Published in final edited form as:
J Orthomol Med. 2012 January 1; 27(1): 9–12.

Schedule Dependence in Cancer Therapy: Intravenous Vitamin C and the Systemic Saturation Hypothesis

Michael J. Gonzalez, DSc, PhD, FACN[1], **Jorge R. Miranda Massari, PharmD**[2], **Jorge Duconge, PhD**[3], **Neil H. Riordan, PhD**[4], and **Thomas Ichim, PhD**[4]

Michael J. Gonzalez: michael.gonzalez5@upr.edu

[1]University of Puerto Rico, Medical Sciences Campus, RECNAC 2 Project, School of Public Health, Dept. Human Development, Nutrition Program, GPO Box 365067, San Juan, PR 00936

[2]University of Puerto Rico, Medical Sciences Campus, School of Pharmacy, Dept Pharmacy Practice, 3100 N Hillside Ave. Wichita, KS 67219

[3]University of Puerto Rico, Medical Sciences Campus, School of Pharmacy, Dept. Pharmaceutical Sciences, 3100 N Hillside Ave. Wichita, KS 67219

[4]Riordan Clinic, 3100 N Hillside Ave. Wichita, KS 67219

Abstract

Despite the significant number of in vitro and in vivo studies to assess vitamin C effects on cancer following the application of large doses and its extensive use by alternative medicine practitioners in the USA; the precise schedule for successful cancer therapy is still unknown. Based on interpretation of the available data, we postulate that the relationship between Vitamin C doses and plasma concentration x time, the capability of tissue stores upon distribution, and the saturable mechanism of urinary excretion are all important determinants to understand the physiology of high intravenous vitamin C dose administration and its effect on cancer. Practitioners should pay more attention to the cumulative vitamin C effect instead of the vitamin C concentrations to account for observed discrepancy in antitumor response. We suggest that multiple, intermittent, short-term intravenous infusions of vitamin C over a longer time period will correlate with greater antitumor effects than do single continuous IV doses of the same total exposure. This approach would be expected to minimize saturation of renal reabsorption, providing a continuous “dynamic flow” of vitamin C in the body for optimal systemic exposure and clinical outcomes. This prevents the “systemic saturation” phenomena, which may recycle vitamin C and render it less effective as an anticancer agent. Nonetheless, more pharmacokinetic and pharmacodynamic studies are needed to fully understand this schedule-dependence phenomenon.

Introduction

The pharmacokinetics and pharmacodynamics of intravenous (IV) vitamin C (Ascorbic Acid, Ascorbate, AA) has been partially described by various groups.[1–7] Nevertheless, the

Correspondence to: Michael J. Gonzalez, michael.gonzalez5@upr.edu.

Competing Interests
The authors declare that they have no competing interests.

issues of schedule dependence and dosage in relation to cancer therapy have not been thoroughly discussed.

The use of large doses of AA has been utilized for the treatment of cancer by various groups.[8–10] The inhibitory action on cancer cells by AA has been described since 1952.[11] High concentrations of AA may induce apoptotic cell death in tumour cell lines, possibly via its pro-oxidant action.[12] Moreover, high doses of AA in the presence of oxygen favour the formation of hydrogen peroxide, providing an additional mechanism of anticarcinogenic action.[12] Another anticarcinogenic action induce by high doses of AA is angiogenesis inhibition.[13] Our group has also observed that higher concentrations of AA increase adenosine triphosphate production probably by increasing mitochondrial electron flux.[14] In contrast to this, lower concentrations of AA display antioxidant properties that may prevent the activation of oxidant-induced apoptosis and prevent the formation of hydrogen peroxide.[15] These concentration dependent behaviours of AA may in part explain the seemingly contradictory results reported previously on AA effects on cancer.

Discussion

IV Vitamin C

The concentrations of AA toxic to cancer cells in vitro can be achieved clinically by intravenous administration. Currently, IV AA is used extensively by alternative medicine practitioners in the USA (11,233 patients treated in 2006 and 8,876 patients in 2008).[16] Clinical studies evaluating AA in cancer outcome have been done.[17–19] As much as a 70-fold difference in plasma concentrations is expected between oral and IV administration, depending on dose. As a matter of fact, the pharmacokinetics of orally administered vitamin C has been early postulated to be dose-dependent, as the fraction absorbed decreased with increasing dose due probably to a saturable intestinal pump-mediated absorption mechanism.[5]

In addition, the systemic clearance of vitamin C seems to be increased with accumulative exposure, a process that has been well-described by Hickey et al in the so-called “Dynamic-Flow Model.”[4] Briefly, under physiological conditions, vitamin C is normally removed through glomerular filtration by kidneys, but a fraction of this filtered amount is returned into the body by capacity-limited tubular reabsorption. Thus, this concentration-dependent tubular reabsorption of vitamin C by the kidneys is saturated at supra-physiological levels of ascorbate and, therefore, a shorter terminal vitamin C elimination half-life is observed in individuals who receive excessively high amounts of vitamin C by continuous IV infusion. We think an IV schedule affording very high doses (>100 g) or continuous infusions will overload the body stores for vitamin C, as well as block its dynamic flow processes. In this context, it is necessary to take control of the dosing schedule for vitamin C delivery into the body so that the required systemic levels are obtained (i.e., those necessary to have in vivo anticarcinogenic activity, but not too high that can saturate the non-linear recycling process in kidneys and hence increasing the vitamin C clearance).

We have hypothesized that giving vitamin C intravenously by following a fractioned schedule over a longer period (i.e., by multiple-days, intermittent short-term IV infusions of

high doses instead of using the conventional long-term continuous IV infusion administration) will provide the optimal levels for anticarcinogenic activity. Such a schedule is expected to minimize the saturation of renal vitamin C reabsorption while providing a continuous “dynamic flow” of AA in the body for optimal systemic exposure and effect.

We firmly believe that a good understanding of all these mechanisms and their further implementation in clinical practice will yield better therapeutic outcomes. Accordingly, a concentration-function approach to vitamin C provides new insights into its physiology and pharmacology. With IV administration, ascorbate is turned from vitamin to drug, as pharmacologic concentrations are produced that are as much as 100-fold greater than maximal oral dosing.[2]

In some circumstances continuous infusion of IV vitamin C does not seem to be the optimal therapeutic schedule for cancer and repeated administration over a longer time period should be favored. We believe this particular pharmacokinetic-pharmacodynamic behaviour of high dose IV vitamin C can be explained by the Systemic Saturation hypothesis.

Systemic Saturation Concept in Relation to IV Vitamin C

Systemic saturation results when the concentration of AA in plasma and tissues in the body are high enough to produce an adverse effect in the biochemical parameters or metabolism. In this way, AA’s conversion to Dehydroascorbate (DHA) is reversed back to AA. Once this takes place, the prooxidant action is decreased, thus AA anticarcinogenic and/or carcinostatic action is reduced. This physiological phenomenon may occur when high IV doses of AA (100g or more) are given in a continuous sched ule. When high doses of IV AA are given continuously, it overwhelms the cellular biochemical pathways favouring the reversion of DHA to AA. This particular action dismisses AA anticarcinogenic and/or carcinostatic activity. This concept may in part explain the contradictory results reported previously in clinical studies despite in –vitro evidence that high concentrations kill cancer cells. The continuous high dose AA may pose a physiological stress to the body that may cancel or overcome the same physiological mechanisms we are trying to modify.

A pilot pharmacokinetic study of vitamin C at high dose infusions in a cancer patient suggested a dual-phase kinetic behaviour of ascorbate in vitro.[20] This disposition pattern depends on the actual infusion-generated plasma ascorbate concentrations with respect to the saturation cut-off level (ca. 70 μM = 0.123 mg/dL).[4,7] All these parameters are relevant to understand the physiology of high dose IV AA.

Conclusion

While AA alone may not be enough of an intervention in the treatment of most active cancers, it seems to improve quality of life19 and extend survival time.[21–29] It should be considered as part of the treatment protocol for all cancer patients.

Despite multiple in vitro and in vivo studies using different schedules of vitamin C for cancer therapy, the exact administration schedule that maximizes antitumour response remains unknown. Researchers should pay more attention to the cumulative (net) vitamin C

effect instead of the vitamin C concentrations. Again, we speculate that the schedule-dependence in the pharmacokinetics of AA accounts for such a discrepancy. The relationship between AA dose, steady-state plasma concentration, tissue store or cell compartments concentration/distribution, and urinary excretion is important to understand its physiological effect or more related to this discussion, its effect on cancer. In this regard, we suggest that prolonged schedules of intravenous vitamin C would yield greater antitumour effects than would single continuous IV doses of the same total exposure. As such, administration schedules reaching effective antitumour concentrations are more likely to result from intermittent IV infusion delivered on multiple-days. Nonetheless, more pharmacokinetic and pharmacodynamic studies are needed to fully understand this phenomenon.

References

1. Levine M, Conry-Cantilena C, Wang Y, et al. Vitamin C pharmacokinetics in healthy volunteers: evidence for a recommended dietary allowance. PNAS. 1996; 93:3704–3709. [PubMed: 8623000]
2. Riordan NH, Riordan HD, Casciari JP. Clinical and experimental experiences with vitamin C. J Orthomol Med. 2000; 15:201–213.
3. Padayatty SJ, Sun H, Wang Y, et al. Vitamin C pharmacokinetics: implications for oral and intravenous use. Ann Intern Med. 2004; 140:533–537. [PubMed: 15068981]
4. Hickey DS, Roberts HJ, Cathcart RF. Dynamic Flow: A new model for ascorbate. J Orthomol Med. 2005; 20:237–244.
5. Duconge J, Miranda-Massari JR, Gonzalez MJ, et al. Schedule dependence in cancer therapy: what is the true scenario for Vitamin C? J. Orthomol Med. 2007; 22:21–26.
6. Duconge J, Miranda-Massari JR, González MJ, et al. Vitamin C pharmacokinetics after continuous infusion in a patient with prostate cancer. Ann Pharmacother. 2007; 41:1082–1083. [PubMed: 17519294]
7. Duconge J, Miranda-Massari JR, Gonzalez MJ, et al. Pharmacokinetics of vitamin C: insights into the oral and intravenous administration of ascorbate. PR Health Sci J. 2008; 27:7–19.
8. Murata A, Morishige F, Yamaguchi H. Prolongation of survival times of terminal cancer patients by administration of large doses of ascorbate. Int J Vitam Nutr Res Suppl. 1982; 23:103–113. [PubMed: 6811475]
9. Riordan HD, Riordan NH, Jackson JA, et al. Intravenous vitamin C as a chemotherapy agent: a report on clinical cases. PR Health Sci J. 2004; 23:115–118.
10. Verrax J, Calderon PB. Pharmacologic concentrations of ascorbate are achieved by parenteral administration and exhibit antitumoral effects. Free Radic Biol Med. 2009; 47:32–40. [PubMed: 19254759]
11. McCormick WJ. Ascorbic acid as a therapeutic agent. Arch Pediat. 1952; 69:151–155. [PubMed: 14924799]
12. Chen Q, Espey MG, Krishna MC, et al. Pharmacologic ascorbic acid concentrations selectively kill cancer cells: action as a pro-drug to deliver hydrogen peroxide to tissues. Proc Natl Acad Sci U S A. 2005; 102:13604–13609. [PubMed: 16157892]
13. Mikirova NA, Casciari JJ, Riordan NH. Ascorbate inhibition of angiogenesis in aortic rings ex vivo and subcutaneous Matrigel plugs in vivo. J Angiogenes Res. 2010; 18:2. 2. [PubMed: 20150992]
14. Gonzalez MJ, Rosario-Perez G, Guzman AM, et al. Mitochondria, energy and cancer: the relationship with ascorbic acid. J Orthomol Med. 2010; 25:29–38. [PubMed: 23565030]
15. Frei B, Stocker R, England L, et al. Ascorbate: the most effective antioxidant in human blood plasma. Adv Exp Med Biol. 1990; 264:155–163. [PubMed: 2244489]

16. Padayatty SJ, Sun AY, Chen Q, et al. Vitamin C: intravenous use by complementary and alternative medicine practitioners and adverse effects. PLoS One. 2010; 5(7):e11414. [PubMed: 20628650]

17. Riordan HD, Casciari JJ, González MJ, et al. A pilot clinical study of continuous intravenous ascorbate in terminal cancer patients. PR Health Sci. 2005; 24:269–276.

18. Hoffer LJ, Levine M, Assouline S, et al. Phase I clinical trial of i.v. ascorbic acid in advanced malignancy. Ann Oncol. 2008; 19:1969–1974. [PubMed: 18544557]

19. Vollbracht C, Schneider B, Leendert V, et al. Intravenous vitamin C administration improves quality of life in breast cancer patients during chemo-/radiotherapy and aftercare: results of a retrospective, multicentre, epidemiological cohort study in Germany. In Vivo. 2011; 25:983–990. [PubMed: 22021693]

20. González MJ, Mora EM, Miranda-Massari JR, et al. Inhibition of human breast carcinoma cell proliferation by ascorbate and copper. PR Health Sci J. 2002; 21:21–23.

21. Cameron E, Pauling L. Supplemental ascorbate in the supportive treatment of cancer: Prolongation of survival times in terminal human cancer. Proc Natl Acad Sci USA. 1976; 73:3685–3689. [PubMed: 1068480]

22. Cameron E, Pauling L. Supplemental ascorbate in the supportive treatment of cancer: Reevaluation of prolongation of survival times in terminal human cancer. Proc Natl Acad Sci USA. 1978; 75:4538–4542. [PubMed: 279931]

23. Morishige F, Murata A. Prolongation of survival times in terminal human cancer by administration of supplemental ascorbate. J Int Acad Prev Med. 1979; 5:47–52.

24. Murata A, Morishige F, Yamaguchi H. Prolongation of survival times of terminal cancer patients by administration of large doses of ascorbate. Int J Vitam Nutr Res Suppl. 1982; 23:101–113.

25. Hoffer A, Pauling L. Hardin Jones biostatistical analysis of mortality data for cohorts of cancer patients with a large fraction surviving at the termination of the study and a comparison of survival times of cancer patients receiving large regular oral doses of vitamin C and other nutrients with similar patients not receiving those doses. J Orthomol Med. 1990; 5:143–154.

26. Hoffer A, Pauling L. Hardin Jones biostatistical analysis of mortality data for a second set of cohorts of cancer patients with a large fraction surviving at the termination of the study and a comparison of survival times of cancer patients receiving large regular oral doses of vitamin C and other nutrients with similar patients not receiving these doses. J Orthomol Med. 1993; 8:157–167.

27. Gonzalez NJ, Isaacs LL. Evaluation of pancreatic proteolytic enzyme treatment of adenocarcinoma of the pancreas, with nutrition and detoxification support. Nutr Cancer. 1999; 33:117–124. [PubMed: 10368805]

28. Riordan HD, Riordan NH, Jackson JA, et al. Intravenous vitamin C as a chemotherapy agent: a report on clinical cases. PR Health Sci J. 2004; 23:115–118.

29. Padayatty SJ, Riordan HD, Hewitt SM, et al. Intravenously administered vitamin C as cancer therapy: Three cases. Can Med Assoc J. 2006; 174:937–942. [PubMed: 16567755]