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Vitamin C in Cancer Treatment: Where Pharmacokinetics Speaks

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Editorial

One of the critical elements for a drug to be effective is the ability of the drug to reach its target organ in an effective concentration. The dynamic interactions among drug absorption, distribution, metabolism, and excretion determine the plasma concentration of a drug, and dictate the amount of free drug that reaches the target site, and therefore, influence the ultimate outcome the drug may provide. These basic principles in pharmacology state the importance of pharmacokinetics. In this article, we shall focus on one example that vividly demonstrates the importance of pharmacokinetics – the research on high dose vitamin C as treatment for cancer.

The claim for using large dose of vitamin C (ascorbate) to treat cancer was advocated in the 1970s by Linus Pauling, the two-time Nobel laureate, first based on his theory of "orthomolecular medicine", and then supported by clinical data from Ewan Cameron, a Scottish surgeon. Cameron embellished the hypothesis that ascorbate inhibited the enzyme hyaluronidase, which otherwise destroyed collagen so that cancers could metastasize [1]. With only minimal *in vitro* data, Cameron treated terminally ill cancer patients with high doses of vitamin C - 10 grams per day intravenously for up to 10 days followed by 10 grams per day orally indefinitely. He had at least one spectacular success: a 45-year-old truck driver who had lymphoma had intravenous vitamin C without radiotherapy or chemotherapy. Within two weeks the patient became clinically well and able to return to work. He then stopped taking his vitamin C and relapsed, and again began treatment with vitamin C alone. The patient again responded well and was cured [2]. Of course, cancer cases occasionally undergo spontaneous remissions, but in this case the remissions had corresponded exactly with the vitamin C treatment, and it has not been known that a patient with this kind of cancer had undergone two spontaneous remissions. Cameron contacted Linus Pauling, who had his own interests in high-dose vitamin C. Pauling joined and championed Cameron's efforts. Together, they published a retrospective case series in 1976 in the Proceedings of the National Academy of Sciences [3], a paper that created a typhoon in the journal, among cancer scientists and physicians and with the general public. A follow-up paper in the same journal intensified the controversy 2 years later, with additional cases [4]. In both papers, the authors concluded that patients who had high dose vitamin C treatment benefited with improved quality and prolongation of life. Multiple scientific objections were raised: the lack of blinding inherent to a retrospective case-series design, the underlying susceptibility of the rural Scottish patient population to endogenous vitamin C deficiency, the lack of independent pathologic confirmation of diagnosis, and the possibility of a placebo effect [5-7].

Charles Moertel and colleagues at the Mayo Clinic designed two prospective double-blind placebo-controlled trials to attempt to restore scientific balance and civility. Neither, unfortunately, was restored. Enrolled patients in the first trial had prior chemotherapy [5], and in the second trial had none [6]. Both trials, using the same dose that Pauling and Cameron recommended, showed no effect of ascorbate. Sharp debates had been arisen between Pauling and the vitamin C critics. Unfortunately Pauling's objections were drowned by passionate opinions, and the medical community concluded that vitamin C had no place in cancer treatment. Robert Wittes, in an editorial accompanying the second trial, wrote that ascorbate showed no utility in cancer treatment and should not be used. But he added a disclaimer: his conclusions could change if new evidence arose [8].

Pharmacokinetics of vitamin C had not been known at the time, and both sides on the debate neglected one simple thing: Cameron and Pauling used intravenous infusion of 10 grams Vitamin C per day for a week or more followed by daily oral doses, and the Mayo Clinic trials used the same 10 grams dose but only administered orally. Indeed, new evidence rose just from the different pharmacokinetic behaviors of intravenous versus oral vitamin C in large doses.

The pharmacokinetic study on oral vitamin C conducted by Mark Levine and colleagues at NIH was initially purposed to identify a dose-plasma concentration relationship for oral vitamin C ingestion, as a pre-requisite to study the dose-function relationship and to determine the optimal intake of this vitamin. Their results in healthy humans found that vitamin C concentrations in plasma and cells were carefully, or tightly, controlled by multiple mechanisms acting together: bioavailability, or intestinal absorption; tissue accumulation; renal reabsorption and excretion, and utilization rate as a function of homeostasis. Once oral intake of vitamin C exceeded 200 mg daily, the plasma concentration platues at 70~80 uM. Further increase in the dose did not provide obvious increase of concentration in plasma and in cells – the bioavailability drops, intracellular distribution saturated, and the renal excretion accelerated. However, when ascorbate was administered intravenously, tight control was bypassed, until renal excretion restored equilibrium – that could be hours depending on the dose [9-12].

With unequivocal data showing that intravenous ascorbate transiently bypassed tight control of oral doses, the NIH investigators surprisingly realized that pharmacokinetics had been overlooked in the earlier cancer studies [7]. At the doses used in these cancer trials, intravenous administration of ascorbate would produce concentrations around 5 mM which could never be achieved orally. Only high dose intravenous ascorbate was like a drug, producing concentrations that could be 70 to 100-fold higher than maximally tolerated oral doses [7,12]. Indeed, later researches found plasma ascorbate concentrations as high as 20-30 mM were safely achieved with large dose of intravenous ascorbate [13,14]. By contrast, oral intake did not provide plasma concentrations higher than 300 μM [12].

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If intravenous but not oral ascorbate was a drug, then the conclusion that ascorbate was not effective in cancer treatment was based on a false premise and deserved reexamination. Recent researches based on the new pharmacokinetic information have gained advances. High ascorbate concentrations achievable with parenteral administration have been proved cytotoxic to many cancer cells *in vitro* and inhibitory to xenografts *in vivo* [13,15]. Parenteral administrations raised ascorbate concentrations to milimolars both in plasma and in extracellular fluid of tissues [16]. These pharmacologic ascorbate concentrations produced both ascorbate radical and hydrogen peroxide in the extravascular space of tumor xenografts, which act as effecter species and encountered pro-oxidant effects to tumor cells [13,16].

The discovery in pharmacokinetics re-opened the "closed" case of vitamin C in cancer treatment. Plasma concentration is critical. In this case, the anti-oxidant vitamin C turned out to exert pro-oxidant effect in the interstitial fluid in the tumor when raised to pharmacologic concentrations beyond the physiological tight control. Laboratories all over the world repeated and confirmed the anti-cancer activity of high dose parenteral ascorbate. Active researches are going on to identify down-stream molecular mechanisms. Several early phase clinical trials have been carried out [14,17] or are underway confirming the pharmacokinetics and safety of high dose intravenous ascorbate in cancer patients. Using proper design assisted by new information in mechanisms and pharmacokinetics, the controversies on vitamin C and cancer treatment might eventually be clarified with large clinical trials re-evaluating the efficacy. Advantage of using vitamin C in cancer treatment lies with its low toxicity which is especially valuable given the toxic side effects of most of the current standard chemotherapies.

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