S-14-5

Vitamin C Bioavailability

M.MAYERSOHN

Department of Pharmaceutical Sciences, College of Pharmacy, The University of Arizona, Tucson, Arizona USA 85721

I. INTRODUCTION

Vitamin C (ascorbic acid) is a relatively simple, water-soluble organic molecule which is involved in a surprisingly large number of physiological and biochemical functions. Further, the role of the vitamin in modulating the pharmacologic and toxicologic effects of xenobiotics is not well understood.

Humans need to obtain this essential vitamin from exogenous sources since we no longer have the biochemical machinery needed for its biosynthesis. While food is the major source for the daily intake of the vitamin, there are large populations that ingest the pure vitamin in one of several commercial forms. There is relatively little quantitative information about the bioavailability of the vitamin and factors that will affect it. This paper will attempt to provide a concise review of our current knowledge of the oral gastrointestinal (GI) absorption and bioavailability of vitamin C and factors known to or thought to affect those processes.

II. GASTROINTESTINAL ABSORPTION

There is evidence suggesting that the GI absorption of vitamin C involves a specialized transport system. This system appears not to be present in all mammals (e.g., rats, hamster) but was shown to exist in the guinea pig [1]; a species, like the human, which depends upon exogenous sources for vitamin C intake. The transport mechanism was described as having the properties of a gradient-coupled Na^+ -dependent system [1]. Earlier investigations in humans suggested that the vitamin was absorbed by passive diffusion [2,3]. Subsequent studies using isolated segments of human ileum [4,5] and an *in situ* perfusion study in humans [6], however, have concluded that the vitamin is absorbed by a specialized transport system.

There have been several studies in humans which have evaluated vitamin C absorption on the basis of oral dosing and urine excretion data. A study by Stewart and Booth [7] resulted in data (one subject) which, while not analyzed by the investigators, suggested specialized absorption. A more extensive study was reported by Kubler and Gehler [8] whose data were further analyzed by Mayersohn [9]. Figure 1 illustrates the results of those studies whose curves are indicative of a saturable absorption process as has been observed for vitamins B_1 , B_2 and B_{12} . These data are analyzed in Figure 2 to obtain estimates of the parameters of the absorption process; the maximal absorbable amount (V_{max}) and the amount corresponding to one-half of the maximum (k_m). Those estimates along with those obtained from another study [10] indicate substantial variation. The average V_{max} for each of those three studies are 2.46, 0.55 and 0.86 g. The corresponding mean values for k_m are 3.56, 0.68 and 1.31 g.

Fig. 1. (Left) Amount of vitamin C absorbed (y-axis on left) and the % dose absorbed (y-axis on right) as a function of dose. Key: $\square$ (ref. 7); $\circ$, $\bullet$ (ref. 8,9).

Fig. 2. (Right) Amount of vitamin C absorbed as a function of the amount absorbed/dose. Key: $\bullet$ (ref. 7); $\circ$ (ref. 8,9).

It is clear that these absorption parameters need to be better defined but this preliminary analysis suggests large inter-subject variation in absorption of vitamin C. Indeed, we have noted the possibility of there being "good" and "poor" absorbers of the vitamin, but more data are needed to verify that suggestion [10].

III. FACTORS AFFECTING VITAMIN C ORAL BIOAVAILABILITY

1. Divided Doses. A potential practical means for improving the oral absorption efficiency of the vitamin would be to divide a single large dose into smaller doses ingested during the day [9]. The improvement in absorption efficiency for doses of 2, 6 and 15 g is shown in Figure 3. There has been experimental verification of this suggestion as noted in Figure 4 [10].

Fig. 3. (Left) Increase in the absorption efficiency of vitamin C as a function of the number of divided doses per day for total daily doses of 2, 6 and 15 g. Simulations based upon ref. 9.

Fig. 4. (Right) Percentage vitamin C dose absorbed in each of 3 subjects following 1 g oral administration as a solution on an empty stomach (control), following a meal (food) and upon divided doses (0.125 g every 0.25 hr x 8 doses).

2. Food. The influence of food on the bioavailability of vitamins

is of general practical interest. Examining absorption in the presence and absence of food may also serve to probe the likely sites of absorption along the GI tract. Experiments with vitamin C [10], as summarized in Figure 4, indicate that the presence of food promotes absorption. These data suggest that the major site of vitamin C absorption is high in the small intestine. Therefore, any factor which delays gastric emptying or promotes retention high in the small intestine, should result in an increase in the bioavailability of the vitamin (e.g., anticholinergic drugs).

3. Dosage Form. There have been relatively few studies that have examined the influence of dosage form on the bioavailability of vitamin C. The results of one study are summarized in Figure 5 [11]. The most interesting observation is that the "timed-release" form provided the lowest bioavailability in all subjects. Perhaps this is not surprising on the basis that the vitamin is most efficiently absorbed high in the small intestine, yet such dosage forms are designed to release their contents gradually over the length of the GI tract. The data, however, represent results from a small population and only one formulation of that type of dosage form. Additional studies need to be conducted to verify this observation and to be able to make general rules.

Fig. 5 (Left). The influence of different oral dosage forms on the bioavailability of vitamin C in 4 subjects [11].

Fig. 6 (Right). The influence of age in normal human males on the absolute oral bioavailability of vitamin C.

4. Age. Considerable controversy remains and little data are available concerning the efficiency of vitamin absorption as it is influenced by age in humans. Although there are general suggestions to the effect that gastrointestinal absorption is impaired in the elderly this is not the case for most drugs [12,13] and our preliminary data suggest that it is not true for vitamins C and B₂ [Lopez-Anaya and Mayersohn, unpublished]. The data in Figure 6 illustrate the absolute oral bioavailability of vitamin C (compared to an intravenous dose) as a function of age in normal male subjects. These data suggest the lack of a relationship between oral bioavailability and age in humans.

SUMMARY

The above brief review indicates that the bioavailability of vitamin C in humans is complex and that our current understanding of that process and factors that influence it are incomplete. It is important that an overall pharmacokinetic scheme be developed and tested to completely describe the complex dispositional and absorption processes of the vitamin. Such information will provide a better understanding of the absorption and disposition of the vitamin per se. Furthermore, that information will permit us to better understand how those factors influence the participation of the vitamin in events associated with maintenance of health.

REFERENCES

- [1] Stevenson, N.R., and Brush M.K. (1969): Existence and Characteristics of Na⁺-Dependent Active Transport of Ascorbic Acid in Guinea Pig. *Amer. J. Clin. Nutr.*, **22**, 318-326.
- [2] Nicholson, J.T.L., and Chornock, F.W. (1942): Intubation Studies of the Human Small Intestine. XXII. An Improved Technic for the Study of Absorption; its Application to Ascorbic Acid. *J. Clin. Invest.*, **21**, 505-509.
- [3] Spencer, R.P., Purdy, S., Hoeldtke, R., Bow, T.M., and Markulis, M.A. (1963): Studies on Intestinal Absorption of L-Ascorbic Acid-1-C¹⁴. *Gastroenterology*, **44**, 768-773.
- [4] Stevenson, N.R. (1974): Active Transport of L-Ascorbic Acid in the Human Ileum. *Gastroenterology*, **67**, 952-956.
- [5] Mellors, A.J., Nahrwold, D.L., and Rose, R.C. (1977): Ascorbic Acid Flux Across Mucosal border of Guinea Pig and Human Ileum. *Amer. J. Physiol.* **233**, E374-E379.
- [6] Nelson, E.W., Lane, H., Fabri, P.J., and Scott, B. (1978): Demonstration of Saturation Kinetics in the Intestinal Absorption of Vitamin C in Man and the Guinea Pig. *J. Clin. Pharmacol.*, **18**, 325-335.
- [7] Stewart, J.S., and Booth, C.C. (1964): Ascorbic Acid Absorption in Malabsorption. *Clin. Sci.*, **27**, 15-22.
- [8] Kubler, W., and Gehler, J. (1970): Zur Kinetik der enteralen Ascorbinsaure-Resorption: Ein Beitrag zur Berechnung nicht dosisproportionaler Resorptionsvorgange. *Internat. Z. Vit. Forschung*, **40**, 442-453.
- [9] Mayersohn, M. (1972): Ascorbic Acid Absorption in Man-Pharmacokinetic Implications. *Eur. J. Pharmacol.*, **19**, 140-142.
- [10] Yung, S., Mayersohn, M., and Robinson, J.B. (1981): Ascorbic Acid Absorption in Man: Influence of Divided Dose and Food. *Life Sci.*, **28**, 2505-2511.
- [11] Yung, S., Mayersohn, M., and Robinson, J.B. (1982): Ascorbic Acid Absorption in Humans: A Comparison among Several Dosage Forms. *J. Pharm. Sci.*, **71**, 282-285.
- [12] Mayersohn, M. (1982): The "Xylose Test" to Assess Gastrointestinal Absorption in the Elderly: A Pharmacokinetic Evaluation of the Literature. *J. Gerontol.*, **37**, 300-305.
- [13] Mayersohn, M. (1986): Special Pharmacokinetic Consideration in the Elderly, in *Applied Pharmacokinetics*, 2nd ed., ed. by Evans, W.E., Schentag, J.J., and Jusko, W.J., Applied Therapeutics, Spokane, Washington, 1986.