Pyruvate Clinical Applications Adumbrates a Revolutionary Medical Advance

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Pyruvate in Oral Rehydration Salt

On the 50th anniversary of clinical application with WHO-guided oral rehydration salt/solution (ORS) and oral rehydration therapy (ORT), prestigious journals, Lancet and JAMA, published articles for the memory last year [1,2]. In 1978, the Lancet hailed the ORS for oral treatment of diarrhea and cholera as a most medical advance in past century because of the survival of a couple of million lives by the ORT worldwide per year [3].

The findings in intestinal physiology in 1950s that Sodium-Glucose co-transporters exist in intestinal epithelium in mammalian are the base of ORS theory, by which sodium easily with glucose is actively and rapidly absorbed and water is passively and massively passed through the intestinal barrier. WHO-ORS consists of powders of sodium bicarbonate or citrate, sodium chloride, potassium chloride and glucose, which is called WHO-ORS I or II. Citrate-based reduced osmolarity one with less sodium chloride and glucose is known as WHO-ORS III, which may be more effective for non-cholera patients with diarrhea [4]. In last decades, due to its superiority of sodium and water absorption, the ORS has been promoted to rescue young patients with burns for vast rehydration with or without intravenous infusion. Currently, the ORT has been one of guidelines in burn shock resuscitation and it is also effective in resuscitation of burns in adults [5,6].

Since 2012, we have innovated pyruvate-enriched ORS (Pyr-ORS) by equimolar pyruvate of sodium salt to replace bicarbonate or citrate in WHO-ORS (I or II) and do so in reduced osmolar WHO-ORS (III), also [7-10]. Intriguing findings are that Pyr-ORS reveals great superiorities in resuscitation of hemorrhagic and burn shock in animal models, particularly in severe acidosis correction, visceral blood flow preservation, organ and intestinal barrier protection and survival improvement, compared with WHO-ORSs. Opposite bicarbonate or citrate, pyruvate of sodium salt holds biological and pharmacological properties that benefit critically ill patients: increase of anoxia/hypoxia tolerance, reversal of hypoxic lactic acidosis, anti-oxidative stress and inflammation, protection of mitochondria and anti-apoptosis and so on [11-16]. Therefore, pyruvate is a modulator of glucometabolic disorders and a protector of multi-organ function in numerous insults. It may be critical of pyruvate protection that exogenous pyruvate preserves the key metabolic enzyme, pyruvate dehydrogenase (PDH) activity. As demonstrated with intravenous (IV) pyruvate in severe injured animals, oral pyruvate in Pyr-ORS can mostly reactivate the depressed PDH (see below), enhance nicotinamide adenine dinucleotide oxidized/reduced form (NAD+/NADH) ratio by the pyruvate reductive reaction with lactate dehydrogenase (LDH), coupled with the NADH oxidative reaction, promoting the regular glycolysis pathway [12,17]. Thereby, pyruvate with its hypoxia-inducible factor-1 (HIF-1) stimulation, in both hypoxia and normoxia, enables to improve glucose oxidative metabolism to preserve cell function in various insults [12].

Notably, a recent finding showed that oral Pyr-ORS improved diabetes status: significantly reduced body weight and fasting blood sugar level and robustly raised blood insulin level. Surprisingly, oral pyruvate in Pyr-ORS reversed the declined PDH activity by high...
glucose (HG) stimulation with inhibition of pyruvate dehydrogenase kinase (PDK) promoted by HG in diabetic db/db mice. These changes of enzyme activities were confirmed in the investigation of HK-2 cell line in HG, in vitro. As a result, the typical glucometabolic Warburg effect-like disorder in diabetes was mostly corrected [18]. Another discovery in the same diabetic model was that oral Pyr-ORS significantly decreased the advanced glucose end products (AGEs) in renal tissues and protected kidney function (submitted data for publication), as demonstrated previously [19,20].

Prior studies illustrated that oral pyruvate in large doses can improve diabetes and pancreatic insulin secretion, mitochondrial disorders in children and adults [21-23]. However, single pyruvate is malabsorption and a large dose of pyruvate is gastrointestinal irritative, but a regular dose less than 25 g as a single ingestion is not functional well and no blood pyruvate is raised if only 7.0 g/d is orally taken for 7 days [24,25]. The Pyr-ORS was, thus, created by replacement of alkaliens in ORS with equimolar pyruvate, so that a regular amount of pyruvate can be sufficiently absorbed from intestine with enough glucose in Pyr-ORS to robustly increase pyruvate levels in blood and tissues to function ideally [10,26], a comparable target obtained as intravenously infused pyruvate [17]. Therefore, oral pyruvate in Pyr-ORS would prevent from multi-organ dysfunction and reverse disorders of glucometabolic pathways and acid-base balance in critical care patients subjected to various pathogen insults [8-10].

Pyruvate in Fluid Resuscitation

Generally, sodium pyruvate powders in aqueous solutions are not stable at pH over 5.0 at room temperature [27]. However, pyruvate fluids for clinical uses (from 28 mM in pyruvate Ringer’s solution to 154 mmol/L pyruvate saline) are long-term stable, if the pH of solutions is adjusted to lower than pH 5.0, at room temperature [28]. Pyruvate systemically protects cells/tissues in either anaerobic or anerobic conditions, including red blood cells (RBCs) [11], particularly preserves PDH activity as a PDH activator, like dichloroacetate (DCA), and corrects hypoxic lactic acidosis [12,17,29,30], so that it would be more superior than citrate, acetate, lactate, bicarbonate and chloride as current anions in medical fluids in protection of cell function against various injuries in clinical settings [12,13,31,32].

In addition to pyruvate specific benefits in IV resuscitation, experimental pyruvate-based peritoneal dialysis solutions also showed the advantages in peritoneal dialysis and peritoneal resuscitation from shock in animal studies [33-35], the similarity as demonstrated with pyruvate-enriched priming solution in experimental bypass surgery [11]. The advantages of pyruvate resuscitation mainly are rapid correction of hypoxic lactic acidosis, distinct multi-organ protection, specific preservation of visceral blood flow and intestinal barrier and profound increment of survival. Accordingly, IV or oral pyruvate is not only a volume extender, but also a therapeutic agent to protect multi-organ function and against metabolic disturbances simultaneously in fluid resuscitation. Due to its stability, superiority and safety without clinical toxicity [28,36,37], there is highly possible to manufacture pyruvate-enriched fluids, IV or oral solutions (Pyr-ORS), for dealing with critical care patients in near future.

Pyruvate in Anti-Aging and Beyond

NAD+, a star molecule for anti-aging, is well recognized in health and diseases [38]. However, pyruvate may be theoretically more beneficial than NAD+ in protection against aging: 1) exogenous pyruvate generates NAD+ by the LDH reduction free of energy on the 1:1 basis, thus, one pyruvate molecule administrated basically equals to one NAD+ given; 2) pyruvate has additional beneficial properties that NAD+ does not own, among which the following pyruvate actions play a critical role in protection of cell function: reactivation of the PDH activity, correction of lactic acidosis, exertion of direct anti-oxidative/nitrosative stress and inhibition of AGES formation; PDH inhibition, oxidative stress, acidosis and AGES deposition are involved in pathogenesis of degenerative nervous diseases. Therefore, pyruvate shows robust neuroprotection in many animal studies [26,39]. A recent report demonstrated that pyruvate was equimolarly more beneficial than NAD+ in cell function, in vitro [40]. Besides, it is worthwhile to note that pyruvate may inhibit cancer in certain conditions as several studies substantiated [41,42].

Although ethyl pyruvate (EP) has been extensively investigated with even better benefits than sodium pyruvate in cell protection, the phase II clinical trial was failed ten years ago, compared with effective clinical trials with sodium pyruvate [21-23,36,37], making the EP prospect compromising [43].

Considering iatrogenic drawbacks of normal saline and lactate Ringer’s solution in fluid resuscitation from critical care patients, the novel pyruvate solutions, such as pyruvate/chloride saline ([Na+] 154 mMol/L, [Pyr-] 50 mMol/L, [Cl-] 104 mMol/L) and pyruvate Ringer’s solution ([Pyr-] 28 mMol/L) in crystalloids and colloids [12,28,44], may be the new generation of resuscitation fluids. Pyr-ORS as an alternative to IV-fluid use as the first-line medicine for fluid therapy would improve overall treatment outcomes of various diseases [45]. Therefore, Pyr-ORS would prompt ORT prevalence in critical care and pre-hospital rescue, particularly in a large scale. It may also prevent and treat diabetes and aging as a function drink in a big population. The prospect of pyruvate applications may be another most important medical advance this century.

References


