



## Brief Communication

## Halitosis in cystinosis patients after administration of immediate-release cysteamine bitartrate compared to delayed-release cysteamine bitartrate

Martine Besouw<sup>a,\*</sup>, Albert Tangerman<sup>b</sup>, Elisabeth Cornelissen<sup>c</sup>, Patrice Rioux<sup>d</sup>, Elena Levtchenko<sup>a</sup><sup>a</sup> Department of Pediatric Nephrology, University Hospitals Leuven, Herestraat 49, 3000 Leuven, Belgium<sup>b</sup> Center for Dentistry and Oral Hygiene, Department of Periodontology, University of Groningen, University Medical Center Groningen, P.O. Box 30.001, 9700 RB Groningen, The Netherlands<sup>c</sup> Department of Pediatric Nephrology, Radboud University Nijmegen Medical Centre, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands<sup>d</sup> Raptor Pharmaceutical Corporation, 9 Commercial Blvd, Suite 200 Novato, CA 94949, USA

## ARTICLE INFO

## Article history:

Received 7 June 2012

Received in revised form 27 June 2012

Accepted 27 June 2012

Available online 6 July 2012

## Keywords:

Cysteamine

Cystinosis

Dimethylsulfide

Halitosis

## ABSTRACT

Halitosis due to dimethylsulfide (DMS) generation is a major side effect of cysteamine in the treatment of cystinosis. Recently, an enteric coated formulation of cysteamine bitartrate (RP103) administered twice daily was demonstrated to be non-inferior for lowering WBC cystine levels compared to the non-enteric coated formulation (Cystagon®), administered 4 times per day. Since both formulations had different pharmacokinetic profiles, we compared DMS breath levels after administration of either RP103 or Cystagon® in four cystinosis patients. Although cysteamine areas under the curve (AUCs) were comparable, AUC of DMS was lower after the administration of RP103 compared to Cystagon®. This observation is of importance in cystinosis patients, since halitosis hampers compliance with cysteamine therapy.

© 2012 Elsevier Inc. All rights reserved.

## 1. Introduction

Cystinosis is a lysosomal storage disease caused by mutations in the *CTNS* gene, encoding the lysosomal cystine transporter cystinosin. Mutations result in intralysosomal cystine accumulation in all tissues. Patients generally present within the first year of life with generalized proximal tubular damage (called renal Fanconi syndrome), resulting in polyuria, polydipsia and failure to thrive. If untreated, the disease progresses to end-stage renal disease around the age of 10 years. As cystine accumulates in all cells throughout the body, extra-renal organs are also affected, including the eyes, various endocrine organs, muscles and the central nervous system [1].

Cystinosis is treated by the administration of cysteamine. The drug enters the lysosome through a yet unknown transporter. Once inside, it cleaves the accumulated cystine resulting in the formation of cysteine and cysteine–cysteamine disulfide. The first can exit the lysosome via the cysteine transporter, the latter uses a yet unidentified cationic amino acid transporter [1]. The currently most widely used formulation of the drug is cysteamine bitartrate (trade name Cystagon®, Mylan Pharma, USA). The cystine depleting effect of the drug lasts no longer than 6 h, and the drug should be administered 4 times

per day [2]. In 2007 it was demonstrated that cysteamine administration directly into the small intestine led to higher cysteamine plasma levels with higher area under the curve (AUC), compared to gastric administration [3]. These findings prompted the development of an enteric coated formulation of cysteamine bitartrate, called RP103 (Raptor Pharmaceutical Corporation, USA), which can be administered twice daily [4,5]. Recently, a phase III clinical trial comparing the effect of the enteric coated RP103 on white blood cell cystine levels with Cystagon® was completed. The results demonstrated non-inferiority of RP103 compared to Cystagon® for lowering WBC cystine levels, even with an average total daily steady-state dose of RP103 that was 82% of the established dose of Cystagon® [6].

Next to the necessity to administer Cystagon® 4 times daily, the compliance with cysteamine therapy is further hampered by the fact that the administration of cysteamine causes halitosis. In 2007 we showed that halitosis after Cystagon® administration is caused by the metabolism of approximately 3% of the total amount of ingested cysteamine into dimethylsulfide (DMS) and, although to a lesser extent, methanethiol (MT) [7]. Since the new, enteric coated formulation of cysteamine bitartrate has a different pharmacokinetic profile, we studied the amount of DMS in expired air after ingestion of RP103 compared to Cystagon®.

## 2. Patients and methods

Four patients who participated in the phase III clinical trial with RP103 were included (Table 1) [6]. Their age ranged between 11 and 13 years, glomerular filtration rate (GFR) is between 49 and

Abbreviations: AUC, area under the curve; DMS, dimethylsulfide; MT, methanethiol; GFR, glomerular filtration rate; HPLC, high-performance liquid chromatography.

\* Corresponding author. Fax: +32 16 343842.

E-mail addresses: [martine.besouw@uzleuven.be](mailto:martine.besouw@uzleuven.be) (M. Besouw), [atangerman@hotmail.com](mailto:atangerman@hotmail.com) (A. Tangerman), [m.cornelissen@cukz.umcn.nl](mailto:m.cornelissen@cukz.umcn.nl) (E. Cornelissen), [prioux@raptorpharma.com](mailto:prioux@raptorpharma.com) (P. Rioux), [elena.levtchenko@uzleuven.be](mailto:elena.levtchenko@uzleuven.be) (E. Levtchenko).

**Table 1**  
Patients' characteristics and test results.

Pt	Sex	Age (years)	GFR (mL/min/1.73 m <sup>2</sup> )	Daily cysteamine dose (g/m <sup>2</sup> )		WBC cystine level (nmol 1/2 cystine/mg protein)		Cysteamine AUC (mg·h/L)		DMS AUC (nmol·h/L)	
				Cystagon®	RP103	Cystagon®	RP103	Cystagon®	RP103	Cystagon®	RP103
1	M	13	89.7	1.3	1.2	0.6	0.2	1.2	1.5	16.3	8.2
2	M	11	161.7	1.5	1.5	0.2	0.3	0.7	0.5	5.3	2.6
3	M	20	53.5	1.3	1.2	0.3	0.7	1.3	1.2	8.8	4.4
4	M	15	49.0	1.7	1.5	0.7	1.6	0.5	0.5	2.5	1.2

162 (normal >90) mL/min/1.73 m<sup>2</sup>, and all patients were male. Breath samples were collected in balloons as described before [7] and were measured on the same day. Samples of 1.0 mL breath air were extracted with plastic containers and subsequently measured with the portable gas chromatograph OralChroma™ (Abilit Corporation, Japan) [8]. For Cystagon®, breath samples were collected before administration and at 30 min, 1, 2, 3, 4 and 6 h thereafter. For RP103, breath samples were collected before administration and at 1, 2, 3, 4, 5, 6, 8, 10 and 12 h thereafter. Cysteamine plasma levels were measured at the same time points using reversed-phase high-performance liquid chromatography (HPLC). The AUC was calculated using the trapezoid rule. The Wilcoxon signed-rank test was used for statistical analysis, and values were considered statistically significant at  $p < 0.05$ .

### 3. Results

The results of cysteamine plasma measurements and DMS breath measurements are shown in Fig. 1 and Table 1. The median daily dose of cysteamine was 1.43 (range 1.27–1.74) g/m<sup>2</sup> under Cystagon® and 1.33 (range 1.15–1.53) g/m<sup>2</sup> under RP103. No statistical significant difference was observed between white blood cell cystine levels after Cystagon® (median 0.5, range 0.2–0.7 nmol 1/2 cystine/mg protein) and RP103 (median 0.5, range 0.2–1.6 nmol 1/2 cystine/mg protein), and between cysteamine plasma AUC after Cystagon® (median 1.0, range 0.5–1.3 mg·h/L) and RP103 (median 0.8, range 0.5–1.5 mg·h/L). The median DMS AUC under Cystagon® was 7.0 (range 2.5–16.3) nmol·h/L and median DMS AUC under RP103 was 3.5 (range 1.2–8.2)

nmol·h/L ( $p = 0.068$ ). In all studied patients a decrease in DMS breath levels was found after administration of RP103, compared to Cystagon®. The patients with the highest DMS AUC showed the most prominent decrease. MT was detected in small amounts in only 2 patients, and in the remaining two patients MT levels were undetectable.

### 4. Discussion

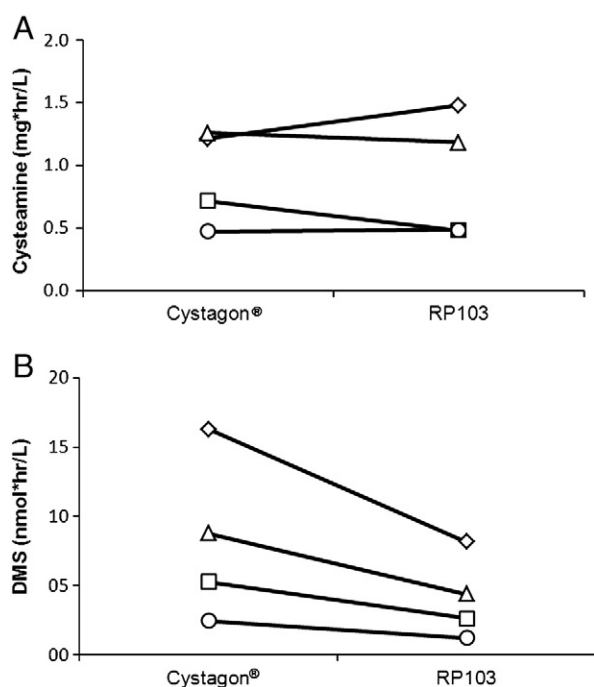
Recently, a phase III clinical trial has proved non-inferiority of the enteric coated RP103 compared to Cystagon® in lowering white blood cell cystine levels [6]. Since halitosis remains a major problem after the administration of cysteamine, we performed a study in 4 patients to compare the excretion of DMS and MT in expired air after ingestion of either compound. DMS AUC was lower after ingestion of RP103 in all studied patients, although the difference was not statistically significant. In line with previous results, the peak of cysteamine plasma levels preceded the peak of DMS breath levels by approximately 1 h [7]. The threshold level to cause an objectionable smell is 0.5 nmol/L for MT and 1.0 nmol/L for DMS [9]. The threshold for MT was crossed only occasionally in 2 patients. In contrast, DMS breath levels were above the threshold at every time point in all studied patients. Therefore, it is obvious that halitosis in these patients is caused by DMS.

Since the difference in DMS AUC did not reach statistical significance in this small cohort, DMS excretion should be further analyzed in a larger population. Whether patients indeed subjectively experience less annoyance with bad breath under RP103 treatment compared to Cystagon®, should be further evaluated in a larger group. Unfortunately, there is still no way to further diminish DMS excretion or to mask its odor. However, in the phase III trial, several patients could be treated with lower total daily doses of cysteamine if treated with RP103 [6]. This would decrease cysteamine peak levels in plasma, which in turn will cause a decrease in peak DMS breath levels and will thus result in a further decline of DMS AUC.

In conclusion, we demonstrate that the administration of RP103 results in a trend towards less DMS excretion, with equal cysteamine AUC compared to Cystagon®. This observation is of importance for improving compliance with cysteamine therapy in cystinosis patients.

### References

- [1] W.A. Gahl, J.G. Thoene, J.A. Schneider, Cystinosis, *N. Engl. J. Med.* 347 (2002) 111–121.
- [2] E.N. Levtchenko, C.M. van Dael, A.C. de Graaf-Hess, M.J. Wilmer, L.P. van den Heuvel, L.A. Monnens, H.J. Blom, Strict cysteamine dose regimen is required to prevent nocturnal cystine accumulation in cystinosis, *Pediatr. Nephrol.* 21 (2006) 110–113.
- [3] M.C. Fidler, B.A. Barshop, J.A. Gangoiti, R. Deutsch, M. Martin, J.A. Schneider, R. Dohil, Pharmacokinetics of cysteamine bitartrate following gastrointestinal infusion, *Br. J. Clin. Pharmacol.* 63 (2007) 36–40.
- [4] J.A. Gangoiti, M. Fidler, B.L. Cabrera, J.A. Schneider, B.A. Barshop, R. Dohil, Pharmacokinetics of enteric-coated cysteamine bitartrate in healthy adults: a pilot study, *Br. J. Clin. Pharmacol.* 70 (2010) 376–382.
- [5] R. Dohil, M. Fidler, J.A. Gangoiti, F. Kaskel, J.A. Schneider, B.A. Barshop, Twice-daily cysteamine bitartrate therapy for children with cystinosis, *J. Pediatr.* 156 (2010) 71–75.
- [6] C.B. Langman, L.A. Greenbaum, M. Sarwal, P. Grimm, P. Niaudet, G. Deschenes, E. Cornelissen, D. Morin, P. Cochat, D. Matossian, S. Gaillard, M.J. Bagger, P. Rioux, A randomized controlled crossover trial with delayed-release cysteamine bitartrate



**Fig. 1.** Area under the curve of cysteamine plasma levels (A) and DMS breath levels (B) after ingestion of Cystagon® or RP103 in 4 cystinosis patients.

- in nephropathic cystinosis: effectiveness on white blood cell cystine levels and comparison of safety, *Clin. J. Am. Soc. Nephrol.* 7 (2012) 1112–1120.
- [7] M. Besouw, H. Blom, A. Tangerman, A. de Graaf-Hess, E. Levtchenko, The origin of halitosis in cystinotic patients due to cysteamine treatment, *Mol. Genet. Metab.* 91 (2007) 228–233.
- [8] A. Tangerman, E.G. Winkel, The portable gas chromatograph OralChroma: a method of choice to detect oral and extra-oral halitosis, *J. Breath Res.* 2 (2008) 017010.
- [9] A. Tangerman, E.G. Winkel, Intra- and extra-oral halitosis: finding of a new form of extra-oral blood-borne halitosis caused by dimethyl sulphide, *J. Clin. Periodontol.* 34 (2007) 748–755.