Amrik Sahota et al., Androl Gynecol: Curr Res 2017, 5:3
DOI: 10.4172/2327-4360-C1-005

L-cystine diamides as a novel therapy for cystinuria

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Background: Cystinuria is characterized by excessive excretion of cystine in the urine and cystine stones in the kidneys and, to a lesser extent, in the bladder. Cystine analogs such as cystine dimethylester (CDME) inhibit cystine crystal growth through binding to specific crystal surfaces, thus providing a novel therapeutic approach for cystinuria. We synthesized a series of L cystine diamides as cystine crystal growth inhibitors that would have greater stability and bioavailability compared with CDME. The most effective inhibitor to date is L cystine bis(N'-methylpiperazide), denoted LH708. Here, we evaluate the effectiveness of LH708 in inhibiting cystine stone formation in Slc3a1 knockout male mice, which serve as a model for cystinuria.

Methods: Mice age three months were screened for bladder stones by computed tomography (CT). Only mice that did not have stones were used for this study. Mice were treated with LH708 (150 μmol/kg) or water alone by stomach tube daily for 60 and CT scans were done on days 30 and 60. Bladder stone volume was determined using image analysis software.

Results: Nineteen mice were treated with LH708 and five of them showed stones at day 30. The same mice were stone-positive at day 60, and there was a significant increase in stone volume between the two scans (28.15 versus 64.70 mm^3, p=0.0005). Twenty-four mice were treated with water alone and 15 of them showed stones at day 30. Five of these mice died between the two scans, but an additional three were stone-positive at day 60. There was a significant increase in stone volume at the second scan (20.74 versus 52.67 mm^3, p=0.0001). Overall, 26% of mice formed stones in the LH708 group versus 75% in the water group.

Conclusion: These data strongly support the evaluation of LH708 as a potential therapy for cystinuria.

Biography

Amrik Sahota is a Professor in the Department of Genetics, Rutgers University, Piscataway, NJ. He is also a Clinical Professor in the Department of Pathology and Laboratory Medicine and in the Division of Urology, Department of Surgery, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ. He is a fellow of the American College of Medical Genetics and Genomics, National Academy of Clinical Chemistry, Royal Society of Biology (UK), and the Royal College of Pathologists (UK). He is board-certified in Clinical Molecular Genetics by the American Board of Medical Genetics and Genomics and in Molecular Diagnostics by the American Board of Clinical Chemistry. His research interests are in genetic disorders of urolithiasis, mouse models for human disease, and molecular diagnostics.

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