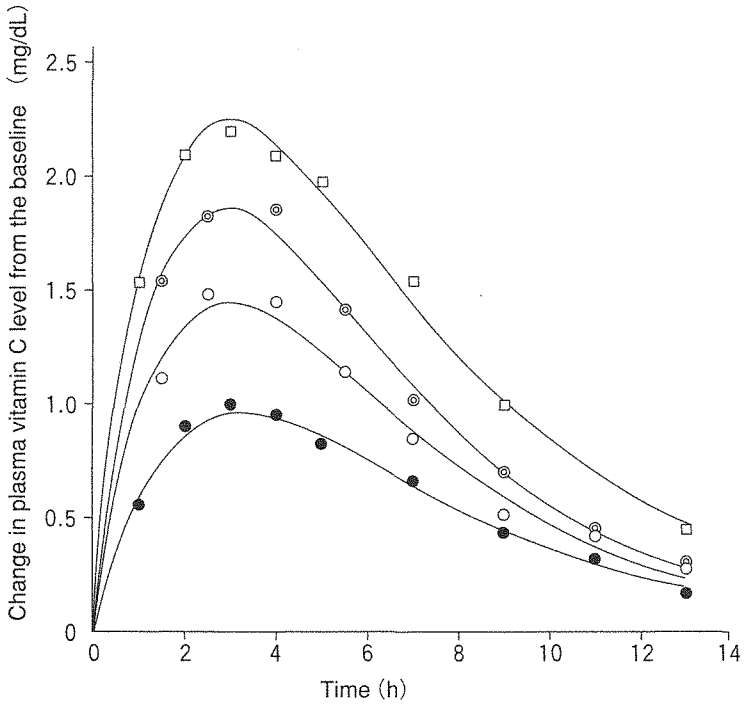

Fig. 2 Typical Simulated Curve for the Change in Plasma Vitamin C Level from the Baseline reported by Kübler (saturated body pool).
●, 1,500mg; ○, 3,000mg; ◎, 6,000mg; □, 12,000mg.

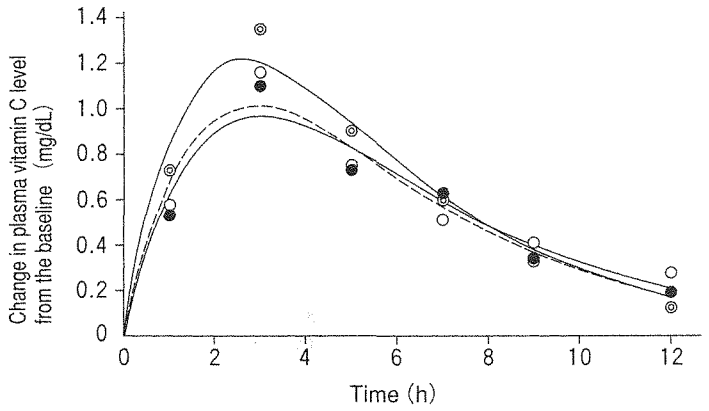

Fig. 3 Typical Simulated Curve for the Change in Plasma Vitamin C Level from the Baseline reported by Melethil (saturated body pool).
●, 500mg; ○, 1,000mg ; ◎, 2,000mg.

or may be degraded by intestinal enzymes and bacteria.

When the V/F ratio was plotted against the dose administered, a linear relation was obtained as shown in Figure 4. The value of the V/F ratio at D=0 was 19.9 liters. This can be assumed to be the distribution volume for vitamin C, and it seems to be a reasonable volume for a water-soluble vitamin. Three explanations for the dose-dependence of the

Table 2 Pharmacokinetic parameters determined from the simulation of plasma vitamin C profiles using data reported by Kübler and Melethil

	Data from Kübler				Data from Melethil		
Dose(g)	1.5	3.0	6.0	12.0	0.5	1.0	2.0
Ka (h^{-1})	0.38	0.39	0.41	0.52	0.41	0.41	0.42
Ke (h^{-1})	0.26	0.29	0.30	0.20	0.27	0.31	0.35
V/F (L)	68	88	138	294	23	42	66

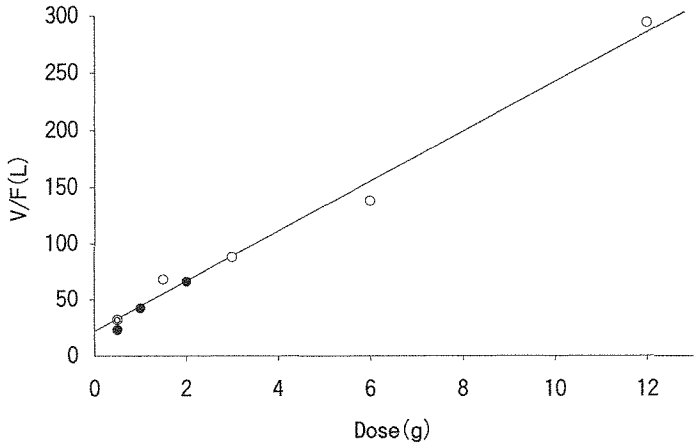

Fig. 4 Relationship between the V/F Ratio Estimated by Simulation and the Dose of Vitamin C Administered.
○, Kübler's data; ●, Melethil's data; ◎, Murata's data

V/F ratio can be suggested. One is that the fraction of the dose absorbed (F) decreases as the dose administered increases. The second is that the distribution volume (V) increases with increasing dose levels. The third is that F decreases and V simultaneously increases with an increase in the dose administered.

At present, insufficient data are available to draw any conclusions about this issue. However, if only F decreases with increasing dose levels and V remains at 19.9 liters, F should be about 0.63, 0.50, 0.16, and 0.07 at doses of 500, 1000, 5000, and 12000 mg, respectively. The daily urinary excretion of the substance in the steady-state corresponds to the amount excreted after a single dose. The mean urinary excretion of vitamin C above the baseline level at doses of 250 and 500 mg in the 44-week study was 121.3 and 208.1 mg/day, respectively[13]. Therefore, the fraction of the dose absorbed calculated from the urinary excretion was respectively 0.59 and 0.50 at doses of 250 and 500 mg, taking into account that the urinary excretion of vitamin C after intravenous administration is 82.6%[14]. These values were comparable with those estimated by our simulation. Therefore, there seems to be a strong possibility that F decreases as the dose of vitamin administered is increased.

References

1. Branchard, J., K. A. Conrad, R. A. Mead, and P. J. Garry (1990). Vitamin C disposition in young and

elderly men. *Am. J. Clin. Nutr.*, **51**, 837-845.

2. Zetler, G., G. Seidel, C. P. Siegers, and H. Iven (1976). Pharmacokinetics of ascorbic acid in man. *Eur. J. Clin. Pharmacol.*, **10**, 273-282.
3. Kallner, A., D. Hartmann, and D. Hornig (1979). Steady-state turnover and body pool of ascorbic acid in man. *Am. J. Clin. Nutr.*, **32**, 530-539.
4. Kitamori, N.(1992). Some considerations on the pharmacokinetic analysis of vitamins. in *Proceedings of the 1st International Congress on Vitamins and Biofactors in Life Science* , pp. 442-445.
5. Melethil, S., M. B. Subrahmanyam, C. J. Chang, and W. D. Mason, (1987). Megadose of vitamin C: a pharmacokinetic evaluation. *Ann. N.Y. Acad. Sci.*, **498**, 491-493.
6. Mayersohn, M.(1972). Ascorbic acid absorption in man: pharmacokinetic implications. *Eur. J. Pharmacol.*, **19**, 140-142.
7. Melethil, S., W. D. Mason, and C. J. Chang (1986). Dose-dependent absorption and excretion of vitamin C in humans. *Int. J. Pharm.*, **31**, 83-89.
8. Murata, A., S. Hirata, M. Matsuoka, Y. Hibi, T. Kashihara, N. Kitamori, H. Tamai, and M. Mino (1990). Plasma concentration and urinary excretion of vitamin C after oral administration of sustained-release preparations in healthy adult males. *Vitamins (Japan)*, **64**, 285-294.
9. Brenner, G. (1975). Enterale Ascorbinsäureresorption beim Menschen nach Applikation einer mikroverkapselten Retardpräparation. *Med. Klin.*, **70**, 1219-1222.
10. Murata, A., R. Baba, M. Matsuoka, H. Otsuka, T. Takeuchi, and Y. Itokawa (1989). Plasma levels and urinary excretion of vitamin C after oral administration of vitamin C preparations in healthy male adult. *Vitamins (Japan)*, **63**, 133-139.
11. Kübler, W., and J. Gehler (1970). Zur Kinetik der enteralen Ascorbinsäure-Resorption: ein Beitrag zur Berechnung nicht dosisproportionaler Resorptionsvorgänge. *Internal. Z. Vit. Forschung*, **40**, 442-453.
12. Yamaoka, K., and Y. Tanigawara (1983). *Introduction to Pharmacokinetics using a Microcomputer*. Nankodo,Tokyo.
13. Murata, A., C. Kobayashi, M. Matsuoka, H. Otsuka, M. Kitagawa, M. Mino, M. Kimura, and Y. Itokawa (1991). Changes in the plasma concentrations and urinary excretion of vitamin C in healthy male adults during long-term ingestion of a multivitamin preparation. *Vitamins (Japan)*, **65**, 557-565.
14. Yung, S., M. Mayersohn, and J. B. Robinson (1978). Ascorbic acid elimination in humans after intravenous administration. *J. Pharm. Sci.*, **67**, 1491-1492.

ビタミンCの血漿濃度-時間プロフィールと薬動学的解析

柏原　俊夫*・北森　信之*・村田　　晃
（生物機能化学講座・*武田薬品工業㈱製剤研究所）
平成7年11月6日　受理

要　　約

著者ら，Kübler ら，Melethil らの，500，1000，1500，2000，3000，6000，12000 mg のビタミンCを健康な成人に径口投与したときの，血漿ビタミンC濃度の変化量のデータを用いて，ビタミンCの血漿濃度-時間プロフィールのシミュレーションを行った．シミュレーションには，最小二乗法により実測値にフィットする曲線が得られるようにモデル式の定数を選ぶ．山岡らのコンピュータ・プログラムを使用した．この結果，次のことが分かった．

ビタミンCの薬物動態は，one-compartment モデルにフィットする．Tmax（最高濃度到達時間）は3時間で，投与量とは関係がない．これは，ビタミンCの吸収過程に Michaelis Menten kinetics がそのまま適用できないことを示している．なお，最高濃度到達時間が3時間と比較的長いことは，Ka が小さいことで説明できる．投与量に対してV/F（分布容積と吸収率の比）をプロットすると，直線関係になる．投与量がゼロのときの外挿値は約20であり，水溶性ビタミンの分布容積として妥当な値である．分布容積は一定で，投与量の増加につれて吸収率が低下すると仮定すれば，吸収率は，500，1000，5000，12000 mg 投与で，それぞれ63，50，16，7％となる．

これまでのビタミンC投与に関する一連の研究を総合して考えると，野菜・果物からの摂取を基本に，多くの人で，更に適量のビタミンCを補給する必要があるといえる．補給する場合，bioavailability の観点からすると，1回の摂取量は250～500 mg が適当といえよう．1日に1000，2000 mg を摂取するときは，3～4回に分けて摂取するのがよかろう．