Intravenous Ascorbic Acid: Protocol for its Application and Use

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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 IVAA 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

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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 is 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, tachycardia 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 IAAAs (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% NaCl 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.
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Table 1. Osmality 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).

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

Table 2. Final volume (cc)

<table>
<thead>
<tr>
<th>Ascorbic acid (g)</th>
<th>Sterile water</th>
<th>Ringer’s lactate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>250</td>
<td>250</td>
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<tr>
<td>15</td>
<td>250</td>
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<tr>
<td>30</td>
<td>500</td>
<td>500</td>
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<tr>
<td>60</td>
<td>750</td>
<td>750</td>
</tr>
<tr>
<td>75</td>
<td>750</td>
<td>1,000</td>
</tr>
<tr>
<td>100</td>
<td>1,000</td>
<td>1,250</td>
</tr>
</tbody>
</table>

-Remember to subtract AA quantity from bag or fluid.

The dose can be gradually increased over time but the
infusion rate should not exceed 1gm 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 scrobutic 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 esta 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.

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