

Orphan Drugs 2020: Tailored inhibition of cystine stone formation as a therapy for cystinuria - Sahota A - Rutgers University, USA.

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Abstract:

Cystinuria, a typical genetic disorder of cystine transport, which is characterized by rapid and excessive excretion of cystine through urine and recurrent cystine stones within the kidneys and, to a lesser extent, within the bladder. Males generally are more severely affected than females. The disorder may cause chronic renal disorder in many patients. The cystine transporter can also be a heterodimer which consists of the rBAT (encoded by SLC3A1) and b0,+AT (encoded by SLC7A9) subunits joined by a disulfide bridge. The molecular basis of cystinuria is understood in great detail, and this information is now getting used to define genotype-phenotype correlations. Currently, the treatments for cystinuria include the administration of thiol drugs for the more severe cases and increased fluid intake to increase cystine solubility. These drugs, however, have poor patient compliance thanks to adverse effects. Thus, there's a requirement to scale back or eliminate the risks related to therapy for cystinuria. Four mouse models for cystinuria can be described and these models provide a resource for evaluating the efficacy and safety of latest therapies for cystinuria. We are evaluating a replacement approach for the treatment of cystine stones supported the inhibition of cystine crystal growth by cystine analogs. Our studies about cystinuria indicate that the cystine diamides are effective in preventing cystine stone formation within the Slc3a1 knockout mouse model for cystinuria. In addition to growth of crystal, aggregation of crystal is required for stone formation. Male and feminine mice with cystinuria have comparable levels of crystalluria, but only a few female mice form stones. The identification of things that inhibit aggregation of cystine crystal in female mice may provide insight into the gender difference in disease severity in patients with cystinuria.

Cystinuria genotypes:

Cystinuria genotypes are classified as Type A or Type B. Type A is caused by mutations in SLC3A1 and Type B by mutations in SLC7A9. Clinical symptoms in the A and B sub-groups are similar and there is no apparent correlation between genotype and phenotype but, as noted below, relationships between genotypes and phenotypes are now beginning to be delineated. SLC3A1 heterozygotes haven't any apparent phenotype, but SLC7A9 heterozygotes excrete variable levels of COLA within the urine. Few of these latter patients will have stones, but perhaps they are more likely to do so if urine volumes are low or animal-protein ingestion is high.

The percentage of Type A and B genotypes appears to be population-dependent, but the distribution may be skewed by the inevitably small number of patient samples in the various studies. There is a preponderance of mutations in SLC7A9 in the Spanish population, but a higher percentage (55–75%) of mutations in SLC3A1 has been reported in other European populations

(UK, France, Eastern Europe) and an equal distribution has been found in the American population. Approximately 2% of patients have mutations in at least one copy of each gene, but stone formation only occurs if both copies of either gene are abnormal (Type AAB or ABB cystinuria). Mutations haven't been identified or just one mutant allele has been identified in approximately 5% of patients with cystinuria. To date, 241 mutations have been identified in SLC3A1 and 159 mutations in SLC7A9, including atypical cases for both genes, in the Human Gene Mutation Database.

Clinical trials:

The thiol drugs D-penicillamine and tiopronin are part of the standard treatment regimen for cystinuria, but they are associated with significant side effects, including allergic reactions, skin disorders, liver abnormalities, nephrotic syndrome, and blood disorders. Clinical trials are currently in progress aimed at reducing the side effects associated with cystinuria therapy (www.clinicaltrials.gov, accessed November 12, 2018). This include buccillamine, a thiol-binding drug developed from tiopronin (NCT02942420); tolcapton, a vasopressin antagonist which increases output of urine (NCT02538016); and α -lipoic acid, a nutritional supplement that has been shown to increase the cystine solubility in the Slc3a1 knockout mouse model for cystinuria (NCT02910531). The recently completed two clinical trials involved measurement of cystine supersaturation as an indicator of cystine stone recurrence (NCT02120105) and thus the connection between dosage of cystine concentration in the urine (NCT02125721) and cystine binding thiol drugs. An earlier trial involving a mixture of nine Asian Indian herbs collectively mentioned as Cystone didn't decrease urine cystine levels or stone burden in patients with cystinuria (NCT00381849).

Objective:

To estimate the effectiveness of l-cystine dimethyl ester (CDME) in a Slc3a1 knockout mouse model of cystinuria as it acts as an inhibitor of growth of cystine crystal, for the treatment of cystine urolithiasis.

Materials and Methods:

CDME (200 μ g per mouse) or water was delivered by gavage daily for four weeks. Highest doses by gavage or in the water supply were administered to estimate organ toxicity. Urinary amino acids and cystine stones were analyzed to estimate drug efficacy using several analytical methods.

Results:

Treatment with CDME led to a big decrease in stone size compared thereupon of the water group ($P = .0002$), but the amount of stones was greater ($P = .005$). The change in stone size distribution between the two groups was evident by micro computerized tomography. Overall, cystine excretion in urine was an equivalent between the two groups ($P = .23$), indicating that

CDME didn't interfere with cystine metabolism. Scanning microscopy analysis of cystine stones from the CDME group demonstrated a change in crystal habit, with numerous small crystals. l-cysteine methyl ester was detected by using instrument called Ultra Performance Liquid Chromatography-Mass Spectrometer in stones from the CDME group only, indicating that a CDME metabolite was incorporated into the crystal structure. No pathologic changes were observed at the doses tested.

Conclusion:

These data demonstrate that CDME promotes small stones formation but doesn't prevent stone formation, according to the hypothesis that CDME inhibits growth of cystine crystal. Combined with the shortage of observed adverse effects, our findings support the utilization of CDME as a viable treatment for cystine urolithiasis.