

A rational approach for improving the ascorbate antineoplastic activity

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COMMENTARY

A Rational Approach for Improving the Ascorbate Antineoplastic Activity

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INTRODUCTION

There is no doubt today that pharmacological concentrations of ascorbate can be reached in the interstitial fluids after intravenous administration of ascorbate (50–110 g/m² per patient), while oral route fails to do so (1, 2). Consequently, 10–30 mM for 5–6 hr of ascorbate in interstitial fluids may generate cytotoxic levels of H₂O₂ in cancer-sensitive cells. However, even the combination of H₂O₂ with either chemotherapy (3) or oncothermia (4) remains unable to kill all cancer cells. There are several explanations for this failure and one is that the H₂O₂ concentration is too unstable. In order to make H₂O₂ more effective, the peritoneal route of high dose of ascorbic acid is proposed. Daily administration for at least 3 months may improve the outcome.

Gram doses of vitamin C administered orally had been proposed as a potential cancer therapy by Cameron and Pauling since 1976 (5). However, successive clinical trials performed in cancer patients treated with 10 g of once-a-day oral dosage of vitamin C showed no benefit (6). It is understandable why oral dosages of vitamin C do not yield high blood levels owing to a modest bioavailability and renal excretion so that the concentration of H₂O₂ at the levels of neoplastic cells are ineffective (7, 8).

Chen et al. deserved the merit to have clarified this problem: they have shown that, while the maximum tolerated oral dose of even 3 g every 4 hr yields a plasma vitamin C concentration of 220 μmol/L, a 50–100 g dose administered intravenously yields a minimal plasma level of 13,400 μmol/L (and up to 30 mmol/L), that is 61–150-fold higher (9–12). They also proposed that after intravenous administration of vitamin C, this compound, after transfer into the extravascular tissues, generates H₂O₂ and ascorbyl radicals (13). Consequently, the H₂O₂ levels becomes high enough to oxidize and possibly kill some neoplastic cells if these are not protected by catalase or by GSH peroxidase. Verrax and Calderon (14) have amply confirmed that oral and parenteral administration of ascorbate are not comparable, supporting Levine's et al. studies.

It is well established that H₂O₂ can exert a cytotoxic effect on either normal or particular neoplastic cells (15–17). In physiological conditions, normal cells produce most of the

H₂O₂ into the mitochondria and this oxidant acts as an important signaling molecule that is quickly reduced to H₂O by antioxidants. In the case of neoplastic cells, H₂O₂ production is quite variable and some type of neoplasms can be killed by H₂O₂ produced outside the cell. Such a condition appears to happen when ascorbate, in the presence of a so far unknown protein fraction, probably within the alpha 2 globulins (ceruloplasmin or others globulins binding copper or iron) releases H₂O₂ and ascorbyl radicals in sufficient amount able to induce an irreversible oxidation of neoplastic cells (17–19). The H₂O₂ concentration has a paramount relevance and if it is below 10 μM it is usually not noxious, whereas concentrations from 40 μM to 1 mM cause growth arrest, apoptosis, and/or necrosis (20). H₂O₂ readily diffuse across aquaporin channels and, when inside the cell, it is rapidly degraded by scavenging enzymes such as catalase, GSH-peroxidase, or by peroxiredoxins. In normal cells, 80–90% of H₂O₂ is rapidly reduced, but what happens in the great variety of neoplastic cells remains uncertain. It is possible that some neoplastic cells, being unable to reduce intracellular H₂O₂, are killed and it seems that this is the case when extracellular H₂O₂ reaches a high concentration depending upon the ascorbate level in the neoplastic capillary environment. Recently, as a concomitant mechanism, it has been observed that ascorbate itself promotes lymphocyte development via an epigenetic arrangement giving an insight into the part of ascorbate-mediated enhancement of immune function (21). It appears obvious that at least some types of cancer must be sensitive to H₂O₂, but some species produce themselves H₂O₂ and have an antioxidant defence.

Such a composite situation emphasizes the importance to deliver not only a large dose of ascorbate (80–100 g) but above all to maintain a constant level of H₂O₂ in the neoplastic environment. It has been already proved that ascorbate acts as a prodrug and cannot generate H₂O₂ in whole blood (9). In any case, formation of H₂O₂ in plasma is promptly reduced. What is important therefore is the concentration of H₂O₂ and ascorbyl radical as inducer of peroxidation in the extracellular environment.

Owing to the so-far observed killing effect on some neoplastic cells, the crucial question is whether the intravenous

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infusion of ascorbate is the best method to achieve an extracellular concentration of H_2O_2 as high or higher than 20 mM. The elimination of ascorbic acid is variable and dose-dependent because of its nonlinear pharmacokinetics. The half-life is obviously influenced by the rapid ascorbate transfer from blood to extravascular fluids, by renal filtration, several organs uptake and some degradation. In such a case the level of H_2O_2 in extracellular fluids raises quickly but remains sustained for a rather short time. The half-life of ascorbate in plasma of participants in a trial was approximately between 60 and 80 min (7), while in the culture medium it was of about 3 hr (22). Owing to the normal schedule of ascorbate administration every other day, a relevant problem is that a significant concentration of H_2O_2 among neoplastic cells last a too shorter time, while to be really effective it should remain at high levels for longer periods. An approximate calculation of the area under curve shows that high concentrations of H_2O_2 are brief, possibly unable to both kill all the neoplastic cells and prevent the insurgency of a resistance mechanism.

Is there a better administration route?

Between 1985 and 1992, evaluating the pharmacokinetic and pharmacodynamic of interferons, it was realized that the most proficient route of administration of these compounds was their administration via lymphatics (23–25). At that time, the subcutaneous route was selected because, by injecting interferons mixed with 60 mg human albumin in a 3 mL volume, it was possible to markedly enhance the absorption via cutaneous lymphatics. This so-called intralymphatic administration was found to decrease and delay the renal elimination of interferons, to enhance their biological activity and reduce general side effects. However, this route is not feasible in the case of ascorbate.

Due to the massive ascorbate dosages, a potential alternative to the intravenous administration is the use of the intraperitoneal route. In fact, the peritoneal membrane is a dynamic dialyzer, and the peritoneal cavity for at least five decades has been widely used in patients with a partial renal dysfunction (in such a case the patient becomes able to replace the peritoneal fluid a few times a day).

For the delivery of ascorbate solution, only a light and small intraperitoneal catheter appears necessary and the patient himself may learn how to replace the liquid under antiseptic technique for preventing peritoneal infection. The ascorbate solution must be prepared by the hospital pharmacists, according to validated standard operative procedures. Summarily, the scheduled amount of pure ascorbic acid should be solubilized in the adequate volume of water for injections, and the resulting hypertonic solution must be neutralized and sterilized to be used at once. Physiologically, the peritoneal cavity is almost virtual but it has a surface of not less than 1700 cm², hence 1 L of ascorbate, if homogeneously distributed, yields an almost imperceptible liquid layer. The liquid is absorbed mostly by great capacity lymphatics, which preferentially drain into the left thoracic duct ending into the angle of the junction of the left subclavian vein with the left internal jugular vein. Ascorbate will then mix with the blood pool and it will be redistributed into all

organs. Renal loss of ascorbate will diminish and its half-life will be prolonged and the H_2O_2 levels in neoplastic organs, although at a slightly lower concentration than after IV infusion, will be sustained for longer time. In order to maintain a fairly constant and effective H_2O_2 levels in the neoplastic environment, the patient ought to perform one infusion daily. In order to ascertain the efficacy of this route, the peritoneal infusion should be continued for at least three months. This is possible as pharmacological levels of ascorbate are well-tolerated with the exception of renal impairment or glucose-6-phosphate dehydrogenase deficiency (26–28). Moreover, the H_2O_2 may prove to be far more effective in the case of peritoneal carcinomatosis as it occurs for ovarian cancer. This may avoid the need of extensive and traumatic peritonectomy and the use of toxic chemotherapy (29). Other abdominal tumors such as pancreatic cancer, liver, gastric, colon, and prostatic cancer may be usefully treated provided that the interstitial concentration of H_2O_2 is maintained for long periods at an effective concentration. By considering the pioneering and intensive efforts by Levine's group in showing the ascorbate efficacy in some neoplasms, it may be worthwhile to evaluate the intraperitoneal approach.

In conclusion, beside Levine and collaborators, several other groups have advocated the use of intravenous high dosages of ascorbate in neoplastic patients on the basis of the killing activity of H_2O_2 on tumoral cells (16, 30–33). Recently, the combination of ascorbate and chemotherapy has been evaluated (2, 34), but so far clinical results have been meagre. This may depend upon either the various sensitivity to H_2O_2 and malignancy of neoplastic cells or on their ability to become resistant during the discontinuous presence of H_2O_2 in the neoplastic environment (35). If this hypothesis is correct, the daily administration of ascorbate via intraperitoneal route for a long period may change the outlook that at the moment remains uncertain. However, whenever possible, it would be proficient to first evaluate the sensitivity of different neoplasms to H_2O_2 as well as the most effective combination with chemotherapeutic drugs (36, 37). So far, intravenous ascorbic acid appears able to reduce fatigue (38) and to prevent cancer-associated sepsis (39).

It is hoped that the oncologists may be interested in evaluating the intraperitoneal route and in any case we would be glad to help anyone else.

DECLARATION OF INTEREST

The authors report no conflict of interest. The authors alone are responsible for the content and writing of the paper.

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