

# Clinical Utility of Pharmacological Ascorbate in Veterinary Oncology

Kendra V. Pope, DVM

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## Author Contact:

Integrative Oncology & Veterinary Wellness  
252 Broad St., Suite 3  
Red Bank, NJ 07701  
Phone: (732) 268-8553  
Email: info@drkendrapope.com

## Abbreviations

<b>C<sub>max</sub></b>	<b>Maximum concentration</b>
<b>CRI</b>	<b>Constant rate infusion</b>
<b>G6PD</b>	<b>Glucose-6-phosphate dehydrogenase</b>
<b>PK</b>	<b>Pharmacokinetics</b>

## Abstract

Pharmacological ascorbate has had a prominent role in oncology and integrative treatment of cancer for many decades. The use of and interest in the agent as well as anecdotal evidence for its benefit for veterinary patients is commonly discussed. Recently, more evidence is mounting for its use and benefit to both human and veterinary patients. This literature review evaluates the history and use of pharmacological ascorbate in cancer patients as well as biological activity and available data for use in veterinary patients. Researched mechanisms of activity against cancer cells and the available data regarding dosing, frequency, and administration in animals are reviewed. Potential clinical concerns of treatment and use alongside conventional cancer treatment are examined. Although the exact dosing, frequency, and protocols for maximal effectiveness are not yet established, this review offers a clear and thorough understanding of available evidence and literature regarding pharmacological ascorbate.

## Introduction

The role ascorbate (vitamin C) plays in the prevention and treatment of cancer is a long-documented and controversial relationship deserving of ongoing conversation. A substantial body of literature supports potential antitumor

effects of ascorbate in vitro and in vivo, documenting cytotoxicity of cancer cells and disruption of tumor growth in animal models (1). Over the years, numerous epidemiological studies have highlighted a decreased incidence of cancer and improved survival in patients with higher dietary intake or higher plasma levels of vitamin C (2). What continues to be a hotly debated topic is whether vitamin C has any therapeutic effects in the treatment of cancer, with original trials dating back to the 1950s when McCormick hypothesized that ascorbate protects against cancer by increasing collagen synthesis (3). In the 1970s, Cameron and Campbell treated 50 patients who had various types of advanced cancer with high doses of oral ascorbate, IV ascorbate, or both and noted several tumor responses following treatment (4). These findings were followed by Cameron and Pauling, who published the results of 100 patients with terminal cancer for whom conventional therapy was no longer considered useful. Patients were treated with 10 g of IV ascorbate for 10 days, followed by 10 g orally for an indefinite amount of time. The ascorbate-treated patients were compared to 1,000 retrospective controls who had similar disease but did not receive ascorbate or any other definitive anticancer therapy. The patients who received ascorbate survived 300 days longer than the controls (5, 6). Criticism of the reports included the retrospective nature of the trial, the lack of controls or blinding, and the

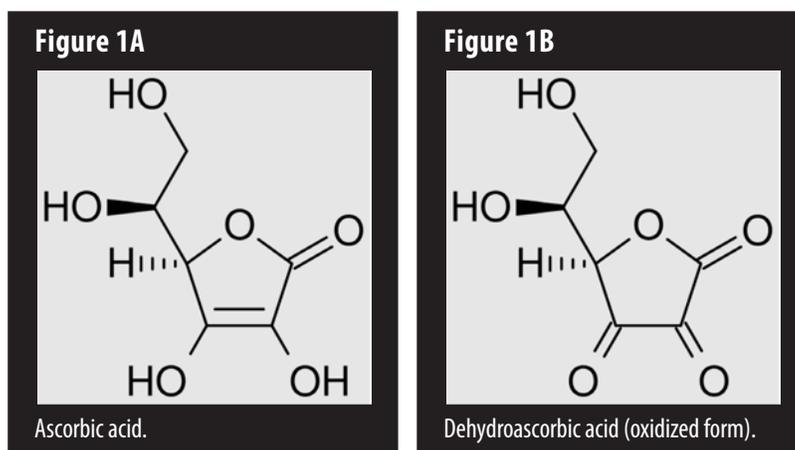
fact that the patients who were studied may have been at risk for endemic vitamin C deficiency (7). The Mayo Clinic attempted to repeat Cameron and Pauling's results in a randomized placebo-controlled trial in patients with advanced cancer, but they failed to detect any clinical benefit after daily oral administration of 10 g of ascorbate (8). Because the study noted no significant difference between the ascorbate-treated and placebo-treated groups, the scientific community dismissed ascorbate's role in cancer treatment (9). The fundamental difference between the 2 data sets is believed to be the oral versus IV route of ascorbate, which is now known to result in significantly altered pharmacokinetics (PK) of the vitamin (1). Recently, with a greater understanding of tumor biology, as well as the discovery that IV ascorbate produces plasma concentrations that are much higher than those produced by oral ascorbate, there has been renewed interest in ascorbate as an anticancer agent (7). The benefit or utility of ascorbate in veterinary oncology has not been reported, although protocols are described and used commonly within the integrative oncology and holistic communities. The biochemistry for the functions of vitamin C is principally the biochemistry of ascorbate, and therefore, the remainder of this literature review uses the term *pharmacological ascorbate* to distinguish the functioning of ascorbate as a drug from its biochemistry as vitamin C, similar to a recent publication (10). The current understanding of pharmacological ascorbate for use in cancer patients and a review of the available information regarding pharmacological ascorbate in veterinary oncology are discussed below.

### Biological Activity, Synthesis, and Absorption

Although vitamin C is commonly known for its role in immunity, it also plays many important roles in metabolic pathways throughout the body. Vitamin C primarily functions as an antioxidant and free radical scavenger as well as a regulator of collagen synthesis, where it is involved in hydroxylation of prolyl and lysyl residues of procollagen. It contributes to catalysis by donating electrons to metal ion cofactors of hydroxylase enzymes and is also a potent enhancer of iron absorption (11). It also serves primary functions in drug, steroid, and tyrosine metabolism as well as electron transport, which is essential for synthesis of L-carnitine, an important carrier of acyl groups across mitochondrial membranes. Because vitamin C protects against free radical damage induced by the oxidative burst of neutrophils and stimulates the phagocytic

effects of leukocytes, it plays an important role in immune system function. Larger doses play a protective role against carcinogenesis, acting as a nitrate scavenger reducing nitrosamine-induced carcinogenesis (12). Processed foods high in nitrates and nitrites, such as bacon and sausage, are often supplemented with vitamin C to reduce the carcinogenic capability of the resultant nitrosamines (13). Vitamin C also plays a role in prevention of gingivitis and periodontal disease and may have some benefit in exercise stress recovery (12, 14).

Most higher animals that synthesize vitamin C do so from carbohydrate precursors, such as glucose and galactose. This production occurs in the hexuronic acid pathway of the liver or the kidney as a result of the activity of the enzyme L-gulonolactone oxidase (15). Because humans, as well as other primates, the guinea pig, a few bat species, insects, fishes, and some birds, lack this enzyme, they cannot synthesize vitamin C and must meet their requirements via foods (16). In these species, vitamin C is absorbed by a saturable, carrier-mediated, active-transport mechanism that is sodium dependent. Species that can synthesize vitamin C absorb it strictly by passive diffusion with an absorption efficiency greater than 80% (12). Following absorption, vitamin C is ubiquitously distributed within the cells of the body, both in animals capable of synthesizing the vitamin as well as those dependent on dietary vitamin C, with the highest levels found in the pituitary and adrenal glands as well as white blood cells, skeletal muscles, liver, spleen, brain, and pancreas (12, 15). Under physiologic conditions, vitamin C exists as ascorbate, a weak acid that cannot cross most membranes readily. To enter tissues, vitamin C as ascorbic acid first has to be oxidized to dehydroascorbic acid (Figure 1A,B), transposed by facilitative diffusion via glucose



(Figures by Stanislaw Gackowski from Wikipedia.org)

transporters (17, 18). Once inside the cell, dehydroascorbic acid is quickly reduced back to ascorbic acid by an intracellular enzyme (dehydroascorbic acid reductase), which uses reduced glutathione to complete this pathway (12, 19).

### Requirements and Deficiency

Under normal conditions, dogs and cats have no dietary requirement for vitamin C, because they can synthesize this vitamin. However, they have one-quarter to one-tenth the ability to synthesize vitamin C when compared to other mammals because the rate of vitamin C synthesis in liver tissue is lower than it is in other animal species, such as ruminants, rodents, and rabbits (14). Dogs have been documented to synthesize vitamin C in the liver at a rate of 5 µg/mg of protein per hour, whereas cows, rats, and rabbits had rates of 68, 39, and 23 µg/mg of protein per hour, respectively (14). During stress or intense exercise, the vitamin C requirement may exceed the synthetic capacity of the liver. Even for species that do synthesize vitamin C, it has been shown that the synthesizing capacity of the liver can vary widely from animal to animal, suggesting a possible supplementary need for the vitamin in individuals under certain conditions or disease states (20, 21). Starvation or lack of optimum food supplies affects vitamin C synthesis, and mean plasma vitamin C concentration was found to be significantly lower in dogs after they were fasted (22). Satisfactory and reliable procedures to assess vitamin C levels in animals have not been developed because of limited knowledge concerning the vitamin's metabolic functions (23). Information regarding adequacy has been determined by analysis of vitamin C concentrations in serum (plasma), leukocytes, whole blood, or urine. Normal circulating plasma levels are reported at 4 µg/mL in dogs and 3 µg/mL in cats (12). When measuring plasma levels in animals, precautions need to be taken to protect the vitamin in solution and to select an assay that measures the vitamin and no other substances (23). Commercial vitamin C testing is not readily available for the veterinary practitioner.

Although the clinical manifestation of overt vitamin C deficiency, such as weakness, fatigue, bone pain, loose teeth, and hemorrhages of the skin, musculature, adipose tissue, and certain organs, would not be expected in species capable of synthesizing vitamin C, the development of scurvy has been reported in dogs (24, 25). Vitamin C deficiency has also been reported to be associated with canine hypertrophic osteodystrophy, with evidence supporting the

use of vitamin C (100-200 mg) orally or intramuscularly to enhance recovery (26, 27). Vitamin C has also been administered to pregnant bitches with hip dysplasia, resulting in puppies with no evidence of the disease (28). As in dogs, vitamin C synthesis in cats is lower than in other species; however, repeated trials have failed to demonstrate a need for dietary vitamin C in cats (23). Successful growth and reproduction are routinely obtained in cats with commercial and purified diets containing no supplemental vitamin C (29).

### Anticancer Mechanisms of Action

Various possibilities for mechanisms of action of anticancer activity for pharmacological ascorbate have been researched and proposed. Originally considered a biological response modifier, pharmacological ascorbate was believed to increase extracellular collagen production and strengthen the extracellular matrix, therefore walling in tumors (30). Subsequent laboratory data have shown that pharmacological ascorbate is toxic to a variety of cancer cell lines with extracellular concentrations as low as 100 to 200 µM (3). However, for most cancer cell lines, pharmacological ascorbate concentrations causing a 50% decrease in cell survival are less than 5 mM, with normal cells (lymphocytes, monocytes, fibroblasts) being insensitive up to 20 mM of ascorbate (3).

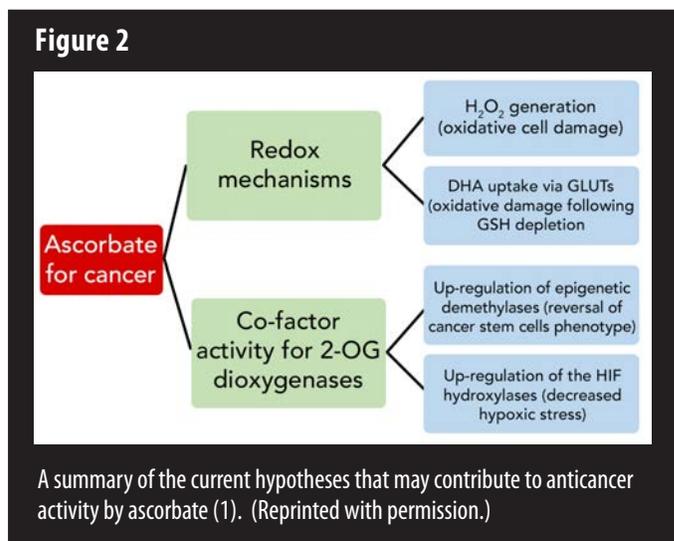
At physiological concentrations, vitamin C is a potent free radical scavenger, protecting cells against oxidative damage (31). However, in extracellular concentrations greater than 1 mM, pharmacological ascorbate leads to pro-oxidant effects through the reduction of transition metal ions, such as iron and copper. Upon their reduction by ascorbate, these metal ions can react with hydrogen peroxide or lipid hydroperoxides to produce either hydroxyl radicals or lipid alkoxy radicals via the Fenton reaction (15). Interestingly, these effects can only be achieved in extracellular fluid, not whole blood, because red blood cells contain large quantities of catalase and peroxidases that efficiently quell Fenton chemistry to protect hemoglobin from oxidative damage (32). The buildup of hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) within the extracellular tissues is then preferentially toxic toward tumor cells via a variety of mechanisms: increased cell cycle arrest, p53 up-regulation, decreased ATP levels, compromised mitochondrial function, suppression of anti-oxidant gene expression, cell death by apoptosis, activation of ataxia telangiectasia mutated (ATM)/adenosine monophosphate-activated protein kinase (AMPK) pathway, inhibition of mammalian target of rapamycin (mTOR), or

induction of angiogenesis inhibition (15, 33-36). Anticancer effects have also been demonstrated with pharmacological ascorbate levels well below 1 mM, potentially including modification of cell survival pathways involving p53 (37). In cultured colorectal cancer cells harboring KRAS or BRAF oncogene mutations exposed to high levels of pharmacological ascorbate, increased oxidative stress via accumulation of reactive oxygen species (ROS) and inactivation of glyceraldehyde 3-phosphate dehydrogenase (GAPDH) led to an energetic crisis and cell death (38). In addition, there is increasing evidence that perturbations in cancer cell metabolism result in increased steady-state levels of ROS, including superoxide and H<sub>2</sub>O<sub>2</sub>, capable of disrupting cellular iron metabolism, increasing labile iron pools, and therefore sensitizing cancer cells to pharmacological ascorbate toxicity through disruptions in iron metabolism (39). The most current hypotheses suggest that the anticancer activity of pharmacological ascorbate reflects either its redox, pro-oxidant, or enzyme cofactor activity (1) (**Figure 2**).

### Dosing, Frequency, and Duration

Despite the significant number of *in vitro* and *in vivo* studies that have been performed to assess the effects of pharmacological ascorbate on cancer, well-established dosing guidelines have not yet been recognized. In humans, as much as a 70-fold difference in plasma concentrations is expected between oral and IV administration, depending on the dose (34). Human studies of pharmacological ascorbate have determined that therapeutic, cytotoxic plasma levels cannot be achieved through oral administration, and therefore, IV or IP injection is required (34, 40). In addition, it is believed that multiple infusions (15-125 g) given over hours are required to achieve and maintain proposed therapeutic plasma levels due to the rapid clearance of ascorbate (10). Research is ongoing to determine the most effective administration schedule in the treatment of cancer.

In general, high intake of vitamin C is considered to be of low toxicity (12). Upon oral ingestion, ascorbic acid is readily absorbed from the intestine; however, large doses are actually associated with a decrease in its absorption (41). In humans, complete plasmatic saturation occurs at 1,000 mg daily (~100 mM), with bioavailability of vitamin C complete at 200 mg as a single dose and decreasing above 500 mg and higher due to urinary excretion (42). In 2001, Wang et al. investigated the PK of orally administered vitamin C in healthy Beagle dogs using 2 forms of the supplement—crystalline ascorbic acid and Ester-C® (a) (28). Ester-C®, a



combination of ascorbic acid, dehydroascorbic acid, and calcium as well as minor amounts of smaller metabolites of ascorbic acid, showed a higher rate and degree of absorption compared to ordinary ascorbic acid when given to rats (43). In the study by Wang et al., 8 dogs were orally administered 15 mg/kg of ascorbic acid as well as 15 mg/kg Ester-C®, and 6 dogs were orally administered 50 mg/kg of ascorbic acid as well as 50 mg/kg Ester-C®. Animals were not administered any vitamins prior to the study, were fed a regular diet that did not contain ascorbic acid, and were sampled after an overnight fast. No statistical differences were seen in PK parameters between the groups, and no increased bioavailability of Ester-C® was noted. The maximum concentration (C<sub>max</sub>) of plasma ascorbic acid after administration for the 15 mg/kg group was 23.9 (±9.5) μmol/L, and the C<sub>max</sub> for the 50 mg/kg group was 43.9 (±14.2) μmol/L. In agreement with human studies, the area under the curve (AUC), calculated after low and high doses of ascorbic acid, demonstrated a lack of linear dose proportionality, independent of supplement form, which is believed to be due to increased clearance that occurred as plasma concentration increased. Interestingly, maximum absorption concentration occurred within 3 hours. However, a second absorption peak was noted 6 to 10 hours after administration, lasting a total of 2 to 3 hours in one-third of the performed experiments. The authors hypothesized that the secondary peak might result from a secondary absorption process, such as enterohepatic recycling that may occur in species that synthesize ascorbic acid (28). This process has been noted to occur in rats (44). In 2009, Hesta et al. evaluated the effects of a variety

of orally administered antioxidants in healthy dogs for greater than a 1-month administration period (20). Average dosing of ascorbic acid was 0 mg/kg, 2.7 mg/kg, and 5.4 mg/kg, noting a trend ( $P = 0.056$ ) for an increased plasma vitamin C concentration based on quantity of ascorbic acid supplementation. The authors noted this concentration was significantly influenced by time, with concentrations increasing with increased time of administration. They also noted that CD4-positive lymphocytes increased with increasing quantity of vitamin C supplementation and hypothesized that plasma concentrations would be higher if doses were divided over several times a day, as suggested elsewhere (45).

Scott et al. reported on 4 Greyhounds who were treated with 1 g of pharmacological ascorbate orally or IV, with peak plasma concentrations significantly greater when pharmacological ascorbate was administered IV (mean:  $0.33 \pm 0.06$  mM) compared to orally (mean:  $0.03 \pm 0.01$  mM) (45). Peak concentrations were achieved within 6 minutes of administration, with plasma levels falling rapidly back to baseline (mean: 0.01 mM) within 6 hours. The authors suggested that vitamin C must be administered orally multiple times a day to maintain plasma concentrations above normal. Although well-established treatment protocols have not been reported for veterinary oncology patients, a commonly accepted historical protocol is often employed (Marty Goldstein, DVM, personal email communication, January 2017). Recently, 7 dogs and 1 cat were reported to have received 125 to 1,000 mg/lb of pharmacological ascorbate IV for 3 consecutive days for the adjuvant treatment of multiple cancers, with minimal side effects (46). In a recent publication by Musser et al., the authors sought to determine the PK profile of IV ascorbate in healthy Beagle dogs as well as the effects of pharmacological ascorbate on canine osteosarcoma cell lines (10). Trial subjects were administered a low-dose (550 mg/kg) infusion during the first trial day, which was escalated to 2,200 mg/kg for administration on the second trial day. The author chose at least a 2-day washout period between each dose, and the infusion was given over 6 hours (12.5 mL/hour for the 550-mg/kg dose; 50 mL/hour for the 2,200-mg/kg dose) via an infusion pump in order to achieve a steady-state plasma ascorbate concentration. Pharmacological ascorbate was combined with sterile water to achieve a 500-mg/mL ascorbate solution with a targeted osmolarity between 500 and 900 mOsm/L. Blood was sampled at 12 time points: immediately prior to the pharmacological ascorbate infusion; at 0.5, 1, 3, 5, and 6 hours during the infusion period;

and at 6.5, 7, 8, 10, 12, and 16 hours during the post-infusion period. The mean initial plasma ascorbate concentration for the 8 dogs at the 550-mg/kg ascorbate dose (~4 g) was 0.02 mM ( $\pm 0.01$  mM). Over the course of the 6-hour infusion, this peaked to 2.14 mM ( $\pm 0.54$  mM). Once the infusion was completed, ascorbate levels fell sharply below therapeutic levels and returned to near baseline by 6 hours post infusion. The mean initial plasma ascorbate concentration for the 8 dogs at the 2,200-mg/kg dose of ascorbate (~15-21 g) was 0.02 mM ( $\pm 0.01$  mM). Over the course of the 6-hour infusion, this peaked to  $8.6 \pm 2.1$  mM, with ascorbate levels falling sharply and returning to near baseline 6 hours post infusion (10). In another recent publication seeking PK data of pharmacological ascorbate in healthy Beagle dogs, 1 group received a single constant rate infusion (CRI) of 1,500 mg/kg of pharmacological ascorbate, whereas the second group received a single CRI of 3,000 mg/kg of pharmacological ascorbate over 4 hours (47). Ascorbic acid was diluted in sterile water to achieve an osmolarity between 700 and 1,000 mOsm/L, and infusion was maintained below 1 gm/kg/hour. The Cmax of the 1,500-mg/kg group was  $12.44 \pm 0.18$ , and the Cmax for the 3,000-mg/kg group was  $26.86 \pm 9.33$ . The authors concluded that both groups maintained plasma ascorbic acid levels above the minimum therapeutic concentration (0.3 mM) from 1 to 10 hours after administration, but the time for which the plasma concentration remained above 10 mM was 2 hours at 1,500 mg/kg and 4.5 hours at 3,000 mg/kg, respectively. Therefore, 3,000 mg/kg was considered more suitable than 1,500 mg/kg to achieve approximate human pharmacological concentration in dogs (47).

Although doses required to obtain plasma levels of vitamin C with in vitro anticancer activity are documented to be achievable and well tolerated, the exact administration schedule that maximizes antitumor response remains unknown. It has been postulated that the relationship between vitamin C doses and plasma concentration over time, the capability of tissue stores upon distribution, and the saturable mechanism of urinary excretion are all important determinants in humans to understand the physiology of pharmacological ascorbate dose administration and its effect on cancer (48). Conventionally, in human cancer care, long-term continuous IV infusions are considered most common, with many practitioners recommending 2 to 3 infusions weekly, advocating for 15 to 25 infusions prior to determining response to treatment (49). Alternatively, a fractioned schedule over a longer period, as well as CRIs, bolus applications, and combination therapy with oral

and intramuscular administration, have been described (48, 50). Nonetheless, more PK and pharmacodynamic studies are needed to fully understand the most effective administration schedule in both humans and animals, as well as the creation of multimodal clinical trials using pharmacological ascorbate alongside other integrative therapies, as routinely done in clinical practice.

### **Safety and Clinical Considerations**

Pharmacological ascorbate has been used for many decades by complementary and alternative medicine providers and physicians, with few side effects reported (2). Of 9,328 human patients surveyed, only 1% reported minor side effects, including lethargy, fatigue, change in mental status, and vein irritation (51). Phase 1 safety trials of pharmacological ascorbate in humans indicate most adverse events were mild and only possibly or probably related to the treatment. Treatment-related nausea and headache were fairly common in all cohorts, with some patients having moderate to severe hyponatremia and hypokalemia. Other reported adverse events were hypertension, insomnia, abnormal urine color, loss of appetite, fatigue, chills, and hyperglycemia (52). Pharmacological ascorbate was determined to be safe in tumor-bearing dogs when administered at a dose of 125 to 1,000 mg/lb IV for 3 consecutive days (46). One self-limiting episode of diarrhea was observed at 500 mg/lb. Blood urea nitrogen, creatinine, ionized calcium, and urine specific gravity were monitored daily in this patient population, and serum biochemical testing and urine specific gravity were not determined to be significantly different following pharmacological ascorbate infusion. In a recent publication, pharmacological ascorbate infusions of 550 mg/kg and 2,200 mg/kg were well tolerated by all dogs, with 1 dog experiencing a grade 1 veterinary cooperative oncology group-common terminology criteria for adverse events (VCOG-CTCAE) vomiting during the higher dose infusion and another showing VCOG-CTCAE grade 1 nausea/ptyalism (10). No changes in complete blood count or chemistry panels were noted during the course of this study for any dog. Blood gas analysis revealed statistically significant changes in pre- and post-ascorbate calcium, sodium, potassium, chloride, bicarbonate, partial pressure of carbon dioxide, anion gap, lactate, and glucose measurements; however, the pH was not significantly different pre- and post-ascorbate administration. The authors concluded that most of the blood gas analysis changes, although mathematically significant, were considered to be mild and are likely due to analytical

interference caused by high concentrations of ascorbate in the plasma. A similar, recently published trial investigated the tolerability of 1,500 mg/kg and 3,000 mg/kg of IV pharmacological ascorbate, noting only mild diarrhea as an adverse event observed in 1 dog receiving 3,000-mg/kg dosing (47). Urine pH was also monitored between groups in this study, with no significant difference noted.

A minor product of vitamin C metabolism is oxalate, which has the potential to form calcium oxalate crystals in individuals predisposed to renal stone formation (2). A single study reported that 1 human patient with a history of renal calculi developed a kidney stone following 2 weeks of continuous IV infusion of pharmacological ascorbate (53). Acute oxalate nephropathy has also been reported in several human cases following IV pharmacological ascorbate administration; however, the patients all exhibited existing renal dysfunction (54). In individuals with normal renal function, IV pharmacological ascorbate infusions of up to 1,500 mg/kg of body weight resulted in less than 0.5% conversion into oxalic acid; however, IV pharmacological ascorbate is cautioned in patients with renal dysfunction due to the inability of the kidneys to clear high circulating concentrations (55). Lim et al. evaluated microscopic urine sediment in healthy dogs following IV infusions of pharmacological ascorbate of 1,500 mg/kg and 3,000 mg/kg to confirm the presence of oxalate crystals. Following these single infusions, crystals including oxalate were not observed. The authors concluded that the production of urine oxalate not only depends on urine ascorbic acid but also on other metabolic factors, including thiamine, making it difficult to assess the impact of pharmacological ascorbate on urine. Serial monitoring of urine pH as well as sediment for oxalate crystal formation in patients receiving pharmacological ascorbate therapy was recommended (47).

Due to 2 case reports of hemolytic anemia in glucose-6-phosphate dehydrogenase (G6PD)-deficient individuals following 80 g of IV ascorbate, human patients are typically screened for G6PD deficiency prior to IV pharmacological ascorbate administration (56, 57). Lower ascorbate doses typically used for quality-of-life improvement (70-140 mg/kg) are considered unlikely to precipitate hemolytic anemia in G6PD-deficient individuals due to lack of *in vivo* hydrogen peroxide generation at these doses (49). However, there is evidence in the literature to indicate that lower levels than previously considered (5-10 g) may cause oxidation (58, 59). Practically, G6PD screening is

recommended in human patients receiving infusions of 20 to 25 g or more (49, 60). Deficiencies have not been routinely reported in companion animals, and commercial testing is not readily available. In a single report published in 1976 by Smith et al., after screening 3,300 dogs, only 1 dog was reported to have a mild deficiency in G6PD (61). On March 21, 2016, in the author's personal email communication with John Harvey, DVM, PhD, DACVP, the veterinary pathologist involved in testing for this deficiency, it was noted that they have since been able to identify a horse, but no dogs, with G6PD deficiency. It was also noted that Smith et al. were unable to demonstrate increased susceptibility to oxidants in the dog that had the mild G6PD deficiency (61).

Intravenous ascorbate is also well known to interfere with many point-of-care glucose meters, even at low gram doses (62). Intravenous ascorbate can cause either false-positive or false-negative results, depending on the biochemistry used in the monitor, and therefore, caution is required for patients needing regular glucose monitoring (2). Patients with diabetes who rely on glucometer readings for administration of insulin are not recommended to use these results for at least 8 hours after IV ascorbate administration; however, IV ascorbate does not interfere with laboratory-based glucose tests, which use absorbance photometric rather than electrochemical detection and can be used for blood glucose readings in the interim if needed (49, 62, 63). This known interference has been used by some clinicians as a convenient method for determining peak plasma vitamin C concentrations in human patients receiving IV pharmacological ascorbate infusions (64). Based on data provided by Ma et al., a blood sample obtained and tested on a glucometer at completion of IV infusion, subtracted by the baseline glucometer reading, can be used as an approximate estimation of blood ascorbate concentration after IV pharmacological ascorbate (>50 mg/dL, or 2.8 mM). However, this measurement is not accurate in detecting lower or baseline blood ascorbate. The currently accepted goal in oxidative therapy is 350 to 400 mg/dL (20-23 mM) as measured post infusion by standard lab high-performance liquid chromatography techniques. Similar findings have not been investigated or performed in companion animals; however, in the author's experience, point-of-care glucometer readings show blood glucose levels that increase concomitantly based on the dose of pharmacological ascorbate administered. At the

time of publication of this article, the author was in collaboration with a commercial laboratory assisting in validation of a point-of-care diagnostic to determine plasma levels of vitamin C in companion animals (b).

### **Combination With Conventional Cancer Treatments**

Due to the antioxidant activity identified for vitamin C, the potential interaction between pharmacological ascorbate and conventional cancer treatments, such as chemotherapy and/or radiation therapy, have long been discussed and debated because theoretical concerns exist for the ability of vitamin C to inactivate free radicals created by conventional cancer treatment. Concerns that pharmacological ascorbate might reduce the effectiveness of standard chemotherapy and/or radiation therapy have not been demonstrated through clinical research, and in actuality, numerous reports suggest that pharmacological ascorbate may actually increase the efficacy of several chemotherapeutic drugs and radiation in vitro (65-67). Espey et al. demonstrated that pharmacological concentrations of ascorbate with gemcitabine resulted in a synergistic cytotoxic response in pancreatic tumor cell lines, with gemcitabine-ascorbate combinations showing enhanced inhibition of growth compared to gemcitabine alone (68). Animal studies have indicated that concurrent administration of pharmacological ascorbate to numerous different chemotherapeutic agents, such as paclitaxel, carboplatin, melphalan, carfilzomib, bortezomib, cisplatin, and temozolomide, synergistically decreased xenograft tumor growth and increased survival (35, 69-71). No difference in the antitumor activity of the chemotherapeutic agents dacarbazine and valproic acid was noted when combined with pharmacological ascorbate in a murine melanoma model (72). Cell culture studies as well as animal models have shown radio-sensitizing effects of vitamin C in combination with ionizing irradiation; however, 1 animal model showed radio-protective effects to the tumor (73-75). In the study showing protective effects, radiation treatment was carried out only 2 hours after IP administration of pharmacological ascorbate, whereas in the other studies radiation treatments were administered on day 3 or 5 following administration of ascorbate. Additional studies using positron emission tomography (PET) imaging showed tumoristatic activity when pharmacological ascorbate and radiation therapy were used alone; however, when combined, tumoricidal activity was observed (76). It has also been identified that pancreatic cancer, non-small cell lung cancer, and glioblastoma mul-

tiforme cells treated with pharmacological ascorbate are more sensitive to concurrent or subsequent treatment with ionizing radiation and chemotherapy, whereas normal cells are spared (77). Pharmacological ascorbate also enhanced pancreatic tumor cell radiation cytotoxicity while offering potential protection to normal surrounding tissue from radiation damage.

Human trials have shown no adverse effects from combining pharmacological ascorbate with a number of different chemotherapeutic agents, including carboplatin, paclitaxel, decitabine, cytarabine, aclarubicin, gemcitabine, erlotinib, and temozolomide (2). Vitamin C is routinely administered in combination with arsenic trioxide to enhance its efficacy in the treatment of refractory multiple myeloma, and numerous case reports indicate that pharmacological ascorbate administered IV can be safely used with chemotherapy and radiotherapy and could potentially enhance the effects of conventional cancer therapy (78-80). At the time of publication of this manuscript, a pilot study is currently enrolling patients to evaluate the benefits of pharmacological ascorbate concurrently with carboplatin chemotherapy in dogs with appendicular osteosarcoma following amputation (81).

Although pharmacological ascorbate has been reported to increase the efficacy of several chemotherapeutic drugs either *in vitro* or *in vivo* as well as in combination with radiation therapy, it is important to note that the activity of some agents seems to decrease when pharmacological ascorbate is used simultaneously (15). Evidence exists for direct inactivation of a chemotherapy drug, bortezomib, *in vitro*; however, clinical trials have not been performed to determine if such reactions occur *in vivo* (82). In addition, it has been observed that cells exposed to dehydroascorbic acid (which allows intracellular loading of ascorbate) might be protected against arsenic trioxide or tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) *in vitro*, requiring further investigations to determine if this also occurs *in vivo* (83, 84). Importantly, it should also be noted that the oral supplementation of vitamin C (together with other antioxidants) seems to have no influence on the outcome of patients undergoing chemotherapeutic regimens, suggesting that oral pharmacological ascorbate does not protect cancer cells from oxidant damage induced by chemotherapy (85). Additional points to note are that various chemotherapeutic agents act via different mechanisms of action, not all of which are via oxidative mechanisms (86). If the chemotherapeutic agent

does not act via oxidative mechanisms, concurrent pharmacological ascorbate administration may not be an issue and may actually be synergistic (2). The relatively short half-life of vitamin C in circulation due to rapid renal clearance is notable, estimated at less than 2 hours in humans and approximately 3.5 hours in dogs (10), which would allow for further avoidance of interactions with timing of conventional treatment and ascorbate infusions if additional precautions were believed to be necessary.

## Conclusions

Pharmacological ascorbate has been used for decades alongside conventional cancer treatment or as an adjunct to integrative care in the treatment of cancer in both humans and animals. Although well-established dosing protocols have not been established within the human or veterinary communities, ongoing research exists to continue demonstrating anticancer activity and tolerance of infusions, as well as utility and efficacy surrounding various dosing of these protocols. Evidence has also always existed surrounding the benefit of pharmacological ascorbate to quality of life in cancer patients either with or without conventional cancer treatment, showing reduced pain, fatigue, insomnia, nausea, and vomiting and improved appetite and tolerance to chemotherapy and/or radiation therapy (2, 35, 73). Discrepancies in oral versus IV administration as well as developing nuances in identifying specific metabolic differences and variations in tumor microenvironments between patients likely contribute to the difficulty in proving efficacy among varied clinical trials. Additional information regarding the specific inflammatory, metabolic, and genetic profiles of specific cancers as well as baseline vitamin C concentrations of each patient will likely be needed to develop the most effective dosing strategy for individual patients. Pharmacological ascorbate has been shown to be synergistic with chemotherapy and/or radiation therapy in various *in vitro* clinical trials. Fewer *in vivo* trials exist in humans, with only 1 trial currently enrolling patients to prove safety in combination with chemotherapy in dogs. However, combination therapy seems to be of low risk, especially if infusions are administered on different days than conventional cancer treatments. Additional trials will be needed to establish the optimal dose, frequency, and duration of IV ascorbate as well as safety and efficacy in combination with various therapies in the treatment of cancer.

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## Endnotes

- a. Ester-C®, The Ester C Company, Holbrook, NY 11741
  - b. VDI Laboratory, LLC, Simi Valley, CA 93063
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