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Betaine

Updated: September 26, 2017.

OVERVIEW

Introduction

Betaine is a modified amino acid consisting of glycine with three methyl groups that serves as a methyl donor in several metabolic pathways and is used to treat the rare genetic causes of homocystinuria. Betaine has had only limited clinical use, but has not been linked to instances of serum enzyme elevations during therapy or to clinically apparent liver injury.

Background

Betaine (bee' ta een) is a naturally occurring modified amino acid that is used therapeutically to treat genetic homocystinuria. Homocystinuria can be caused by several inherited defects in sulfur amino acid metabolism, the most common of which are cystathionine β-synthase deficiency (CβS) and 5,10-methylenetetrahydrofolate reductase (MTHRF) deficiency. Typically, plasma levels of homocysteine and methionine are elevated while cysteine is decreased. Children with these deficiencies develop mental retardation, ocular lens dislocations, skeletal deformities and early onset atherosclerosis. Most evidence indicates that the high levels of homocysteine are the major cause of the clinical complications. Therapy of homocystinuria includes a low methionine diet, pyridoxine, a cofactor for cystathionine beta-synthase, and betaine which results in a decrease in homocysteine levels and amelioration of the clinical manifestations. Betaine is believed to act by increasing methylation reactions, one of which causes homocysteine to be metabolized to methionine. Betaine is an important nutrient that can be obtained from foods (such as beets), synthesized endogenously from choline, or provided as a supplement in patients with impaired folate status or inherited deficiencies of enzymes involved in transsulfuration pathways. The liver is rich in betaine but levels may be somewhat reduced in patients with liver disease. Betaine was approved as an orphan drug for use in homocystinuria in 1996 and is available as a powder for reconstitution in bottles of 180 grams under the brand name Cystadane. The typical dose is 3 to 10 grams twice daily. Side effects are dose related and can include gastrointestinal upset with diarrhea, bloating, cramps, dyspepsia, nausea and vomiting. Rare, but potentially severe side effects include excessive increases in serum methionine concentrations which may lead to life-threatening cerebral edema.

Hepatotoxicity

In small, open label trials of betaine therapy for homocystinuria as well as in small controlled trials of betaine in other conditions (Alzheimer disease, nonalcoholic steatohepatitis), serum enzyme elevations and clinically apparent liver injury were not reported. Indeed, in some studies, betaine has been associated with significant declines in preexisting serum enzyme elevations in a proportion of patients with nonalcoholic fatty liver disease.

Likelihood score: E (unlikely cause of clinically apparent liver injury).

Mechanism of Injury

Betaine is a naturally occurring modified form of glycine that aids in the transsulfuration pathways converting homocysteine to methionine. Administration of betaine even in high doses (6 to 20 grams daily) has not been linked to hepatotoxicity.

Drug Class: Genetic Disorder Agents

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Betaine – Cystadane®

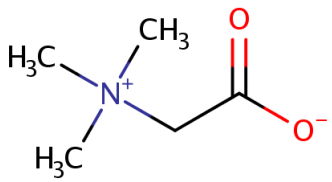
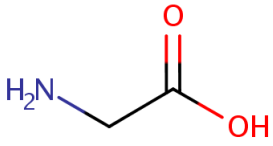
DRUG CLASS

Genetic Disorder Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULAS AND STRUCTURES

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Betaine	107-43-7	C5-H11-N-O2	
Glycine	56-40-6	C2-H5-N-O2	

ANNOTATED BIBLIOGRAPHY

References updated: 26 September 2017

Abbreviations used: CβS, cystathionine β-synthase; MTHFR, 5,10-methylenetretrahydrofolate reductase.

Zimmerman HJ. Hepatotoxicity. The adverse effects of drugs and other chemicals upon the liver. 2nd ed. Philadelphia. Lippincott, 1999.

(Textbook of drug induced liver injury published in 1999; does not discuss betaine).

Elsas L J II, Acosta PB. Homocystinuria. Nutritional support of inherited metabolic disease. In, Shils ME, Olson JA, Shihe M, Ross AC. Modern Nutrition in Health and Disease. 9th ed. Baltimore: Williams & Wilkins, 1999, pp. 1035-40.

(Textbook of nutrition and therapeutics).

Smolin LA, Benevenga NJ, Berlow S. The use of betaine for the treatment of homocystinuria. J Pediatr 1981; 99: 467-72. PubMed PMID: 7264811.

(Two children with severe homocystinuria were treated with betaine [6.4 to 9.2 g daily] and both had prompt decline in homocysteine levels and improvement in clinical symptoms despite concurrent increases in serum methionine levels).

Wilcken DE, Wilcken B, Dudman NP, Tyrrell PA. Homocystinuria--the effects of betaine in the treatment of patients not responsive to pyridoxine. N Engl J Med 1983; 309: 448-53. PubMed PMID: 6877313.

(Among 10 patients with homocystinuria due to CβS deficiency who were treated with betaine [3 g twice daily] for up to 5-13 months, all had rapid decline in plasma homocysteine levels and several had improvements in clinical symptoms, while side effects were mild and no patient developed "abnormalities of hepatic, renal or bone marrow function").

Benevenga NJ. Betaine in the treatment of homocystinuria. N Engl J Med 1984; 310: 265-6. PubMed PMID: 6690948.

(Letter in response to Wilcken [1983] discussing the possible role of alternate pathways of methionine catabolism in the effects of betaine on homocysteine levels in homocystinuria).

Wendel U, Bremer HJ. Betaine in the treatment of homocystinuria due to 5,10-methylene tetrahydrofolate reductase deficiency. Eur J Pediatr 1984; 142: 147-50. PubMed PMID: 6381059.

(In a 3 year old girl with MTHFR deficiency, betaine therapy [6-20 g daily] resulted in a decrease of homocysteine levels to trace amounts and a partial improvement in clinical symptoms "without apparent harmful effects and without signs of a disturbed liver function").

Wilcken DE, Dudman NP, Tyrrell PA. Homocystinuria due to cystathionine beta-synthase deficiency--the effects of betaine treatment in pyridoxine-responsive patients. Metabolism 1985; 34: 1115-21. PubMed PMID: 3934499.

(Among 6 patients with homocystinuria with adequate control using pyridoxine alone, methionine challenge led to an increase in serum homocysteine levels, which was blunted by betaine therapy [6 g daily]; no mention of adverse events).

Gahl WA, Bernardini I, Chen S, Kurtz D, Horvath K. The effect of oral betaine on vertebral body bone density in pyridoxine-non-responsive homocystinuria. J Inherit Metab Dis 1988; 11: 291-8. PubMed PMID: 3148071.

(Among 5 patients with homocystinuria not responsive to pyridoxine who were treated with betaine [3 g twice daily] or placebo in a 1 year crossover design, betaine led to significant decreases in homocysteine levels and inconsistent changes in serum methionine values, but had no effect on bone mineral density, and "no side effects or intolerance of medication occurred in any patients").

Holme E, Kjellman B, Ronge E. Betaine for treatment of homocystinuria caused by methylene tetrahydrofolate reductase deficiency. Arch Dis Child 1989; 64: 1061-4. PubMed PMID: 2629632.

(A 24 day old girl with homocystinuria due to MTHFR deficiency had a complete clinical remission with betaine therapy [3-6 g daily]; side effects were not discussed).

Betaine for homocystinuria. Med Lett Drugs Ther 1997 Jan 31; 39: 12. PubMed PMID: 9025725.

(Concise review of the mechanism of action, clinical efficacy, adverse events and costs of betaine shortly after its approval in the US as orphan drug therapy for homocystinuria; side effects included nausea, vomiting and diarrhea; no mention of ALT elevations or hepatotoxicity).

Andersson HC, Marble M, Shapira E. Long-term outcome in treated combined methylmalonic acidemia and homocystinemia. Genet Med 1999; 1: 146-50. PubMed PMID: 11258350.

(Among 8 patients with methylmalonic acidemia and homocystinemia treated with betaine and dietary restriction for 2-11 years, no long term adverse effects were noted).

Miglio F, Rovati LC, Santoro A, Setnikar I. Efficacy and safety of oral betaine glucuronate in non-alcoholic steatohepatitis. A double-blind, randomized, parallel-group, placebo-controlled prospective clinical study. Arzneimittelforschung 2000; 50: 722-7. PubMed PMID: 10994156.

(Among 191 patients with nonalcoholic steatohepatitis treated with betaine [combined with diethanolamine gluconate and nicotinamide ascorbate] or placebo for 8 weeks, serum ALT levels decreased by 11% [43 to 38 U/L] on betaine compared to slight increases on placebo [41 to 43 U/L] and other side effects were mild; no mention of worsening of ALT levels or hepatotoxicity).

Abdelmalek MF, Angulo P, Jorgensen RA, Sylvestre PB, Lindor KD. Betaine, a promising new agent for patients with nonalcoholic steatohepatitis: results of a pilot study. Am J Gastroenterol 2001; 96: 2711-7. PubMed PMID: 11569700.

(Among 10 patients with nonalcoholic steatohepatitis treated with betaine [10 g twice daily] for 12 months, all had a decrease or stable levels of ALT and side effects were mild but included nausea, loose stools, abdominal cramps and body odor, and "there were no adverse events noted in hematology of blood chemistry results").

Yaghmai R, Kashani AH, Geraghty MT, Okoh J, Pomper M, Tangerman A, Wagner C, et al. Progressive cerebral edema associated with high methionine levels and betaine therapy in a patient with cystathionine beta-synthase (CBS) deficiency. Am J Med Genet 2002; 108: 57-63. PubMed PMID: 11857551.

(A 10 year old girl with homocystinuria due to CβS deficiency developed marked increases in serum methionine levels while on betaine therapy [6 g daily] and subsequently developed progressive cerebral edema, which resolved after stopping betaine and restricting methionine intake; there were mild and transient ALT elevations at the time of admission).

Lowering plasma homocysteine. Med Lett Drugs Ther 2003; 45: 85-6. PubMed PMID: 14576622.

(Concise review of methods of lowering plasma homocysteine levels as an approach to decrease atherosclerotic events, largely by use of folate and vitamin B12 supplements which together can lower levels by 7-25%, but have not been shown to decrease severe cardiovascular outcomes).

Ueland PM, Holm PI, Hustad S. Betaine: a key modulator of one-carbon metabolism and homocysteine status. Clin Chem Lab Med 2005; 43: 1069-75. PubMed PMID: 16197300.

(Review of the role of betaine in one carbon metabolism and its effects on homocysteine levels; "no side effects have been observed" with betaine therapy).

Yokoi K, Ito T, Ohkubo Y, Sumi S, Ueta A, Sugiyama N, Togari H. Long follow up of betaine therapy in two Japanese siblings with cystathionine beta-synthase deficiency. Pediatr Int 2008; 50: 694-5. PubMed PMID: 19261122.

(Two Japanese sisters with homocystinuria [CβS deficiency] were treated with betaine for more than 12 years with partial success; no mention of ALT elevations or clinically apparent liver injury).

Chaabene-Masmoudi A, Mesrati F, Zittoun J, Landrieu P. Insidious peripheral neuropathy occurring under treatment in infantile MTHFR deficiency. J Inherit Metab Dis 2009; 32 Suppl 1: S303-6. PubMed PMID: 19697151.

(A 15 year old girl with homocystinuria [MTHFR deficiency] on long term betaine therapy [4 g daily for more than 10 years] developed a progressive peripheral neuropathy that did not respond to further increases in betaine dose).

Abdelmalek MF, Sanderson SO, Angulo P, Soldevila-Pico C, Liu C, Peter J, Keach J, et al. Betaine for nonalcoholic fatty liver disease: results of a randomized placebo-controlled trial. Hepatology 2009; 50: 1818-26. PubMed PMID: 19824078.

(Among 55 patients with nonalcoholic steatohepatitis treated with betaine [10 g twice daily] or placebo for one year, there were no differences in changes in ALT, AST or homocysteine levels between the two groups, and "no clinically apparent hepatotoxicity [ALT or AST ≥3X baseline value], rise in total bilirubin value of 2X normal, or severe adverse event was reported").

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al.; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. Gastroenterology 2015; 148: 1340-52. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, none were attributed to betaine).

Huemer M, Mulder-Bleile R, Burda P, Froese DS, Suormala T, Zeev BB, Chinnery PF, et al. Clinical pattern, mutations and in vitro residual activity in 33 patients with severe 5, 10 methylene tetrahydrofolate reductase (MTHFR) deficiency. J Inherit Metab Dis 2016; 39: 115-24. PubMed PMID: 26025547.

(Retrospective analysis of 33 subjects with homocystinuria and MTHFR deficiency found worse outcomes in those with lower residual enzyme activity, and betaine therapy [in 31 patients] appeared to improve biochemical and clinical features; no mention of ALT elevations or hepatotoxicity).

Day CR, Kempson SA. Betaine chemistry, roles, and potential use in liver disease. Biochim Biophys Acta 2016; 1860: 1098-106. PubMed PMID: 26850693.

(Review of the chemistry, distribution, metabolic functions and potential for use of betaine in chronic liver disease, focusing upon alcholic and nonalcoholic liver disease where hepatic levels of betaine may be insufficient).

Sookoian S, Puri P, Castaño GO, Scian R, Mirshahi F, Sanyal AJ, Pirola CJ. Nonalcoholic steatohepatitis is associated with a state of betaine-insufficiency. Liver Int 2017; 37: 611-9. PubMed PMID: 27614103.

(Serum levels of betaine were found to be lower in patients with nonalcoholic steatohepatitis than in those with fatty liver alone and lower levels were associated with worse histologic features of nonalcoholic fatty liver).