684

CLINICAL SCIENCES

Intravenous Ascorbic Acid: Protocol for its Application and Use

HUGH D. RIORDAN, MD*; RONALD B. HUNNINGHAKE, MD*; NEIL H. RIORDAN, MS; PA*
JAMES J. JACKSON, PhD*; XIAOLONG MENG, PhD*; PAUL TAYLOR, BS*; JOSEPH J. CASCIARI, PhD†;
MICHAEL J. GONZÁLEZ, DSC, PhD, FACN†; JORGE R. MIRANDA-MASSARI, PharmD‡;
EDNA M. MORA, MD**; NORBERTO ROSARIO, MD††; ALFREDO RIVERA, BSN‡‡.

High dose intravenous (IV) ascorbic acid (AA) has been used as therapy for infectious disease from bacterial and viral origin and adjuvant therapy for cancer. In this publication we describe a clinical protocol that has been developed over the past twenty years utilizing high dose IV AA as therapy for cancer. This includes principles of treatment, rationale, baseline workup, infusion protocol, precautions and side effects.

Key words: Intravenous ascorbic acid, Intravenous vitamin C, Cancer

High dose intravenous ascorbic acid (IAA) has been used as a therapy for bacterial infection, viral infection, and as adjuvant therapy for Cancer (1-7). The treatment rationale for the use or IAA in treatment of cancer has been described in detail elsewhere (7-9). In general cancer patients have depressed circulatory, cellular and tissue ascorbate levels and reserves. Ascorbate administered in pharmacological doses enhances various parameters associated with better prognosis (7,8). There is also evidence that physiologically attainable concentrations by intravenous administration are selectively toxic to cancer cells (3-7,10); contrary to the limited levels of ascorbate that can be reached by oral intakes. Moreover, there is evidence of synergism between the conventional methods for cancer treatment (surgery, radiation and chemotherapy) when utilized with ascorbate (11-13).

Principle of Treatment

Over 21 years of clinical experience using intravenous ascorbate in cancer patients indicate that the best responses are obtained when maintaining a continuous high plasma ascorbate level (3-7,10,14). Initially, doses of 15g per infusion were used, once or twice per week. These doses improved patient's sense of well being, reduced pain and in many cases improved survival times beyond predictions of experienced oncologists. Later using 30 grams of IAA, twice per week, it was found that metastatic lesions in lung and liver of a man with primary renal cell carcinoma disappeared in a matter of weeks (3). At the time it was believed that IAA was helpful to cancer patients solely through two mechanisms; by increasing production and strengthening extra cellular collagen (in this manner preventing metastasis and further tumor growth) and by improving immune function (immune cell's activity and interferon). Subsequently, resolution of bone metastases in a patient with primary breast cancer was reported using infusions of 100 grams once or twice per week (4). Now it is known that other mechanism(s) exists by which ascorbic acid (AA) and its salts are capable of cytotoxic activity against malignant tissue. AA is preferentially toxic to tumor cells (5), this preferential toxicity has been detected in multiple tumor cell types *in vitro* (14).

Also, plasma concentrations of AA required for killing tumor cells have been achieved in humans (5,10). Others have described *in vivo* toxicity of AA in multiple tumor types and in animal models, even in animals bearing human tumors (15-20).

Treatment Rationale

From previous studies (4,10,14), we concluded that:

- tumor cells are more susceptible to high dose ascorbate induced peroxidation products (mainly H_2O_2) due to their relative deficiencies in antioxidant enzymes, mainly catalase and superoxidase dismutase.
- concentrations of ascorbate high enough to kill tumor cells can be achieved in humans by IAA administration.

From *the Center for the Improvement of Human Functioning, Biocommunications Research Institute, Wichita, KS, the †RECNAC II Project, School of Public Health, Department Human Development, Nutrition Program, the University of Puerto Rico, Medical Sciences Campus, the ‡School of Pharmacy, Dept. of Pharmacy Practice University of Puerto Rico, **the Puerto Rico Cancer Center and Surgery Division Medical Sciences Campus, PR, ††VA Medical Center, Dept. Nursing, IV Team San Juan, PR, and the ‡‡Tabor Collage-Wichita, KS.

Address for correspondence: Dr. Michael J. González, University of Puerto Rico, Medical Sciences Campus, RECNAC II Project, Department Human Development, Nutrition Program, PO Box 365067, San Juan, PR 00936-5067.

Samples of human serum from patients receiving IAA confirmed that AA concentrations *in vivo* can reach levels that are cytotoxic to tumor cells *in vitro*. Using densely populated monolayers, a three–dimensional hollow fiber tumor model with the use of human serum as a growth medium to closely mimic the in-vitro environment it was found that an AA plasma concentration of 400 mg/dL effectively kills tumor cell types (14). Earlier it was reported that 40 mg/dL of plasma AA was adequate to kill tumor cells but this data was generated from *in-vitro* studies utilizing sparsely populated cell monolayers and standard tissue culture medium. Interestingly, human serum has been reported to decrease ascorbic acid cytotoxicity in cancer cells (10). This action is probably due to its antioxidant capacity. IAA is actually an off-label treatment, therefore, an appropriate informed consent must be read, understood and signed by the patient.

As with any cancer treatment it is important to establish certain baseline data before starting treatment, in order to monitor future therapeutic response. Such baseline data may vary depending upon the type and extent of the particular cancer of the patient being treated. It is necessary to include the patients weight, full hematological profile, SMAC-20 profile, G6PD test, measurement of serum tumor marker proteins if present and clinical and radiological measurements (CAT-Scan, MRI if appropriate) and; if possible, a performance on the Karnovsky scale.

Precautions and side effects. The side effects of IAA are rare. However, there are contraindications and potential side effects that should be considered. Although it has only been reported once in the literature, tumor necrosis, hemorrhage and subsequent death after a single intravenous 10 gm dose of ascorbic acid, as reported by Campbell and Jack (21), should be the highest concern for the safety of IAA in cancer patients; for this reason, it its advisable to begin with a small dose. Patients with highly anaplastic, rapid growing tumors with heavy tumor load should be carefully monitored.

Clinically those patients will present sudden pain in the areas of tumor deposit, swelling, tumor hemorrhage (internal and external), hyperpyrexia, severe hypertension, tachychardia and azotemia (2). This extremely rare complication can be fatal and must be vigorously treated. If suspected, the ascorbate infusion should be immediately discontinued and the patient treated as for septic shock. It has been reported that after such event, residual tumor has considerably decreased in size or even disappeared. (2,21). Although, highly dangerous, this reaction might also be termed as the best possible response to ascorbate treatment of widespread malignancy.

Another report describes acute oxalate nephropathy in a patient with bilateral ureteric obstruction and renal insufficiency who received 60gram IAAs (22); there is also a report of a patient with colon carcinoma, receiving daily IAA, who developed nausea and vomiting requiring hospitalization for dehydration (Hanson J, personal communication). Both of these cases show the need to assess the patient's renal function, hydration status and voiding capacity.

Although rare, hemolysis can occur in patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency, due to its oxidative capacity and increased formation of hydrogen peroxide (23,24). Localized pain and stinging sensation at the infusion site can occur if the infusion rate is too fast or 0.9% NaCI is used as a carrier solution. Dextrose should never be used as a carrier solution since glucose may stimulate tumor growth by enhancing glycolysis. Since ascorbate may work as a chelating agent, some individuals may experience tremors due to hypocalcemia.

Rivers (25) reported that high dose IAA is contraindicated in renal insufficiency, chronic hemodialysis patients, unusual forms of iron overload and oxalate stone formers. However, two reports (26,27) show that magnesium oxide (300mg/d, orally) and vitamin B6 (10mg/d, orally) inhibit oxalate stone formation in recurrent stone formers and can be provided to the patients. Given the amount of fluid which is used as a vehicle for the ascorbate and the sodium hydroxide/sodium bicarbonate used to adjust the pH, any condition which can be adversely affected by increased fluid or sodium such as: congestive heart failure, ascites, edema, hypertension, is relatively contraindicated. Ascorbate is preferably given by intravenous drip. It should never be given IV push as the osmolality of high doses are capable of sclerosing peripheral veins. An IV fluid osmolality of less than 1,200 mOsm will be tolerated well by most patients. (Table 1)

Infusion solution. In high dose ascorbate therapy many intravenous solutions are hypertonic. This does not seem to present a problem as long as the infusion rate is low enough and the toxicity does not exceed 1,200 milliOsm (mOsm). When infusing AA it should be mixed with Ringer's lactate (RL) solution when of up to 25 grams and/or sterile water for larger amounts. We recommended the use of sodium ascorbate/ascorbic acid mixture containing 0.91 moles of sodium per moles of ascorbate (500 mg AA/mL, pH range 5.5-7.0, Merit Pharmaceuticals, Los Angeles, California, Maclaskey Pharmaceuticals, Wichita, Kansas, Bioniche Pharm, London, Ontario, Canada.) Table 1 shows the osmolalities of commonly prepared solutions and Table 2 shows the final volume to maintain normal osmolality.

Infusion. As indicated in the precautions, a small starting dose of 15gm AA in 250ml RL over 1hr is recommended and the patient is observed closely for any adverse event.

Table 1. Osmolality of various amounts of sodium ascorbate/ascorbic acid in sterile water and Ringer's Lactate (mOsm; isotonic = 300 mOsm). Hypotonic mixtures are underlined; useful mixtures from isotonic to 1200 mOsm are in bold. An equal volume of IV solution is removed from the bag or bottle, prior to adding concentrated sodium ascorbate/ascorbic acid solution (500mg/mL).

Sodium ascorbate/ascorbic acid (gm.)	Final volume of sterile water				Final volume of Ringer's lactate			
	250	500	750	1000	250	500	750	1000
1	39	19	13	10	336	318	312	309
15	579	290	193	145	843	572	481	436
30	1158	579	386	290	1386	843	662	572
60	2316	1158	772	579	2472	1386	1024	843
75	2895	1448	965	724	3015	1658	1205	979
100	3860	1930	1287	965	3920	2110	1507	1205

Table 2. Final volume (cc)

Ascorbic acid (g)	Sterile water	Ringer's lactate
1	250	250
15	250	250
30	500	500
60	750	750
75	750	1,000
100	1,000	1,250

-Remember to substract AA quantity from bag or fluid.

The dose can be gradually increased over time but the infusion rate should not exceed 1 gm AA per min., 0.5 gm/min is well tolerated by most patients. Although there is variability due to scheduling and tolerance, a typical protocol may consist of the following infusions:

week 1: 1 x 15gm.	infusion per day	2-3 per week
week 2: 1 x 30gm.	infusion per day	2-3 per week
week 3: 1 x 65gm.	infusion per day	2-3 per week
week 4: 1 x 100gm.	infusion per day	2-3 per week

The dose is then adjusted to achieve transient plasma concentrations of 400mg/dL, 2-3 infusions per week or 200 mg/dL if taking oral lipoic acid (300 mg bid). This protocol should be followed for at least a year. The goal of the infusions is to raise plasma ascorbate concentration above cytotoxic levels for tumor cells as long as possible. The AA molecule is very similar to glucose, which greatly facilitates its entrance into the malignant cell. Because the ascorbate is so readily cleared by the kidney, the optimal infusion rate will result in tumor cytotoxic plasma levels of ascorbate for the largest periods of time and hopefully, maximum tumor cell lysis. Patients are advised to supplement orally with at least 5 gm. daily when no infusion is given, in order to maintain basal tissue levels and prevent a rare, but possible scorbutic rebound effect.

Resumen

El ácido ascórbico (AA) en altas dosis intravenosas (IV) ha sido utilizado como terapia para enfermedades infecciosas de origen bacteriano y viral, así como terapia adyuvante contra cancer. En ésta publicación describimos un protocolo clínico que ha sido desarrollado durante los pasados veinte años utilizando AA en altas dosis IV como terapia para cancer. Este trabajo incluye principios de tratamiento, fundamentos científicos, laboratorios y pruebas iniciales, protocolo de infusión y efectos secundarios.

References

1. Klenner FR. Observations on the dose and administration of ascorbic acid when employed beyond the range of a vitamin in human pathology. J Appl Nutr 1971;23:61-88.
2. Cameron E. Protocol for the use of vitamins C in the treatment of cancer. Med Hypotheses 1991; 36:190-194.
3. Riordan HD, Jackson JA, Schultz M. Case study: high-dose intravenous vitamin C in the treatment of a patient with adenocarcinoma of the kidney. J Ortho Med 1990;5:5-7.
4. Riordan NH, Jackson JA, Riordan HD. Intravenous vitamin C in a terminal cancer patient. J Ortho Med 1996;11:80-82.
5. Riordan NH, Riordan HD, Meng XL, Li Y, Jackson JA. Intravenous ascorbate as a tumor cytotoxic chemotherapeutic agent. Med Hypotheses 1995;44:207-213.
6. Riordan HD, Jackson JA, Riordan NH, Shultz M. High dose intravenous Vitamin C in the treatment of a patient with renal cell carcinoma of the kidney. J Ortho Med 1996;11:80-82.
7. Riordan HD, Jackson JA, Hunninghake RE, Riordan NH. High dose intravenous Vitamin Cand long time survival of a patient with cancer of the head of the pancreas. J Ortho Med 1995;10:87-88.
8. Cameron E, Pauling L, Leibovitz B. Ascorbic acid and cancer: a review. Cancer Res 1979; 39:663-681.
9. González MJ, Mora E, Riordan NH, Riordan HD, Mojica P. Rethinking vitamin C and cancer: an update on nutrition oncology. Cancer Pre Intl 1998; 3:215-224.
10. Riordan NH, Riordan HD, Casciari JJ. Clinical and experimental experiences with intravenous vitamin C. J Ortho Med 2000; 4:201-213.
11. Ringsdorf, WM JR, Cheras Kin E. Vitamin C and human wound healing. Oral Surg Oral Med Pathol 1982; 53:231-236.
12. Kennedy M, Bruninga K, Mutlu EA, Lo sordo J, Choudhary S, Keshavarzian A. Successful and substantial treatment of chronic radiation proctitis with antioxidants vitamins E and C. Ann J Gastroenterol 2001; 96:1080-1084.
13. Fujimoto J, Mori T, Takai S. Amelioration of pulmonary toxicity of bleomycin by free radical scavengers. Gan To Kagaku Ryoho 1990; 17:946-949.
14. Casciari JJ, Riordan NH, Schmidt TL, Meng XL, Jackson JA, Riordan HD. Cytotoxicity of ascorbate, lipoic acid and other ahoxidants in hollow fibre in vitro tumors. Brit J Cancer 2001; 84:1544-1550.
15. Cohen MJ, Krasnow SH. Cure of advanced Lewis lung carcinoma (LL): a new treatment strategy. Proceedings of AACR 1987; 28:416.

16. Lupulesco A. Vitamin C inhibits DNA, RNA and protein synthesis in epithelial neoplastic cells. Intl J Vit Nutr Res 1991; 61-125-129.
17. Varga JM, Airoldi L. Inhibition of transplantable melanoma tumor development in mice by prophylactic administration of Ca-ascorbate. Life Sciences 1983; 32:1559-1564.
18. Pierson HF, Meadows GG. Sodium ascorbate enhancement of carbidopa-levodopa methyl ester antitumor activity against pigmented B-16 melanoma. Cancer Res 1983; 43:2047-2051.
19. Charkrabarti RN, Dasgupta PS. Effects of ascorbic acid on survival and cell-mediated immunity in tumor bearing mice. IRCS Med Sci 1984; 12:1147-1148.
20. Tsao CS, Dunham WB, Ping YL. In vivo antineoplastic activity of ascorbic acid for human mammary tumor. In vivo 1988; 2:147-150.
21. Campbell A, Jack T. Acute reactions to mega ascorbic acid therapy in malignant disease. Scot Med J 1979; 21:151.
22. Wong K, Thomson C, Bailey RR, McDiarmid S, Gardner J. Acute oxalate nephropathy after a massive intravenous dose of vitamin C. Aust NZ J Med 1994;24:410-411.
23. De Flora A, Benatti U, Morelli A, Guida L. Oxidant damage of normal and glucose-6- phosphate dehydrogenase(G6PD-deficient red blood cells are enhanced by iron-EDTA complex. Biochem Int 1983; 281-290.
24. Stocks J, Dormandy TL. The autooxidation of human red cell lipids induced by hydrogen peroxide. Brit J Haematol 1971; 20:95-111.
25. Rivers JM. Safety of high-level vitamin C ingestion. In: Third Conference on AA. Ann NY_Acad Sci 1987; 498:95-102.
26. Rattan V, Sidhu H, Vaidyanathan S, Thind SK, Nath R. Effect of combined supplementation of magnesium oxide and pyridoxine in calcium-oxalate stone formers. Urol Res 1994; 22:161-5.
27. Prien El, Gershoff SF. Magnesium oxide-pyridoxine therapy for recurrent calcium oxalate calculi. J Urol 1974; 112:509-512.