Review of Evidence for Determining Your Vitamin C Dosage

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ABSTRACT

Evidence is presented to support your decision about vitamin C (AA) supplementation. The Recommended Daily Allowance for men of AA has been raised from 60 to 90 mg. Because higher doses may be more beneficial, the Food and Nutrition Board has established an Upper Limit for safety of 2,000 mg per day. Studies of AA dosage for humans demonstrated that 500 mg twice a day is the lowest oral dosage that provides significant saturation of blood plasma. One study endorsed 200 mg from dietary sources for the RDA. Recently several studies have indicated the benefit of high levels of AA to maintain the brain and heart, reduce damage from stroke, brain trauma, and cataracts, and lower the risk of cancer metastasis and colds. Evidence is presented consistent with the hypothesis that people, especially older people and soldiers in combat environments at risk for brain trauma, will benefit if they maintain the saturating level of AA that can be obtained with supplements.

INTRODUCTION

In 1956, Denham Harman, founder of AGE, proposed the free radical (ROS) theory of aging (Beckman and Ames 1998b). Linus Pauling proposed megadoses of the water-soluble antioxidant vitamin C (ascorbic acid, AA) to trap free radicals, recommending dosages up to 16 g per day (Pauling 1970). In 1994, King et al (1994) discovered that 500 mg of AA taken orally every 12 hr were sufficient to provide continuous excretion of excess AA into the urine. In 1996, a similar study by Levine M et al (1996) confirmed those results, showing that that dosage provides the highest statistically significant concentration in plasma for protection from free radical damage. But they recommended only 200 mg AA consumed from dietary sources as the RDA, based on the plasma AA level necessary to saturate certain white blood cells.

The Food and Nutrition Board of the Institute of Medicine raised the RDA for AA for men and women to 90 and 75 mg resp., with an Upper Limit for safety established at 2 g per day. This review describes recent studies relevant to the selection of a daily intake of AA for health maintenance.

EVIDENCE

HOW CONCENTRATIONS IN DIFFERENT TISSUES AFFECT FUNCTION

In addition to serum and white blood cell concentrations of vitamin C, there are many other tissues in which high AA concentrations are important to maintain. Some studies below reflect the metabolic and antioxidant functions of AA in controlling cell differentiation through nutrition signaling. In a process called nutrient signaling, described only in the past decade, nutrients can transform metabolic processes as hormones do (Bhalla and Iyengar 1999; Ordman 2008). AA signals cell differentiation of brain and heart stem cells described below.

BRAIN : Taking 500 mg of vitamin C twice daily may lessen Alzheimer's, stroke, and head trauma damage. Stroke is the leading cause of disability worldwide (Zweifler 2003), and head trauma is common in war veterans. Several studies reveal the value of elevated levels of AA for protecting brain function. First, in humans with Alzheimer's and mild cognitive impairment, tissues and biofluids show evidence of oxidative stress (Su et al 2008). Cognitive decline in aging dogs is lessened simply by adding antioxidants to the diet. The deposition of amyloid-beta is decreased (Araujo et al 2005).

AA is a water-soluble antioxidant that crosses the blood-brain barrier. AA is produced in the liver of most mammals. Hibernating animals naturally store high concentrations of AA in the brain for protection from the metabolic stress that accompanies arousal (T[illegible]en et al. 2001). In humans, brain stroke damage continues when blood flow resumes. AA substantially prevented this reperfusion injury (Rozell 1998). Polidori et al (2001) show that AA is much lower in plasma for those with head trauma or intracranial hemorrhage compared to healthy subjects, while other antioxidants such as vitamin E are unaffected. Even at a dose of 200 mg AA/day, ischemic stroke-related lipid peroxidation decreased significantly in humans (Polidori et al 2005).

Via nutrient signaling, AA may exert effects on brain maintenance and recovery. How neural progenitor cells (NPCs) differentiate is determined by the redox state of the brain (Adler 2008). In the reducing environment produced by AA, NPCs become neurons. Under oxidizing conditions, astrocytes are formed. Prozorovski et al (2008) conclude that nontoxic manipulation of redox conditions in the brain influences NPC fate to produce neurons. People are able to generate new neurons throughout their entire lives (Song et al. 2005). High AA concentrations in the brain maintain the potential to generate new neurons.

HEART: The benefits of AA for the circulatory system include improved circulation and heart health. AA reverses the endothelial dysfunction caused by oxidative stress (Levine GN et al 1996). As with brain stem cells mentioned above, sufficient AA causes embryonic stem cells to differentiate into cardiac myocytes (Takahashi et al 2003).

TABLE 1: SUMMARY OF POTENTIAL DAMAGE BY OXIDATIVE STRESS AND BENEFITS OF AA INTAKES OF 500 MG TWICE A DAY TO HUMANS

BRAIN	ROS contribute to Alzheimer's (Su et al 2008) AA reduces cognitive decline (Araujo et al 2005) AA reduces reperfusion injury (Rozell 1998) AA reduces damage from head trauma (Polidori et al 2001) AA generates new neurons (Prozorovski et al 2008)
HEART	AA reverses endothelial dysfunction (Levine GN et al 1996). AA generates new cardiac myocytes (Takahashi et al 2003) AA (500 mg twice daily) protects plasma (Moser et al 2006)
EYES	AA reduced cataract odds 64% (Valero et al 2002)
COLDS	AA (500 mg) reduced frequency of colds by 66% (Saszuki et al 2006)
CANCER	AA reduced mutations causing metastases (Ishikawa et al 2008)
SAFETY	Upper Limit established at 2,000 mg AA daily (Food and Nutrition Board 2000) Up to 2,000 mg AA daily is safe (Hathcock et al 2005)

Abbreviations: AA- ascorbic acid (Vitamin C)
ROS-Reactive oxygen species (free radicals)

PLASMA: Heinz bodies reflect ROS damage to red blood cells (RBCs). Johnston and Cox (2001) measured Heinz bodies in RBCs (Beutler et al. 1995) in college students. They concluded that the antioxidant protection afforded by short-term vitamin C supplementation is maximal at the 500–1000 mg dosage. When taken in conjunction with 400 IU of vitamin E, a fat-soluble antioxidant, Moser et al (2006) concluded that 500 mg of AA taken twice daily was superior to 200 mg in reducing Heinz bodies, while vitamin E with minimal AA prevented protein carbonyl and TBARS damage.

CATARACTS: A major study in Europe shows that blood levels of AA above 49 μmol/L were associated with a 64% reduced odds for cataract (Valero et al 2002). US daily value for AA provides only about 20 μmol/L, while 500 mg twice daily provides about 75 μmol/L.

COLDS: Evidence for any benefit of AA for preventing or treating colds remains controversial. A meta-analysis by Douglas and Hemila (2005) evaluated 55 comparative studies treating colds with oral doses of 200 mg of AA per day, and found at most limited evidence for any benefit in prevention or treatment of colds. Although twice-a-day dosing is necessary to maintain elevated serum AA, I have not been able to locate any studies conducted with this requirement. Recently Saszuki et al (2006) reported that the risk of getting a cold decreased in response to single doses of AA. In a study over the range from 50 to 500 mg AA daily, the risk of contracting three or more colds during a 5 yr period was decreased 66% by daily intake of 500 mg.

CANCER: Research has demonstrated that mutations of mitochondria accumulate with age (Beckman and Ames 1998a). Each mitochondrion generates about 4,000 free radicals per second (Gredilla et al 2001; Myers and Bosmann 1974). In human tumors, mitochondrial DNA mutations occur at high frequency. Ishikawa et al (2008) demonstrated that pretreatment of tumor cells in mice with free radical scavengers prevents those cells from metastasizing. By prevention of mitochondrial DNA mutations, a mechanism to maintain a high concentration of antioxidants in mitochondria could reduce the risk of metastatic tumors. A review by Frei and Lawson (2008) also shows many recent studies demonstrating that millimolar vitamin C by i.v. infusion will kill cancer cells but not normal cells.

SAFETY: There are periodic reports that taking large amounts of AA over long periods of time may be harmful. But even doses of 10 g/day in adults have not been reported to cause harm in reliable scientific studies. Doses above 2,000 mg daily may cause diarrhea and gastric disturbance in some people. In addition, too much AA distorts results of tests commonly used to measure the amount of glucose in urine and blood. Combining oral anticoagulant drugs and excessive amounts of AA can produce abnormal results in blood-clotting tests (e.g., lowering prothrombin time).

However, while media reports periodically raise concern about taking AA and vitamin E supplements, those reports are based on misinterpretations of peer-reviewed studies. In response, a major review by numerous authorities, John N Hathcock, Angelo Azzi, Jeffrey Blumberg, Tammy Bray, Annette Dickinson, Balz Frei, Ishwarlal Jialal, Carol S Johnston, Frank J Kelly, Klaus Kraemer, Lester Packer, Sampath Parthasarathy, Helmut Sies and Maret G Traber (2005), was titled " Vitamins E and C are safe across a broad range of intakes". They provided numerous human studies justifying the tolerable Upper Limit (UL) established by the Food and Nutrition Board, which is 1,000 mg daily for vitamin E and 2,000 mg daily for AA.

DISCUSSION

Physicians accept the role of AA as a vitamin for immediate health benefits such as prevention of scurvy. Ever since Harman's free radical theory of aging and anti-nuclear activist Linus Pauling's proposal to take megadoses of AA as an ROS scavenger to maintain long-term health, people have found higher doses controversial. Periodically, the media report erroneous findings, like those of Podmore et al (1998) that AA may cause DNA mutations. The press has failed to report their erroneous technique and the ULs established in 2000 defining the safety of antioxidant nutrients.

The dosages still advocated actively in the literature are three. They are: 90 mg, found in most diets, providing the Daily Value, sufficient to prevent scurvy; 200 mg, the highest intake likely through a conscientious diet, sufficient to saturate certain WBCs; and 500 mg twice a day, which can be obtained only through oral supplements, and is the highest dosage necessary and sufficient for oral dosage saturation of plasma in vivo. Given the likely benefits of higher plasma levels reflected in Table 1, along with the safety of those levels, greater education should be provided to people to help alleviate the expense and suffering that may be caused by inadequate AA intake.

CONCLUSION

As documented above, 500 mg of vitamin C taken every 12 hrs may reduce many major causes of chronic disease and aging decline, not to mention colds. The safety and benefit of vitamin C supplements is of critical importance, especially those in war zones or of advancing years. People ought to be informed of the safety and benefit of vitamin C supplements.

REFERENCES

Adler EM (2008) Science signaling: Sirtuin to become astrocytes. Science 320: 291
Araujo JA, Studzinski CM, Head E, Cotman CW, Milgram NW (2005) Assessment of nutritional interventions for modification of age-associated cognitive decline using a canine model of human aging. AGE 27: 27-37
Beckman KB, Ames BN (1998a) Mitochondrial aging: open questions. Ann N Y Acad Sci 854: 118-27
Beckman KB, Ames BN (1998b) The free radical theory of aging matures. Physio. Rev. 78: 547-81
Beutler E, Lichtman MA, Coller BS, Kipp TJ (1995) Williams hematology. 5th edn. McGraw-Hill, New York, L26
Bhalla US, Iyengar R (1999) Emergent properties of networks of biological signaling pathways. Science 283: 381–387
Douglas RM, Hemila H, D'Souza R, Chalker EB, Treacy B (2004) Vitamin C for preventing and treating the common cold. Cochrane Database Syst Rev. 4: CD000980.
Douglas RM, Hemila H (2005) Vitamin C for Preventing and Treating the Common Cold. PLoS Medicine 2: e168
Food and Nutrition Board, Institute of Medicine. (2000) Dietary reference intakes for vitamin C, vitamin E, selenium, and carotenoids. Washington, DC: National Academy Press
Frei B, Lawson S (2008) Vitamin C and cancer revisited. PNAS 105: 11037-11038
Gredilla R, Sanz A, Lopez-Torres M, Barja G (2001) Caloric restriction decreases mitochondrial free radical generation at complex I and lowers oxidative damage to mitochondrial DNA in the rat heart. FASEB Journal 15: 1589-1591
Hathcock JN, Azzi A, Blumberg J, Bray T, Dickinson A, Frei B, Jialal I, Johnston CS, Kelly FJ, Kraemer K, Packer L, Parthasarathy S, Sies H,Traber MJ (2005) Vitamins E and C are safe across a broad range of intakes. AJCN 81: 736-745
Ishikawa K, Takenaga K, Akimoto M, Koshikawa N, Yamaguchi A, Imanishi H, Nakada K, Honma Y, Hayashi J (2008) ROS-Generating Mitochondrial DNA Mutations Can Regulate Tumor Cell Metastasis. Science 320: 661-664
Johnston CS, Cox SK (2001) Plasma-saturating intakes of vitamin C confer maximal antioxidant protection to plasma. JACN 20: 623-627
King G, Beins M, Larkin J, Summers B, Ordman AB (1994) Rate of Excretion of vitamin C in human urine. AGE 17: 87-92
Levine GN, Frei B, Koulouris SN, Gerhard MD, Keaney JF, Vita JA (1996) Ascorbic acid reverses endothelial vasomotor dysfunction in patients With coronary artery disease. Circulation 93: 1107-1113
Levine M, Conry-Cantilena C, Wang Y, Welch RW, Cantilena LR (1996) Vitamin C pharmacokinetics in healthy volunteers: Evidence for a recommended dietary allowance. PNAS USA 93: 3704-9
Moser LR, Ordman AB (2006) Design for a study to determine optimal dosage of ascorbic acid and alpha-tocopherol in humans. AGE 28: 77-84
Myers MW, Bosmann HB (1974) Mitochondria! Protein Content and Enzyme Activity of Reuber Hepatoma H-351. Cancer Research 34: 1989-94
Ordman AB (2008) Pilot study for an age and gender-based nutrient signaling system for weight control. AGE 30: 201-8
Pauling, L (1970) Vitamin C the Common Cold. W.H.Freeman, San Francisco
Podmore ID, Griffiths HR, Herbert KE, Mistry N, Mistry P, Lunec J (1998) Vitamin C exhibits pro-oxidant properties. Nature 392: 559
Polidori MC, Mecocci P, Frei B (2001) Plasma vitamin C levels are decreased and correlated with brain damage in patients with intracranial hemorrhage or head trauma. Stroke 32:898-902
Polidori MC, Pratic D, Ingegni T, Mariani E, Spazzafumo L, Del Sindaco P, Cecchetti R, Yao Y, Ricci S, Cherubii A, Stahl W, Sies H, Senin U, Mecocci P (2005) Effects of vitamin C and aspirin in ischemic stroke-related lipid peroxidation: Results of the AVASAS Study. BioFactors 24:265–274
Pray WS (2006) Nonprescription Product Therapeutics. 2nd ed. Baltimore, MD: Lippincott Williams & Wilkins. 235-264.
Prozorovski T, Schulze-Topphoff U, Glumm R, Baumgart J, Schroter F, Ninnemann O, Siegert E, Bendix I, Br[illegible]tle O, Nitsch R, Zipp F, Aktas O (2008) Sirt1 contributes critically to the redox-dependent fate of neural progenitors. Nat. Cell Biol. 10: 385-394
Rozell N (1998) Of Ground Squirrels, Vitamin C and stroke. Alaska Science Forum Article 1378 Sasazuki S, Sasaki S, Tsubono Y, Okubo S, Hayashi M, Tsugane S (2006) Effect of vitamin C on common cold: randomized controlled trial. Eur J Clin Nutr 60: 9-17
Song H, Kempermann G, Wadiche LO, Zhao C, Schinder AF, Bischofberger J (2005) New neurons in the adult mammalian brain: Synaptogenesis and functional integration. J Neurosci 25: 10366-10368
Su H, Gornitsky M, Geng G, Velly AM, Chertkow H, Schipper HM (2008) Diurnal variations in salivary protein carbonyl levels in normal and cognitively impaired human subjects. AGE 30: 1-9
Takahashi T, Lord B, Schulze PC, Fryer RM, Sarang SS, Gullans SR, Lee RT (2003) Ascorbic acid enhances differentiation of embryonic stem cells into cardiac myocytes. Circulation 107: 1912-1916.
Toein O, Drew KL, Chao ML, Rice ME (2001) Ascorbate dynamics and oxygen consumption during arousal from hibernation in Arctic ground squirrels. Am J Physiol Regul Integr Comp Physiol 281: R572-R583
Valero MP, Fletcher AE, De Stavola BL, Vioque J, Alepuz VC (2002) Vitamin C is associated with reduced risk of cataract in a Mediterranean population. J. Nutr. 132: 1299-1306
Zweifler RM (2003) Management of acute stroke. South Med J 96: 380–385