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Two Grams BID Is an Oral Dosage of Vitamin C to Reduce the Risk of Recurrence of Superficial Bladder Carcinoma

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Abstract

Background: Continuous exposure to millimolar (mM) Vitamin C (AA) *in vitro* kills cancer cells. For superficial bladder carcinoma (SBC), standard chemotherapy is instillation of Bacillus Calmette-Guerin. The recurrence rate with this therapy is 91%. But high dosage vitamins including AA reduced the recurrence to 41%. Aim: To determine the oral dosage of AA that causes the highest concentration of AA [AA] in the bladder. Method: We conducted a clinical trial of 14 people who took various dosages of AA, and analyzed the [AA] in their urine. Results: AA above 2 g twice a day was not absorbed. But that intake produced a bladder [AA] above 1 mM in all participants. Conclusion: Taking 2 g of AA BID will increase [AA] in the bladder to a level likely to kill cancer cells that cause SBC. Taking that dosage 2 consecutive days a week is likely to reduce the recurrence rate of SBC substantially.

Keywords

Cancer, Vitamin C, LUTS, Superficial Bladder Carcinoma

1. Introduction

Linus Pauling proposed that taking megadoses of Vitamin C (ascorbic acid, AA) has many benefits. Among his results [1] are that AA significantly prolonged the fraction of survivors at times after date of onset of terminal stage (untreatable) cancer patients. Many patients had received an oral dose of 10 g daily.

AA enhances survival of cancer patients *in vivo* when properly administered IV (intravenously) rather than

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orally [2]. "Observational reports described ascorbate, given in pharmacologic doses of 10 g daily, as effective in treating some cancers and in improving patient well-being" [2] (**Figure 1** [3] [4]). Ongoing research continues to improve the effectiveness of AA in killing cancer cells [5]. Subsequently, the same dose had no effect on patient well-being and survival in two double-blind placebo-controlled trials, and AA was discarded as a treatment modality [6] [7]. Recent clinical evidence, however, indicates that the role of AA in cancer treatment should be examined anew [8]. The originally reported observational studies used IV and oral AA, but the subsequent double-blind placebo-controlled studies used only oral AA. It was not recognized that the route of AA administration might produce large differences in plasma concentrations. Recent pharmacokinetics studies in men and women show that 10 g of AA given IV are expected to produce plasma concentrations of nearly 6 mM, which are 75-fold higher than those concentrations from the same oral dose [8] [9]. The maximum serum concentration achievable by oral AA is 80 μM. The potential of IV AA to treat cancer is being explored [10], in at least 8 clinical trials currently [11].

It is estimated that 73,510 people will be diagnosed with and 14,880 will die of cancer of the urinary bladder in 2012 [12]. Developed in 1976 by Morales [13], normal chemotherapy for superficial bladder carcinoma (SBC) is instillation with intravesical *Bacillus Calmette-Guerin* (BCG). However, such cancers "commonly exhibit a very aggressive behavior and carry a grave prognosis", and the 5-year recurrence rate is 91%. Lamm [14] developed a megavitamin protocol that reduces recurrence to just 41%. However, many bladder oncologists do not use this modification.

When Lamm was publishing his megavitamin protocol, he was unaware of Ordman's discovery [15] that AA must be taken twice a day (BID) to maintain elevated levels in the serum, a result we showed next for calcium [16] and eventually assumed for all water-soluble nutrients. In 1994, we published in AGE [15] that when people consume AA orally, AA intake above 500 mg is excreted in the urine over 12 hr, and that 500 mg must be consumed twice a day to guarantee continuous excretion of excess in the urine (**Figure 2**). Levine [9] showed the relationship between oral AA dosage and serum levels, confirming Ordman's conclusion that 500 mg AA BID produces the highest statistically significant serum concentration of Vitamin C [AA] in people. That [AA] is about 80 μM, while the RDA (recommended daily allowance) produces only about 25 μM. The RDA is established by the US Food and Nutrition Board to reduce the risk of deficiency likely to cause short-term illness in

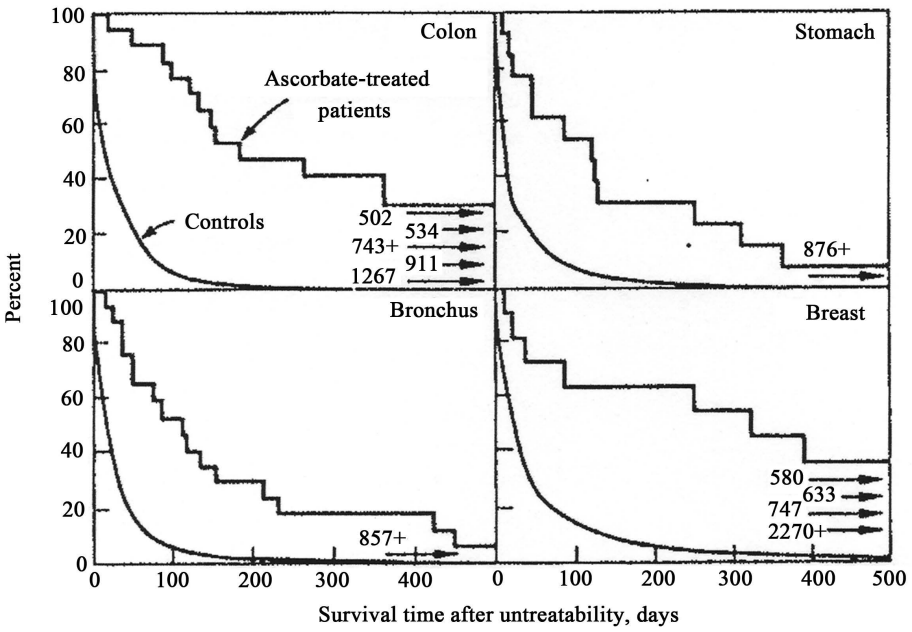

Figure 1. Fraction of survivors at times after date of onset of terminal stage (untreatability) of AA-treated patients with primary cancer of colon, stomach, bronchus, or breast, compared with that for matched controls (10 per ascorbate-treated patient). Many patients were given 10 g daily orally, but a variety of other AA treatments were used. Copyright 1976 National Academy of Sciences, USA [4].

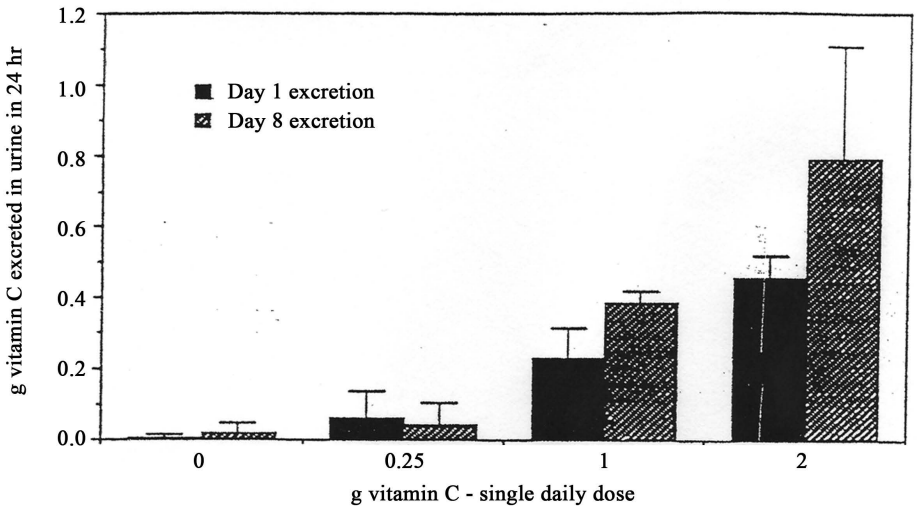

Figure 2. Relationship of dose of AA to total urinary excretion. Individuals took AA daily at 8 am for 8 days. All urine was collected during the first and last day. Each bar represents the mean for 5 individuals [14].

the US population. Recent studies indicate 40% of Americans take AA supplements [17].

In his megavitamin treatment, Lamm also did not note that the 2 g of AA was probably the active ingredient. Chen *et al*. [2] demonstrated in tissue culture that 5 cancer cell lines had EC_{50} values of <4 mM but normal cells were unaffected by 20 mM (**Figure 3**). They proposed the mechanism by which AA kills cancer cells without harming normal cells. Extracellular but not intracellular AA mediated cell death, which occurred by apoptosis and pyknosis/necrosis. Cancer cells catalyzed the generation of hydrogen peroxide from AA, while normal cells did not. Although AA addition to medium generated H_2O_2, AA, in addition to blood, generated no detectable H_2O_2 and only trace detectable AA radical. However, it is still accepted among many oncologists, e.g. at the Mayo Clinic web site, that high dose IV AA is ineffective [18]. Yet AA is used intravenously with cancer patients and increases efficacy in conjunction with a variety of chemotherapies, as reviewed by Levine at NIH [19]. A survey indicated more than 8800 patients were treated with IV AA in 2008 [20].

Current SBC treatment with BCG does not include the megavitamin protocol. In reviewing Lamm's result, Ordman noticed that Lamm's megavitamin included 2 g AA daily. In contrast to intravenous AA required to elevate serum concentrations to treat most cancers, oral AA is absorbed into the serum, and removed by the kidneys through the bladder in urine. Since AA kills cancer cells without harming healthy ones, we realized that an oral dose of AA could be found that would provide the maximum continuous [AA] in the bladder, and that this might significantly and safely reduce the recurrence of SBC.

Normal daily urine output is estimated 0.5 to 2 liters. Given that doses above 500 mg AA BID are excreted, we hypothesized that taking 2 g AA BID would produce a urine [AA] of approximately 14 mM, a level demonstrated to kill cancer but not harm normal human cells.

The objective of this study is to confirm our hypothesis that 2 g AA BID will produce a [AA] in the urine high enough to be able to kill cancer cells on the inner lining of the bladder.

2. Materials and Methods

2.1. Study Population

Beloit College Institutional Review Board approval was received before experimentation began. Fourteen students age 18 - 22 weighing 47 to 141 kg volunteered to participate in the trial.

2.2. Regimen and Compliance

The subjects took 2 g of AA (four Spring Green 500 mg tablets) at 9 am and again at 9 pm. Participants wrote down when doses were taken, and confirmed this to those collecting their urine.

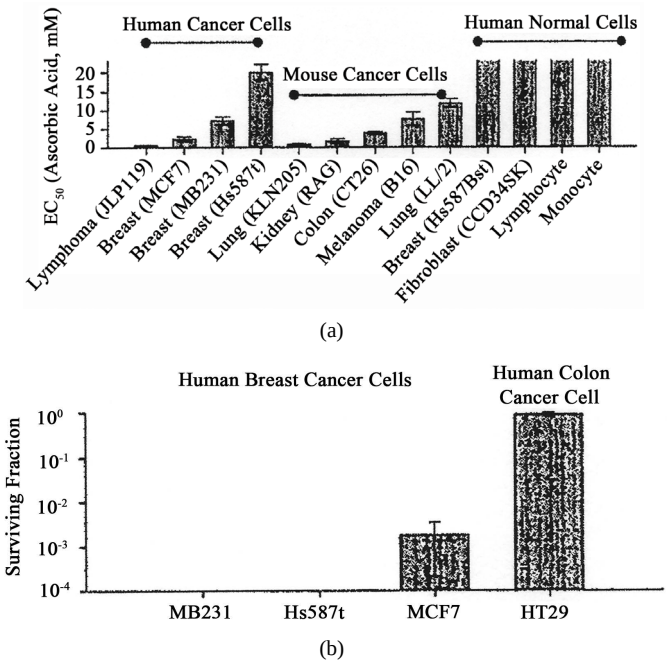

Figure 3. Effects of pharmacologic [AA] on cancer and normal cells. (a) EC_{50} values of ascorbate in human and mouse cancer cells and normal humans cells. All cells were treated with AA for 1 hr, washed, and recultured without AA. EC_{50} values were determined 18 - 22 hr later. (b) Colony formation of cancer cells in soft agar after 1 hr treatment with 5 mM AA. Surviving fraction, expressed in log scale, indicates number of treated colonies compared with matched untreated control cells. Copyright 2005 National Academy of Sciences, USA [2].

2.3. Sampling

Urine samples were collected 5 to 12 hours after the second dose was consumed.

2.4. Study Endpoints and Laboratory Methods

Oxalic acid was immediately added to stabilize the AA. The samples were put on ice until they were assayed with dichlorophenol-indophenol (DCIP) [21] in the next few hours. The [AA] of the samples was determined with an Ocean Optics spectrophotometer at 520 nm. This procedure was repeated twice with the same subjects.

3. Results

The results of the exploratory trial were used to determine a 2 g AA BID dosage (**Table 1**) and BID dosing (**Table 2**) that would produce the highest [AA] in the bladder. The pilot trial showed that dosages above 500 mg BID were necessary to guarantee continuous excretion from the bladder, and that dosages above 2 g BID were not absorbed from the intestine. After the peak concentration was achieved, it was maintained continuously during a week that the dosage was taken. Neither larger nor more frequent doses raised urinary [AA] any further.

The participants for this trial were from 18 to 22-year-old non-smokers and stated they were of good health, with most being male (**Table 3**). **Table 4** illustrates the results of the trial. The difference [AA] within individuals in the two trials likely results from different volumes of urine production. Three of the 14 reported minor indigestion.

Comparison of the maximum AA achieved vs. the level required to kill cancer cells:

Table 5 shows that bladder [AA] achieved by 2 g AA BID is likely to kill SBC cells *in vivo*. The AA levels ranged from 2.7 to 27.8 mM AA, which is much greater than the 2 mM level required to kill cancer cells *in vitro* [2].

Table 1. Effect of BID dose on the urinary [AA].

AA Dosage Taken Twice a Day	Urinary [AA]
1 g	1 mM
2 g	6 mM
3 g	7 mM
6 g	6 mM

Table 2. Effect of frequency of dosing on urinary [AA].

Dosage	Frequency	Urinary [AA], mM
1 g	Hourly	6 mM
1 g	Every 12 hr	1 mM
2 g	Every 12 hr	6 mM

Table 3. Characteristics of participants.

Person	Gender	Weight (kg)	Exercise (min/week)
1	M	102	900
2	M	93	840
3	F	79	0
4	M	77	1080
5	M	93	780
6	F	47	0
7	F	53	225
8	M	141	n.d.
9	M	90	1200
10	F	66	100
11	M	65	240
12	M	69	0
13	M	76	300
14	M	68	240

Table 4. Effect of BID dose on the urinary [AA]—Variation among participants.

Person	Gender	[AA], mM	[AA], mM
		1st trial	2nd trial
1	M	2.66	
2	M	2.68	
3	F	3.85	
4	M	4.09	
5	M	5.64	6.40
6	F	6.37	
7	F	6.68	9.53
8	M	7.40	8.32
9	M	7.41	10.72
10	F	8.46	10.62
11	M	8.57	23.20
12	M	9.56	11.40
13	M	11.90	20.21
14	M	14.57	27.80
Range Females = 3.85 to 10.62 mM			
Range Males = 2.66 to 27.8 mM			

Table 5. Comparison of the maximum [AA] achieved vs. the level required to kill cancer cells.

Condition	[AA], mM in medium	Dosage	Duration	Result	Ref.
SBC in the bladder	n.d.	2 g once daily	12 hr	Recurrence reduced from 91% to 41%	[14]
SBC in the bladder	2.7 to 27.8	2 g BID	Continuous	Clinical trial planned	here
Cancer cells in tissue culture	2	*In vitro* 2 mM continuous	1 hr	Nearly 100%	[2]
Normal cells in tissue culture	20	*In vitro* 20 mM continuous	1 hr	100% survival	[2]

4. Discussion

Taking 2 g AA raises the concentration of AA filtered by the kidneys to a maximum of approximately 6 mM. Our previous work [15] demonstrated that when AA is taken orally, the concentration in urine rises over 4 hr, remains elevated for the next 12 hr, and then falls rapidly, unless another dose of AA has been consumed. A single daily dose of 2 g will elevate the bladder concentration for at most 12 hr. Our results show that a 2 g dose is the most that will be absorbed. While **Figure 3** shows that exposure of cancer cells to AA of 1 hr is sufficient to kill them, providing a longer exposure *in vivo* seems prudent. Higher and more frequent doses shown in **Table 1** and **Table 2** did not raise urinary AA further, so excess AA must not be absorbed into the serum, and be disposed through the intestines. To maintain the 6 mM [AA] continuously, taking the dosage every 12 hr is necessary and sufficient.

AA is approved by the US Food and Drug Administration as a GRAS (generally recognized as safe) substance. Two-time Nobel Prize winner Linus Pauling took 16 g daily for years without side effects. In the latest statement issued by the Food and Nutrition Board for the USDA, the chair of the panel on antioxidants, Maret Traber, set the upper limit for AA at 2 g daily [22]. Using this level chronically may cause diarrhea in a few individuals. A review states clearly that high dosages of AA cause no apparent harm [19]. One hazardous side effect of AA is that wound healing takes longer, so it should not be consumed within a week of bleeding. Another side effect of high doses of supplemental AA that is documented in peer-reviewed literature was reported in 2011, when it was shown that taking AA supplements regularly causes LUTS in 21% of older men [23]. LUTS is lower urinary tract symptoms, specifically more difficulty with and frequency of urinating, similar to prostate hyperplasia. It remains unclear whether AA contributes to kidney stones. AA can be biochemically metabolized to oxalic acid, and oxalic acid forms kidney stones. For this reason many physicians believe that consuming AA increases the risk of kidney stones. However, a reduction in the risk for kidney stones was observed in those who take AA supplements [24]. A 2013 study by Thomas *et al.* [25] reported a 0.15% increased risk in a Swedish population that takes single doses of 1 g or more through supplements. Other documented effects of AA are beneficial. These include a minor reduction in blood pressure [26], a reduction in cortisol levels [27], and a reduction in the risk of stroke damage [28]-[30].

In order to reduce the chance of causing LUTS, and considering that cancer often develops tolerance for many forms of chemotherapy, the proposal to conduct a clinical trial on those with SBC will include 2 g AA BID two consecutive days per week. We are assuming that AA will be processed by the kidneys of SBC patients as it is by our healthy volunteers. Our pre-trial involved participants taking 2 g of Vitamin C twice a day (4 g daily) to achieve a maximal concentration of AA in the bladder. Previously, it was thought that there was no benefit in taking more than 2 g of Vitamin C per day, but our research indicates that taking a higher dose, 4 g per day, will increase the concentration of AA in the bladder. We predict that the increased amount of AA in the bladder will help to prevent or treat SBC by killing any new cancer cells as soon as they develop in the bladder. This method may provide a cure for SBC.

5. Conclusion

Research about urinary excretion of AA indicates that the AA level in the bladder can be elevated simply by oral consumption. The maximum [AA] ranged from 2.7 to 27.8 mM, by consuming 2 g AA BID. For people with SBC, this method provides a level of AA in the bladder that can kill cancer cells, not harm normal tissue, and is likely to significantly reduce the rate of recurrence from 91% to no more than 41%, and potentially much less.

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Abbreviations

AA: ascorbic acid/vitamin C;
BID: in divided does, twice a day;
BCG: Bacillus Calmette-Guerin;
IV: intravenously;
SBC: superficial bladder carcinoma;
LUTS: lower urinary tract sypmtoms;
DCIP: dichlorophenol-indophenol;
GRAS: generally recognized as safe.

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