Estimating the turnover time of high intravenous intake of vitamin C

Alfred Wong

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Xymega Corporation, Vancouver, Canada

Correspondence to:
Xymega Corporation, Post Office Box 34173, Vancouver V6J 4N1, Canada
aw688@xymega.com

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SUMMARY

Background: *Intravenous dosing is generally recognized to be the only effective means of maintaining a high concentration of vitamin C in the plasma. High dosing of vitamin C has been reported to be beneficial in, among other things, improving the quality of life as well as survival time of patients with terminal cancer. There is a paucity of information on the depletion of vitamin C in plasma at the high dosing regimen.*

Methods: *The primary human-subject data reported by Levine et al. and Riordan et al. were used in this analysis. It is generally recognized that chemical kinetic studies could be used to deduce the underlying mechanism involved in the transport of vitamin C from the plasma into the cell structure.*

Results: *A single rate constant was found to be essentially applicable to describe the rate of depletion of vitamin C from the plasma of healthy volunteers as well as for cancer patients, over the range of intravenous administration of 200 mg to 60,000 mg.*

Conclusion: *The application of first-order reaction kinetics has been shown to provide a means to estimate the depletion time at any intravenous high dosing of vitamin C.*

Key words: *Ascorbic Acid; Injections, Intravenous; Neoplasms; Pharmacokinetics; Dose-Response Relationship, Drug; Models, Biological*

INTRODUCTION

Vitamin C (syn. ascorbic acid) is an essential micronutrient which is involved in biological and biochemical functions in humans. This vitamin could not be synthesized *in situ* by humans. The principal sources for humans are either routine consumption of fruits and vegetables, or through on-purpose oral or intravenous intake of vitamin C supplement.

The tolerable upper intake level of vitamin C, by oral means, is generally cited to be in the range of 2,000 mg per day for adults (1). This level corresponds approximately to the optimum daily intake first advocated by Pauling (2) nearly 4 decades ago. Some of the adverse side effects of chronic high (oral) dosing have been observed to be diarrhea and hyperoxaluria (3).

The physiological barrier to oral administration to attain a higher concentration in the plasma is due to intestinal absorption and renal excretion of vitamin C (4). Indeed, if the renal function was impaired, a high concentration of vitamin C (as administered orally) in the plasma can be expected (5). Padayatty et al. (6) have found vitamin C concentration in the plasma to vary substantially with the route of administration.

The safe chronic intake of as much as 40 grams per day has been reported previously for the treatment of various viral and bacterial infections (2). The use of very high doses of vitamin C to treat terminal cancer patients was first proposed in the late 1950s. Cameron and Pauling (7, 8) reported the significant extension of life of cohorts of terminal cancer patients by several hundred days.

The science of vitamin C treatment of cancer patients have not been investigated actively for the past few decades because neither the vitamin C molecule nor the therapeutic use of vitamin C is patentable. The interest of vitamin C therapy has however been renewed recently with the publication of several notable case studies in which vitamin C-treated cancer patients were reported to live an additional 3 to 10 years, after their first prognosis of the final stage of terminal cancer (9-15).

Present knowledge suggests that Vitamin C is transported readily from the circulating plasma into malignant cells to mediate the subsequent formation of cytotoxic H_2O_2 (16-18). In in-vitro studies, non-malignant cells were found to be not affected by such vitamin C treatment (17, 19-24). Duconge et al. (25) have recently reviewed current state of knowledge pharmacokinetics of vitamin C from both oral and intravenous perspectives.

There is no means available presently to the medical practitioners for setting the frequency of intravenous administration of high doses of vitamin C. We have undertaken this investigation to estimate the depletion time of intravenous administration of high doses of vitamin C in plasma.

METHODS

The primary human-subject data reported by Levine et al. (26) and Riordan et al. (27) are used in this analysis.

Chemical kinetic studies could be used to deduce the underlying mechanism involved in the transport of vitamin C from the plasma into the cell structure (28-29). First-order reactions are the most common. A first-order reaction is defined as one for which, at a given temperature, the rate of the reaction depends only on the first power of the concentration of a single reacting species.

In the case of vitamin C concentration in the plasma, the kinetic study began with the assumption that the reaction(s) causing vitamin C decrease is essentially first-order. The classical first-order reaction can be expressed as

$$\frac{-dc}{dt} = kc, \text{ where } c = \text{concentration and } t = \text{time} \quad \ldots\ldots(1)$$

Upon integration, equation (1) is transformed to the convenient form of

$$\log c = -kt + \log c_0, \text{ where } c_0 \text{ is the initial concentration} \quad \ldots\ldots(2)$$

A plot of log *c* versus *t* would yield a straight line, of which the slope is the rate constant value *k*.

RESULTS

As given in Figure 1 and 2, Levine et al. (26) have reported that both oral and intravenous dosing of Vitamin C would reach rapidly similar background value of about 80 μM, at the two example doses of 200 mg and 1,250 mg of Vitamin C. Healthy volunteers were the test subjects. In this study, this limiting value, i.e., 80 μM, was used as the terminal value for the selection of experimental data for the estimation of the first-order rate constant.

It may be noted in Figure 2, the maximum value reached with an oral intake of 1,250 mg of Vitamin C was approximately 150 μM, more than 10 times less than the threshold pharmacological concentration noted in *in vitro* studies of Chen et al. (17).

In the data set of Riordan et al. (27), the experiments were made under a repeat dosing regimen, i.e., injection of vitamin C was made at pre-set intervals, on cancer patients. The plasma vitamin C level was never allowed to reach the background value in their study.

Figure 3 shows the estimation of first-order rate constant, using the published data of Levine et al. (26) and Riordan et al. (27). A cursory review of the slope of the four curves suggested that the data might be pooled to provide a single average rate constant. The specific calculation involves the use of the individual rate constant (from Figure 3) and the application of an arbitrary common initial concentration (*viz*., 60,000 mg vitamin C). As given in Figure 4, the degree of correlation of the best-fit curve was generally satisfactory. The estimated rate constant could be inserted into equation (2) to give

$$\log c = -0.156t + \log c_0 \quad \ldots\ldots(3)$$

where t is time in hours, and c_0 is the initial concentration in μM

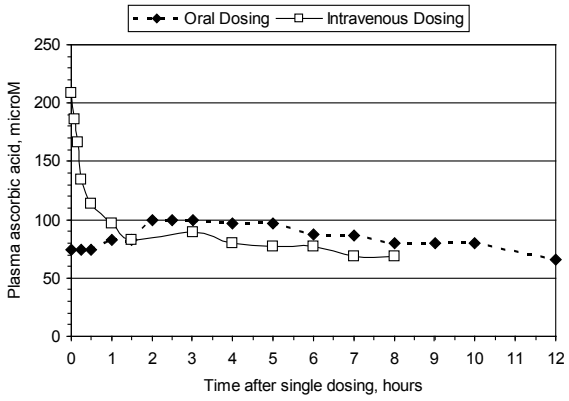

Figure 1. Plasma vitamin C profile after single dosing of 200 mg for subject #3

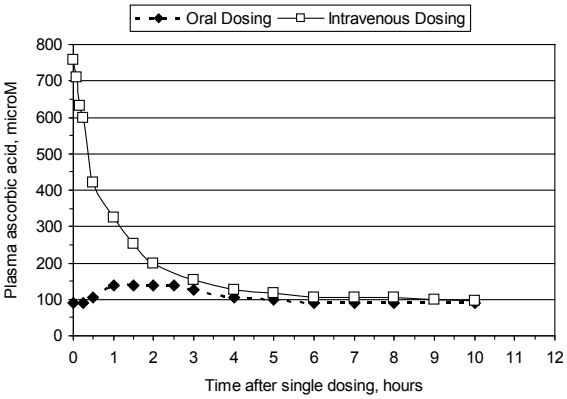

Figure 2. Plasma vitamin C profile after single dosing of 1,250 mg for subject #3

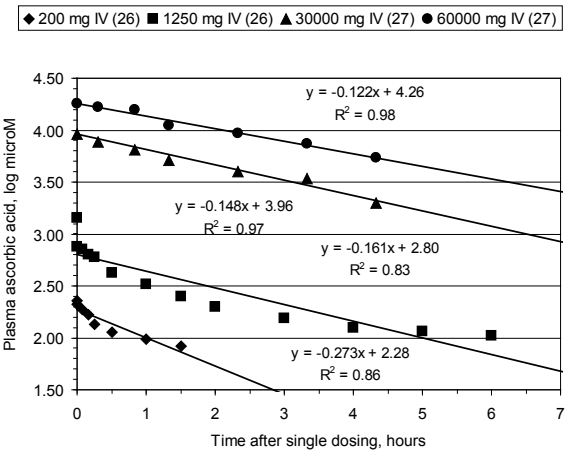

Figure 3. Rate constant for first-order kinetics (references)

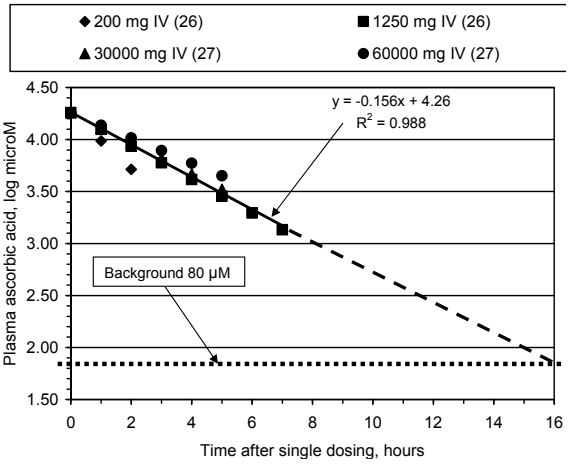

Figure 4. Estimated first-order rate constant using pooled data (references)

DISCUSSION

It is interesting to note that a single rate constant is essentially applicable to describe the rate of depletion of vitamin C from the plasma of healthy volunteers as well as for cancer patients, over the range of intravenous administration of 200 mg to 60,000 mg. This observation also suggests that the transport of vitamin C from the plasma across the cell

membranes to be unaffected by the physiological status of the cells. It follows that the depletion of vitamin C might indeed be very small in mediating the formation of cytotoxic H_2O_2 to react with cancerous cells. This possibility remains to be proven.

In *in vitro* studies of human Burkitt's lymphoma cells, Chen et al. (17) has found the effective pharmacologic concentration to be about 2,000 μM vitamin C. If this threshold concentration in the plasma was required for therapeutic activity in human patients, then the time interval required for repeated injection of 60,000 mg vitamin C could be calculated to be about every 8 hours.

CONCLUSION

Despite the limited availability of experimental data, we have developed a protocol for the estimation of depletion time of intravenously-administered vitamin C from the plasma. This preliminary assessment could now provide the medical professionals with a means to set the time interval of repeated dosing of vitamin C to maintain a threshold value for, among other things, the therapeutic treatment of patients afflicted with cancer.

Conflict of interest

We declare no conflicts of interest.

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