

# Enteric-Coated Cysteamine Bitartrate for the Treatment of NAFLD in Children



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## ABSTRACT

**Background.** Non-alcoholic fatty liver disease (NAFLD) is common in children. Hepatic fat accumulation and oxidative stress contribute to its pathogenesis. The thiol agent cysteamine bitartrate (Cystagon®) readily crosses cellular membranes and is FDA approved for the treatment of the lysosomal storage disorder cystinosis. Cysteamine is a scavenger of reactive oxygen species and a potent antioxidant through increased intracellular glutathione production.

**Aim.** Evaluate the safety and potential efficacy of enteric-coated (EC) cysteamine therapy for NAFLD in children.

**Method.** Children >10 y with biopsy proven NAFLD and elevated ALT were treated with twice-daily EC-Cysteamine for 6 months. Drug dosage was increased as tolerated over 9d to maximum (1000mg). Monthly physical examination, AST/ALT, weight/ body mass index (BMI). Subjects with >50% sustained reduction in ALT reached end-point for the study. GI symptom scores (maximum score 14) were measured.

**Results.** 11 of 13 children (11-17y, mean 14.0y) were enrolled and completed EC-Cysteamine therapy (final dose range 200-1000mg, mean 695mg or 7.6mg/kg body weight /dose). For these 11 patients the mean ALT levels at baseline and after 6 months EC-Cysteamine were 120.2 and 54.5 iu/l, respectively (p<0.004), and for AST levels were 60.3 and 35.7 iu/l, respectively (p=0.02). Of the 11 subjects, primary end-point was reached in 7 and normalization of ALT/AST levels in 6. The mean BMI was 34.5 at baseline and 34.2 kg/m<sup>2</sup> after treatment (p=0.37). Although the mean symptom scores at baseline (1.1) and after 6 months EC-Cysteamine (0.7) were similar, some patients did initially report mild GI symptoms which either resolved spontaneously or with dose reduction. No major adverse events were reported.

**Conclusions.** EC-Cysteamine reduces ALT and AST levels in children with NAFLD without reduction in BMI. Transient GI symptoms may be due to rapid initial drug dosing. Further studies are required to evaluate optimal cysteamine dose and effect on liver histology in NAFLD patients.

## BACKGROUND

Non-alcoholic fatty liver disease (NAFLD) is the commonest cause of chronic liver disease in North America, representing a spectrum of histologic abnormalities which are characterized by the finding of a predominantly macrovesicular hepatic steatosis. The pathogenesis of NAFLD is unclear, but, insulin resistance plays a primary role and patients will often have underlying metabolic syndrome (including obesity, diabetes and hypertriglyceridemia). Whereas insulin resistance plays an important role in the development of steatosis, exactly how NASH arises is unclear, but, does involve oxidative stress through the excessive production of reactive oxygen species (ROS) or decreased anti-oxidant activity.

The thiol agent cysteamine is a potent anti-oxidant agent and most likely induces intracellular glutathione production. Cysteamine effectively traverses the cellular membranes and is FDA approved for the treatment of the intra-lysosomal storage disease cystinosis. Previously cysteamine was shown to be hepato-protective following acetaminophen toxicity. The formulation of commercially available cysteamine (Cystagon®) was recently altered in order to reduce the frequency of drug ingestion and possible upper gastrointestinal adverse events. In this pilot study we determine the effect the new formulation, EC-cysteamine, on specific markers in children NAFLD.

## METHODS

### Subjects and screening

Children >10 years with biopsy-proven NAFLD and an ALT level of 50 iu/l or above, who have undertaken lifestyle changes (such as diet and exercise) for at least three months, were recruited from the Pediatric Gastroenterology, Hepatology and Nutrition database. The study was approved by an IRB at UCSD and written assent/consent was obtained from all subjects/guardians. Subjects were evaluated at the General Clinical Research Center, UCSD.

	NAS	EC-Cysteamine Dose in mg (twice daily)	BMI (kg/m <sup>2</sup> )		ALT iu/l		AST iu/l		Cytokeratin 18 U/L		Adiponectin ug/mL	
			Pre Drug	Post Drug	Pre Drug	Post Drug	Pre Drug	Post Drug	Pre Drug	Post Drug	Pre Drug	Post Drug
01	4	1000	34.4	31.8	55	18	39	17	226	218	8.1	7.9
04	6	1000	32.5	32.1	286	137	121	55	2345	1120	7.2	10.3
09	5	200	24	24.8	61	23	48	26	218	224	14.4	14.2
10	4	900	48.3	49.8	122	92	67	53	1744	1829	7.8	6.8
11	5	450	26.2	25.6	133	38	64	26	695	151	8.9	14.3
12	3	1000	36	36.5	113	28	56	20	858	189	6.1	10.1
13	3	900	36.1	35.9	85	53	44	33	699	408	8.1	9.1
14	6	300	28.8	27.9	70	72	43	37	662	837	11.1	16.5
15	4	300	26.3	26.7	102	40	49	27	826	293	2.7	8.4
19	3	1000	37.8	36.9	88	52	54	77	1829	743	3.8	4.2
20	5	600	49.3	48.1	207	46	78	22	810	190	8.2	11.0
MEAN		695	34.5	34.2	120.2	54.5	60.3	35.7	992	546	7.8	10.3

Table. Patient characteristics with changes in BMI, AST/ALT, cytokerin 18 and adiponectin levels compared with baseline following treatment with EC-Cysteamine for 6 months. Serum levels of cytokerin 18 decreased and those of adiponectin increased following treatment with EC-cysteamine.

### Treatment and Monitoring

Cystagon® (Mylan, West Virginia) was enterically-coated with Eudragit® at The Coating Place, WI., resulting in capsule dispersion at intestinal pH 5.5-6. EC-cysteamine dosage was started at 300mg bid and increased as tolerated over 9 days to a maximum of 1000mg bid for a total of 6 months treatment. Vital signs, weight/body mass index, ALT/AST values were measured monthly. Markers of oxidative stress and fibrosis were measured before and after treatment. Subjects also received monthly diet and exercise advice from a nutritionist.

Common upper GI symptoms, included heartburn, pain, nausea and vomiting, were monitored using a 7-point symptom score (maximum score 14). Halitosis and body odor were also recorded.

Subjects who had ≥50% reduction from baseline or normalization (according to age) of ALT reached primary end-point for the study. After completion of treatment with EC-cysteamine, subjects were reassessed every 2 months with ALT/AST, weight/body mass index and physical examination for a further 6 months.

## RESULTS

Thirteen of 20 children screened for this study were enrolled. Data from 11 subjects (mean age 14.0 years, 10 male), who completed 6 months of treatment, was used in the final analysis. There were 7 Hispanics, 3 Caucasian, 1 Asian-Pacific

In four subjects, the dose of EC-cysteamine was increased to 1000 mg, the remaining subjects remained on lower doses (range 200 and 900 mg bid) as tolerated. See Table.

The mean ALT levels at baseline and after 6 months of treatment were 120.2 and 54.5 iu/l, respectively (p<0.004), and for AST the levels were 60.3 and 35.7 iu/l, respectively (p=0.02). Primary end-point was reached in 7 subjects and normalization of ALT and/or AST levels in 6 subjects. Following EC-cysteamine therapy, 10 patients completed monitoring to the end of the study and had mean ALT and AST levels of 73.9 and 38.7 iu/l. The mean BMI values were 34.5 at baseline, 34.2 after 6months EC-cysteamine treatment and 35.1 kg/m at the end of the study.

Initially, some mild upper GI symptoms were reported. Most symptoms resolved spontaneously or with dose reduction and were attributed to the rapid initial dose increase. The mean symptom scores at baseline and after 6 months EC-Cysteamine were 1.1 and 0.7, respectively. Some patients experienced body odor and/or halitosis. Three patients were lost to follow-up during the study.

In NAFLD, serologic levels of cytokerin 18 are elevated and those of adiponectin are decreased. The changes of these serologic marker levels are shown in the Table.

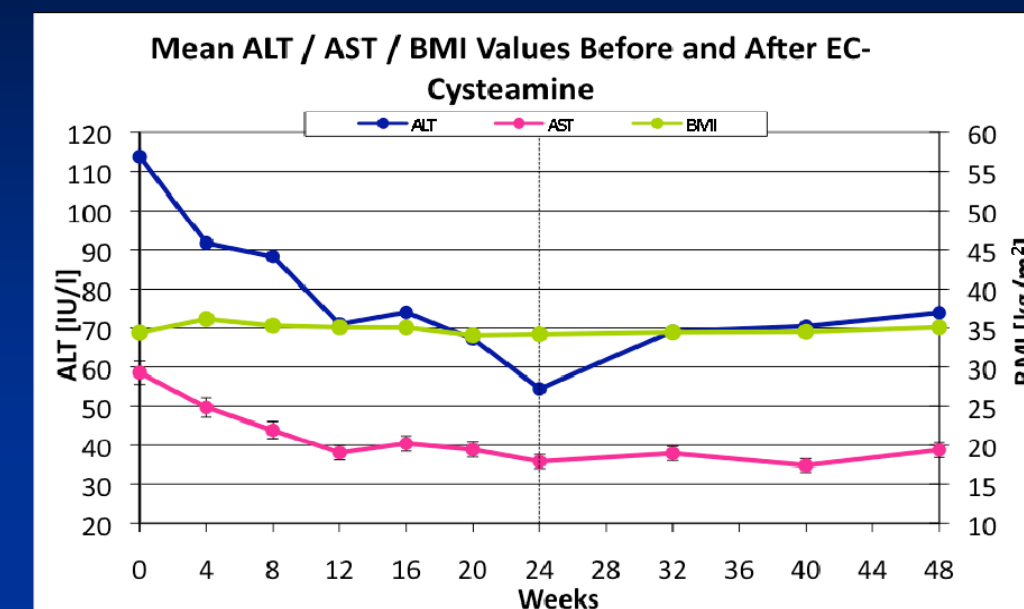


Figure. Mean ALT and AST levels during EC-cysteamine therapy (0-24 weeks, N=11) and after therapy (24-48 weeks, N=10). There was no significant change in mean BMI.

## CONCLUSIONS

1. EC-cysteamine, taken twice daily for 6 months, reduces ALT and AST levels in most of the pediatric subjects with NAFLD.
2. Cytokeratin 18 levels decreased and adiponectin levels increased in response to EC-Cysteamine therapy.
3. The reduction in mean AST was sustained for 6 months after completing EC-cysteamine therapy.
4. Transient GI symptoms reported resolved with or without EC-Cysteamine dose reduction. Symptoms were most likely due to rapid initial drug dosing to maximal levels.

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