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Stability of extemporaneously prepared cinacalcet oral suspensions

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Stability of extemporaneously prepared cinacalcet oral suspensions

Abstract

Purpose The stability of extemporaneously prepared cinacalcet suspensions over 90 days was evaluated.

Methods Cinacalcet 5-mg/mL suspension was prepared by triturating 30-mg cinacalcet tablets. Twelve 30-mL batches were prepared with a 1:1 mixture of Ora-Plus and either Ora-Sweet or Ora-Sweet SF (sugar free). Three suspensions of each kind were stored at both room temperature and refrigerated conditions. A 1-mL sample was taken from each bottle at 0, 7, 18, 32, 64, and 90 days. Each sample was assayed using high-performance liquid chromatography (HPLC). A new HPLC method for evaluating drug peaks of pure cinacalcet was developed. Stability was defined as retention of at least 90% of the initial drug concentration.

Results The HPLC method established in this study serves as a novel assay for evaluating cinacalcet oral suspensions. For all suspensions tested at individual conditions, the concentration remained above 90% of the initial concentration for 90 days of storage with the exception of Ora-Plus and Ora-Sweet SF suspensions stored under refrigeration, which were stable for 64 days. Usual sedimentation of the suspensions occurred over time but resolved with agitation; there was no other change in visual appearance of the suspensions over the course of the 90-day study. The color and odor of the suspensions throughout the study remained unchanged with respect to the initial time point.

Conclusion Extemporaneously compounded cinacalcet 5-mg/mL oral suspensions prepared with a 1:1 mixture of Ora-Plus and either Ora-Sweet or Ora-Sweet SF and stored in 2-oz amber polypropylene plastic bottles were stable for at least 64 days at room temperature and under refrigeration.

Comments

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Title: Stability of extemporaneously prepared cinacalcet oral suspensions

ABSTRACT:

Purpose: Cinacalcet is the only calcimimetic drug available for use in the United States. It is indicated for the treatment of primary hyperparathyroidism, secondary hyperparathyroidism in patients with chronic kidney disease (CKD) receiving dialysis, and parathyroid carcinoma. Cinacalcet is only available as 30, 60, and 90 mg oral tablets and is not commercially available in an oral liquid dosage form. A liquid dosage form would facilitate accurate dosing and easier administration for children and for adults who are unable to swallow tablets. The objective of this study is to determine stability for extemporaneously prepared cinacalcet suspensions over a 90-day period.

Methods: Cinacalcet 5 mg/mL suspension was prepared by triturating 30 mg cinacalcet tablets. Twelve 30-mL batches were prepared with a 1:1 mixture of Ora-Plus and either Ora-Sweet or Ora-Sweet SF (sugar free). Three suspensions of each kind were stored at both room temperature and refrigerated conditions. A 1 mL sample was taken from each bottle at 0, 7, 18, 32, 64, and 90 days. Each sample was assayed using high-performance liquid chromatography. Stability was defined as retention of at least 90% of the initial drug concentration.

Results: The concentration of cinacalcet remained above 90% for at least 64 days in both types of suspensions stored under both conditions.

Conclusions: Extemporaneously compounded cinacalcet 5 mg/mL oral suspensions prepared with 1:1 mixture of Ora-Plus and either Ora-Sweet or Ora-Sweet SF and stored in two-ounce amber polypropylene plastic bottles were stable for at least 64 days at room temperature and under refrigeration.

Key words: stability, HPLC, pediatrics, dosage forms, drug delivery, cinacalcet

INTRODUCTION

Cinacalcet is a calcimimetic that lowers parathyroid hormone (and subsequently serum calcium) by increasing the sensitivity of the calcium-sensing receptor on the parathyroid gland.[1] It is indicated for the treatment of primary hyperparathyroidism, secondary hyperparathyroidism in patients with chronic kidney disease (CKD) receiving dialysis, and parathyroid carcinoma. It is the only calcimimetic drug available for use in the United States and is commercially available as 30, 60, and 90 mg oral tablets.[1] The FDA has approved cinacalcet for use in adults but not in the pediatric population. In fact, a 2013 clinical trial of cinacalcet in children was halted by the FDA due to a report of subject death secondary to hypocalcemia.[2] Despite the warning from the FDA, pediatric clinicians may consider its use for patients with unusually high parathyroid hormone levels due to dietary and/or medication noncompliance. Untreated hyperparathyroidism can lead to musculoskeletal disorders, cardiac events, calcifications, and increased mortality. Pediatric literature from several observational case series and case reports suggest a weight-based dose of 0.25-1.25 mg/kg/dose. [3, 4] However, it is difficult to administer an accurate dose using the commercially available tablets. A need currently exists for an extemporaneous formulation of cinacalcet in order to facilitate accurate dosing and provide an easier way of administration for both children and adults who are unable to swallow tablets. The objective of this study is to determine stability for extemporaneously prepared cinacalcet suspensions over a 90-day period.

METHODS

Suspension preparation

Cinacalcet 5 mg/mL oral suspensions were compounded using cinacalcet (Amgen Inc.) 30 mg tablets[a] as the drug source. Five 30 mg tablets were triturated in a glass mortar and 15 mL of Ora-Plus suspending agent[b] was added in parts. The resulting suspension was transferred to a precalibrated 2 ounce amber bottle. The authors pre-calibrated the bottles by measuring 30 mL of purified water (the desired final product volume) in a graduated cylinder and transferring the water into the amber bottle. The amber bottle was then marked at the level to which it was filled by the measured volume of water, then emptied and allowed to dry. This step was performed to ensure that the final volume of the product was accurate, as a second check against the volume demarcations provided by the manufacturer. The mortar was washed with portions of either Ora-Sweet[c] or Ora-Sweet SF[d] (sugar free), completing the transfer of drug and suspending agent into the precalibrated amber bottle[e] for a final volume of 30 mL. The detailed procedure for suspension compounding is provided in Appendix 1 (this procedure can be further used as a reference compounding procedure for such suspensions). This procedure was completed twelve times, and for 6 replications Ora-Sweet SF (sugar-free) was used in place of Ora-Sweet. Four conditions were tested (Ora-Plus/Ora-Sweet at room temperature, Ora-Plus/Ora-Sweet SF at room temperature, Ora-Plus/Ora-Sweet under refrigeration, Ora-Plus/Ora-Sweet SF under refrigeration) with 3 replications for each condition. For each of the twelve suspensions, the bottles were thoroughly shaken manually and then a 1 mL sample was withdrawn with an Eppendorf pipette periodically from 0 to 90 days after compounding. These samples were stored in 2 mL polypropylene microcentrifuge tubes and frozen at -20˚C until reverse-phase high-performance liquid chromatography (HPLC) analysis was performed.

Reverse-Phase High-Performance Liquid Chromatography

Samples of cinacalcet oral suspension were thawed at room temperature and agitated manually. A 625 µL portion of each sample was transferred to a 25 mL volumetric flask. The sample was diluted to a final volume of 25 mL in a volumetric flask with 50:50 v/v deionized water: acetonitrile (ACN). This dilution was sonicated for 15 minutes then stored under refrigeration for 24-48 hours to allow the drug to fully extract into solution. After extraction, 1 mL of the diluted sample was withdrawn and filtered using a 0.45 micron syringe filter[f] and transferred to an HPLC vial.

One of the samples from t=18 days (Ora-Plus/SF, room temperature) was prepared using an alternate method (scaled down by a factor of 5) because of limited sample availability. To prepare the same concentration as our primary method, 125 µL of this sample was brought to a volume of 5 mL with 50:50 water: acetonitrile in a volumetric flask. The remaining procedure was identical, including 15 minutes of sonication and 24-48 hours extraction before filtration and HPLC analysis.

Reverse phase HPLC analysis was performed on a Shimazdu LC-2010A HT liquid chromatograph instrument[g] using Phenomenex Kinetex 5 micrometer EVO C18 column, 100 Å, 150 x 4.6 mm[h]. A gradient method was used with mobile phase A consisting of deionized water with 0.1% trifluoroacetic acid (TFA) and mobile phase B consisting acetonitrile with 0.1% TFA. The percent mobile phase A:percent mobile phase B ratio was adjusted as follows: 0-3 minutes 70:30, 3-10 minutes 40:60, 10-18 minutes 10:90, 18-25 minutes 70:30. A flow rate of 1 mL/min was used, with an injection volume of 10 µL. The detector wavelength was set to 270 nm for the analysis. Column temperature was maintained at 25°C. HPLC data was collected and analyzed by Shimadzu LCSolution software.

Method development

Various HPLC methods for analyzing cinacalcet have been described elsewhere previously.[5-7] However, established methods that could effectively analyze pure cinacalcet were unable to properly evaluate cinacalcet suspensions due to excipients in the commercially available suspending agents. Excipients co-absorbed at the same wavelength as the active pharmaceutical ingredient on the HPLC column so a new method was developed to resolve these peaks from the drug peak. With methanol as the organic component of the mobile phase on a C18 column, sharp peak shape and resolution of peaks were not achieved even when pH and oven temperature were adjusted (pH adjusted from 2.49 to 4.83 and oven temperature varied from 25˚C to 30˚C). Switching from a C18 to an F5 column did not improve peak shape and tailing. Tailing was evident when using orthophosphoric acid to adjust mobile phase pH, and drug and excipient peaks overlapped when the mobile phase contained acetic acid. These issues were resolved by switching to 0.1% trifluoroacetic acid (TFA) in the mobile phase, a gradient method and a run time of 25 minutes. This resulted in sharp drug peaks that were well resolved from the excipients. The HPLC method established in this study serves as a novel assay for evaluating cinacalcet oral suspensions.

Standard curve

Standard concentrations of pure cinacalcet were prepared by first making a stock solution of 10 mg pure cinacalcet powder[i] (Amgen Inc.) in 10 mL of 70:30 acetonitrile:water. Portions of this stock solution were further diluted with 50:50 acetonitrile: water to prepare the following cinacalet concentrations: 50, 100, 150, 200, 250, and 300 µg/mL. A 1 mL aliquot of each of these 6 concentrations was transferred to an HLPC vial and analyzed in triplicates using the same method as described above.

Forced degradation

A forced degradation study was performed to verify that the method could indicate stability and resolve degradation products from the parent drug. Samples were subjected to acid, base, peroxides (oxidation), heat, and sunlight (UV) for seven days to observe resulting degradation products. Specifically the forced degradation conditions tested were 0.1 M hydrochloric acid at 60˚C, 0.1 M sodium hydroxide at 60˚C, 2.4% hydrogen peroxide at 60˚C, heat (60˚C), and ambient sunlight[5,6]. A fresh stock solution was prepared using pure cinacalcet powder in 10 mL of 50:50 acetonitrile:water. Five 2 mL aliquots of the stock solution were transferred to volumetric flasks and brought to a final volume of 10 mL with 50:50 acetonitrile:water (with the exception of sample 3 for which 3% hydrogen peroxide was used to complete the final volume of 10 mL resulting in a final concentration of 2.4% hydrogen peroxide). These 200 µg/mL standards were subjected to degradation conditions. At three and seven days post preparation, 1 mL portions were analyzed with the established HPLC method. Sample 1 was prepared using 0.1M hydrochloric acid, and sample 2 was prepared with 0.1M sodium hydroxide. Sample 3 was prepared with 3% hydrogen peroxide (final concentration of 2.4% hydrogen peroxide). Samples 4 and 5 were prepared in 50:50 acetonitrile:water (to mimic the mobile phase). Samples 1-4 were stored at 60˚C, while sample 5 was stored at room temperature near a window, exposed to ambient sunlight.

Forced degradation sample 3 (2.4% H_2O_2) demonstrated significant degradation, with 7% of the expected concentration remaining after 3 days and 3% remaining after 7 days. Major degradation peaks were well separated from the drug peak as shown in Figure 1. For all other degradation conditions (acid, base, heat, and sunlight) the concentration remained unchanged after 7 days. Cinacalcet is a relatively stable molecule but forced degradation has been previously observed

under oxidative conditions.[6] Our method was able to detect degradation and resolve degradation products from the parent drug.

RESULTS AND DISCUSSION

A linear standard curve was obtained between the concentrations of 50-300 µg/mL with R^2=0.9969. The average retention time was 5.036 minutes. A representative chromatogram is provided in Figure 2. HPLC analysis of degradation samples produced a sharp drug peak with an average retention time of 5.031 minutes. This was well separated from the peaks created by the suspending agent excipients, which eluted at ≤4.3 minutes. For all suspensions tested at individual conditions, the concentration remained above 90% of the original concentration for 90 days of storage with the exception of Ora-Plus/OraSweet SF suspensions stored under refrigeration which were stable for 64 days. Usual sedimentation of the suspensions occurred over time, but resolved with agitation and apart from that there was no change in visual appearance of the suspensions over the course of the 90-day study. The color and odor of the suspensions throughout the study remained unchanged with respect to the initial time point. All vehicles were commercially available and contained effective preservatives to prevent microbial growth. Ora-Plus served as the suspending vehicle while Ora-Sweet and Ora-Sweet SF provided flavor and sweetness.

Despite meticulous compounding techniques, initial concentrations for cinacalcet suspensions ranged from 4.86 ±0.15 mg/mL to 5.38 ±0.31 mg/mL. United States Pharmacopoeia guidelines allow for tablet potency to vary within ± 10% of the label claim.[8] It is possible that tablet potency contributed to variation in the concentration of these suspensions. A trend was observed

with the initial concentration of cinacalcet preparations being higher than the expected concentration of 5 mg/mL.. Considering all the oral suspensions were prepared with same batch of cinacalcet tablets from the same manufacturer, on the same day, the variability among the tablets was documented to be consistent. Authors believe this is a valid observation for this study and worthy of documenting for colleagues in academia, pharmaceutical industry and pharmacy. Thus, observing the initial concentration at day "zero" is even more essential for such stability studies as they provide additional information about the compounded product being evaluated. Additionally, a trend was observed in the degradation profile of the each of the samples from the initial concentration and results remain to be consistent across the different samples being evaluated in this study as shown in Table 1.

For three time points noted in Table 1, only 2 replications (instead of 3 as for the other time points) were analyzed due to sample availability. For one of these replications, the method was established after one of the three samples had already been analyzed. For the other two replications, the samples were compromised due to the integrity of the storage container, so those samples were omitted from the analysis. The 64-day sample in Ora-Plus/Ora-Sweet under refrigeration had an average of 99 ±10% of the original concentration. This is one of the time points for which n=2, resulting in the wider standard deviation. Upon review of the chromatogram no degradation peaks were seen. Also, these same suspensions were stable at 90 days (104 ±10%) indicating that degradation did not occur. Similarly, a wide standard deviation was evident at the 7 day time point for the suspensions in Ora-Plus/Ora-Sweet stored at room temperature. However, no degradation peaks were evident on the chromatograms and the samples were stable for the remaining time points. At the 90 day time point, Ora-Plus/Ora-Sweet SF samples stored refrigeration could no longer be considered stable as the concentration range

dropped below 90% (98 ±12%). However the other three conditions tested remained stable through the 90 day time point.

Cinacalcet 30, 60, and 90 mg tablets contain the same active and inactive ingredients as well as the same film coating according to product labeling.[1] Therefore, bioavailability or therapeutic effectiveness would not be expected to vary if suspensions are prepared with the 60 or 90 mg tablets rather than the 30 mg tablets.

LIMITATIONS

Limitations of this study include the fact that the study samples were subjected to freezing before analysis due to the unavailability of an established HPLC method to analyze cinacalcet suspensions. An extraction method was conducted to ensure complete drug removal from the suspensions and it would be ideal to have an HPLC method that could be used without an extraction step. Continuous temperature monitoring of storage locations was not performed daily. However the samples were stored in the same location (lab shelf for room temperature and 4°C for under refrigeration) in a hermetically sealed 2 ounce amber bottle. In future studies a temperature monitor/probe for each location is recommended.

CONCLUSION

Extemporaneously compounded cinacalcet 5 mg/mL oral suspensions prepared with 1:1 mixture of Ora-Plus and either Ora-Sweet or Ora-Sweet SF and stored in two-ounce amber polypropylene plastic bottles were stable for at least 64 days at room temperature and under refrigeration. Extended storage of compounded cinacalcet suspensions can lead to significant cost savings and is more convenient for the patient population relying on such oral suspensions.

FOOTNOTES

[a]Sensipar® (cinacalcet HCl) 30 mg tablets. Amgen Inc, Thousand Oaks, CA, lot 1050983 and 1050037.

[b]Ora-Plus suspending vehicle. Perrigo, Minneapolis, MN.

[c]Ora-Sweet flavored vehicle syrup. Perrigo, Minneapolis, MN.

[d]Ora-Sweet SF flavored sugar-free vehicle syrup. Perrigo, Minneapolis, MN.

[e]Sixty-milliliter amber oval prescription bottles with child-resistant closures. Total Pharmacy Supply.

[f]Syringe filter, nylon, 0.45µm, 13mm diameter. CELLTREAT Scientific Products. Pepperell, MA

[g]HPLC 2010A HT with LCSolutions. Shimazdu Scientific Instruments, Marlborough, MA.

[h]Kinetex 5 micrometer EVO C18 column, 100 Å, 150 x 4.6 mm. Phenomenex Inc. Torrance, CA.

[i]Cinacalcet (AMG-073) HCl. Purity >99%. Batch number S126002.

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KEY POINTS

- A need currently exists for an extemporaneous formulation of cinacalcet in order to facilitate accurate dosing and provide an easier way of administration for both children and adults who are unable to swallow tablets.
- The study demonstrates the preparation and stability of a compounded oral suspension of cinacalcet HCl using commercially available cinacalcet 30 mg tablets.
- The compounded suspensions were analyzed using HPLC analysis and they remained stable for at least 64 days at room temperature and under refrigeration.

APPENDIX

Appendix 1 Procedure for compounding cinacalcet 5 mg/mL oral suspensions (30 mL batch)

1. Count out five 30-mg Sensipar® (Amgen) tablets.
2. Crush the tablets from step 1 in a glass mortar and triturate to a fine powder.
3. Add 15 mL of Ora-Plus suspending agent in parts and triturate until a smooth suspension is obtained.
4. Transfer the resulting suspension from step 3 to a precalibrated amber 2 ounce prescription bottle.
5. Wash the mortar with portions of either Ora-Sweet or Ora-Sweet SF (sugar free), completing the transfer of drug and suspending agent into the precalibrated amber 2 ounce prescription bottle for a final volume of 30 mL.
6. Shake the suspension to ensure uniform drug distribution.
7. Label the bottle "Shake Well Before Use" and assign an expiration date of 64 days after preparation. Suspension may be refrigerated or stored at room temperature.

Figure 1 Chromatogram of cinacalcet forced degradation under oxidation conditions

Figure 2 Chromatogram of cinacalcet 300 mcg/mL

Suspension	Mean ± S.D. Actual Initial Drug Concentration (mg/mL)	Mean ± S.D. % Initial Concentration Remaining				
		Day 7	Day 18	Day 32	Day 64	Day 90
Ora-Plus/Ora-Sweet, room temperature	5.38 ±0.31	108 ±14	111 ±7	103 ±8	103 ±5	104 ±12
Ora-Plus/Ora-Sweet SF, room temperature	4.86 ±0.15	110 ±8	108 ±3	102 ±7	107 ±5	104 ±9
Ora-Plus/Ora-Sweet, refrigeration	5.1 ±0.45	105 ±12	101 ±1[a]	103 ±2	99 ±10[a]	104 ±10
Ora-Plus/Ora-Sweet SF, refrigeration	5.19 ±0.24	106 ±4	94 ±3	93 ±3	96 ±4[a]	98 ±12
	[a]n=2 due to sample availability					

Table 1: Stability of cinacalcet oral suspensions in two vehicles at room temperature and refrigeration