Identifiers: NCT03342001 Unique Protocol ID: HP-00076671

Brief Title: Hypothyroidism Treated With Calcitonin

Protocol: 11/9/2017

Lay Summary

1 * Provide a summary of the background and purpose of the study in language that can be understood by a person without a medical degree.

It is known that a proportion of patients with hypothyroidism despite serum TSH levels being within the normal reference range, (Wiersinga, Duntas, Fadeyev, Nygaard, & Vanderpump, 2012) may continue to express symptoms of hypothyroidism. Common symptoms include fatigue, muscle pain, weight gain, and mood changes. Saravanan et al. reported in a large community-based survey that patients on levothyroxine even with a normal TSH showed significant impairment in psychological well-being compared with age- and sex-matched controls (Hospital et al., 2002). These patients are challenging to manage and are often unhappy with they care.

Established treatment of hypothyroidism is levothyroxine. Thyroid follicular cells synthesize and secrete thyroxine and triiodothyronine. However, even when people are receiving adequate levothyroxine replacement therapy, their quality of life may not improve. Calcitonin (CT) is also produced by the thyroid gland, parafollicular cells. Their levels are not tested in hypothyroidism because the exact role of calcitonin in human health and disease is not fully known. CT has long been thought to play an important role in bone and mineral homeostasis, particularly with respect to its ability to regulate calcium metabolism. CT has been found in fish, reptiles, birds, and mammals. Salmon-derived CT is 50–100 times more potent than human CT. Hence, salmon CT (sCT) has been used for medicinal purposes.

There is a need for further research in order to understand the nature of persisting symptoms in patients on thyroid hormone replacement despite a serum TSH within the reference range. Calcitonin has been shown to alleviate pain in patients with bone or mineral disorders. To date, the use of calcitonin for relief of hypothyroid symptoms has not been studied.

1 * Describe the purpose, specific aims, or objectives of this research. State the hypothesis to be tested:

The primary objective of our study is to evaluate the efficacy of low dose salmon calcitonin (sCT) on health-related quality of life in levothyroxine treated hypothyroid patients with persistent symptoms despite adequate biochemical correction. We hypothesize that sCT replacement will significantly reduce some of the hypothyroid symptoms. This is a proof of concept pilot study.

-- Determine whether sCT alters plasma levels of Calcium, PO4, PTH

-- Determine steady-state levels of CT before and after 6 weeks of treatment

2 * Discuss the research design including but not limited to such issues as: probability of group assignment, potential for subject to be randomized to placebo group, use of control subjects, etc.:

This is a pilot study. Volunteer patients with hypothyroidism will be given a daily nasal spray supplement with salmon calcitonin 200 units, for 6 weeks. Blood samples will be taken at Day 0 (baseline) and at the end of 6 weeks. Thyroid, parathyroid hormone and electrolytes status will be assessed by measuring the levels of TSH, FT4, TT3, PTH, Calcium, Albumin, and PO4 in these samples. Participants will complete a quality of life survey at baseline and at 6 weeks, using a disease specific questionnaire, which was created to detect impaired well-being in subjects with thyroid problems. We modified items from the ”City of hope” questionnaire (“Quality of Life -THYROID VERSION,” ).

There will be no randomization. Adverse side effects will be recorded during the study.

3 * Describe the relevant prior experience and gaps in current knowledge. Describe any relevant preliminary data:

It is known a proportion of people with hypothyroidism have persistent symptoms despite biochemical euthyroidism on thyroid hormone therapy. There are no good treatments currently available for such patients. Conflicting data exists on using T3 n this population. It is known that patients after thyroidectomy and many with Hashimotos have low calcitonin levels. This is a proof of concept pilot study to determine whether calcitonin replacement may be beneficial.

4 * Provide the scientific or scholarly background, rationale, and significance of the research and how it will add to existing knowledge:

It is known that a proportion of patients with hypothyroidism despite serum TSH levels being within the normal reference range, (Wiersinga, Duntas, Fadeyev, Nygaard, & Vanderpump, 2012) may continue to express symptoms of hypothyroidism. Common symptoms include fatigue, muscle pain, weight gain, and mood changes. Saravanan et al. reported in a large community-based survey that patients on levothyroxine even with a normal TSH showed significant impairment in psychological well-being compared with age- and sex-matched controls (Hospital et al., 2002). These patients are challenging to manage and are often unhappy with they care.

Established treatment of hypothyroidism is levothyroxine. Thyroid follicular cells synthesize and secrete thyroxine (T4) and triiodothyronine (T3). However, even when people are receiving adequate levothyroxine replacement therapy, their quality of life may not improve. Also, treatment with combined T4 and T3 has been attempted with equivocal metabolic and QoL outcomes.

Calcitonin (CT) is also produced by the thyroid gland, parafollicular cells. Their levels are not tested in hypothyroidism because the exact role of calcitonin in human health and disease continues to be elucidated. It has long been thought to play an important role in bone and mineral homeostasis, particularly with respect to its ability to regulate calcium metabolism. CT has been found in fish, reptiles,

birds, and mammals. Salmon-derived CT is 50–100 times more potent than human CT. Hence, salmon CT (sCT) has been used for medicinal purposes. Calcitonin levels have been found to be decreased in hypothyroidism (Poppe et al, 1999; Borges et al, 1998).

To date, the use of calcitonin for relief of hypothyroid symptoms has not been studied. However, the use of calcitonin has shown improvements in QoL in patients with osteoporosis and osteoarthritis (Shohrati et al, 2015; Esenyel et al, 2013).

1 * Provide a summary of current literature related to the research: If you uploaded a separate research protocol document in the 'Research Protocol' page, cite the applicable section and page numbers from that document in the answer box below.

Saravanan P1, Chau WF, Roberts N, Vedhara K, Greenwood R, Dayan CM. (2002). Psychological well-being in patients on " adequate " doses of L -thyroxine : results of a large , controlled community- based questionnaire study, 577–585.

Quality of Life -THYROID VERSION. (n.d.). Retrieved from http://prc.coh.org/QOL-Thy.pdf

Wiersinga, W. M., Duntas, L., Fadeyev, V., Nygaard, B., & Vanderpump, M. P. J. (2012). 2012 ETA Guidelines: The Use of L-T4 + L-T3 in the Treatment of Hypothyroidism. European Thyroid Journal, 1(2), 55–71. https://doi.org/10.1159/000339444

Poppe K, et al. Calcitonin reserve in different stages of atrophic autoimmune thyroiditis. Thyroid. 1999 Dec;9(12):1211-4.

Esenyel et al. Effects of calcitonin on knee osteoarthritis and quality of life. Reumatolo Int (2013)33:423–427

Shohrati et al. Effect of Nasal Calcitonin on the Health-Related Quality of Life in Postmenopause Women Affected With Low Bone Density. Iran Red Crescent Med J. 2015 July; 17(7): e6613.

Borges et al., Calcitonin deficiency in early stages of chronic autoimmune thyroiditis. Clin Endocrinol (Oxf). 1998 Jul;49(1):69-75.

Study Procedures

If you uploaded a separate research protocol document in the 'Research Protocol' page, cite the applicable section and page numbers from that document in the answer boxes below. (If this study is a collaborative UM/VA study please list each procedure that is being conducted and the locations where it is being conducted.)

1 * Describe all procedures being performed for research purposes only (these procedures would not be done if individuals were not in the study) and when they are performed, including procedures being performed to monitor subjects for safety or to minimize risks:

-Recruit biochemical euthyroid patients with persistent symptoms of hypothyroidism and investigate the efficacy of calcitonin on improving quality of life.

-Patients will be enrolled if have diagnosis of hypothyroidism and currently euthyroid on hormone replacement (nl TSH within 60 days of study initiation, or if not done will be drawn at first visit)

-Patients will be provided with calcitonin spray for 6 weeks, while receiving usual clinical care. Quality of life will be assessed by Qol questionnaire at pre and post intervention and blood samples will be collected at initial visit and 6 weeks. Patient will be screened using inclusion and exclusion criteria. If they agree to be part of the study they will be given the questionnaire and have blood drawn (clinical care, if not already done within 60 days of visit) prior to distribution of calcitonin.

-Calcitonin will be stored and dispensed by the Midtown Hospital pharmacy, which has SOP's for storing and dispensing study drug

- If blood testing not available, will do screening blood tests on visit 1 and if qualify for study, will have separate visit to initiate calcitonin

- If the participant has an abnormal lab value disqualifying them from the study, he/she will be informed and appropriate medical care will be given. Participant will not be allowed to take part in study any longer

- At 3 week point will have phone interview with subject to assess for side effects and medication compliance

- Handout to be given to pt to record compliance and adverse events

-At the end of 6 weeks, all participants will return to the CDE to complete the quality of life survey again. Will also assess for symptoms and side effects from calcitonin and about compliance with medication. At this time blood will be drawn again (clinical care).

- All subjects taking any study drug will be included in ITT analysis. If the subject misses > 30% of doses, will have subanalysis of subjects who took drug regularly vs. not, and will add additional participants to add power to outcomes.

-All screening labs will be done after the consent is signed and screening labs will be reviewed for eligibility prior to the administration of the study drug.

2 * Describe all procedures already being performed for diagnostic or treatment purposes (if not applicable to the study, enter "N/A"):

Blood draws

3 * Describe the duration of an individual participant's participation in the study:

The duration of an individuals participation will be 6 weeks.

4 * Describe the amount of time it will take to complete the entire study:

The duration of the entire study is expected to be completed in less than 2 years.

Study collection should be finished in approximately 12 months and data analysis should take approximately an additional 6 months.

5 * Describe any additional participant requirements:

Participants will not have any additional requirements that are not outlined above.

Sample Size and Data Analysis

If you uploaded a separate research protocol document in the 'Research Protocol' page, cite the applicable section and page numbers from that document in the answer boxes below.

1 * Provide the rationale and sample size calculations for the proposed target population:

This is a pilot study and sample of convenience

2 * Provide the plan for data analysis. Include in the description the types of comparisons that are planned (e.g., comparison of means, comparison of proportions, regressions, analysis of variance, etc.), which is the primary comparison/analysis, and how the analyses proposed will relate to the primary purposes of the study:

Primary outcome to be measured is mean change in QoL before and after CT. All subjects taking any study drug will be included in ITT analysis. If the subject misses > 30% of doses, will have subanalysis of subjects who took drug regularly vs. not, and will add additional participants to add power to outcomes. This is a pilot study to prove concept and it is understood may not be powered adequately.

1 * Describe whether results (study results or individual subject results, such as results of investigational diagnostic tests, genetic tests, or incidental findings) will be shared with subjects or others (e.g., the subject's primary care physicians) and if so, describe how it will be shared:

The results of the study will not be shared with the individual subjects or primary care physicians individually. This is a pilot study aiming to demonstrate the effects of calcitonin on quality of life in patients with hypothyroidism. Results may be presented at national conferences and published in peer-reviewed journals.

ID: VIEW4E02808CBD800

Name: v2_Sharing of Results

HP-00076671

View: v2_Research with Drugs or Biologics

Research with Drugs or Biologics

You indicated on the "Type of Research" page that your study involves use of unapproved drug(s)/biologic(s) or approved drug(s)/biologic(s) whose use is specified in the protocol AND/OR evaluation of food(s) or dietary supplement(s) to diagnose, cure, treat, or mitigate a disease or condition.

1

* List all drugs/biologics to be administered in this study. Be sure to list each drug/biologic with its generic name only.

| | Drug Name | FDA Approved | IND Number | PI IND Holder |
|---|---|---|---|---|
| View | calcitonin | yes | no | |

List inclusion criteria (List each Inclusion Criteria individually, using the ADD button):

| | Number | Criteria |
|---|---|---|
| View | 1 | Age 18-89 |
| View | 2 | TSH wnl (0.4-4.5) |
| View | 3 | on levothyroxine therapy |

List exclusion criteria (List each Exclusion Criteria individually, using the ADD button):

| | Number | Criteria |
|---|---|---|
| View | 1 | pregnant, planning to get pregnant, or up to 6 months post partum |
| View | 2 | Current or previous thyroid cancer |
| View | 3 | Congenital hypothyroidism |
| View | 4 | any tobacco use |

| | | |
|---|---|---|
| View | 5 | prescribed proton pump inhibitors |
| View | 6 | prescribed steroids |
| View | 7 | prescribed armour thyroid |
| View | 8 | Unstable medical conditions (CKD, Cirrhosis etc) |
| View | 10 | Pituitary disease |
| View | 11 | Hypocalcemia |