

Dichloroacetate is a Novel Safe Treatment for Beta-ketothiolase Deficiency: Towards Better Therapeutic Outcomes (An Original Article)

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Abstract Beta-ketothiolase deficiency (BKTD) is an inborn error of ketone bodies and isoleucine metabolism. Patients with BKTD manifest during late infancy and early childhood with recurrent episodes of ketoacidosis (accumulated acetoacetate and β -hydroxybutyrate) that may be refractory to treatment and life-threatening. BKTD is exaggerated by fasting, starvation and catabolic conditions. Dichloroacetate (DCA) is a safe effective treatment for both lactic acidosis and non-Hodgkin's lymphoma. DCA is non-toxic and non-carcinogenic at therapeutic doses. DCA toxic doses are hundred times (1-2 gram/l) more than the therapeutic doses. In experimental models of ketosis, DCA reduces ketonemia and ketonuria while significantly lowering blood glucose. Importantly, DCA was reported to divert pyruvate (amino group acceptor) to form alanine in transamination reactions to regenerate α -ketoglutarate from glutamate) to oxidative pathways to form acetyl CoA that is oxidized in Krebs cycle. That inhibits first step of isoleucine catabolism (transamination step) and consequently blocks formation of acetoacetate and β -hydroxybutyrate. That alleviates ketone bodies-induced refractory metabolic acidosis. On biochemical and pharmacological bases, we suggest DCA as a novel evidence-based adjuvant and life-saving treatment for BKTD. Moreover, 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 isoleucine catabolism, increased ketone bodies formation and decreased ketone bodies utilization). DCA relieves most of these. Biochemically, DCA and ketone bodies (acetoacetate and β -hydroxybutyrate) are structural analogs derived from acetic acid. In neonatology, DCA improved neonatal septicaemia-induced refractory metabolic acidosis that did not respond to conventional sodium bicarbonate. In conclusion, DCA is strongly suggested to treat BKTD.

Keywords: Dichloroacetate, beta-ketothiolase deficiency, antimetabolite, pharmacological antagonist, ketone bodies, acidosis, isoleucine

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1. Introduction

Beta-ketothiolase (mitochondrial acetoacetyl-CoA thiolase [T2]; EC 2.3.1.9; encoded by *ACAT1* gene) is a vital enzyme for ketone bodies and isoleucine metabolism [1]. Beta-ketothiolase deficiency (BKTD) is a rare autosomal recessive disorder characterized by an inborn error of isoleucine catabolism and affecting ketone body metabolism. Its clinical features are characterized by intermittent ketoacidotic episodes that are associated with clinical signs and symptoms of toxic encephalopathy e.g. lethargy, hypotonia, vomiting, tachypnea, and coma in some patients, with an onset during infancy or toddlerhood [2].

In ketone bodies synthesis in the liver, T2 catalyzes the formation of acetoacetyl-CoA from two acetyl-CoA molecules. In extrahepatic ketone body utilization, T2 is responsible for the thiolytic cleavage of acetoacetyl-CoA into two molecules of acetyl-CoA (Figure 1) [1]. In isoleucine catabolism, T2 catalyzes the thiolysis of 2-methylacetoacetyl-CoA to acetyl-CoA and propionyl-CoA (a glucogenic substrate) (Figure 2). Branched-chain aminotransferase catalyzes the first reaction in the catabolic pathway of branched-chain amino acids, a reversible transamination that converts branched-chain amino acids into branched-chain ketoacids [3] (Figure 3).

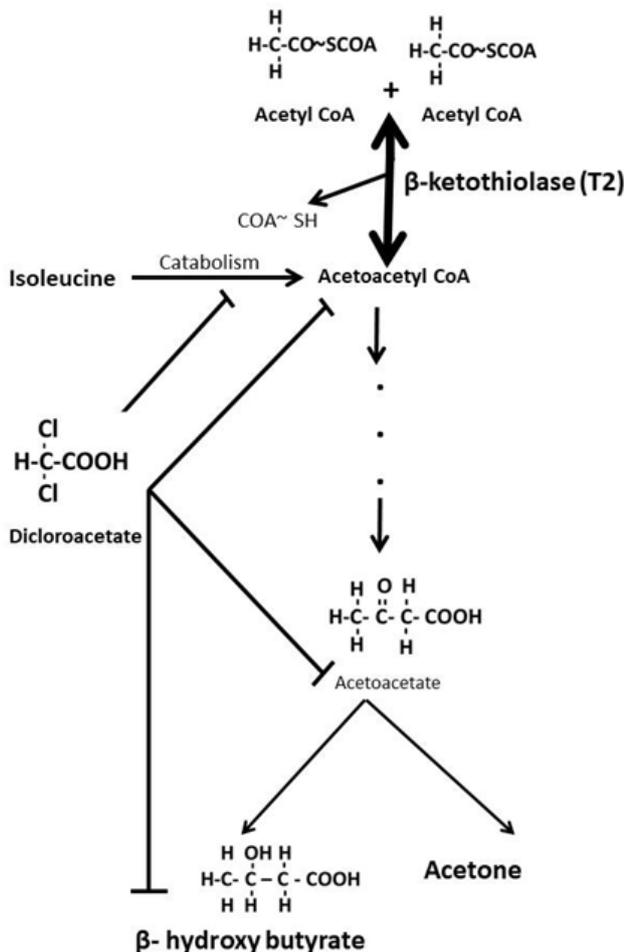


Figure 1. Role of β -ketothiolase in ketone bodies synthesis (ketogenesis) and oxidation. DCA can prevent ketogenesis and inhibit further isoleucine catabolism (minimizing further acetoacetate formation and related ketoacidosis)

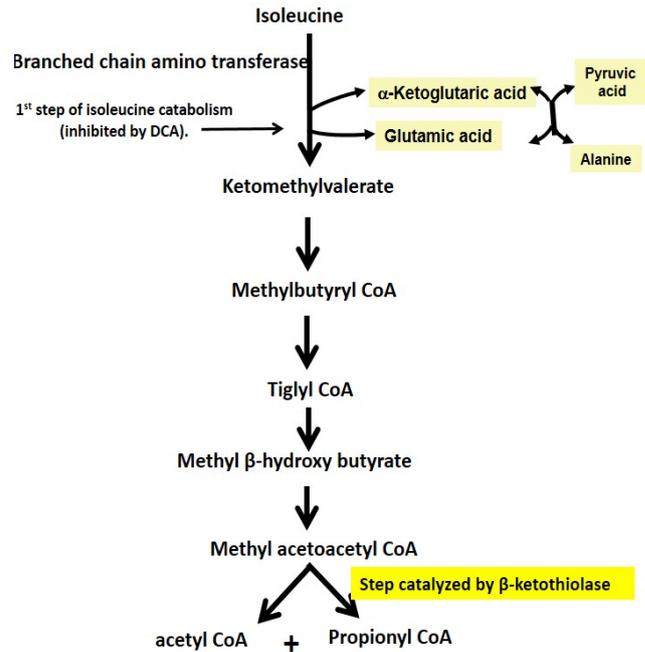


Figure 2. Biochemical bases and consequences of β -ketothiolase (BKT) deficiency. BKT plays a vital role in catabolism of isoleucine. BKT cleaves methylacetoacetyl CoA into acetyl CoA and propionyl CoA. Deficiency of BKT results in the accumulation of acetoacetate and lack of ketone bodies utilization. Fortunately, 1st step of isoleucine catabolism (transamination step) is reported to be indirectly inhibited by dichloroacetate (DCA). DCA inhibits first step of isoleucine catabolism preventing ketone bodies formation and subsequent refractory metabolic acidosis. That may suggest a promising role of DCA in treating BKT deficiency.

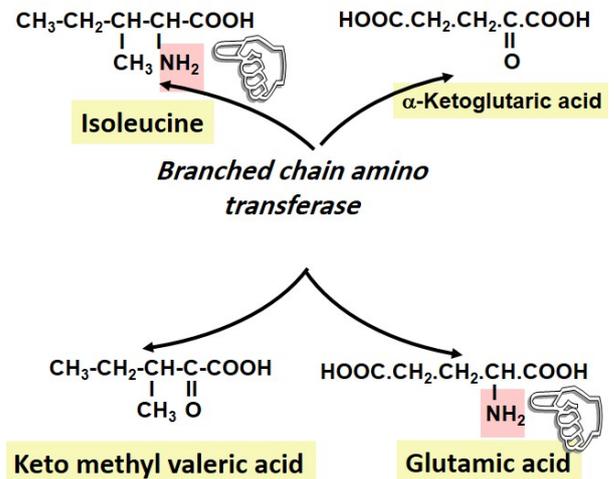


Figure 3. Transamination of isoleucine is vital for its catabolism. Alanine aminotransferase (ALT, GPT). The reaction is readily reversible. However, during amino acid catabolism, ALT enzyme functions in the direction of glutamate synthesis

Beta-ketothiolase deficiency (BKTD; MIM# 203750, 607809) is an inborn error of ketone body and isoleucine metabolism. Patients with BKTD usually manifest during late infancy and early childhood with recurrent episodes of ketoacidosis. A history of ketogenic triggers e.g. prolonged fasting, febrile illness and/or high protein intake is usually present. Frequency and severity of ketoacidotic episodes vary among patients. A considerable proportion of patients develop severe episode/s, commonly with

encephalopathy and/or hemodynamic collapse. Death or permanent neurological abnormalities (e.g., gait/movement disorders, hypotonia, and mental retardation) are well-documented possible complications [4]. Based on that, in ketoacidoses of BKTD, source ketone bodies are both fatty acids catabolism and impaired isoleucine catabolism.

In addition, some patients with BKTD may develop chronic neurological impairment (mainly extrapyramidal manifestations) independent of the frank ketoacidosis. This could be attributed to accumulated isoleucine catabolic metabolites (particularly 2-methylacetoacetate and 2-methyl 3-hydroxybutyrate) (Figure 2). Therefore, BKTD should be considered not only as a defect in ketone body utilization but also as a defect in isoleucine catabolism with the potential for insidious cerebral toxicity [1]. Strategies for treating BKTD should include reducing metabolic acidosis, inhibiting ketogenesis, stimulating ketone bodies utilization, inhibiting lactate formation (anaerobic metabolism), relieving metabolic effects exerted by the accumulated ketones (acetoacetate and β -hydroxybutyrate), and decreasing isoleucine catabolism (Figure 2) [1-4]. Most of these may be achieved using the acetate analog dichloroacetate (DCA).

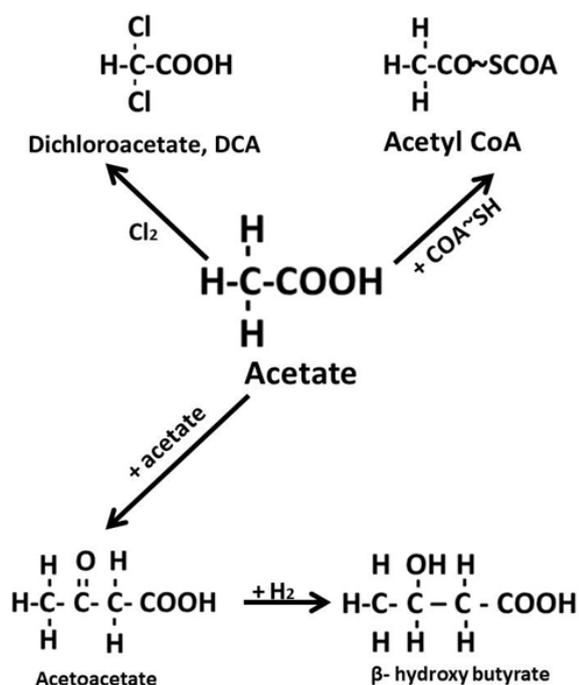


Figure 4. Some acetate derivatives of biological importance. Acetyl CoA, acetoacetate, β -hydroxybutyrate and dichloroacetate (DCA) are acetate analogs. An evident pharmacological antagonism was reported between acetate and DCA. An evident pharmacological antagonism was reported between ketone bodies and DCA as regard effects on arterial blood pH where DCA treats metabolic acidosis

DCA is a derivative of acetic acid by replacing two hydrogen atoms by two chloride atoms (Figure 4). There is no evidence or report that therapeutic doses of DCA are carcinogenic or toxic. DCA is quite safe at therapeutic doses. Biochemically, both DCA and ketone bodies (acetoacetate and β -hydroxybutyrate) are structural analogs derived from acetic acid (Figure 4).

Table 1. Key clinical features of beta-ketothiolase (BKT, T2) deficiency [1]

• Decreased ketone bodies utilization.
• Ketone bodies accumulation and metabolic acidosis
• Ketonemia and ketonuria
• Fasting ketoacidotic crisis
• \pm Refractory metabolic acidosis

2. The Hypothesis/Theory

1. On biochemical and pharmacological bases and in light of a previous report [5], we hypothesize that DCA is a promising adjuvant treatment (with insulin/glucose) for treating BKTD. That is because DCA inhibits isoleucine catabolism upstream of the step catalyzed by beta-ketothiolase (before formation of acetoacetyl-CoA). Hence, DCA participates in decreasing the formation of (1) isoleucine catabolic intermediates, which are neurotoxic, thereby decreasing the incidence of chronic neurological impairment and (2) acetyl-CoA is the precursor of ketogenesis, thereby decreasing ketoacidosis.
2. DCA decreases lipolysis and serum free fatty acids [6]. It is well-known that oxidation of free fatty acids gives acetyl-CoA that is the main source for ketogenesis in the liver. Therefore, DCA decrease ketone body production and consequently decreases the severity of BKTD.
3. DCA is an antimetabolite of acetate (precursor of ketogenesis) [7], acetoacetate (ketone body) and β -hydroxybutyrate (ketone body) [8]. Thus DCA decreases ketone bodies formation (through antagonizing acetate).
4. Being a structural analog to acetate and ketone bodies (acetoacetate and β -hydroxybutyrate), DCA may act as a pharmacological antagonist to ketone bodies i.e. DCA will alleviate the refractory metabolic acidosis induced by ketone bodies accumulation [9] due to BKTD and other causes.
5. Based on that, DCA is promising as a sole treatment (or adjuvant treatment to insulin/glucose) for treating BKTD in acute episodes as well as a long-term prophylaxis for potential chronic neurological impairment.

3. Evaluation of the Hypothesis/Theory

In experimental models of ketosis, DCA reduces ketonemia and ketonuria while significantly lowering blood glucose [10]. DCA inhibits alanine formation (from pyruvate) through activating pyruvate oxidation to form acetyl CoA to start Krebs cycle and other metabolic pathways. This decreases pyruvate transamination to form alanine. That secondarily disturbs branched-chain amino acid transamination (by limiting the amino group acceptors necessary to form alanine in transamination reactions to regenerate α -ketoglutarate from glutamate). α -ketoglutarate is essential for isoleucine transamination and subsequent catabolism (Figure 3) [5]. This is supported by

the report that DCA increases lactate/pyruvate ratio [11]. This minimizes pyruvate availability for transamination of branched chain amino acids and inhibits their further catabolism i.e. decreases the severity of BKTD.

Blackshear et al. reported a marked decrease in the concentration of ketone bodies (acetoacetate and β -hydroxybutyrate) after DCA treatment to rats where DCA inhibited the production of ketone bodies during severe ketoacidosis [12]. That was supported by another report where DCA infusion induced a maximal decrease in serum ketone bodies (acetoacetate and β -hydroxybutyrate) after a prior small increase [12]. Interestingly, DCA did not affect insulin-induced serum clearance of ketone bodies [12].

4. Evidences that DCA Antagonizes Ketone Bodies Effects Particularly Acidosis

DCA inhibits extrasplanchnic ketone bodies uptake evidenced by DCA-induced inhibition of β -hydroxybutyrate oxidation by rat diaphragm muscle [9]. That was supported by DCA-induced increase in serum ketone bodies [12,13].

Table 2. Evidences that DCA is strongly suggested for treating BKTD

- DCA interferes with isoleucine metabolism (at the 1st step before Beta-ketothiolase step i.e. before formation of acetoacetyl-CoA from isoleucine [5] (i.e. DCA relieves BKTD-induced chronic cerebral toxicity and ketoacidosis).
- DCA prevents ketone bodies formation (as DCA antagonizes acetate, the precursor of ketogenesis) [7,12,13]
- DCA structurally antagonizes acetoacetate and β -hydroxybutyrate i.e. DCA may antagonize ketoacidosis-induced decreased blood pH. This is evidenced by DCA-induced increased blood pH and bicarbonate [8,14]
- DCA did not affect insulin-induced serum clearance of ketone bodies [12,13]
- DCA antagonizes metabolic effects (particularly metabolic acidosis) [12,13]. This can be generalized to ketone bodies-induced acidosis.
- DCA increased arterial blood pH in patients with diabetes mellitus and hyperlipoproteinemia [15]. This can be generalized to ketone bodies-induced acidosis.
- DCA administration is accompanied by increased blood pH and bicarbonate. This report was in experimental animals [14] and same results were proved in human patients [16].
- DCA infusion induced a maximal decrease in serum ketone bodies (acetoacetate and β -hydroxybutyrate) after a prior small increase [12,13].

5. Empirical Data

DCA and ketone bodies are structural analogs to acetate. This may suggest competing effects and pharmacological antagonism between DCA and ketone bodies. This is evidenced by the report that infusion of DCA into rats with severe diabetic ketoacidosis over four hours caused a

marked decrease in blood ketone bodies concentration [12,13]. Recently, Being an analog of acetate (precursor of ketogenesis), DCA was recently suggested as a competitive inhibitor of ketogenesis and ketone bodies effects [8]. DCA was reported to significantly decrease ketone bodies formation [13] and antagonize acetate [7]. In experimental models of ketosis, DCA reduced ketonemia and ketonuria while significantly decreased blood glucose. However, DCA inhibited peripheral ketone bodies uptake and did not increase ketone bodies utilization [12,13], which can be minimized upon combining DCA with insulin/glucose.

6. Consequences of the Hypothesis/Theory

Table 3. Therapeutic benefits of DCA for treatment of BKTD

- DCA inhibits further catabolism of isoleucine and prevents ketone bodies formation and related metabolic acidosis.
- This is supported by the report that DCA increases lactate/pyruvate ratio [11]. This minimizes pyruvate availability for transamination of branched chain amino acids and inhibits their further catabolism i.e. decreases the severity of BKTD.
- DCA prevents excess accumulation of isoleucine catabolic intermediates, which are neurotoxic, thereby decreasing the incidence of chronic neurological impairment in BKTD.
- DCA alleviates effects of accumulated ketone bodies in BKTD
- DCA treats refractory acidosis that may be associated with BKTD.
- DCA enhances aerobic metabolism and minimizes the ongoing anaerobic metabolism that may be associated with BKTD.
- DCA prevents muscle fatigue, wasting and weight loss in prolonged recurrent attacks of BKTD.

7. Conclusion

Our hypotheses carry a lot of hope in introducing DCA as a novel potential promising and life-saving adjuvant treatment to glucose/insulin for treating BKTD and related metabolic disorders through alleviating the refractory acidosis and progressive metabolic derangements following isoleucine catabolism and related ketosis.

Conflict of Interest

The authors declare that there is no conflict of interest

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