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Pharmacokinetics of enteric-coated cysteamine bitartrate in healthy adults: a pilot study

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Cysteamine bitartrate is taken lifelong, every 6 h and for the treatment of cystinosis. Recent studies using cysteamine for for other diseases such as neurodegenerative disorders adopt the same dosing regimen for cysteamine. Regular cysteamine bitartrate (Cystagon) may cause upper gastrointestinal symptoms in some patients.

WHAT THIS STUDY ADDS

- This is the only study that provides pharmacokinetic data for cysteamine delivered in an enteric-release preparation in normal subjects. EC-cysteamine is very well tolerated and does not cause increased gastrin concentrations, even at relatively high doses.
- EC-cysteamine at the higher dose results in better drug uptake as measured by C_{max} and AUC and is more likely to be effective.

AIMS

Cysteamine bitartrate (Cystagon®) is the approved treatment for cystinosis. Poor compliance and patient outcome may occur because the drug needs to be taken every 6 h and in some patients causes gastrointestinal symptoms due to hypergastrinaemia. A formulation of cysteamine requiring twice daily ingestion would improve the quality of life for these patients. This study compares the pharmacokinetics and gastrin production following cysteamine bitartrate non-enteric-coated and cysteamine bitartrate enteric-coated in normal healthy subjects.

METHODS

Enteric-coated cysteamine was prepared. Following single doses of cysteamine bitartrate non-enteric-coated 450 mg and cysteamine bitartrate enteric-coated 450 mg and 900 mg, serial plasma cysteamine and gastrin concentrations were measured. Two subjects also received cysteamine bitartrate non-enteric-coated 900 mg. Gastrointestinal (GI) symptoms were recorded.

RESULTS

Six healthy adults (mean age 20.7 years, range 18–24 years; mean weight 59.3 kg) received drug. All post-dose gastrin concentrations were within the normal range (<100 pg ml^{-1}). The t_{max} following cysteamine bitartrate non-enteric-coated (mean and SD is 75 ± 19 min) was shorter than cysteamine bitartrate enteric-coated (220 ± 74 min) ($P = 0.001$), but only the C_{max} and AUC estimates following 900 mg cysteamine bitartrate enteric-coated were significantly greater than any of the other preparations or doses ($P < 0.05$). One patient had GI symptoms following both 900 mg cysteamine bitartrate non-enteric-coated and cysteamine bitartrate enteric-coated.

CONCLUSION

Although patient numbers were low, single high doses of cysteamine bitartrate enteric-coated were better tolerated than similar doses of cysteamine bitartrate non-enteric-coated in the healthy subjects and all had normal gastrin concentrations. The delayed t_{max} following cysteamine bitartrate enteric-coated suggested that the cysteamine was released enterically.

Introduction

Nephropathic cystinosis is a rare autosomal recessive disease caused by abnormal intra-lysosomal accumulation of the amino acid cystine within various tissues [1]. Without treatment patients will develop end-stage renal failure, usually before 10 years of age, and may require renal transplantation. Cysteamine bitartrate (Cystagon®, Mylan, Morgantown, WV) lowers intracellular cystine concentrations by reacting with intra-lysosomal cystine to form the mixed disulfide of cysteamine and cysteine, which then leaves the lysosome via the lysine transport system [2]. Regular treatment with cysteamine has been shown to improve growth and to reduce the rate of progression of renal and thyroid failure in children with cystinosis [3, 4].

White blood cell (WBC) cystine concentrations estimate body cystine concentrations and are used to monitor efficacy of cysteamine therapy in patients with cystinosis. The long-term outcome for these patients is improved by maintaining low intracellular cystine concentrations which is achieved by taking cysteamine bitartrate non-enteric-coated every 6 h throughout the day [5, 6]. This dosing regimen impedes quality of life and not surprisingly contributes to poor long-term compliance with therapy, particularly in adolescents and adults [5]. Cysteamine bitartrate may also cause upper gastrointestinal symptoms in some patients with cystinosis and this may arise through gastrin-mediated gastric acid-hypersecretion [7–9].

A recent study showed that the maximum plasma cysteamine concentration (C_{max}) was achieved when drug was directly delivered through a naso-enteric tube into the small intestine (SI) as compared with the stomach and colon in both cystinosis patients and normal controls [10, 11]. As a result, WBC cystine concentrations remained depressed longer in subjects with cystinosis. From that study we hypothesized that targeted enteric delivery of oral cysteamine bitartrate would prolong drug effectiveness and hopefully necessitate fewer daily doses [10].

In this study we report the pharmacokinetics of cysteamine bitartrate non-enteric-coated and a cysteamine bitartrate enteric-coated in normal control subjects and show that, at equivalent doses, the plasma cysteamine C_{max} and AUC for both formulations are similar to that obtained in the previous enteric-tube study [11].

Methods

The University of California at San Diego (UCSD) Human Research Protection Program approved this study. Informed consent was obtained. Study subjects were admitted to the UCSD, General Clinical Research Center.

Subjects

Six healthy adults (two male, four female) with a mean age of 20.7 years (range 18–24 years) and a mean weight of 59.3 kg (range 52.0–66.4 kg) were enrolled. Subjects were asked to discontinue acid suppressants, antibiotics, non-steroidal anti-inflammatory drugs, pro-kinetic agents and anti-histamines 2 weeks prior to admission. Baseline chemistry, *Helicobacter pylori* serology, complete blood count and urinalysis were performed upon admission. Serum pregnancy tests were performed for women.

All doses of cysteamine bitartrate non-enteric-coated and cysteamine bitartrate enteric-coated are expressed as base.

Enteric-coated cysteamine bitartrate

Cysteamine bitartrate non-enteric-coated capsules normally disperse within the stomach. The capsules (150 mg) were coated with Eudragit L30D 55 (Rohm GmbH & Co KG, Germany), triethylcitrate and hydroxypropylmethylcellulose so that they would disperse in the small intestine at pH 5.5–6. The coating took place at The Coating Place Inc. (Verona, WI) using a Model 600 Wurster coating unit.

Samples of the coated capsules were tested before use and remained intact in 0.1N HCl at 37°C for 2 h, but readily dissolved within 30 min when placed into $NaHCO_3$ solution at pH 6.8 and 37°C.

Study outline

Following an overnight fast, except for water, subjects received a single dose of cysteamine bitartrate non-enteric-coated 450 mg (day 1), cysteamine bitartrate enteric-coated 450 mg (day 2) and cysteamine bitartrate enteric-coated 900 mg (day 3). Patients remained fasted for 4 h after drug ingestion. Two patients (DB and AB) also received cysteamine bitartrate non-enteric-coated 900 mg on day 4. Following drug ingestion blood samples were taken for plasma cysteamine concentrations (at baseline, 15, 30, 45, 60, 75, 90, 105, 120, 135, 150, 165, 180 min, and 3.5, 4, 4.5, 5, 6, 8, 10, and 12 h) and for serum gastrin concentrations (at baseline, 0, 30, 60, 90, 120 min, 3 h and 4 h). Gastrin (pg ml^{-1}) was measured using the Diagnostic Products Corporation (Los Angeles, Calif) gastrin^{125} radioimmunoassay-kit. The coefficients of variation for gastrin vary with blood concentration and range from 6.8% at 50 pg ml^{-1}, 6% at 110 pg ml^{-1} to 4% at 331 pg ml^{-1}. Plasma cysteamine was measured using tandem mass spectroscopy (API 4000 LC/MS/MS; Applied Biosystems, Foster City, California) with previously described methods [8, 12]. For cysteamine, the recovery, precision and linearity were established over an analytical measurement range) from 1 to 150 µmol l^{-1}; at 1 µmol l^{-1} the CV was 4.8%.

Statistical analysis

Mixed model restricted maximum likelihood (REML) repeated measures analyses of variance with subjects as a random effect were performed on plasma cysteamine pharmacokinetic parameters (t_{max}, C_{max} and AUC) and contrasts were used to test differences between means for the

drug administrations (SAS Software, version 9.2 – Cary, NC). The basic idea behind REML estimation is to find the set of weights for the random effects in the model that minimize the negative of the natural logarithm times the likelihood of the data (the likelihood of the data can vary from 0 to 1, so minimizing the negative of the natural logarithm times the likelihood of the data amounts to maximizing the probability, or the likelihood, of the data). The statistical analysis of random effects is accomplished by using the random effect model, if all of the independent variables are assumed to have random effects, or by using the mixed model, if some of the independent variables are assumed to have random effects and other independent variables are assumed to have fixed effects. A significant difference was defined when $P < 0.05$.

Results

Subjects

Baseline chemistry, *Helicobacter pylori* serology, complete blood count and urinalysis were normal in all subjects. All subjects remained asymptomatic except subject 5 who had a single episode of emesis 3.5 h after receiving cysteamine bitartrate enteric-coated 900 mg. The same patient, 1 h after taking cysteamine bitartrate non-enteric-coated 900 mg, felt very nauseous and vomited forcefully, and 45 min later appeared pale and lethargic. The lethargy and pallor lasted 1 h and there were no reported haemodynamic changes.

Gastrin concentrations

These remained within normal limits (<100 pg ml^{-1}) in all subjects. Of 135 gastrin measurements, 84 (64%) were reported below the detectable concentration of <25 pg ml^{-1} and so the midpoint level of 12.5 pg ml^{-1} was used for statistical calculations. The mean gastrin concentrations for all measurements from all subjects on days 1, 2, 3 and 4 were 19.8 (95% CI 16.7, 22.9), 18.4 (95% CI 15.2, 21.7), 16.3 (95% CI 14.1, 18.6) and 26.2 pg ml^{-1} (95% CI 21.6, 30.9), respectively. There was a statistical difference in gastrin concentrations following cysteamine bitartrate non-enteric-coated 900 mg *vs.* other forms or dosages ($P < 0.01$), but no significant difference between other forms or dosages (Table 1).

Cysteamine pharmacokinetics

The mean and SD for t_{max} following 450 mg cysteamine bitartrate non-enteric-coated (75 ± 19 min, 95% CI 55, 95 min) was significantly shorter than from 450 mg cysteamine bitartrate enteric-coated (220 ± 74 min, 95% CI 142, 298 min) ($P < 0.001$) and 900 mg cysteamine bitartrate enteric-coated (255 ± 78 min, 95% CI 173, 337 min) ($P < 0.001$). The t_{max} values after 450 mg and 900 mg cysteamine bitartrate enteric-coated were not significantly different ($P = 0.469$).

The plasma cysteamine profiles, individual and mean, for the six subjects receiving varying doses of cysteamine bitartrate non-enteric-coated and cysteamine bitartrate enteric-coated are shown in Figure 1A, B. These figures show that mean and SD for plasma cysteamine C_{max} concentrations estimated from all subjects were not significantly different between cysteamine bitartrate non-enteric-coated 450 mg (40.4 ± 15.8 μM, 95% CI 23.8, 57.0 μM) and cysteamine bitartrate enteric-coated 450 mg (41.6 ± 18.8 μM, 95% CI 21.9, 61.3 μM) ($P = 0.832$). The C_{max} after cysteamine bitartrate enteric-coated 900 mg (84.2 ±

Table 1

Gastrin concentrations following cysteamine bitartrate non-enteric-coated and cysteamine bitartrate enteric-coated. Mean gastrin concentrations were calculated from measurements every 30–60 min for 4 h after drug ingestion. Normal gastrin concentrations are <100 pg ml^{-1}. One subject vomited 1 h after receiving cysteamine bitartrate non-enteric-coated 900 mg (gastrin concentration 37 pg ml^{-1}) and 3.5h after receiving cysteamine bitartrate enteric-coated 900 mg (gastrin concentration 29 pg ml^{-1} at 3 h and 33 pg ml^{-1} at 4 h)

Formulation and dosage (number of patients)	Mean gastrin concentration (pg ml^{-1}) (number of specimens)	Standard deviation for gastrin	Cysteamine bitartrate enteric-coated 450 mg (SE)	Cysteamine bitartrate enteric-coated 900 mg (SE)	Cysteamine bitartrate non-enteric-coated 450 mg (SE)	Cysteamine bitartrate non-enteric-coated 900 mg (SE)
Cysteamine bitartrate non-enteric-coated 450 mg (*n* = 6)	19.8 (39)	9.7	—	***P* = 0.01 (2.78)	**P* = 0.38 (1.85)	**P* = 0.53 (1.83)
Cysteamine bitartrate non-enteric-coated 900 mg (*n* = 2)	26.2 (14)	8.1	—	—	***P* = <0.002 (2.77)	***P* = 0.0001 (2.75)
Cysteamine bitartrate enteric-coated 450 mg (*n* = 6)	18.4 (40)	10.1	—	—	—	**P* = 0.28 (1.82)
Cysteamine bitartrate enteric-coated 900 mg (*n* = 6)	16.3 (42)	7.2	—	—	—	—

Statistically significant difference in gastrin response between different doses and formulations is ** ($P < 0.05$) and non-significant is * ($P > 0.05$). Cysteamine bitartrate enteric-coated and cysteamine bitartrate non-enteric-coated dosages are shown with *P* values and also standard error (SE) in parenthesis.

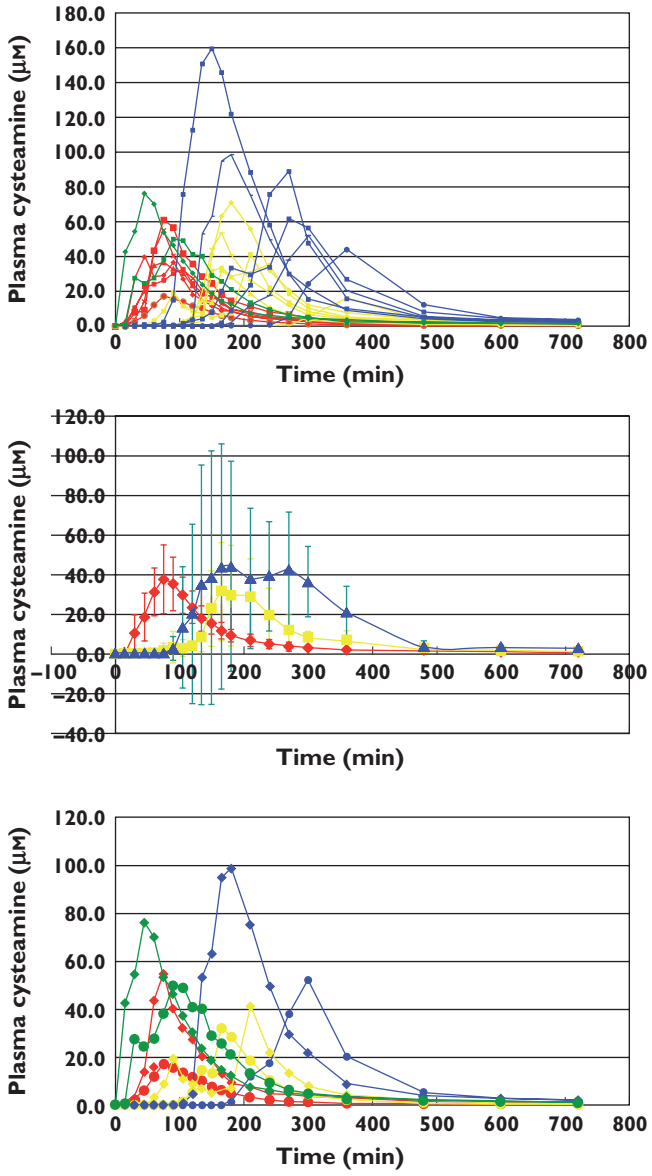

Figure 1

(A) Plasma cysteamine concentrations in six subjects (1–6) after a single dose of cysteamine bitartrate non-enteric-coated 450 mg (red), cysteamine bitartrate enteric-coated 450 mg (yellow) and cysteamine bitartrate enteric-coated 900 mg (blue) and from two patients (5 and 6) after cysteamine bitartrate non-enteric-coated 900 mg (green). (B) The mean plasma cysteamine concentrations in the six subjects (1–6) after cysteamine bitartrate non-enteric-coated 450 mg (red), cysteamine bitartrate enteric-coated 450 mg (yellow) and cysteamine bitartrate enteric-coated 900 mg (blue). The 'double-peak' appearance of the of the mean concentration profiles following 900 mg cysteamine bitartrate enteric-coated represents a wide distribution of t_{max} values rather than sustained release of the formulation. Error bars are standard deviation. (C) Plasma cysteamine concentrations in two patients (5 with diamonds and 6 with circles) after a single dose of cysteamine bitartrate non-enteric-coated 450 mg (red), cysteamine bitartrate enteric-coated 450 mg (yellow), cysteamine bitartrate non-enteric-coated 900 mg (green) and cysteamine bitartrate enteric-coated 900 mg (blue). Subject 5 vomited 1 h after receiving cysteamine bitartrate non-enteric-coated 900 mg and 3.5h after receiving cysteamine bitartrate enteric-coated 900 mg

42.2 μM, 95% CI 39.9, 128.5 μM) was significantly greater than cysteamine bitartrate non-enteric-coated 450 mg ($P = 0.01$) and cysteamine bitartrate enteric-coated 450 mg ($P = 0.02$) (see Table 2).

In the six subjects the mean AUC for plasma cysteamine after cysteamine bitartrate enteric-coated 900 mg (11814 ± 4951 μM min, 95% CI 6616, 17012 μM min) was significantly higher than cysteamine bitartrate non-enteric-coated 450 mg (4860 ± 1659 μM min, 95% CI 3118, 6602 μM min) ($P < 0.002$) and cysteamine bitartrate enteric-coated 450 mg (5194 ± 2220 μM min, 95% CI 2863, 7525 μM min) ($P = 0.002$); the difference for AUC between cysteamine bitartrate non-enteric-coated and cysteamine bitartrate enteric-coated 450 mg was not significant ($P = 0.425$). The mean plasma cysteamine profiles in subjects 5 and 6 who also took cysteamine bitartrate non-enteric-coated 900 mg are shown in Figure 1C. The mean t_{max}, mean C_{max} and AUC following cysteamine bitartrate non-enteric-coated 900 mg was 67.5 min, 63.1 μM and 8323 μM min, respectively. The t_{max} values for cysteamine bitartrate enteric-coated 900 mg and cysteamine bitartrate non-enteric-coated 900 mg were significantly different ($P = 0.002$) but not C_{max} ($P = 0.2$) or AUC. For subjects 5 and 6, following cysteamine bitartrate non-enteric-coated 900 mg ingestion the C_{max} and AUC were not significantly different compared with any other formulation or dose (*vs.* cysteamine bitartrate non-enteric-coated 450 mg, $P = 0.2$ and *vs.* cysteamine bitartrate enteric-coated 450 mg, $P = 0.24$).

Table 2 also shows the pharmacokinetic data and compares it with data from a previous study when cysteamine solution was infused through a naso-enteric tube directly into the stomach and then into the small intestine (SI) [11]. The C_{max} values following tube delivery of 500 mg (base) cysteamine into the stomach and SI were 39.5 and 51.1 μM which were similar to C_{max} values when 450 mg cysteamine bitartrate non-enteric-coated and cysteamine bitartrate enteric-coated were ingested (40.4 and 41.6 μM, respectively). The mean AUC measurements following cysteamine bitartrate enteric-coated 900 mg were more than double the measurements when cysteamine bitartrate enteric-coated 450 mg was taken.

Discussion

Although cysteamine therapy is currently being evaluated for the treatment of neurodegenerative disorders such as Huntington's disease, it is still only FDA approved for cystinosis. Lifelong, regular 6-hourly therapy will help sustain low intracellular cystine concentrations and reduce the rate of renal and thyroid deterioration as well as improving growth in children [4, 6, 13]. Poor compliance with therapy including the exclusion of the early morning dose from the daily regimen will, however, alter the outcome and likely necessitate earlier kidney transplantation [5]. One possible

Table 2

Mean plasma cysteamine C_{max}, t_{max} and AUC data from present study, following ingestion of varying doses of cysteamine bitartrate non-enteric-coated and cysteamine bitartrate enteric-coated

	*Cysteamine solution 500 mg			Cysteamine bitartrate non-enteric-coated 450 mg			Cysteamine bitartrate non-enteric-coated 900 mg			Cysteamine bitartrate enteric-coated 450 mg			Cysteamine bitartrate enteric-coated 900 mg		
	t_{max} (min)	C_{max} (μmol l^{-1})	AUC(0,∞) (μM min)	t_{max} (min)	C_{max} (μmol l^{-1})	AUC(0,∞) (μM min)	t_{max} (min)	C_{max} (μmol l^{-1})	AUC(0,∞) (μM min)	t_{max} (min)	C_{max} (μmol l^{-1})	AUC(0,∞)	t_{max} (min)	C_{max} (μmol l^{-1})	AUC(0,∞) (μM min)
*Direct tube delivery into stomach (n = 8)	50 (±26)	39.5 (±16.4)	3613 (±1384)	—	—	—	—	—	—	—	—	—	—	—	—
*Direct tube delivery into SI (n = 8)	21 (±6)	51.1 (±20.7)	3988 (±1659)	—	—	—	—	—	—	—	—	—	—	—	—
†Oral ingestion of capsule(n = 6)	—	—	—	75 (±19)	40.4 (±15.8)	4860 (±1659)	—	—	—	220 (±74)	41.6 (±18.8)	5194 (±2220)	255 (±78)	84.2 (±42.2)	11 814 (±4 951)
‡Oral ingestion of capsule(n = 2)	—	—	—	75 (75)	36.1 (17.2–54.9)	3873 (±1695)	67.5 (45–90)	63.1 (50–76.2)	8323 (±894)	187.5 (165–210)	36.9 (32.3–41.4)	4143 (±720)	240 (180–300)	75.5 (52–98)	10 128 (±2 795)

*Data are also provided from a previous study when cysteamine bitartrate 500 mg (base) in solution was delivered directly by naso-enteric tube into the stomach and then into the small intestine [11]. All doses of cysteamine bitartrate non-enteric-coated and cysteamine bitartrate enteric-coated are expressed as base. †In this study all healthy control subjects (1–6) received cysteamine bitartrate non-enteric-coated 450 mg and cysteamine bitartrate enteric-coated at 450 and 900 mg doses. ‡In addition, two control subjects (5 and 6) also received cysteamine bitartrate non-enteric-coated 900 mg. Standard deviations and ranges are shown in parenthesis.

way to improve compliance would be a formulation of cysteamine requiring fewer daily doses and in particular elimination of the 01.00–02.00 h morning dose. Our previous pharmacokinetic studies, using a naso-enteric tube to deliver cysteamine into the stomach and SI, yielded similar results for mean plasma cysteamine C_{max} and AUC measurements for both normal subjects and patients with cystinosis [10, 11]. The previous study from Dohil *et al.* also showed that C_{max} and AUC for plasma cysteamine correlated with longer WBC cystine depletion in patients with cystinosis [10]. We speculate that a higher plasma cysteamine concentration that persists for a longer time will get more of this drug into various organs and allow cystinosis patients to take the drug less frequently.

Cysteamine bitartrate non-enteric-coated capsules (gel-caps) usually disperse in the stomach. The mean t_{max} following 450 mg and 900 mg cysteamine bitartrate non-enteric-coated ingestion at about 75 min was significantly less than for the cysteamine bitartrate enteric-coated formulation which was 220 min or more. This suggested that by enterically coating cysteamine bitartrate non-enteric-coated the capsule dispersion was delayed, most likely occurring within the SI.

In this reported 'proof-of-concept' study we hoped to show that enteric-release cysteamine would yield similar pharmacokinetics (C_{max} and AUC) to those obtained from the naso-enteric tube study in normal subjects where drug was infused directly into the stomach, the small intestine and the colon [11]. This seemed to be the case as the mean C_{max} and AUC following the small intestinal tube delivery of 500 mg cysteamine solution (n = 8, 51.1 ± 20.7 μM and 3988 ± 1659 μM min, respectively) were similar to C_{max} and AUC (n = 6, 41.6 ± 18.8 μM and 5194 ± 2220 μM min, respectively) following oral ingestion of 450 mg cysteamine bitartrate enteric-coated (for C_{max} P = 0.39 and for AUC P = 0.26) (Table 2). However, when 900 mg cysteamine bitartrate enteric-coated was ingested the mean AUC (11 814 μM min) was increased to more than double that seen with 500 mg cysteamine solution (through the tube) and as expected the mean C_{max} was also higher (84.2 μM).

In patients with cystinosis receiving cysteamine solution (500 mg cysteamine base) directly through the enteric tube, the mean plasma cysteamine C_{max} and AUC (55.8 μM and 4299 μM min for SI and 35.5 μM and 3006 μM min for stomach) were significantly higher and the WBC cystine depletion was prolonged when drug was delivered into the SI as compared with the stomach [10]. A higher C_{max} and AUC are therefore more likely to be achieved following delivery/release of the drug into the SI compared with the stomach.

Although only two patients (5 and 6) were studied following 900 mg of both cysteamine bitartrate non-enteric-coated and cysteamine bitartrate enteric-coated the absorption of cysteamine was slightly better following enteric-release, but the difference did not reach statistical significance; the mean C_{max} and AUC values were 63.1 μM

and 8323 μM min with cysteamine bitartrate non-enteric-coated and 75.5 μM and 10 128 μM min with cysteamine bitartrate enteric-coated.

All but one (number 5) control subjects tolerated cysteamine. As reported previously, only some patients with cystinosis who take regular cysteamine therapy will suffer GI symptoms such as nausea, vomiting and abdominal pain [8]. These symptoms often occur 30–60 min after drug ingestion, usually correlate with C_{max} and may be associated with gastric acid hypersecretion. The symptoms of subject 5 also coincided with the C_{max} and also with her highest measurement for serum gastrin (although still within the reported normal range) following both cysteamine bitartrate enteric-coated and cysteamine bitartrate non-enteric-coated 900 mg. She had a single episode of emesis following 900 mg cysteamine bitartrate enteric-coated (C_{max} 98.7 uM, AUC 12 923 μM min) and after taking 900 mg cysteamine bitartrate non-enteric-coated (C_{max} 76.2 μM and AUC 8955 μM min) she developed severe nausea and vomiting followed by pallor with lethargy that lasted for 1 h. Why these symptoms occur only in some individuals, particularly following high dose cysteamine, remains unclear. Although it would seem more likely that symptoms (such as lethargy) arise from a 'central' effect due to high plasma cysteamine concentrations, in the case of patients who have GI symptoms (such as nausea, vomiting, abdominal pain) there may also be a topical effect on the gastric mucosa and this might account for worse GI symptoms with high dose cysteamine bitartrate non-enteric-coated compared with the same dose of cysteamine bitartrate enteric-coated. In previous studies of children with cystinosis who suffered regular upper GI symptoms, a single dose of cysteamine (patient's regular dose) resulted in an increase in mean gastrin concentration from 48.8 pg ml^{-1} at baseline to 73.9 pg ml^{-1} at 30 min post drug ingestion to a peak of 85.9 pg ml^{-1} at 2 h. This correlated with a rapid increase in gastric acid secretion which peaked at 30–60 min after cysteamine ingestion. What is interesting is that these patients with regular GI symptoms would typically complain of symptoms 30–60 min after drug ingestion and not after 2 h (despite the sustained elevation of blood gastrin concentrations at 2 h post-ingestion). This would suggest that it is the rapid initial increase in gastrin-mediated gastric acid secretion, through a possible topical effect of cysteamine on gastric mucosa, that more likely causes GI symptoms in susceptible patients. This may explain why cysteamine bitartrate enteric-coated, by avoiding the 'topical' effect of cysteamine on the gastric mucosa, causes fewer GI symptoms [8, 9].

Following the development of an assay to measure plasma cysteamine [14] a project giving intraperitoneal cysteamine to rats was undertaken in the Schneider laboratory. In these animals sacrificed at 6 min almost 10% of the injected cysteamine was found in the liver, much more than in any other organ. Unfortunately these data were not published. It is possible therefore that following oral ingestion, a significant amount of cysteamine will remain or be metabolized in the liver. This may explain why in our present study there was little difference in C_{max} and AUC measurements within these normal subjects when they receive 450 mg of cysteamine bitartrate non-enteric-coated and cysteamine bitartrate enteric-coated. However, when they receive 900 mg cysteamine bitartrate enteric-coated the C_{max} and AUC are dramatically improved. This would certainly have implications for patients with cystinosis in whom a higher plasma C_{max} and AUC has been shown to correlate with longer WBC cystine depletion. It may also have implications for patients with other disorders such as Huntington's and Batten's disease if cysteamine therapy proves effective for them.

In conclusion, although our patient numbers were low, our study does suggest that single high doses of cysteamine bitartrate enteric-coated were better tolerated than similar doses of cysteamine bitartrate non-enteric-coated in healthy subjects and all subjects had normal gastrin concentrations. The delayed t_{max} following cysteamine bitartrate enteric-coated suggests that the cysteamine is released enterically.

Competing interests

Drs Dohil and Schneider are consultants for Raptor Pharmaceutics and have stock options. The other authors do not have any conflict of interest to declare.

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