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Pharmacokinetics of Six-Carbon Analogues of L-Glucose in Tumour-Bearing Humans (Series I: Ascorbate)

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Abstract

Several molecules with such a number of carbon atoms and stereometric properties as to behave like structural analogues of L-glucose are of great clinical importance in the treatment of solid tumours with antimetabolites. Pharmacological agents similar to natural substrates but bearing no intrinsic activity provide a way to competitively inhibit various rate-limiting reactions within cancer cells, disrupting their energy metabolism. Since the catalytic activity of lactic dehydrogenase A, hexokinase 2 and possibly others is hindered by structural analogues, a proper characterization of these promising non-toxic molecules is useful to researchers and clinicians both from a theoretical and practical standpoint. The fact that most L-Glucose analogues also possess germicidal properties in addition to their oncolytic and angiostatic attributes is especially useful in the field of clinical oncology, plagued by secondary immunosuppression and comorbidities of an infectious origin.

Keywords: Competitive inhibition; Structural analogues; Ascorbate; Metabolic cancer therapy

Preliminary considerations

$C_6H_7O_6^-$ is the L-enantiomer of ascorbate, the conjugate base of L-ascorbic acid, stemming from selective deprotonation at the 3-hydroxy group. Required for a range of essential metabolic reactions in all living organisms -from bacteria to metazoans, with specific molecular receptors and transporters conserved across numerous taxa- the ascorbate ion and its oxidized counterpart, dehidro-ascorbate, have multiordinal roles in all mammals as a metabolite, a vitamin and an a cofactor to at least fifteen enzymes [1-3]. Table 1 shows six, out probably hundreds of, biochemical reactions in which ascorbate/dehydroascorbate has a crucial involvement.

H+ + monodehydro-L-ascorbate radical + NADH = L-ascorbate + NAD+
O_2 + L-ascorbate = L-dehydroascorbate + H_2O
O_2 + dopamine + L-ascorbate = H_2O + monodehydro-L-ascorbate radical + (R)-noradrenaline
L-ascorbate + all-trans-antheraxanthin = all-trans-zeaxanthin + L-dehydroascorbate + H_2O
L-dehydroascorbate + glutathione = L-ascorbate + glutathione disulfide
O_2 + H_2O + L-ascorbate = oxalate + L-threonate + H+

Table 1: Examples of the involvement of ascorbate/dehydroascorbate as an electron donor/acceptor in physiological reactions.

Relevant to the present analysis, as it illustrates their molecular similarities, a phenomenon frequently reported by doctors is a pronounced -though illusory- hyperglycemia upon the intravenous injection of pharmacological doses of ascorbate [4]. L-ascorbate is one of several six-carbon structural analogues of L-glucose. Due to the stereometric similarities amongst both molecules (Figure 1), "hyperglycemic" readings are obtained under the above-mentioned circumstances when blood glucose measurements are conducted through hand-held glucometers. Such false-positive results come about only when glycaemia is gauged through the glucose oxidase

determination method, but not when the hexokinase method is performed. The fact that electrochemical sensors cannot tell both molecules apart illustrates the underlying mechanism of competitive inhibition by structural analogues, a safe and cost-effective tool for the metabolic treatment of solid tumours.

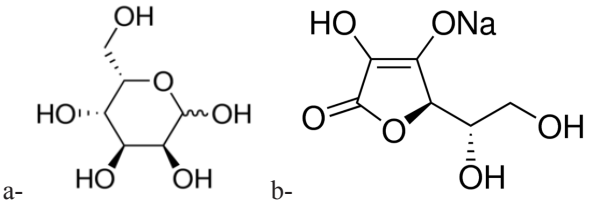

Figure 1: Stereometric similarities amongst the molecular array of L-glucose ($C_6H_{12}O_6$) and sodium ascorbate ($C_6H_7NaO_6$), one of its closest structural analogues. The broad denomination "hexose" (six-carbon sugar) aptly describes the fundamental structure of both molecules. Intramolecular condensations create pyran and furan rings, respectively. Structural depiction from Sigma Aldrich [5].

On the dose-dependent effect of ascorbate

Regarding competitive inhibition with structural analogues such as 2-Deoxy-Glucose ($C_6H_{12}O_5$) or Glucosamine Sulfate ($C_6H_{13}NO_5$), a dose-dependent effect has been observed [6,7]. In vitro experiments with tridimensional tumour models cultivated in human serum, have shown that achieving cytostatic and angiostatic effects require ascorbate concentrations in the mill molar range [8-10]. According to our clinical experience, plasma concentrations of ascorbate equal to or in excess of 300 mg/dl are a requirement for deterministic degrees of effectiveness as an antitumor agent [11,12]. Therefore, in homo, all therapeutic interventions with structural analogues of L-glucose should consider the Minimum Inhibitory Concentration (MIC) or rather, a minimum cytostatic concentration (MCC) of each effector. From the germicidal perspective, the MIC is defined as the lowest concentration that completely inhibits visible growth of the microorganism as perceived by the unaided eye, following proper incubation with a standard inoculum of approximately 10^5 colony-forming units per millilitre (CFU/ml) [13].

From the enzymological perspective, competitive inhibition by structural analogues has also a MIC requirement, related to the law of mass action. Early empirical determinations gave rise to the assertion that the velocity of a reaction is proportional to the concentration of the reactants. Said axiom can be expressed as $V \propto [R]$. In any solution of substances with a given affinity, increasing the concentration of reactants will increase the probability of collision of their molecules, ergo, the physicochemical interactions, in a supra-exponential manner [14]. Although with a much higher degree of complexity, parallel occurrences are expected in biological systems. As per the above-stated law of mass action, any therapeutical intervention with doses leading to plasma concentrations under the MIC threshold will either render small, stochastic effects or be altogether ineffectual.

Several controlled studies have looked at survival times of different murine models such as BALP/C mice with implanted S180 sarcomas following daily injections of 500 mg/kg of ascorbate [15]. At interstitial concentrations of 180 mg/dl, the percentage of tumour growth inhibition approached 50%, escalating to ~ 65% once the intra-tumour ascorbate level went above 360 mg/dl. At a dose of 700 mg/kg/day, the median post-implantation survival time for the control group was 35.7 days, while that for the treatment group was 50.7 days. There is little doubt concerning the dose-dependent effect of sodium ascorbate. Whether by direct selective cytotoxicity, metabolic disruption, immune activation, angiogenesis inhibition and/or other biological response modifications, pharmacological concentrations of ascorbate approaching MCC in and around the neoplastic cells appear to be of value [16-19].

Prior safety and efficacy assessments

The intravenous use of large doses of sodium ascorbate is generally regarded as safe, with a median lethal dose (LD_{50}) of 8,000 mg/kg and a therapeutic index (T_i) of several digits [20-22]. In a study of twenty-four patients suffering from terminal cancer and unable to benefit from standard therapy, Hoffer, et al. reported no adverse effects following several rounds (three times per week) of intravenous ascorbate at doses of 0.4 g/kg to 1.5 g/kg [23]. Although no objective tumour remissions could be attained through said intervention, those patients reached C_{max} levels well above 180 mg/dl without any negative side effects but several positive ones, such as longer survival and enhanced quality of life. Riordan et al. reported having treated over 900 patients with numerous intravenous doses of ascorbate, ranging from 30 to 60 grams, with no negative side effects [24]. As a coadjuvant, given in conjunction with the chemotherapeutics gemcitabine and erlotinib to patients with metastatic pancreatic cancer, intravenous ascorbate has also proven safe [25], while high-dose parenteral ascorbate has been proven to enhance chemo sensitivity and reduce the systemic toxicity of chemotherapy in patients suffering from ovarian cancer [26]. Reports from multiple laboratories in a wide spectrum of animal models of mesothelioma, hepatocarcinoma, pancreatic cancer, sarcoma, acute lymphocytic leukaemia, as well as breast, colon and prostate cancer, have confirmed that cytotoxic concentrations of ascorbate can be attained in vivo, inflicting measurable degrees of tumour remission without damaging the host [27-32].

Patients, materials and methods

Twenty patients, 8 females, 12 males, were selected to evaluate their pharmacokinetic response to pharmacological doses of sodium ascorbate through the intravenous route. Ages

ranged from 35 to 72 years ($\bar{x}$= 53.6), while body weight ranged from 65 kg to 80 kg. All subjects had a confirmed diagnosis of cancer. Following catheterization of either the cephalic or basilic vein from both arms, a three way stopcock with a Luer lock (Discofix) was attached to the Jelco catheter (Smith Medical), connecting an IV bag to each distal port. Once the intravenous route was secured and kept permeable by a continuous drip (7 drops per minute) of saline solution, the procedure was carried out by means of two separate infusion pumps (Medifusion DI-2000-DEAM), attached to the left and right arms respectively, set at 280 drops per minute each. The administered dose was 2 grams per kilogram of body weight, resulting in a mean dose of 140 grams (90-150). The combined total output of both infusion pumps was 560 drops/minute, resulting in a constant solute intrusion rate of 2 grams per minute. Blood samples were drawn from any suitable segment of the dorsal venous arch of the foot, or the distal portion of the saphena magna, on either lower limb. Close and constant attention was paid to developing signs and symptoms throughout the tests by trained medical personnel. Measurements were taken at 15-minute intervals, carefully registering every discernible and/or referred changes in the patient's state. Blood specimens were immediately sent to the laboratory at a consistent pace, under the direct supervision of the technical director or the chief technician in order to minimize preanalytical errors. The analysis of plasma content of ascorbate was performed by high-pressure liquid chromatography coupled with electrochemical detection (EC-HPLC).

Inclusion criteria

Subjects with inborn G6PD deficiencies -therefore prone to haemolytic anaemia due to fragility of erythrocytic membranes when placed in contact with strong reducing agents such as ascorbate- were excluded. Even when exhibiting a normal renal function, patients having undergone nephrectomy or presenting with renal agenesis, as well as patients under dialysis -which could potentially create an artefact in the volume of distribution (V_d) or any other pharmacokinetic parameter- were also not included. No patients with coronary artery disease were admitted in the study. Before each individual test, written informed consent was obtained, and both patients and their close relatives were previously instructed in every instance on the necessary preparations and precautions.

Results

At a dose of 2.000 mg/kg and a constant solute intrusion rate of 2 grams per minute, peak levels of plasma ascorbate were in the range of 389-686 mg/dl ($\bar{x}$ 439, $\tilde{x}$ 467), with C_{max} consistently occurring at 60-75 minutes. In 75% of subjects, beyond the 2nd measurement interval (T_{30}) plasma levels remained above 300 mg/dl for ~60 minutes, demonstrating that ascorbate concentrations with known cytostatic and antiangiogenic activity (extrapolated from both in vitro and in vivo studies) can be achieved with tolerable doses in tumour-bearing humans [33-35]. Taking into consideration previous reports from these authors and others regarding intravenous injections of 30, 60 and 100 grams of ascorbate, linear pharmacokinetics were demonstrated, i.e. C_{max} and AUC increase with dose.

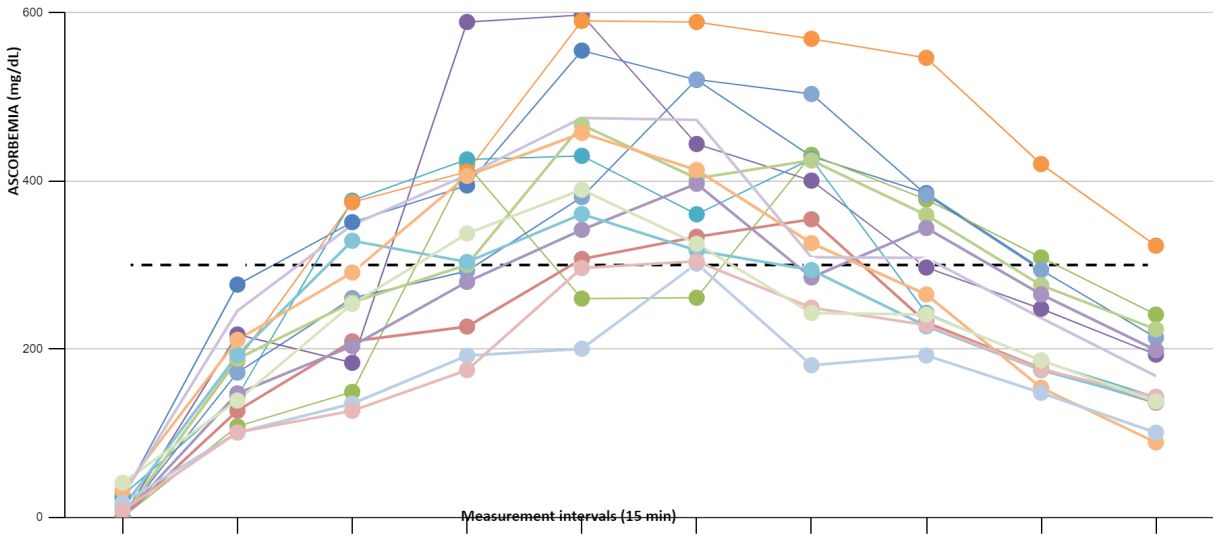

Figure 2: Plasma levels of sodium ascorbate (ascorbemia) in 20 tumour-bearing patients, measured at 15-minute intervals, during and following a 70 minute-long infusion of 2.000 mg/kg body weight, at a constant solute intrusion rate of 2 grams/minute. Maximum plasma concentrations (C_{max}) occurred at 60-75 minutes, coinciding with the end of the programmed, simultaneous administration through infusion pumps A and B. Minimum cytostatic concentration (MCC) was pre-defined by our laboratory as 300 mg/dl (dotted horizontal line).

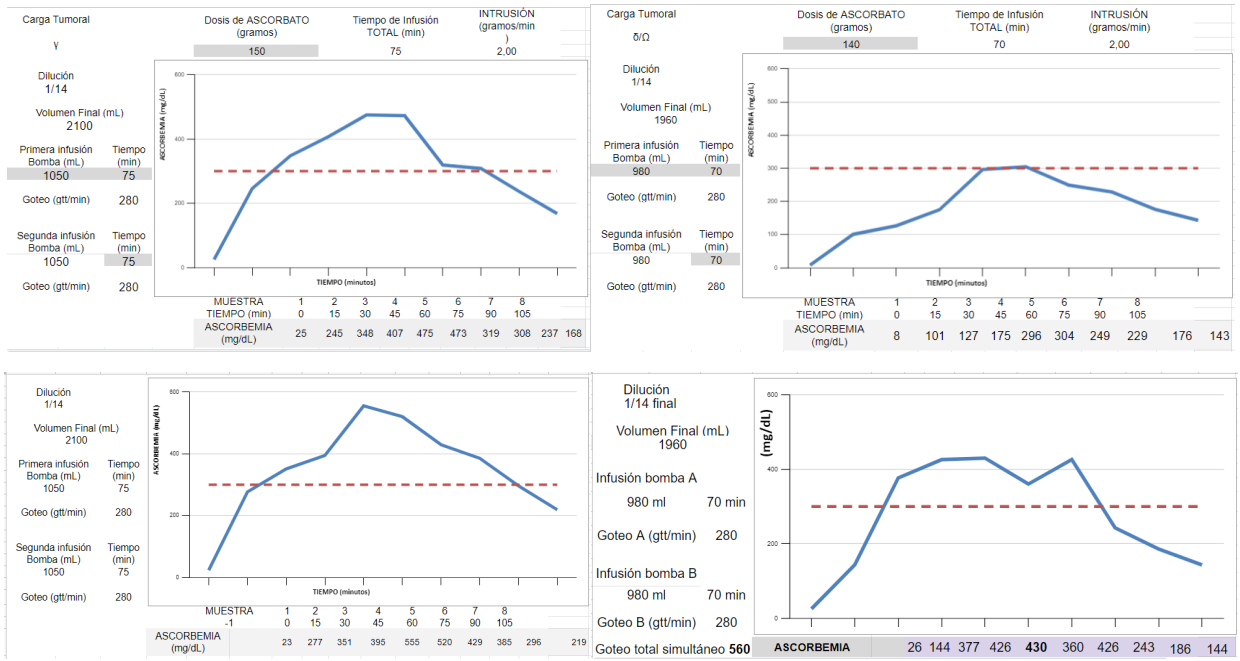

Figure 3: Individual examples of the test, showing the Area under the Curve (AUC) in relation to de Minimum Cytostatic Concentration (MCC).

Discussion

Ascorbate has proven selectively cytotoxic to anaplastic cells in a concentration-, dose- and time-dependent fashion [36-39]. This is a well-described phenomenon in other clinical fields. For instance, the bactericidal effect of aminoglycosides or fluoroquinolones is concentration-dependent [40]. Bactericidal and cytostatic agents work optimally when the C_{max} and, by extension, the AUC, exceed the MIC by a factor of 1 or 2 orders of magnitude. Optimal concentration ranges have been calculated for laboratory animals and subsequently extrapolated to human subjects [41]. The C_{max}/MIC ratio should exceed 10 for optimum dosing of antibiotics and cytostatics, whereas the 24-hour interval AUC to MIC ratio (AUC_{24}/MIC) should exceed 100 in the case of fluoroquinolones [40,41]. When designing therapeutical interventions with structural analogues, pharmacokinetic and pharmacodynamic parameters are cardinal determinants of the efficacy of antimetabolites. Clinically effective dosage regimens and susceptibility breakpoints are pivotal in the design of protocols for anti-metabolic interventions, tailored to the specific metabolic tumour signatures as well as the metabolic sub-phenotypes of different hosts.

These authors and others have repeatedly observed that pharmaceutical agents which exhibit concentration-dependent oncolytic activity also have a post-intervention effect (unpublished data). The Post-Intervention Effect (PIE) is defined as the persistence of oncolytic or germicidal effects after drug concentrations at the pathological locus fall below the MIC. Several mechanistic explanations for the PIE both in oncology and infectology have been advanced in relation with different agents and pathogens, including slow triggering apoptotic responses and/or irreversible binding of a pharmaceutical agent to the target site [42,43].

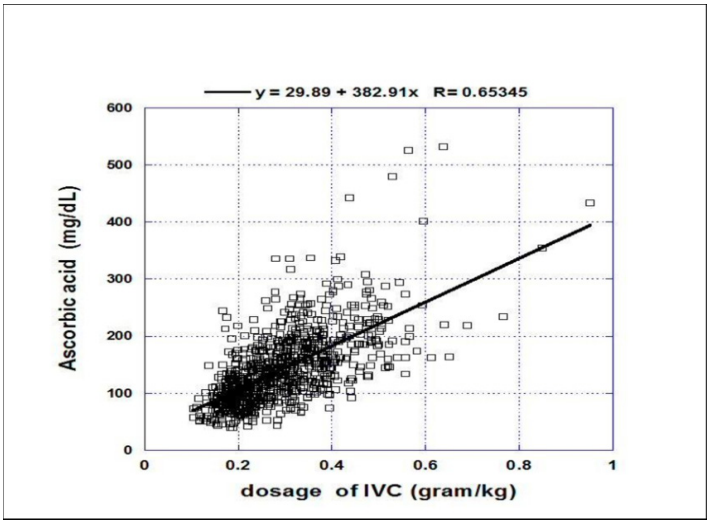

Figure 4: Peak plasma ascorbate concentrations (mg/dL) versus IVC dose (mg/kg) for 900 subjects. Reproduced with permission from Mikirova, et al.: Intravenous ascorbic acid protocol for cancer patients: scientific rationale, pharmacology, and clinical experience [38].

Molecules in several drug classes such as lincosamides, macrolides, penicillins and cephalosporins, all exhibit time-dependent bactericidal power [44,45]. It is conceivable that the oncolytic, selectively cytotoxic effect of several L-Glucose and L-Glutamine analogues is also time-dependant. As serum concentrations of these drugs increase, cytotoxic/antimetabolic killing may plateau, and therapeutic outcomes become dependant on the period that the antimetabolites concentration is registered above the MIC at the pathological locus. This is usually expressed as t > MIC, the fraction of time above the MIC in a 24-hour interval. It should therefore be taken into account that, for time-dependent cytostatic antimetabolites and germicidal drugs, efficacy is fundamentally determined by the extent to which the area under the curve exceeds the minimal inhibitory concentration. As the MIC of a cell line or microorganism increases, these pharmacokinetic targets eventually become unattainable, and microorganisms/cell lines are classified as resistant. Regarding tumour remission, survival and relapse-free periods obtained through antimetabolic interventions, the variability between clinical studies correlates with the dosage employed [46,47]. Poorly designed clinical interventions that use low doses of one or several antimetabolites, can only produce stochastic effects.

Conclusions

Oncolytic and germicidal concentrations of sodium ascorbate can be achieved safely in the clinical setting through intravenous injections, but only at a dose matching or exceeding 1.8 grams/kg body weight and a solute intrusion rate ≥ 2 grams/minute. Though not necessary for improved quality of life, plasma concentrations of ascorbate with a C_{max}/MCC ratio > 1 are a requirement for predictable, deterministic effects on tumour status and overall survival.

Declaration of conflicts of interest

As of this writing, the authors have no conflicts of interest whatsoever, directly or indirectly, by ownership or by affiliation with any brand, company, or institution. No outside contributors had any role in the design, implementation or analysis of our study or the write-up of this paper.

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