

CYSTINOSIS AND ITS TREATMENT

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Cystinosis is a rare inherited disease with an incidence, in developed countries, of about one case in every 200,000 live births. In the past, it was rare for cystinosis sufferers to survive into adulthood. The disease occurs when the mechanism that removes excess cystine breaks down. Cystine then accumulates within body cells preventing these cells from functioning correctly. This initially leads to kidney problems and progresses to other parts of the body, including the thyroid gland, eyes and liver. Impaired growth is yet another symptom of the condition. In this article, the condition and its treatment are described

Nephropathic cystinosis is a rare autosomal recessive disease with an annual incidence rate in Europe of between one in 115,000 and one in 179,000 live births.^{1,2} There are approximately 200 patients in the United Kingdom. The disease manifests itself in raised intracellular levels of the essential amino acid cystine to 50 to 100 times normal levels. Crystals of cystine are present in lysosomes, bone marrow aspirates, leukocytes, cornea and conjunctiva. The disease is characterised by poor growth, renal Fanconi syndrome (impairment in proximal tubule function), renal glomerular failure and involvement of other tissues and organs (see Panel 1).

Cystinosis is fatal if not treated and death occurs in the second decade of life. Treatment begun just after birth can attenuate the rate of renal failure. However glomerular damage present at the time of diagnosis (approximately one year) is irreversible and may result in the need for renal transplant. The condition has been recently reviewed.^{3,4}

Panel 1. Symptoms of cystinosis

- 1 Renal Fanconi syndrome (impairment in proximal tubular function)
- 1 Polyuria (excessive urination)
- 1 Polydipsia (excessive thirst)
- 1 Hypokalaemia (low levels K⁺)
- 1 Hypophosphataemia (low levels PO₄³⁻)
- 1 Crystals of cystine present in lysosomes, bone marrow aspirates, leukocytes, cornea and conjunctiva
- 1 Photophobia, headaches, burning or itching of eyes
- 1 Growth retardation, rickets, muscle myopathy
- 1 Central nervous system involvement, hypothyroidism
- 1 Hepatic and gastrointestinal complications

The disease is caused by a defect in the lysosomal transport mechanism for cystine and results from mutations in CTNS (cystine transport nephrotic syndrome), the gene on chromosome 17 which codes for the cystine transport protein, cystinosin.^{5,6} A number of mutations have been described, as well as a major deletion present in about 50 per cent of cystinosis patients of Western European ancestry (although cystinosis has been described in all major ethnic groups).

CURRENT TREATMENT

Treatment of cystinosis involves administration of glucose and electrolytes to reverse the effects of Fanconi syndrome, as well as corneal and renal transplant. Indomethacin is administered for its sodium, potassium and water retaining action.^{7,8} In some patients, carnitine is used to combat the effects of muscle weakness brought about by urinary loss of free carnitine and subsequent reduction in the transport of fatty acids into muscle tissue⁹ and human growth hormone is used to promote short- and long-term growth in short children with chronic renal failure.¹⁰ Growth hormone may also help improve growth velocity in children with nephropathic cystinosis¹¹ (Panel 2).

The number of medicines taken daily by a cystinosis patient is often considerable, especially when serious medical conditions such as epilepsy or diabetes, are present. These conditions may arise subsequent to

cystinosis, or may be unrelated to the condition. The daily drug regimen of a typical cystinotic patient is presented in Panel 3. This patient is post-transplant and is receiving, in addition to cysteamine and carnitine, treatment for epilepsy, diabetes and hypothyroidism.

The main drug treatment for cystinosis is administration of the aminothiols, cysteamine (mercaptamine, as the bitartrate salt, Cystagon). This compound acts to lower intracellular levels of cysteine by forming a cysteamine-cysteine mixed disulphide within cells, which is structurally similar to the amino acid lysine and can egress the lysosome using the pathway for lysine excretion (Figure 1).¹²

There are major problems, however, with administration of cysteamine. The molecule possesses an offensive taste and smell and irritates the gastrointestinal tract, leading to nausea and vomiting following administration. In addition, cysteamine is excreted in breath and sweat, which leads to halitosis and body odour. Furthermore, some patients exhibit more serious side effects, such as neutropenia. As a result of these problems, patient compliance is poor.

FUTURE TREATMENTS

In an attempt to overcome the problems associated with administration of cysteamine, two recent projects have been established at the University of Sunderland. A team led by Professor Geoff Rowley has attempted the formulation of cysteamine into a sustained release form.¹³ This, it is hoped, will minimise the gastric irritation experienced by patients taking large oral doses of cysteamine and improve patient compliance. A second, more radical approach, pioneered in our own laboratory

Panel 2. Treatments for cystinosis

- 1 Administration of electrolytes, glucose etc, to address imbalance
- 1 Regular renal dialysis
- 1 Renal transplant (requires immunosuppressant therapy)
- 1 Eye drops, corneal transplant
- 1 Indomethacin
- 1 Carnitine
- 1 Growth hormone

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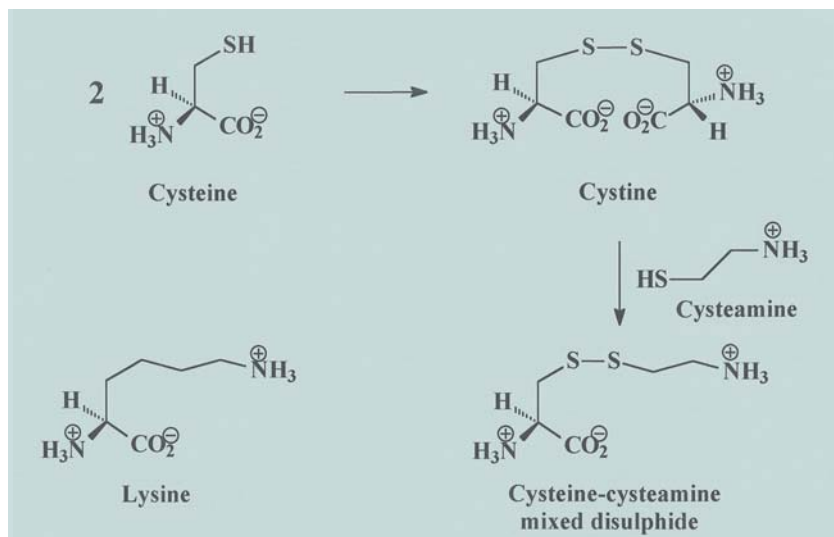


Figure 1: Structural similarity between (a) lysine and (b) cysteine-cysteine mixed disulphide

ries, has concentrated on the design and synthesis of prodrug derivatives of cysteamine. Prodrugs often exhibit desirable improvements over the parent drug, such as increased lipophilicity (which aids uptake

into cells) and improved pharmacokinetic and pharmacodynamic profiles.

We have already synthesised a small number of cysteamine prodrugs and determined their general cytotoxicity in cultures of exponentially growing Chinese hamster ovary cells.¹⁴ Preliminary results indicate that none of the prodrugs tested showed any cell toxicity up to a concentration of 100mM. These compounds are currently being evaluated for their ability to deplete cystine in cultured cystinotic cells. Such research offers hope for the future of cystinosis sufferers. If successful, the prodrug approach for cystinosis will target cysteamine to those cells that need it most, drastically reduce side effects and eliminate the need for repeated daily dosing. The development of prodrugs for cystinosis would be greatly facilitated should a pharmaceutical company decide to adopt this orphan disease.

The discovery of the CTNS gene offers the possibility of improved diagnosis for the

Panel 3. Daily drug regimen for a typical patient with cystinosis

Cysteamine bitartrate	750mg <i>tid</i>
Sodium valproate	500mg <i>bd</i>
Glibenclamide	2.5mg <i>od</i>
Thyroxine	50 mg <i>tid</i> alternate days
Clobazam	10mg <i>bd</i>
Prednisolone	15mg <i>od</i> alternate days
Ciclosporin	0.9ml <i>bd</i>
L-Carnitine	500mg <i>tid</i>
BreathAssure	4 caps <i>tid</i>

This patient is post-transplant and is receiving, in addition to cysteamine and carnitine, treatment for epilepsy, diabetes and hypothyroidism

disease (through mutation detection) and work is under way in Europe and in the United States to establish a knock-out mouse model (an animal with an engineered genetic defect that results in it displaying the symptoms of cystinosis). Study of cystinosis has long suffered from the lack of a naturally occurring animal model. A “mouse with cystinosis” will enable novel therapies to be evaluated quickly. The most far ranging and potentially exciting use for these animals is as a target for gene therapy. Once the mouse model has been developed, work can begin on correcting the defect using a proper functioning CTNS gene. Successful genetic correction of kidney dysfunction in the cystinotic mouse would be a necessary preamble to developing gene therapy for human patients with cystinosis (J. G. Thoene, personal communication).

USEFUL WEBSITES

Cystinosis Foundation UK
www.cystinosis.org.uk

Cystinosis Foundation USA
www.cystinosis.com

Cystinosis Research Network
www.cystinosis.org

Children Living with Inherited Metabolic Diseases (CLIMB)
www.climb.org.uk

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