

Safety of Antimetabolite 2-Deoxy-D-arabinothymine (2DG) as a Coadjuvant Metabolic Intervention in 268 Cancer Patients

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ABSTRACT

Although previously found to be quite safe and potentially useful as a metabolic sensitizer against a wide spectrum of cancer subtypes, 2-Deoxy-D-Arabinohexose, commonly known as 2-Deoxy-D-Glucose (2DG), has remained somewhat ignored in the clinical setting. As a glycolysis inhibitor, 2DG preferentially targets tumour cells, which densely overexpress glucose transporters (GLUTs) in their cytoplasmic membranes, as well as glycolytic and fermentation enzymes hexokinase 2 (HK-2) and lactic dehydrogenase isoenzyme A (LDH-A). The pronounced functional asymmetry, the distinct metabolic phenotypes that set apart neoplastic and normal cells offer a therapeutic window of opportunity to overcome multidrug resistance in the treatment of cancer. Nutripharmacological corrections of blood glucose, followed by the timely introduction of several non-metabolizable structural analogues, is a cost-effective, minimally invasive coadjuvant treatment for solid tumours. Further, our research group has shown that a metabolic intervention with antimetabolites of glucose and pyruvate is strongly enhanced by a systemic suppression of the natural substrates of their catalyzing, rate-limiting enzymes within cancer cells. Here, we demonstrate that 2DG, perhaps the archetypal glucose antimetabolite, is very safe in humans.

KEYWORDS

Structural analogues; 2-Deoxy-D-glucose; Competitive inhibition; Metabolic cancer therapy

INTRODUCTION

Over 90% of all tumour cells described to date exhibit a hypermetabolic phenotype and a high glycolytic flux, while glucose transporters of the GLUT family have been found to be overexpressed in cancer cell membranes by about an order of magnitude [1,2]. There is consensus in the scientific community that increased glucose uptake is a key regulatory axis in the proliferation and biosynthetic capability of neoplastic cells as well as the suppression of programmed cell death [3-6]. Considerable clinical

experience already reported by these authors has made clear that an energy blockade of tumour metabolism is indeed both feasible and safe since it leaves unharmed the organism of the host [7-9]. The aim of the interventions with antimetabolites is the onset of an acute energy disturbance in neoplastic tissues, sparing healthy organs. Such an approach is an exploitation of the functional asymmetry that sets apart neoplastic cells and healthy neighbouring cells, with therapeutic intent. Evidence of such functional asymmetry is readily apparent in positron

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emission tomographies (PET/CT), and it has been found that reductions in the standardized uptake value (SUV_{max}) of neoplastic lesions are positively correlated with survival [10-13]. From the clinical perspective, in the context of competitive inhibition of the rate-limiting enzymes of solid tumours, it is semiologically relevant that neoplastic tissues have such a strong avidity for glucose. This striking hallmark of cancer can be ascertained semi-quantitatively by SUV_{max} calculations [Mbc Region of Interest/(Mbc injected/lean body mass)] [14]. In this regard, PET/CT has provided proof-of-concept for a metabolic approach to cancer treatment. Enzymatic inhibition by structural analogues competing against physiological substrates for the allosteric loci is well understood mechanistically, and antimetabolites of glutamine/glucose/pyruvate are being tested for safety and efficacy.

PRIOR EVIDENCE OF SAFETY

The use of the non-degradable, radioactively-labelled hexose 2-¹⁸F₂FDG (¹⁸FC₆H₁₂O₅) as a means to locate hypermetabolic anaplastic lesions in human patients is now widespread [15-17]. Over two million PET/CTs are being performed every year in the United States alone, each of which routinely involves the injection of 15 mg/kg BW of this analogue (~1200 mg for a 75 kg person). By all accounts, the pharmacological substrate of this radiotracer, 2DG itself, has been reported to be well-tolerated and safe [1]. Given that 2DG has undergone extensive experimentation as an antiepileptic agent as well as an antitumoral agent, there have been trials exploring its safety on humans [18-23]. Additionally, our group has found that physiological ketosis (defined as β -hydroxybutyrate ≥ 1.3 nM/l) offsets glucoprivation. Concerns about neurotolerance to glycolysis inhibitors have been dispelled by the observation that central nervous system cells can aptly extract energy through the oxidation of ketone bodies β -hydroxybutyrate (C₄H₇O₃⁻) and acetoacetate (C₄H₅O₃⁻), which serve as an alternative

fuel during fasting and, as our group has proven, even during a pharmacologically induced, transient removal of blood glucose [9]. Ketone bodies have even been shown to suppress glucose consumption in brain cells [23,24]. Also previously, these authors found that repeated intravenous injections of 2DG, 30 mg/kg BW, were cleared uneventfully by healthy human volunteers, with no discernible organic alterations at any time frame [25].

ELIGIBILITY CRITERIA

Patients were required to be above the age of 21 and below 90, to have a Karnofsky's index performance status ≥ 70 (ECOG performance status of 2 or better), and adequate haematopoietic (hematocrit $\geq 30\%$, platelet count $\geq 100,000/L$), hepatic (ALT ≤ 2.5), and renal (creatinine ≤ 1.5 mg/dl) functions. Patients with a known history or symptoms of coronary artery disease, arrhythmias, uncontrolled hypertension, pericardial effusion, congestive heart failure, G6PD inborn deficiency, coagulopathies, a history of transient ischemic attack, stroke, or any other CNS disorder within the previous 90 days were excluded. Patients with a Body Mass Index (BMI) lower than 19 were not eligible. No restrictions were imposed on previous treatments.

PATIENTS, MATERIALS AND METHODS

Two hundred and sixty-eight tumour-bearing patients, 167 females 101 males, were selected to receive several consecutive doses of 2-Deoxy-D-arabino-hexose in incremental progression, 10 mg/kg to 40 mg/kg BW, by the intravenous route, either daily or every other day, as part of a broader, comprehensive cancer treatment and intended as a metabolic disruptor for cancer cells. Ages ranged from 24 to 89 years ($\bar{x}=59$, $\hat{x}=60$). All patients had a confirmed diagnosis of cancer in a spectrum of tumoral pathologies including cancer to the breast (22.7%), lung (12%), colon (11.5%), prostate (7.8%), uterus (4.1%), kidney (4.1%), ovary (3.7%), stomach (2.6%), bladder (2.2%), liver (2.2%), thyroid (1.1%) as

well as exocrine pancreatic cancer (9.7%), head-and-neck cancer (4.4%), sarcoma (2.6%), glioblastoma (2.2%), multiple myeloma (2.2%), melanoma (1.8%), NH lymphoma (1.8%) and mesothelioma (1.2). All patients had a BMI ≥ 19 , being therefore susceptible to carefully designed, temporary dietary restrictions. Liver and kidney functions (Chemical Analyzer A15, BIOSYSTEMS), as well as hematopoietic status (Haematology Cell Counter Advia 560, SIEMENS), were analyzed in order to assess their overall physiological condition and establish a baseline.

The standard procedure started with the evaluation of the patient's condition and quantification of physiological ketosis by the operator. The required blood ketone level (metabolic threshold) for this interventions was set at 1.5 mM/l, consequently, patients presenting with a ketone/glucose ratio lower than 0,4 were dismissed for the day and received guidance to recalibrate their caloric intake. It is well established that a ketogenic, mildly calorie restricted diet effectively shifts energy metabolism towards beta-oxidation of fatty acids instead of glucose as the main systemic source of ATP production [26]. This fact is of clinical value in the context of interventions with antimetabolites, since it facilitates competitive inhibition [27]. The metabolic shift makes the introduction of non-metabolizable glucose/pyruvate analogues much less disturbing for the healthy tissues of the host, brain cells in particular. It was, therefore, expected that patients presented with a relatively low blood glucose level and above normal ketone levels, which they overwhelmingly did (mean 76 mg/dl and 1.26 mM/l, respectively). Technically, the procedure is described as follows: After catheterization of either the cephalic or basilic vein, a three-way stopcock with a Luer lock (Discofix) is attached to the Jelco catheter (Smith Medical), connecting a IV bag to the distal port. Once the intravenous route has been secured and kept permeable by a continuous drip (7 drops per minute) of isotonic saline solution 0.9% (B

BRAUN) the operator proceeds to administer the corresponding dose of 2-Deoxy-D-arabinohexose, 10% solution (DCM Healthcare). Permeable intravenous access is kept for 90 minutes. Within this group, the adjusted personal dose ranged from 0.5 g to 3 g (\bar{x} = 2.9). Close and constant attention was paid to developing signs and symptoms throughout every session by trained medical personnel. Blood pressure, heart rate, respiratory frequency and oxygen saturation measurements were taken at periodic intervals, carefully registering every discernible and/or referred changes in the patient's physiological and psychological status.

Given that patients undergoing cancer treatments with antimetabolites are routinely required to arrive in a fasting state for their ambulatory treatment with glucose/pyruvate/glutamine analogues, post-intervention termination of fast is accomplished through the ingestion of medium-chain triglycerides and other fats, by means of a high fat/normal protein broth provided (drank at $\approx 60^{\circ}\text{C}$). Upon spontaneous normalization of every and all physiological parameters, from blood glucose to mental acuity, and certainty that they were perfectly capable of managing themselves unaided, patients were released to return home. Follow up communications were systematically carried out over the telephone in the next hours, and trained personnel remained available on call for the remainder of the day.

Before each individual intervention, written informed consent was obtained, and both patients and their close relatives were previously instructed in every instance on the necessary preparations and precautions. A generic copy of the informed consent can be downloaded at <http://www.metabolicstherapy.uk/informedconsent>

OBSERVATIONS

Commonly observed effects were increased thirst (62.6%), increased hunger (70.8%), diaphoresis (31.7%),

drowsiness (22.7%), dizziness (7.8%), involuntary muscle twitching (3.2%). All signs and symptoms were transient and quickly reversed to normal by the end of the intervention. No significant adverse effects were observed, no evidence of any organic perturbation could be found. For patients presenting with mild organ dysfunctions - even though they met eligibility criteria - at the beginning of the study, no signs of worsening could be found. Maximum tolerated doses were arrived at by linear arithmetic progression.

Given the sample size (N = 268), these authors find there is fairly strong evidence of 2DG being a safe pharmacological agent at the above-stated doses and posology. It is worth noting that even the higher dose employed represents a centesimal fraction of its LD50% (8000 mg/kg) for experimental animals [28]. Standard calculation renders the Therapeutic Index (TI) of 2DG a three-digit ratio (LD50/TD = 200), a fact that makes this

antimetabolite fifty-fold safer than popular over-the-counter medications such as aspirin (with a TI of ~ 4).

STUDY LIMITATIONS

Further elucidations are needed into the pharmacokinetics of 2DG in order to gain a deeper understanding of this agent and more precise dosing criteria.

CONCLUSIONS

Glucose structural analogue 2-Deoxy-D-arabinohexose was safe to use through the intravenous route in this group of cancer patients regardless of their underlying pathology subtype or baseline organic status. 2DG is a well-characterized and safe compound that holds great promise for the coadjuvant metabolic treatment of solid tumours.

CONFLICT 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.

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