American Journal of Medical Sciences and Medicine, 2020, Vol. 8, No. 1, 1-5
Available online at http://pubs.sciepub.com/ajmsm/8/1/1
Published by Science and Education Publishing
DOI:10.12691/ajmsm-8-1-1

Dichloroacetate is Cardiotonic and Suggested for Treating Metabolic Acidosis: Alleviating Lactate Effects and Beta-ketothiolase Deficiency (An Original Article)

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Received December 10, 2019; Revised January 11, 2020; Accepted January 22, 2020

Abstract Dichloroacetate (DCA) is an acetate analog that was reported to improve the hemodynamic functions and mechanical efficiency in patients with congestive heart failure. DCA is also known for decades as an activator of pyruvate dehydrogenase (stimulates oxidation of pyruvate to acetyl CoA). This prevents lactate accumulation (stimulating conversion of lactate to form pyruvate then acetyl CoA). Currently, DCA is an effective and safe drug for treating lactic acidosis, a clinical condition due to the accumulation of hydrogen (H+) ions from lactic acid, characterized by blood lactate levels > 5 mM and arterial pH < 7.25. Interestingly, DCA was reported to cause a significant decrease in serum lactate that was accompanied by an increase in arterial blood pH. Moreover, DCA decreases blood lactate levels under various conditions in both man and laboratory animals via diverting pyruvate metabolism (source of lactate) towards oxidation through activating the target enzyme pyruvate dehydrogenase. High serum lactate (due to anerobic metabolism or as a side effect of insulin/glucose therapy) may occur during treatment of beta ketothiolase deficiency (BKTD). In some BKTD patients, serum lactate may increase contributing to the refractory metabolic acidosis. DCA minimized ketone bodies formation (benefits BKTD patients) but not elimination that can be achieved by insulin/glucose treatment. Current insulin/glucose treatment (for BKTD) causes increased glycolysis (i.e. increased lactate production and metabolic acidosis). On biochemical, pharmacological and medical bases, we suggest that can be normalized upon combining insulin/glucose treatment with DCA. In phenformin-induced lactic acidosis, DCA therapy increased arterial pH and bicarbonate, increased intracellular liver pH and cardiac index causing a fall in blood lactate. In hepatectomy-induced lactic acidosis, animals treated with DCA exhibited stabilization of cardiac index, decreased blood lactate, and decreased mortality. That was better in outcome than sodium bicarbonate treatment. We suggest that DCA may exert pharmacological antagonism with ketone bodies effects e.g. acidosis. DCA may be a promising evidence-based adjuvant therapy for acute refractory metabolic acidosis conditions as BKTD and lactic acidosis.

Keywords: *Dichloroacetate, beta-ketothiolase deficiency, lactate, lactic acidosis, ketone bodies, acidosis, isoleucine*

Cite This Article: Amr El-Dardear, Elsayed Abdelkreem, Hussam Baghdadi, Naif Aljuhani, Osama Alhadramy, Mohammed Hassan, Faten M. Omran, Hytham Mahmoud Abdel-Latif, Wafaa A. Abdellah, Azza Mahmoud Ahmed Abouelella, Mohamed Abdel-haleem, Momen El-shazley, Manal Mohamed Helmy Nabo, and

Salah Mohamed El Sayed, Dichloroacetate is Cardiotonic and Suggested for Treating Metabolic Acidosis: Alleviating Lactate Effects and Beta-ketothiolase Deficiency (An Original Article)." *American Journal of Medical Sciences and Medicine*, vol. 8, no. 1 (2020): 1-5. doi: 10.12691/ajmsm-8-1-1.

1. Introduction

Dichloroacetate (DCA) is an acetate analog that was reported to improve the hemodynamic functions and mechanical efficiency in patients with congestive heart failure i.e. DCA is a cardiotonic and metabolic therapy for myocardial ischemia [1]. Moreover, DCA is an acetate derivative that is widely accepted for treating lactic acidosis. Lactic acidosis is a clinical condition due to accumulation of hydrogen (H+) ions from lactic acid, characterized by blood lactate levels >5 mM and arterial pH <7.25. Interestingly, DCA was reported to cause a significant decrease in serum lactate that was accompanied by an increase in arterial blood pH. Moreover, DCA decreases blood lactate levels under various conditions in both man and laboratory animals via diverting pyruvate metabolism (source of lactate) towards oxidation through activating the target enzyme pyruvate dehydrogenase [1-2].

Biochemically, DCA is an acetate analog that is known for decades as an activator of pyruvate dehydrogenase (PDH) (Figure 1), the enzyme that starts aerobic oxidation of pyruvate in Krebs cycle. DCA increases PDH flux more than eightfold (Figure 2) and significantly inhibits the oxidation of acetoacetate and fatty acids [3]. In neonatology, DCA therapy was reported as a novel safe promising treatment for refractory preterm septicaemia in neonates (associated with refractory metabolic acidosis due to group B streptococcus septicaemia and lactic academia) which was also reported to be refractory to conventional sodium bicarbonate [4].

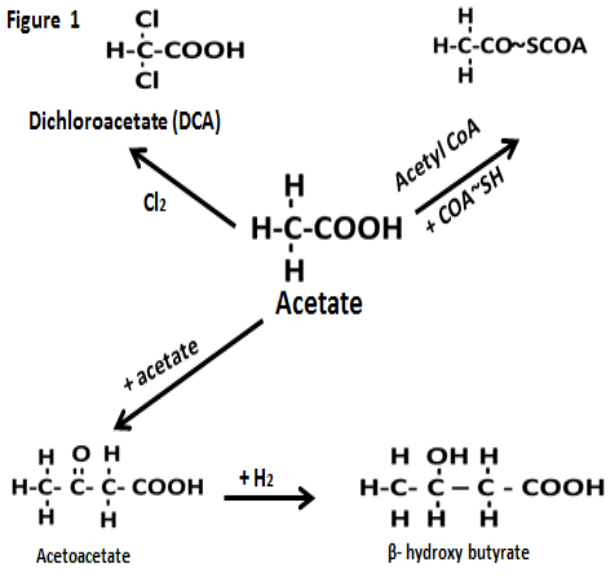

Figure 1. Dichloroacetate (DCA) decreases lactate formation (anaerobic metabolism). DCA stimulates aerobic oxidation of pyruvate to form acetyl CoA via stimulating pyruvate dehydrogenase (PDH) (through inhibiting pyruvate dehydrogenase kinase, PDHK). This is quite promising for treating beta-ketothiolase deficiency (BKTD) due to decreasing anerobic metabolism and related lactate-induced acidosis

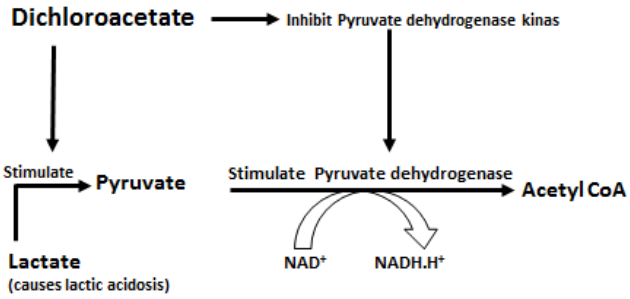

Figure 2. Determining factors of refractory metabolic acidosis in β-ketothiloase deficiency

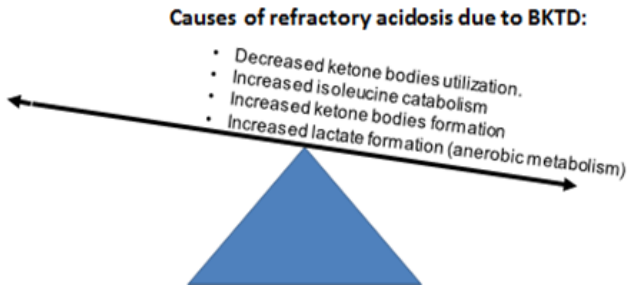

Figure 3. Causes of refractory metabolic acidosis in BKTD

Beta-ketothiolase (T2 enzyme) is an important enzyme for both ketone bodies formation and isoleucine catabolism [5]. During hepatic ketogenesis, T2 directs the biosynthesis of acetoacetyl-CoA from two molecules of acetyl-CoA. During ketolysis, T2 breaks acetoacetyl-CoA into two molecules of acetyl-CoA [5]. In isoleucine catabolism, T2 cleaves 2-methylacetoacetyl-CoA to acetyl-CoA (active acetic acid) and propionyl-CoA (a glucogenic substrate) [5,6].

Beta-ketothiolase deficiency (BKTD) is a rare autosomal recessive disorder disturbing both isoleucine catabolism and ketone body metabolism. Usually, BKTD manifests in infancy to early childhood by intermittent ketoacidotic spells in addition to symptoms of toxic encephalopathy e.g. lethargy, hypotonia, vomiting, tachypnea, and may be coma [6]. A history of ketogenic factors e.g. prolonged fasting, febrile illness and/or high protein intake is usually present. Ketoacidotic spells are quite variable among patients up to encephalopathy and/or hemodynamic collapse. Permanent neurological abnormalities may be present as gait/movement disorders, hypotonia, and mental retardation [7].

1.1. Lactate Levels in BKTD and Status of Ketone Bodies

Lactate levels were reported to be higher than normal in some BKTD patients [8]. So, measuring serum lactate levels may be recommended in all BKTD patients [9] particulary during episodes of metabolic acidosis. During refractory metabolic acidosis (Figure 3), serum lactate (if higher than normal) may play a significant contributing factor for the refractoriness of metabolic acidosis. High serum lactate is likely to be normalized with DCA

treatment [10-14]. Four patients with severe lactic acidosis associated with septic shock were treated with DCA (50 mg/kg body weight). All patients had an expected mortality rate of 90-100%, based on previous studies. In one patient, treatment with DCA was associated with a decrease in blood lactate levels from 11.2 mM before treatment to 0.8 mM 16 h later. Markedly elevated blood pyruvate and alanine levels also decreased to normal. After treatment, the arterial blood pH rose to 7.53, and vasopressor agents were no longer needed to support the blood pressure. Other three patients died with refractory metabolic acidosis [11].

However, increased serum lactate levels may occur as a side effect of insulin/glucose treatment (as given in BKTD). Blackshear reported that the infusion of insulin alone rapidly decreased blood glucose and ketone bodies, but caused an increase in blood lactate and pyruvate [14].

We suggest that can be controlled using DCA. Interestingly, DCA did not affect the insulin effects on blood glucose and ketone bodies. DCA inhibited ketone-body production in severe ketoacidosis [12,13,14].

1.2. Hypothesis

On biochemical, pharmacological and medical bases, we suggest suggest:

- Prescribing DCA as a regular treatment for refractory metabolic acidosis
- Adding DCA to conventional insulin/glucose treatment for treating BKTD.

In few BKTD patients, serum lactate may increase [8] contributing to the refractory acidosis. Current insulin/glucose treatment (for BKTD) causes increased glycolysis (lactate production and metabolic acidosis) that can be normalized upon combining insulin/glucose treatment with DCA.

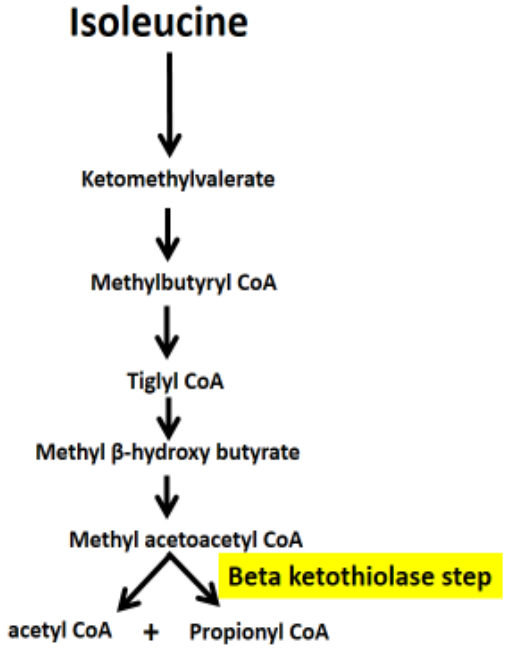

Figure 4. Accumulated acidic metabolites due to beta-ketothiolase deficiency

DCA-induced inhibition of ketone bodies uptake will be alleviated by insulin effects. Causes of refractory metabolic acidosis in BKTD are increased levels of ketone bodies (due to increased acidic metabolites of disturbed isoleucine catabolism (Figure 4), increased ketone bodies formation and decreased ketone bodies utilization) and lactate (due to anerobic metabolism or as a side effect of insulin/glucose therapy). DCA relieves most of these.

Table 1. Role of lactate in metabolic acidosis

• In some BKTD cases, serum lactate may increase (indicating anaerobic metabolism and lactate acidemia) [8,21,22].
• DCA activates pyruvate dehydrogenase (aerobic metabolism) and consequently inhibits lactate formation (a possible contributing cause in metabolic acidosis) [3].

1.3. Evaluation of Hypothesis

As insulin/glucose is well-known to stimulate lactate formation (through stimulating glycolysis) [13], this may add a burden of lactate-based acidosis during treatment of BKTD with insulin/glucose. Interestingly, effects of DCA on glucose metabolism were similar in both healthy and diabetic rats. More interestingly, DCA was reported to significantly decrease the rise in serum lactate and pyruvate due to insulin administration [14].

Interestingly, DCA administration is accompanied by increased blood pH and serum bicarbonate, decreased lactate production, and increased liver lactate extraction in addition to a decrease in tissue lactate levels [10]. All these effects are quite needed when treating any refractory metabolic acidosis particularly acute ketoacidotic episodes of BKTD. DCA alleviates lactate acidemia that may be associated with BKTD.

1.4. Supporting Data to the Suggested Hypothesis

- DCA was reported to improve the clinical outcomes in congenital lactic acidosis [10].
- During liver transplantation surgery, DCA was reported to attenuate lactic acidosis, stabilize the intraoperative acid-base balance and decrease the need for sodium bicarbonate use. Moreover, DCA was reported to decrease postoperative plasma transfusion requirements without exerting any measurable effects on perioperative outcome parameters [15].
- DCA was reported to effectively reduce blood lactate levels in endotoxic shock. Therefore, DCA may be a promising treatment to severe lactic acidosis related to septic shock [16]. DCA given during cardiac arrest caused a more rapid normalization of arterial lactate after successful resuscitation [17].

2. Discussion

Insulin/glucose therapy to BKTD helps in increasing ketone bodies utilization but insulin-induced increased serum lactate may be problematic and enhance the metabolic acidosis. That will certainly benefit from combining insulin/glucose therapy with DCA. DCA is well-known to decrease serum lactate levels. DCA was reported to enhance the ability of rats to exercise at near maximal workloads that may be attributed to DCA-induced decrease in the lactate accumulation rate or

amount [18]. Moreover, DCA proved effective as a treatment for lactic acidosis in dogs [19] and some malignant conditions e.g. non-Hodgkin's lymphoma [20]. In neonates having BKTD, serum lactate may be increased to levels beyond the normal range (indicating anaerobic metabolism and lactate academia).

It is understood that mild to moderate lactic acidosis may exist during acute conditions as dehydration, poor hemodynamics and poor perfusion. However, some neonates with BKTD may have a lactate level of 2.5 mmol/L [21] or even higher (51 mg/dl (that is 5.61 mmol/L) [22]. Both reported BKTD infants in two different studies exhibited serum lactate values more than the normal range (0.26 – 2.21 mmol/L) [23]. Moreover, excess serum lactate may be further exaggerated by insulin/glucose treatment (insulin stimulates glycolysis and lactate production). Relationship of high serum lactate to refractory metabolic acidosis encountered in some cases of BKTD warrants further research investigation.

Regarding suggesting DCA as a suggested treatment for BKTD, two important questions soon arise:

- "Is DCA a recommended treatment for any acute refractory ketoacidosis e.g. during BKTD and in long-term treatment?"
- Is DCA an effective prophylaxis against potential chronic cerebral toxicity caused by accumulated isoleucine-catabolic intermediates?

The answer for both questions is "Yes".

Current treatments for acute BKTD crisis include provision of fluids and glucose/insulin (to inhibit further ketogenesis), bicarbonates (for severe metabolic acidosis but is controversial) and L-carnitine. Insulin/glucose was reported to be effective as it inhibits lipolysis and ketone bodies production [5,24]. However, insulin results in increased serum lactate and pyruvate that may add a further metabolic acidosis burden [14,25]. As insulin stimulates lactate formation (may increase metabolic acidosis and decrease arterial blood pH) [4] while DCA inhibits lactate formation [26], DCA is a recommended adjuvant treatment to insulin/glucose therapy for treating BKTD (to subtract lactate-induced acidosis from the net metabolic acidosis occurring during the acute metabolic ketoacidotic episodes in T2 deficiency patients).

DCA does cause a decrease in ketone bodies formation but not ketone bodies clearance [14,25]. In alloxan-induced diabetes and ketosis in animals, addition of DCA to insulin provoked a rapid and marked reduction in glucosuria with increased urinary excretion of β-hydroxybutyrate and acetone (insulin effect) [27]. The addition of DCA (75 mg/kg/day for 7 days) caused a drop in blood lactate and total lipids and increased urinary excretion of ketone bodies (β-hydroxybutyrate and acetone). High blood β-hydroxybutyrate and acetoacetate concentrations (which were already high at the start) were not affected by combined DCA and insulin treatment [27].

At least, it could be said that DCA does not antagonize insulin effects regarding enhanced ketone bodies clearance that persisted when administering both insulin and DCA together [14,19,25]. In addition, DCA is an evident inhibitor of ketone bodies formation. McAllister et al. suggested a competitive effect for CoA between active pyruvate dehydrogenase and enzymes for ketone bodies oxidation [12]. Based on that, DCA may be regarded as an effective prophylaxis against potential chronic cerebral toxicity caused by accumulated isoleucine-induced catabolic intermediates.

Refractory metabolic acidosis in BKTD is a leading cause of mortality and is multifactorial in origin. It results from increased serum ketone bodies (mainly due to defects in ketone bodies utilization) and the associated increase in anaerobic metabolism and lactate academia. In phenformin-induced lactic acidosis, DCA decreased animal mortality to 22% vs. 89% in those treated with sodium bicarbonate. Interestingly, DCA therapy caused increased arterial pH and bicarbonate, increased intracellular liver cells pH (liver pHi) and cardiac index. DCA also increased liver lactate uptake and decreased blood lactate [19]. In hepatectomy-induced lactic acidosis, animals treated or pretreated with DCA exhibited stabilization of cardiac index, a fall in blood lactate, and about 17% mortality which were better in outcome than treatment with sodium bicarbonate. Sodium bicarbonate treatment was associated with a continuous decrease in cardiac index, rise in blood lactate, and 67% mortality. Animals treated with DCA exhibited improved cardiac index, arterial pH, bicarbonate, and liver pHi with lower mortality rates than those treated with sodium bicarbonate or sodium chloride [19]. In another report, treatment of acidotic animals (having myocardial ischemia and failure) with DCA increased arterial blood pH to 7.53. Interestingly, vasopressor agents were no longer needed to support blood pressure [28]. Based on that, the pharmacological effects of DCA are promising as adjuvants to glucose/insulin for treating BKTD [29]. In clinical practice, therapeutic doses of DCA are far below that.

3. Safety of DCA

There is no evidence or report that therapeutic doses of DCA might be carcinogenic or toxic. In a human study, DCA proved effective as a treatment for some malignant conditions e.g. non-Hodgkin's lymphoma [20]. Although administration of high DCA doses (more than 100 times the reported therapeutic doses) to rodents can result in liver cancer, there is no evidence that DCA (at therapeutic doses) is a human carcinogen. Too high doses of DCA (1-2 g/l) that can never be used in clinical conditions were reported to be carcinogenic. Reported therapeutic doses of DCA (10-50 mg/kg) were never reported to be carcinogenic [30].

4. Conclusion

Our hypothesis confirms that DCA is strongly suggested as a novel, safe and promising adjuvant treatment for metabolic acidosis and BKTD.

Conflict of Interest

The authors declare that there is no conflict of interest.

Financial Support

The authors declare that they did not receive any financial support from any source for this research article.

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