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Pharmacokinetic Studies of Cysteamine Bitartrate Delayed-Release

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Abstract

A twice-daily microsphere formulation of cysteamine bitartrate has been developed for cystinosis and other potential applications. To date, there are no published pharmacokinetic data for cysteamine bitartrate delayed-release in healthy adults. Three randomized open-label, crossover studies to determine the effects of *fasting*, *high fat*, and *carbohydrate* meals on the bioavailability of cysteamine bitartrate delayed-release (600 mg) administered in capsule or sprinkle form to healthy adults. Adverse events were monitored. Fifty-eight adults were studied. Cysteamine absorption ($AUC_{0-24\ hours}$) was the same for capsule and sprinkle forms during all meal/fasting states. The $AUC_{0-24\ hours}$ for capsules while *fasted*, 30 and 120 minutes before a *carbohydrate* meal and during a *high fat* meal were 6,313 ± 329, 4,616 ± 878, 6,691 ± 669, 2,572 ± 295 minutes × μM, respectively, and the mean C_{max} values were 29.4 ± 1.7, 20.7 ± 4.9, 31.6 ± 3.0, and 10.9 ± 1.7 μM, respectively. The mean T_{max} following *fasting* and *high fat* meal were about 3 and 6 hours, respectively. Minor transient GI adverse events occurred. Cysteamine bitartrate delayed-release capsule and sprinkle forms are bioequivalent and optimal absorption occurs during fasting state. High fat diet reduces drug absorption, increases the T_{max} and should be avoided at the time of drug ingestion. Cysteamine bitartrate delayed-release (RP103) is best ingested >30 minutes before a carbohydrate-rich meal.

Keywords

bioavailability, cystinosis, plasma cysteamine levels, RP103, food-effect

Cysteamine bitartrate is an aminothiol agent approved for the treatment of the lysosomal storage disorder cystinosis.[1,2] Nephropathic cystinosis is associated with progressive renal failure, and patients often require renal transplantation. Cysteamine lowers intra-lysosomal cystine by reacting with cystine to form free cysteine and a mixed disulfide and with regular therapy the rate of progression to renal failure can be reduced.[3–5] In cystinosis white blood cell (WBC) cystine levels are used as a surrogate marker and sustained suppression (i.e., <1 nmol ½ cystine/mg protein) is only achieved by giving cysteamine every 6 hours which invariably means having to awaken from sleep.[5,6] Cysteamine may also cause gastrointestinal (GI) symptoms in some patients.[7,8] These factors may contribute to poor compliance with therapy and ultimately necessitating earlier kidney transplantation.[9] In addition to cystinosis, pilot studies have shown that cysteamine has other potential therapeutic applications and is now being evaluated for Huntington's disease and non-alcoholic fatty liver disease (NAFLD).[10,11]

Recently a "proof of concept" study showed efficacy of twice daily delayed-release cysteamine capsules for the treatment of cystinosis, but, only in older subjects who were able to swallow intact capsules.[12–14] Following on from this, a new delayed-release enteric-coated microsphere formulation (RP103, Raptor Pharmaceutical Corp., Novato, CA) was devised which could be ingested within an intact gelatin capsule or as a sprinkle formulation. The latter could be taken orally or via gastrostomy tube by the young and also by older patients with advanced disease and swallowing difficulties.[15]

Little is know about the pharmacokinetics of cysteamine, in particular, the effect of food on the bioavailability of the drug. A recent study showed that the absorption of immediate-release cysteamine (Cystagon®, Mylan Pharmaceuticals, Inc., Morgantown, WV) was significantly impaired when drug was ingested with high fat or high protein diets. Suboptimal drug absorption with

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reduced tissue cysteamine levels may contribute to inadequate tissue cystine depletion and the progression to renal failure despite good compliance with therapy.[16] It is important, therefore, to understand how cysteamine bitartrate delayed-release should be ingested in relation to meals in order to optimize its bioavailability and provide continued tissue cystine depletion.

The aims of this study are to show bioequivalence between cysteamine bitartrate delayed-release administered as intact capsules and as sprinkle form to healthy adults and also to determine the food effect on the bioavailability of this new formulation. This will allow us make recommendations on how and when cysteamine bitartrate delayed-release should be best ingested in relation to meals.

Methods

A series of randomized, open-label, crossover studies were undertaken to evaluate the bioequivalence of cysteamine bitartrate delayed-release ingested as intact or opened capsules and also to determine the dietary conditions required for optimal drug absorption. The studies were performed by Jasper Clinic, Inc. Routine clinical laboratory testing was performed at the Bronson Hospital Clinical laboratory (Kalamazoo, MI). Full informed consent was obtained for each individual.

Three consecutive studies (A, B, C) were undertaken to evaluate serial plasma cysteamine levels in healthy adult subjects after ingesting delayed-release cysteamine under one or more of the following treatment conditions and this required for some patients within each study group to be subdivided into further treatment groups. The specific treatment conditions evaluated included (i) intact cysteamine bitartrate delayed-release capsule ingested during fasting state either alone, with apple sauce or orange juice, (ii) cysteamine bitartrate delayed-release sprinkles (i.e., opened capsules), mixed with apple sauce, ingested during fasting state, (iii) cysteamine bitartrate delayed-release intact capsules and sprinkles ingested within 30 minutes of starting a high fat/high calorie meal, (iv) intact cysteamine bitartrate delayed-release capsules and sprinkles ingested 30 and 120 minutes before a high carbohydrate meal. Ingestion of intact capsules and sprinkles were followed by 240 mL water or orange juice. There was a 3 day washout period between crossover therapy. Each cysteamine bitartrate delayed-release capsule contained 75 mg cysteamine free-base in the form of delayed-release microspheronized beads and a standard dose of 600 mg was used for each study. The complete study dose was ingested in less than 2 minutes. Subjects received cysteamine bitartrate delayed-release following a 10 hours overnight fast. Those who remained fasted did not eat or drink for a further 4 hours.

Subjects

Healthy adults with a body mass index between 18 and 30 kg/m^2 who did not have a history of chronic disease or take regular medications. Vital signs, hematology and chemistry, urinalysis testing were performed before each study period. Subjects with positive testing for hepatitis B or C, HIV, urine drug or alcohol, positive alcohol or pregnancy testing were excluded.

Meals

The high fat/calorie diet was standardized and provided between 800 and 1,000 kcal of which 50% was derived from fat, but, did not contain milk. The high carbohydrate meal was a standardized low pH meal providing 500 kcals from 88% carbohydrate, 6% protein, and 6% fat.

Plasma Cysteamine Levels

Blood samples (2 mL) were taken at baseline, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12, 18, 24 hours after drug ingestion. Plasma cysteamine levels were measured by Bioanalytical Systems, Inc. (West Lafayette, IN) using previously published methodology.[17]

Symptoms

Subjects were closely monitored during the study period for adverse events. These were recorded and evaluated for their nature, seriousness, and relationship to the study medication.

Statistical Analysis

Using GLM procedures in SAS, ANOVA were performed on untransformed T_{max}, k_{el}, and $t_{½el}$ and on ln-transformed $AUC_{0–t}$, $AUC_{0–24\ hours}$, and C_{max} at the alpha level of 0.05. The ratio of means (A/B) and 95% (or adjusted, due to penalty for interim analysis when needed) geometric confidence interval for the ratio of means, based on least-squares means from the ANOVA of the ln-transformed data, were calculated for $AUC_{0–t}$, $AUC_{0\text{-}inf}$, and C_{max}. The BLQ values were treated as zero and included as such in the calculation of mean values used in all figures.

Results

A total of 58 normal healthy adult controls (mean age 34 years, median 31 years, range 19–64 years, 37 males) took part in these studies. The mean BMI was 25.12 kg/m^2 (median 26.0, range 18.4–29.8 kg/m^2). The studies were performed sequentially and the subjects were divided into Study Groups A, B, and C. Routine laboratory blood and urine tests were negative in all. None of the subjects reported any serious adverse events (SAE) during the study and full clinical examination was unremarkable. A summary of the pK data is shown in Table 1.

Table 1. Mean of the C_{max} and T_{max} Values As Well As $AUC_{0-24\ hours}$ Measurements for All Subjects Following Ingestion of Cysteamine Bitartrate Delayed-Release 600 mg During Different Dietary States

Plasma cysteamine	Delayed-release cysteamine (RP103)										Immediate-release cysteamine		
	With meal (high fat)		Fasting				30 minutes pre-meal (high CHO)		120 minutes pre-meal (high CHO)		Fasting	High fat	High protein
	Capsule alone (n = 18)	Sprinkle AS (n = 18)	Capsule alone (n = 4)	Capsule AS (n = 20)	Capsule OJ (n = 20)	Sprinkle AS (n = 40)	Capsule AS (n = 5)	Sprinkle AS (n = 3)	Capsule AS (n = 5)	Sprinkle AS (n = 4)	Capsule Alone (n = 8)	Capsule Alone (n = 8)	Capsule Alone (n = 8)
Mean of	10.9	8.8	26.7	29.4	27.9	28.3	20.7	15.3	31.6	41.2	26.3	22.4	17.2
Cmax μM	(1.7)	(1.1)	(3.3)	(1.7)	(1.2)	(1.4)	(4.9)	(4.0)	(3.0)	(1.5)	(3.5)	(5.6)	(2.6)
[range]	[2.1–25.4]	[2.7–21.5]	[19.3–32.4]	[13.5–46.9]	[19.2–38.7]	[10.6–43.7]	[4.9–31.5]	[7.5–20.8]	[24.4–42.5]	[38–43.9]	[16.5–49]	[7–57.3]	[8–31]
Mean of Tmax	440	346	202	194	202	193	282	200	186	172	71.2	107	120
minutes	(35)	(35)	(14)	(9)	(8)	(12)	(76)	(140)	(15)	(7)	(12.9)	(29)	(23)
[range]	[240–720]	[90–600]	[180–240]	[120–240]	[120–240]	[60–360]	[90–480]	[60–480]	[150–240]	[150–180]	[45–135]	[15–270]	[60–270]
$AUC_{0-24\ hours}$	2,572	2,182	4,881	6,313	5,617	5,980	4,616	3,586	6,691	7,449	3,618	2,799	2,457
min × μM	(295)	(231)	(821)	(329)	(306)	(248)	(878)	(731)	(669)	(278)	(372)	(405)	(353)

The sprinkle AS results represent mean values taken from subjects enrolled in Study Groups B and C. Standard error of the mean is shown in parenthesis. AS is apple sauce and OJ is orange juice. For comparison, previously published data in healthy adults (n = 8) is shown following ingestion of immediate-release cysteamine 500 mg during fasting state, 30 minutes after a high fat/calorie and high protein diets. The mean AUC for plasma cysteamine concentration was about 35–75% higher following cysteamine delayed-release (600 mg) ingestion compared with cysteamine immediate-release (500 mg).

Study Group A

Intact Capsules and Sprinkles During High Fat/ Calorie Diet (n = 18)

Eighteen subjects received 8 intact capsules (600 mg cysteamine) and then 3 days later they ingested the contents of 8 capsules, that is, sprinkle form (mixed in apple sauce) within 30 minutes of commencing a high fat/ calorie meal. Plasma cysteamine levels were undetectable between 0.5 and 12 hours post-ingestion of drug in 72% and 40% of cases after ingestion of intact capsules and sprinkle formulation, respectively. Following capsule and sprinkle ingestion the mean of the C_{max} values was 10.9 (SEM ± 1.7) and 8.8 (±1.1) μM, respectively, the mean of the T_{max} was 440 (±35) and 346 (±35) minutes, respectively, and the $AUC_{0–24\ hours}$ for cysteamine concentration/time was 2,572 (±295) and 2,182 (±231) minutes × μM, respectively. The cysteamine absorption was not significantly different between capsules and sprinkles with high fat diet ($P = .58$). See Figure 1.

Intact Capsules Fasted

Four study subjects were randomly selected from Study Group A to receive intact capsules with water in a fasted state. The mean of their C_{max} and T_{max} levels were 26.7 (±3.3) μM and 202 (±14) minutes, respectively, the mean $AUC_{0–24\ hours}$ was 4,881(±821) minutes × μM. The mean $AUC_{0–24\ hours}$ for these subjects was 1.6-fold higher when fasted compared to when fed with high fat diet.

Study Group B

Intact Capsules Versus Sprinkles Fasted/Apple Sauce

Twenty fasted subjects received 8 intact capsules and then sprinkles 3 days later; both were ingested with 4 oz apple sauce and followed by water. Following fasting capsule/ apple sauce ingestion the mean of the C_{max} and T_{max} values were 29.4 (±1.7) μM and 194 (±9) minutes, respectively, the mean $AUC_{0–24\ hours}$ was 6,313 (±329) minutes × μM. Following fasting sprinkle/apple sauce ingestion the mean of the C_{max} and T_{max} values were 29.4 (±2.1) μM and 190 (±14) minutes, respectively, the mean $AUC_{0–24\ hours}$ was 6,398 (±350) minutes × μM. All estimates of the geometric least squares mean ratios for the parameters $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max} were near 1.00, and the 90% confidence intervals for all comparisons were within the acceptance range for bioequivalence of 0.80–1.25, and there were no significant sequence or period effects observed. See Figure 2.

Intact Capsules Versus Sprinkles 30 and 120 Minutes Before a High Carbohydrate Meal

Subjects from Study Group B were randomized into one of four groups. In subjects who ingested intact capsules with apple sauce 30 and 120 minutes (n = 5 in each group) before a carbohydrate-rich meal the mean of their C_{max} values were 20.7 (±4.9) and 31.6 (±3.0) μM, respectively, the mean of their T_{max} values were 282 (±76) and 186 (±15) minutes, respectively, and the mean $AUC_{0–24\ hours}$ were 4,616 (±878) minutes × μM and

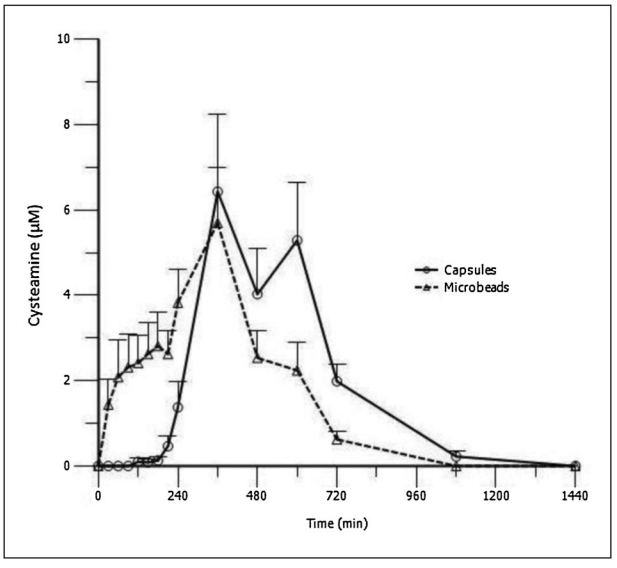

Figure 1. Mean plasma cysteamine concentrations in healthy adults (n = 20) following cysteamine bitartrate delayed-release (600 mg cysteamine-base) ingestion during a high fat diet as either intact capsules or microbead sprinkles (Study Group A). The C_{max} was low with a long T_{max}. SEM bars are shown.

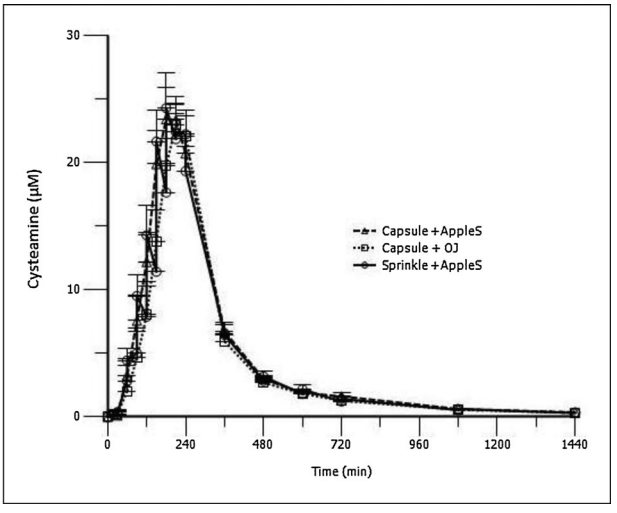

Figure 2. Cysteamine absorption profile was identical following ingestion of cysteamine bitartrate delayed-release as intact capsules with apple sauce or orange juice and with microbead sprinkles either with apple sauce after 10–12 hours nocturnal fasting. SEM bars are shown.

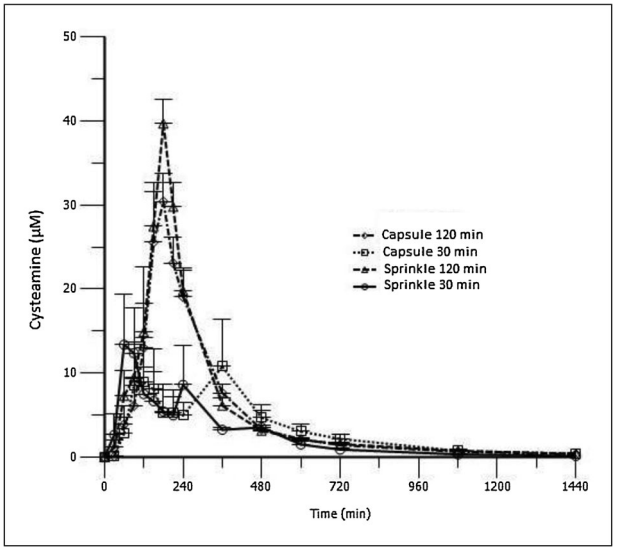

Figure 3. Mean plasma cysteamine levels following ingestion of cysteamine bitartrate delayed-release in intact capsule or sprinkle form 30 and 120 minutes before a high carbohydrate meal. C_{max} and $AUC_{0–24\ hours}$ for cysteamine concentration/time curve were lower when drug was taken closer to the meal. SEM bars are shown.

6,691 (±669) minutes × μM, respectively. In subjects who ingested sprinkles 30 minutes (n = 3) and 120 minutes (n = 4) before eating the mean of their C_{max} values were 15.3 (±4.0) and 41.2 (±1.5) μM, respectively, the mean of their T_{max} values were 200 (±140) and 172 (±7) min, respectively, and the mean $AUC_{0–24\ hours}$ were 3,586 (±731) minutes × μM and 7,449 (±278) minutes × μM, respectively. See Figure 3.

Study Group C

Intact Capsules Fasted/Juice Versus Sprinkles Fasted/Apple Sauce

A further study was undertaken in 20 subjects to determine the absorption of cysteamine following capsule ingestion with an acidic liquid (orange juice [OJ] and also sprinkles taken with apple sauce. Following fasting capsule/OJ ingestion the mean of the C_{max} and T_{max} values were 27.9 (±1.2) μM and 202 (±8) minutes, respectively, the mean $AUC_{0–24\ hours}$ was 5,617 (±306) minutes × μM. Following fasting sprinkle ingestion in the same subjects the mean of the C_{max} and T_{max} values were 27.2 (±1.8) μM and 193 (±12) minutes, respectively, the mean $AUC_{0–24\ hours}$ was 5,562 (±334) minutes × μM. Estimates of the geometric least squares mean ratios for the parameters $AUC_{0–t}$, $AUC_{0–inf}$, and C_{max} indicated minimal differences (<8%) between treatments. The 90% CIs for all comparisons were within the acceptance range for bioequivalence of 80.00–125.00%. Results of the ANOVA for the untransformed apparent terminal elimination rate constant λz, and apparent terminal elimination half-life t½ showed no significant differences between treatments for these parameters ($P > .64$). The point estimate for the median difference in T_{max} values between treatments was 0.0 with a 90% CI of −0.5 to 0.25, indicating no statistically significant difference between treatments.

Symptoms

No SAE were reported and none of the subjects were withdrawn from the study because of treatment-emergent adverse events (TEAE). Seventy-eight TEAEs were reported possibly or probably related to cysteamine bitartrate delayed-release in 28 (48%) of the study subjects and most events were reported as mild/moderate. None of the subjects taking study drug with a high fat meal (Study Group A) had TEAEs. Two subjects (from Study Group B), who initially did not report any symptoms when drug was ingested as intact capsules or sprinkles with apple sauce (without food), following randomization had severe TEAEs when cysteamine bitartrate delayed-release intact capsules were ingested 120 minutes pre-meal. These severe TEAEs occurred about 2–2.5 hours after drug ingestion and included nausea, vomiting, abdominal pain, and headache and resolved after 1–2 hours.

The most frequently reported TEAEs were mild gastrointestinal symptoms and are shown in Table 2. The GI events occurred mostly in fasted patients (Study Group B) about the time of the T_{max} (2–4 hours post-ingestion of drug). Mild nervous system-associated TEAEs were reported in 8 (13.8%) subjects. All symptoms resolved spontaneously.

Table 2. Adverse Events

Serious adverse events (SAE)		
None		
Treatment-emergent adverse events (TEAE)		
Severe		
Nausea, vomiting, abdominal pain, headache	—	2 (3.5%)
Mild/moderate		
Diarrhea	—	14 (24%)
Nausea	—	14 (24%)
Upper abdominal pain	—	6 (10.3%)
Lower abdominal pain	—	5 (8.6%)
Vomiting	—	4 (6.9%)
Headaches	—	4 (6.9%)
Dizziness	—	3 (5.2%)
Somnolence	—	1 (1.7%)

No serious adverse events (SAE) were reported and none of the subjects were withdrawn from the study because of treatment-emergent adverse events (TEAE). The GI events occurred mostly in fasted patients (Study Group B) about the time of the T_{max} (2–4 hours post-ingestion of drug). All symptoms resolved spontaneously.

Discussion

Nephropathic cystinosis is a rare disorder characterized by intralysosomal accumulation of cystine and progression to renal failure.[1] Immediate-release cysteamine therapy taken, every 6 hours around the clock, from the time of diagnosis can significantly deplete intracellular cystine by 90% and this can reduce the rate of progression to kidney failure, improve growth and obviate the need for thyroid replacement therapy.[1,3,4,18] A recent multicenter study showed that using twice daily cysteamine bitartrate delayed-release (RP103), even at a lower total daily dose, was similar to 6-hourly immediate-release cysteamine therapy in maintaining the WBC cystine <1 nmol ½ cystine/mg protein,[19] and now this new formulation is also being evaluated as a potential treatment for NAFLD and Huntington's disease. The cysteamine bitartrate delayed-release capsules presently contain 75 mg cysteamine base compared with the cysteamine bitartrate immediate-release which contain 150 mg. Taking into account the total daily dose of drug is less with cysteamine bitartrate delayed-release most patients are still required to take about 25% more capsules with the new cysteamine bitartrate delayed-release formulation. For this reason twice the number of capsules will be required. Despite this interest in cysteamine bitartrate delayed-release, there are no published data on its pharmacokinetics in healthy adults or any guidelines on how best to ingest the drug in relation to meals. Some patients with cystinosis and neurodegenerative disease may have problems with oral-motor dysfunction and so, as with young children, will have difficulty ingesting intact cysteamine bitartrate delayed-release capsules.[15] Our study shows that cysteamine bitartrate delayed-release has very stable and reproducible fasted pharmacokinetic characteristics, both inter-patient and intra-patient, and even with a relatively small number of patients (20 in each fasted group) there is bioequivalence between the intact capsule and sprinkle form of cysteamine bitartrate delayed-release. This formulation is best ingested at least 30 minutes before a high carbohydrate meal. Cysteamine bitartrate delayed-release should not be taken with a high fat meal. See Table 1.

Concurrent food ingestion does have an effect on cysteamine immediate-release absorption.[20] Some patients with cystinosis take immediate-release cysteamine at meal times in order to diminish GI symptoms. Rather than simply "buffering" gastric acid, food may diminish cysteamine absorption thereby reducing gastrin and gastric acid hypersecretion as well as centrally-triggered symptoms such as emesis.[8,17] The bioavailability of cysteamine is 30% lower when immediate-release cysteamine is ingested with high fat or high protein meals compared with fasting state.[20] The reason for this is unclear, but, it is possible that cysteamine becomes "bound" to protein within the meal and/or that food alters the delivery of drug to the small intestine where its absorption is optimal.[21] Our present study shows a similar effect and when cysteamine bitartrate delayed-release is ingested with a high fat diet the absorption of cysteamine is only 40%, 47%, and 28% of that following ingestion of intact capsules with apple sauce, orange juice and following sprinkles with apple sauce, respectively. This reduction in absorption ($AUC_{0–24\ hours}$ and C_{max}) may also explain why none of the subjects taking drug with high fat diet experienced TEAEs.

Cysteamine bitartrate delayed-release is formulated to release active drug at a pH of 5.5–6.5 in the small intestine.[12,13] When ingested shortly before or with food, the range of T_{max} values was greater (60–720 minutes) than when intact capsule or sprinkles were taken fasted/with apple sauce or orange juice/120 minutes before a high carbohydrate meal (60–240 minutes). This may be because the capsules or sprinkles became mixed into the food within the stomach and the active drug was not readily exposed to the SI absorptive surface. Another factor potentially affecting absorption could be erratic gastric emptying. Control of gastric empting in humans is complex and may be affected by the dietary fat content of food, the type of proteins present and the ratio of solid food to liquid within the stomach.[22–24] Reduced cysteamine absorption during a high fat meal could be due to the effect of dietary fat on gastric emptying.

In a previous pharmacokinetic/pharmacodynamic study of subjects with cystinosis cysteamine solution (500 mg of cysteamine base) was infused through a naso-enteric tube initially into the stomach and then directly into SI 2 days later. The mean AUC for cysteamine concentration/time curve was 3,006 and 4,299 minutes $\times$ μM after intra-gastric and SI delivery, respectively. Following SI delivery the subject's WBC cystine levels remained adequately suppressed for over 12 hours and this was the basis for developing twice daily delayed-release cysteamine. In our present study, the $AUC_{0–24\ hours}$ (following 600 mg cysteamine base) was $>4{,}600$ minutes $\times$ μM in almost all cases except for when capsules or sprinkles were given with a high fat meal. Twice daily cysteamine bitartrate delayed-release is effective in suppressing peripheral WBC cystine levels, however, the dose required ranges from 60% to 100% of the previous total daily dose of immediate-release cysteamine.[12,13,19] One reason for this wide range of doses may be the variable bioavailability of cysteamine due to the erratic delivery of the drug to the SI. Guidelines on the best timing for cysteamine bitartrate delayed-release ingestion may improve absorption and potentially even lower the total daily dose of drug required to maintain low WBC cystine levels.

In a more recent multicenter study, twice daily cysteamine bitartrate delayed-release was shown to be

as effective as 6-hourly immediate-release cysteamine in depleting WBC cystine levels. The mean total daily dose of cysteamine bitartrate delayed-release used was about 1,515 mg/day (or 757 mg/dose) compared with 1,850 mg/day of immediate-release cysteamine and in both cases most subjects ingested drug during or shortly after a meal.[19] Data from our study would suggest that if the dose of cysteamine bitartrate delayed-release was ingested before, rather than during or after meals, a lower dose of drug may be feasible without impacting the level of WBC cystine depletion.

In our studies, mild/moderate GI symptoms were reported in 48% of study subjects when drug was taken during fasting state/CHO diet but not when ingested with high fat diet. Similar findings were found in a recent study using immediate-release cysteamine where 3 of 8 subjects reported GI symptoms when drug was ingested during fasting state or following high protein diet (accepted for publication in this journal). In another study comparing high dose cysteamine immediate-release (900 mg) with similar dose of cysteamine delayed-release in 6 healthy adults only one subject reported GI symptoms and these severe following cysteamine immediate-release.[14] The frequency of reported symptoms in our study may be due to a number of factors. Firstly, cysteamine absorption is greater when drug is taken during fasting than with high fat diet. Secondly, a recent study in rats has shown that cysteamine absorption is greater in naïve than in animals pre-treated with cysteamine (ref.[25] to follow). Better absorption in the Naïve group may be explained by a recent animal study which reports that cysteamine uptake from the intestinal tract is a saturable carrier-mediated process that involves organic cationic transporters.[26] In addition to this, in a recently published study in subjects with NAFLD treated with cysteamine-delayed release subjects frequently reported mild GI symptoms at the start of the study but these spontaneously resolved over the following weeks.[27]

Our study shows that there was no significant difference between cysteamine absorption following intact capsule and sprinkle ingestion in any of the tested fasting/meal states. This confirms bioequivalence between the capsule and sprinkle forms of cysteamine bitartrate delayed-release. Hopefully, this will allow patients with cystinosis and potentially those with neurodegenerative disorders who are unable to swallow intact capsules to receive effective twice daily cysteamine therapy in sprinkle form either mixed in apple sauce by mouth or though a gastrostomy tube. Cysteamine bitartrate delayed-release ingestion is best ingested, with apple sauce or orange juice, at least 30 minutes before eating a carbohydrate-rich meal. High fat content in meals can significantly reduce cysteamine absorption and this may result in higher drug doses being used to suppress WBC cystine levels.

Declaration of Conflicting Interests

The University of California, San Diego has a financial interest in Raptor Pharmaceutics, the company sponsoring this research. Patrice Rioux is Chief Medical Officer of Raptor Pharmaceuticals. Dr. Dohil and the University of California may financially benefit from this interest if the company is successful in developing and marketing a delayed-release cysteamine product. The terms of this arrangement have been reviewed and approved by the University of California, San Diego in accordance with its conflict of interest policies. The other investigators have no conflicts of interest.

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