Brief Communication

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

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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 unidentified transporter. Once inside, it cleaves the accumulated cystine resulting in the formation of cysteine and cysteine–cysteine 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]. This finding prompted the development of a enteric coated formulation of cysteamine bitartrate (RP103), 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
Breath samples were collected in balloons as described before [7] and values were considered statistically significant. Cysteamine plasma levels preceded the peak of DMS breath levels 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


