Vitamin C Pharmacokinetics: Implications for Oral and Intravenous Use

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Background: **Vitamin C at high concentrations is toxic to cancer cells in vitro. Early clinical studies of vitamin C in patients with terminal cancer suggested clinical benefit, but 2 double-blind, placebo-controlled trials showed none. However, these studies used different routes of administration.**

Objective: **To determine whether plasma vitamin C concentrations vary substantially with the route of administration.**

Design: **Dose concentration studies and pharmacokinetic modeling.**

Setting: **Academic medical center.**

Participants: **17 healthy hospitalized volunteers.**

Measurements: **Vitamin C plasma and urine concentrations were measured after administration of oral and intravenous doses at a dose range of 0.015 to 1.25 g, and plasma concentrations were calculated for a dose range of 1 to 100 g.**

Results: **Peak plasma vitamin C concentrations were higher after administration of intravenous doses than after administration of oral doses ($P < 0.001$), and the difference increased according to dose. Vitamin C at a dose of 1.25 g administered orally produced mean (±SD) peak plasma concentrations of 134.8 ± 20.6 μmol/L compared with 885 ± 201.2 μmol/L for intravenous administration. For the maximum tolerated oral dose of 3 g every 4 hours, pharmacokinetic modeling predicted peak plasma vitamin C concentrations of 220 μmol/L and 13 400 μmol/L for a 50-g intravenous dose. Peak predicted urine concentrations of vitamin C from intravenous administration were 140-fold higher than those from maximum oral doses.**

Limitations: **Patient data are not available to confirm pharmacokinetic modeling at high doses and in patients with cancer.**

Conclusions: **Oral vitamin C produces plasma concentrations that are tightly controlled. Only intravenous administration of vitamin C produces high plasma and urine concentrations that might have antitumor activity. Because efficacy of vitamin C treatment cannot be judged from clinical trials that use only oral dosing, the role of vitamin C in cancer treatment should be reevaluated.**

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Vitamin C in gram doses is taken orally by many people and administered intravenously by complementary and alternative medicine practitioners to treat patients with advanced cancer (1, 2). After oral intake, vitamin C plasma concentrations are tightly controlled at 70 to 85 μmol/L for amounts (as much as 300 mg daily) that can be obtained from food (3, 4). However, concentrations achieved by higher pharmacologic doses are uncertain. Despite poor rationale, vitamin C in gram doses was proposed as an anticancer agent decades ago (5). Unblinded studies with retrospective or nonrandom controls reported clinical benefit from oral and intravenous vitamin C administered to patients with terminal cancer at a dosage of 10 g daily (1, 6, 7). Placebo-controlled trials in patients with cancer reported no benefit from oral vitamin C at a dosage of 10 g daily (8, 9), and vitamin C treatment was judged ineffective (10). However, in vitro evidence showed that vitamin C killed cancer cells at extracellular concentrations higher than 1000 μmol/L (11, 12), and its clinical use by some practitioners continues.

We recognized that oral or intravenous routes could produce substantially different vitamin C concentrations (13). We report here that intravenous doses can produce plasma concentrations 30- to 70-fold higher than the maximum tolerated oral doses. These data suggest that the role of vitamin C in cancer treatment should be reexamined, and insights from vitamin C pharmacokinetics can guide its clinical use.

METHODS

Pharmacokinetic Studies in Healthy Persons

The study was approved by the Institutional Review Board of the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health. After we obtained written informed consent, 17 healthy volunteers (7 men, 10 women; age, 19 to 27 years) were studied as inpatients by using a depletion-repletion study design (3, 4). Participants were hospitalized for 3 to 6 months and consumed a vitamin C–deficient diet containing less than 0.005 g of vitamin C per day. At plasma vitamin C concentrations less than 8 μmol/L, persons were depleted without signs of scurvy. Vitamin C, 0.015 g twice daily, was then administered orally until participants achieved a steady state for this dose (0.03 g daily). Participants received successive oral daily vitamin C doses of 0.03 g, 0.06 g, 0.1 g, 0.2 g, 0.4 g, 1.0 g, and 2.5 g until a steady state was achieved for each dose. Bioavailability sampling was conducted at a steady state for vitamin C doses of 0.015 g, 0.03 g, 0.05 g, 0.1 g, 0.2 g, 0.5 g, and 1.25 g. For each bioavailability sampling, vitamin C was administered in the fasting state. After oral administration, blood samples were collected at 0, 15, and 30 minutes and at 1, 1.5,

Context

Clinical studies of vitamin C as a potential anticancer agent have produced inconsistent results despite in vitro evidence that high concentrations kill cancer cells.

Contribution

Pharmacokinetic studies in healthy persons, using a depletion-repletion design, show that intravenous administration can achieve 70-fold higher blood levels of vitamin C than the highest tolerated oral dose.

Cautions

Although this study provides better understanding of the pharmacokinetic issues involved in research on vitamin C, it provides no evidence that vitamin C has any effect on cancer cells and cannot be used to support its clinical use for therapeutic purposes.

–The Editors

2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 19, 22, and 24 hours (3, 4). After intravenous administration at 250 mg/min, blood samples were collected at 0, 2.5, 5, 10, 15, and 30 minutes and at 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 9, and 10 hours. Data obtained from bioavailability samplings were used to determine peak plasma and urine vitamin C concentrations.

Pharmacokinetic Modeling

We used data from 7 men to construct a unique 3-compartment vitamin C pharmacokinetic model with parameters describing saturable absorption, tissue distribution, and renal excretion and reabsorption (14). This model was used to predict peak plasma and urine vitamin C concentrations attained when pharmacologic doses of the vitamin are administered. For intravenous administration, it was assumed that vitamin C was infused at a rate of 1 g/min, and urine output was 100 mL/h.

Vitamin C Assay

Vitamin C was measured by using high-performance liquid chromatography with coulometric electrochemical detection (3, 4, 15).

Statistical Analysis

We compared plasma vitamin C concentration curves (against either dose or time) by repeated-measures analyses of variance (ANOVA). In addition to the repeating factor (dose or time), other factors considered were sex and route of administration. In the comparison of routes of administration at multiple doses, in which sex not only was an important factor itself but also had an important interaction with route, separate ANOVA were determined for men and women to assess the importance of route of administration. Analyses were performed by using DataDesk, version 5 (1995) (Data Description, Inc., Ithaca, New York).

Role of the Funding Source

The funding source had no role in the design, conduct, and reporting of the study or in the decision to submit the manuscript for publication.

Results

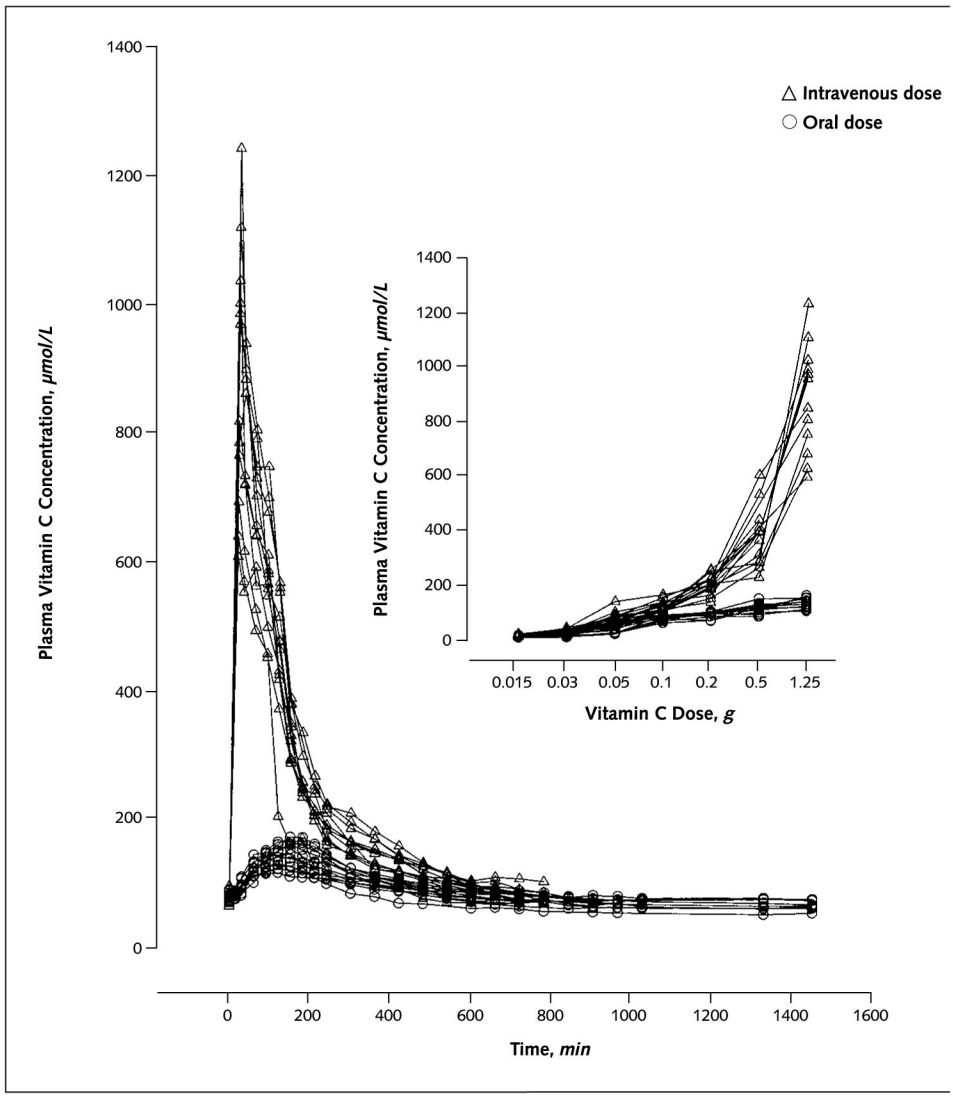
When 1.25 g of vitamin C was given intravenously, plasma concentrations were significantly higher than when the vitamin was given orally ($P < 0.001$ by repeated-measures ANOVA) (**Figure 1**). In addition, plasma concentrations were significantly higher over all doses ($P < 0.001$ by repeated-measures ANOVA) with intravenous compared with oral administration (**Figure 1**, *inset*). At the highest dose of 1.25 g, mean peak values from intravenous administration were 6.6-fold higher than mean peak values from oral administration. When all doses were considered, peak plasma vitamin C concentrations increased with increasing intravenous doses, whereas peak plasma vitamin C concentrations seemed to plateau with increasing oral doses. Urine vitamin C concentrations were higher for the same dose given intravenously compared with that administered by the oral route. At the highest dose of 1.25 g, peak urine concentrations from intravenous administration were approximately 3.5 times higher than from oral administration (data not shown).

The 3-compartment vitamin C pharmacokinetic model that we developed predicted that a single oral dose of 3 g, the maximum tolerated single dose, produced a peak plasma concentration of 206 μmol/L (**Figure 2**, *top*). Peak predicted concentration after a single 1.25-g oral dose was slightly lower at 187 μmol/L. For 200 mg, an amount obtained from vitamin C–rich foods, peak predicted concentration was approximately 90 μmol/L. Plasma concentrations for all of these amounts returned to steady-state values, approximately 70 to 85 μmol/L, after 24 hours. With 3 g given orally every 4 hours, the maximum tolerable (6), peak predicted plasma concentration was approximately 220 μmol/L (**Figure 2**, *top*). By contrast, after intravenous administration, predicted peak plasma vitamin C concentrations were approximately 1760 μmol/L for 3 g, 2870 μmol/L for 5 g, 5580 μmol/L for 10 g, 13 350 μmol/L for 50 g, and 15 380 μmol/L for 100 g (**Figure 2**, *bottom*). Doses of 60 g given intravenously are used for cancer treatment by complementary and alternative medicine practitioners (2). Predicted peak urine vitamin C concentrations were as much as 140-fold higher after intravenous administration compared with oral administration (data not shown).

Discussion

Our data show that vitamin C plasma concentrations are tightly controlled when the vitamin is taken orally, even at the highest tolerated amounts. By contrast, intravenous administration bypasses tight control and results in concentrations as much as 70-fold higher than those

Figure 1. **Plasma vitamin C concentrations in healthy volunteers after intravenous or oral administration of vitamin C.**



Plasma vitamin C concentrations are shown as a function of time after the 1.25-g oral or intravenous dose administered at steady state for that dose in 12 persons (3 men, 9 women). **Inset:** Peak plasma vitamin C concentrations as a function of dose after oral or intravenous administration of vitamin C. Seventeen persons (7 men, 10 women) received doses from 0.015 to 0.1 g, 16 persons (6 men, 10 women) received the 0.2-g dose, 14 persons (6 men, 8 women) received the 0.5-g dose, and 12 persons (3 men, 9 women) received the 1.25-g dose. Persons received each dose while at steady state for that dose.

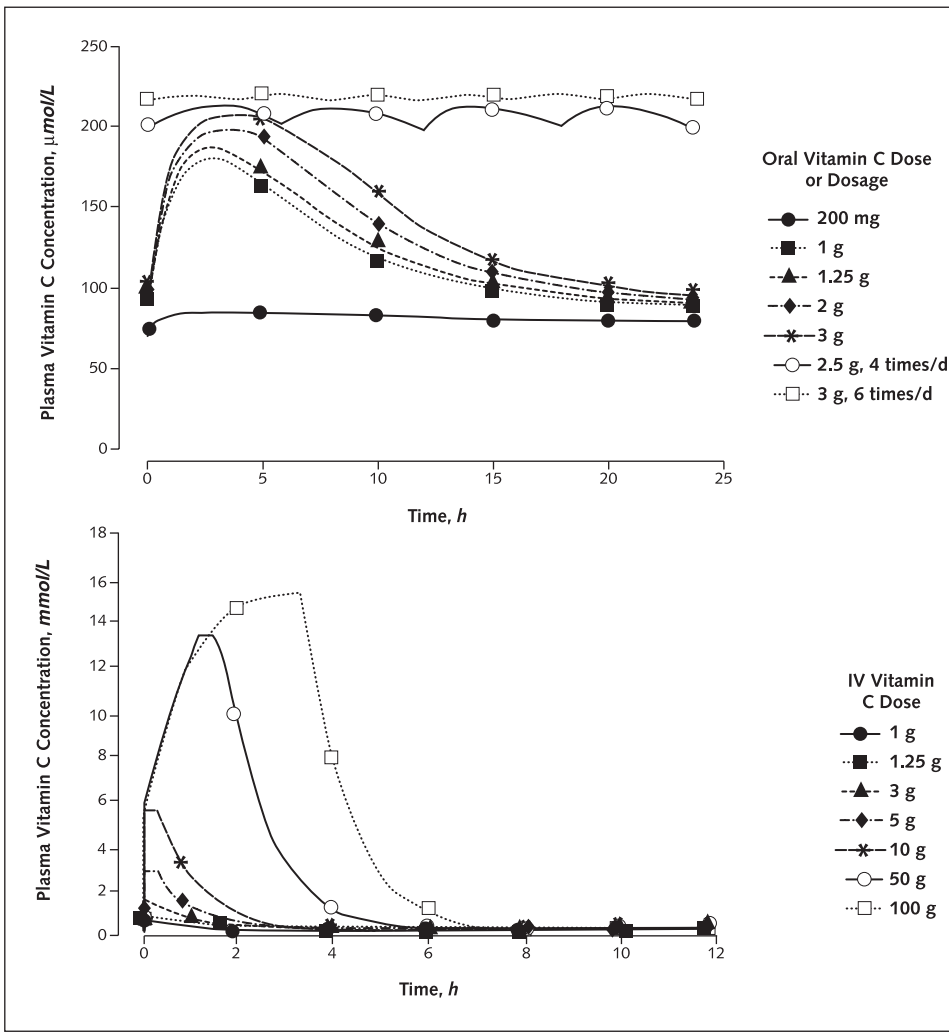
achieved by maximum oral consumption. Both findings have clinical relevance.

Vitamin C oral supplements are among the most popular sold, and gram doses are promoted for preventing and treating the common cold, managing stress, and enhancing well-being (1). Our data show that single supplement gram doses produce transient peak plasma concentrations that at most are 2- to 3-fold higher than those from vitamin C–rich foods (200 to 300 mg daily). In either case, plasma values return to similar steady-state concentrations in 24 hours. Because differences in plasma concentrations from supplements and from food intake are not large, supplements would be expected to confer little additional benefit, a finding supported by available evidence (16, 17).

However, consumption of fruits and vegetables, which contain vitamin C, is beneficial for unknown reasons (16, 17). On the basis of current knowledge and the pharmacokinetics presented here, physicians should advise their patients to consume fruits and vegetables, not vitamin C supplements, to obtain potential benefits.

Just as important, our data show that intravenous administration of vitamin C produces substantially higher plasma concentrations than can be achieved with oral administration of vitamin C. This difference was previously unrecognized and may have treatment implications. Case series published by Cameron, Campbell, and Pauling (l, 6, 7) have been controversial. In these series, several hundred patients with terminal cancer treated with 10 g of vitamin

Figure 2. **Predicted plasma vitamin C concentrations in healthy persons after oral (*top*) or intravenous (*IV*) (*bottom*) administration of vitamin C.**



The 3-compartment pharmacokinetic model used to calculate these values was derived from data in 7 healthy men (3, 14). Baseline values are 70 to 85 μmol/L, the expected steady-state plasma vitamin C concentration for healthy persons with a vitamin C intake of more than 0.2 g/d.

C intravenously for 10 days and then 10 g orally indefinitely were compared with more than 1000 retrospective and prospective controls. Patients treated with vitamin C survived 150 to 300 days longer than controls (1, 6, 7). Other researchers reported benefit consisting of increased survival, improved well-being, and reduced pain (1). All of these studies were uncontrolled, and factors unrelated to intervention may have affected outcome. Two randomized, double-blind, placebo-controlled studies from the Mayo Clinic found no benefit (8, 9). These studies included 200 patients who were treated with 10 g of vitamin C daily. The Mayo Clinic studies were considered to be definitive (10). However, in these studies, vitamin C was given orally, which is in contrast to the intravenous and oral use in other studies. On the basis of our pharmacokinetic data, we conclude that the Mayo Clinic studies, which used oral administration of vitamin C, are not comparable to studies with intravenous administration. The Mayo Clinic studies neither support nor refute possible effects of intravenously administered vitamin C on cancer.

Intravenous vitamin C may have a role in the treatment of cancer as a result of the plasma concentrations that can be achieved only by this route. With consumption of 5 to 9 servings of fruits and vegetables daily, steady-state plasma concentrations are 80 μmol/L or less, and peak values do not exceed 220 μmol/L, even after maximum oral administration of 3 g 6 times daily. By contrast, intravenous vitamin C may produce plasma concentrations as high as 15 000 μmol/L. At extracellular concentrations greater than 1000 μmol/L, vitamin C is toxic to cancer cells, although mechanisms and interpretation are controversial (11, 12, 18). The vitamin C free radical species, ascorbyl radical, is detectable in animals only when they receive intravenous vitamin C equivalent to a 10-g dose in

humans (19). We propose that detectable ascorbyl radical forms only when human plasma concentrations are greater than 1000 μmol/L and that either the radical itself or its unpaired electron induces oxidative damage that can be repaired by normal but not cancer cells. Understanding mechanisms of cytotoxicity may further the investigational use of vitamin C in patients with cancer, used alone or with other agents that potentiate such actions (20). Although minimal data are available, intravenous vitamin C is expected to have little toxicity compared with conventional chemotherapeutic agents (3). In this context and in light of our new pharmacokinetic data, a role for intravenous vitamin C in cancer treatment should be reevaluated.

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