**A randomized controlled trial to assess the effect of dexamethasone on the incidence of the acute phase response following treatment with zoledronic acid**

**Investigators:**

Emma Billington

Greg Gamble

Ian Reid

Department of Medicine

University of Auckland

1. **BACKGROUND**

The potent bisphosphonate zoledronic acid is shown to be effective in the treatment of osteoporosis, Paget’s disease, and hypercalcemia of malignancy [[1-3](#_ENREF_1)]. A single intravenous infusion of zoledronic acid results in an anti-resorptive effect on bone that lasts several years [[4](#_ENREF_4)], and unlike the oral bisphosphonates, the effectiveness of this medication is not limited by issues with absorption and adherence [[5](#_ENREF_5)]. However, treatment with aminobisphosphonates, zoledronic acid in particular, can provoke an inflammatory reaction in some patients, known as an acute phase response (APR) [[6](#_ENREF_6)].

While the clinical manifestations of an APR can be variable, symptoms such as fever, arthralgia, nausea and fatigue are most common [[6](#_ENREF_6)]. APRs typically occur within 72 hours of infusion, and are almost always self-limited, resolving within several days [[6](#_ENREF_6)]. In a post-hoc analysis of the HORIZON-Pivotal Fracture Trial, which evaluated the efficacy of zoledronic acid in postmenopausal osteoporosis, 42.4% of women who received a first dose of zoledronate reported symptoms suggestive of an APR, compared to 11.7% of women who received placebo [[6](#_ENREF_6)]. In a bisphosphonate-naïve population of postmenopausal women, Wark and colleagues observed a significant increase in oral temperature in 63.5% and worsening symptoms suggestive of an APR in 75.9% following an infusion of zoledronic acid. In women that received placebo rather than zoledronic acid, increase in oral temperature was observed in 11.1%, and symptoms suggestive of an APR in 16.7% [[7](#_ENREF_7)].

Although APRs are common, preventative strategies have not been well investigated. In a single study, both acetaminophen and ibuprofen were shown to reduce the incidence of APR by 40-50% [[7](#_ENREF_7)]. A potential preventative role for glucocorticoids has also been considered. In a recent abstract, Chen *et al* described 130 first-time bisphosphonate recipients, 80 who received zoledronic acid and 50 who were given ibandronate. The treatment protocol included the administration of hydrocortisone 100mg intravenously prior to the infusion of bisphosphonate. Patients then received prednisolone 5mg daily for three days following the infusion, as well as regularly scheduled acetaminophen and non-steroidal anti-inflammatory medications. Only 1 patient who received zoledronic acid in this setting developed an APR [[8](#_ENREF_8)]. These results suggest that the frequency of zoledronate-induced APRs may be reduced by the concurrent administration glucocorticoids. However, this study included multiple interventions, each of which has the potential to prevent APRs (intravenous hydrocortisone, oral prednisolone, acetaminophen, and non-steroidal anti-inflammatories), and was uncontrolled.

The aim of the present study is to determine, using a randomized and controlled approach, whether a single dose of a glucocorticoid, given at the time of zoledronic acid infusion, will reduce the incidence of APR compared to placebo. We have chosen to use dexamethasone as the treatment medication as it is easy to administer orally, and has a higher anti-inflammatory potency and longer half-life than other glucocorticoids [[9](#_ENREF_9)]. While long-term glucocorticoid therapy is associated with a number of side effects [[10](#_ENREF_10)], single doses of up to 8mg dexamethasone have been given in the context of dexamethasone suppression tests for several decades, without evidence of significant adverse effects [[11](#_ENREF_11), [12](#_ENREF_12)].

1. **HYPOTHESIS**

That administration of dexamethasone 4mg at the time of zoledronic acid infusion reduces the incidence and/or severity of APR compared to placebo.

1. **AIM**

The aim of this study is to determine whether the daily temperature profile of patients receiving a zoledronic acid infusion is improved by the administration of oral dexamethasone at the time of infusion, compared to placebo. The study will also assess whether there is a decreased incidence and/or severity of symptoms of acute phase response (APR) with oral dexamethasone compared to placebo.

1. **RESEARCH SYNOPSIS**

This protocol describes a prospective randomized-controlled trial of 40 bisphosphonate-naïve individuals undergoing treatment with zoledronic acid for fracture prevention or Paget’s disease.

Individuals meeting inclusion criteria will be randomly and equally allocated to receive one of the following interventions at the time of zoledronic acid infusion:

* 1. Dexamethasone 4mg PO
	2. Placebo tablet PO

At baseline, each participant will undergo oral temperature measurement and will complete a questionnaire relating to symptoms of APR. Daily assessments will continue for 3 days following the intervention. During this time, participants will measure and record their oral temperature three times per day, and will complete the same symptom questionnaire each evening. One day after the intervention, each participant will receive a phone call from a study investigator to encourage compliance with data collection. Four days after the intervention, each participant will receive a second phone call to remind them to return their oral temperature and questionnaire results to the researchers. Fifteen days after the intervention, participants will receive another phone call to inquire about ongoing symptoms.

1. **PARTICIPANT SELECTION**

 5.1 Recruitment Strategy

Participants will be recruited from the Clinical Research Centre (CRC), University of Auckland, or the Bone Clinic, Green Lane Clinical Centre. Eligible patients who require an infusion of zoledronic acid for fracture prevention or treatment of Paget’s disease will be asked by their doctor if they would be interested in taking part in the study. Those who express interest in participating will be approached by one of the study investigators, who will provide them with information about this study and answer any questions. Informed consent will be obtained from patients who wish to participate in the study and meet inclusion criteria.

* 1. Inclusion Criteria
* Females or males aged ≥20 years
* Prescribed zoledronic acid for the first time

 5.3 Exclusion Criteria

* Prior treatment with zoledronic acid
* History of fever, infection, or influenza-like illness within the past week
* Diabetes mellitus
* Uncontrolled hypertension (BP >160/90)
* Treatment with glucocorticoids within the past week
* History of adverse reaction to glucocorticoids in the past
* Major systemic illness, including malignancy
1. **RANDOMIZATION**

Consenting study participants will be assigned a sequential study number. Each number corresponds to sequentially numbered treatment packs, prepared and numbered by study personnel not involved in patient management or endpoint assessment. Treatment allocation will be predetermined using a balanced block design. Briefly, blocks of varying sizes commencing with 20 participants will be created and each row within the block will be assigned a random number (EXCEL 2013 rand() function). Blocks will be balanced for age, to ensure an equal number of participants ≥70 years in each group. Within each block, the rows will be sorted and those 50% of rows with the smallest numbers will be assigned placebo, and the remainder dexamethasone.

Participants, study investigators, and the treating physicians and nurses will be blinded to treatment allocation. To assess adequacy of blinding, four days following the intervention, participants will be asked to indicate whether they think they were randomized to the treatment group or the placebo group.

1. **INTERVENTIONS**
2. Dexamethasone 4mg PO
3. Placebo tablet PO
4. **DATA COLLECTION**

 A synopsis of data collection procedures is presented in Table 1.

 5.1 Visit Schedule

Those who consent to involvement in the study and who meet criteria for inclusion may undergo randomization and receive their zoledronic acid infusion and study intervention on the same day as their Bone Clinic/CRC assessment. If the zoledronic acid infusion is not able to be arranged for the same day (ie. additional time is required for consent or screening), then participants will return to the clinic for randomization and intervention at a later date, once consent and screening are complete.

Participants will receive a phone call from a study investigator the day after the intervention, to encourage compliance with data collection. Participants will be asked to return a record of their oral temperatures and symptom questionnaire results to the study investigators once they have finished collecting this information (four days after the intervention). This will be done using a prepaid envelope, or via email. Participants will receive a phone call four days after the intervention to remind them to return their results to the researchers. Fifteen days after the intervention, participants will receive a final phone call from a study investigator to inquire about ongoing symptoms. A script for telephone symptom enquiry is provided in Appendix 3.

5.2 Baseline Characteristics

At the time of screening, the following information will be obtained either directly from each individual or via review of the medical record:

* Medical history
	+ Chronic illnesses
	+ Malignancy
	+ Fracture history
* Current and recent (within the past week) medication use
	+ Anti-inflammatories (ibuprofen, paracetamol, aspirin)
	+ Glucocorticoids
	+ Vitamin D
* Allergies
* Alcohol consumption
* Smoking status
* Ethnicity
* Most recent serum creatinine level and eGFR
* Most recent serum total calcium level, adjusted for albumin
* Most recent serum blood glucose level, or hemoglobin A1C
* Serum 25-hydroxy vitamin D level (if available)

The following measurements will be obtained at screening:

* Stature will be measured using a Harpenden stadiometer
* Weight will be measured using an electronic scale.
* Blood pressure will be taken using a manual sphygmomanometer.
* In individuals who do not have a recent (collected within 3 months) serum blood glucose level on record, capillary blood glucose will be measured using a portable glucometer.
	+ Those with capillary blood glucose ≥11.0 mmol/L will be excluded from further participation.

5.3 Oral Temperature

Oral temperature will be measured using a digital thermometer. At baseline, three measurements will be obtained, each 1 minute apart. These results will be averaged.

Participants will be taught how to use the digital thermometer, and each participant will be given a thermometer to take home following the intervention. They will be asked to measure oral temperature on the evening of the day of the infusion and then three times per day (before breakfast, mid-afternoon, bedtime) for three days after the infusion. They will be advised not to have any food or drink 30 minutes prior to temperature measurement.

5.4 APR Symptoms

At baseline, participants will complete a questionnaire relating to symptoms of APR (see Appendix 2 for questionnaire). This questionnaire includes four symptoms that are frequently associated with APRs [[6](#_ENREF_6), [7](#_ENREF_7)]. The questionnaire also gives participants the opportunity to describe any additional symptoms, which may pertain to an APR or to an effect of the dexamethasone intervention. Participants are asked to rate the severity of symptoms on a four-point categorical scale (0=absent, 1=mild, 2=moderate, 3=severe).

Each participant will be asked to repeat the APR symptom questionnaire on four consecutive evenings, beginning on the evening of the study intervention and continuing for the next three evenings. They will then be asked to return their questionnaire results to the research centre along with their oral temperature results, by mail or email.

Participants will also receive a telephone call from a study investigator 15 days following the intervention. At this time, participants will be asked whether they have had any symptoms since they last completed the symptom questionnaire (three days following the intervention). They will be asked to list these symptoms, and to rate the maximum severity of each symptom on the same four-point scale used in the questionnaire. They will also be asked to indicate day on which each symptom began, and whether each symptom has now resolved. For symptoms that have resolved, they will be asked to provide the date of resolution. A script for this telephone conversation is provided in Appendix 3.

5.5 Adverse Events

At baseline, participants will be informed that they may take paracetamol 500-1000mg q4-6 hours (not exceeding 4000 mg in a 24 hour period) or an NSAID if they experience APR-related symptoms following their zoledronic acid infusion. They will be asked to document all use of paracetamol, or other medications within 72 hours of infusion.

1. **OUTCOMES**
2. **Primary outcome:** Between-group difference in temperature change from baseline will be compared.
3. **Secondary outcomes:** Between-group difference in change in symptom score from baseline will be compared. Symptom score will be calculated by summing the severity scores for the four APR-related symptoms listed in the questionnaire, and could range from 0-12. Secondary outcomes will also include the proportion of patients in each group who have a significant increase in oral temperature following intervention, defined as an increase of at least 1oC (to a temperature above 37.5oC) from baseline, the difference in proportion of patients in each group reporting worsening severity of at least one APR-related symptom (a change of ≥2 severity units on the four-point scale), and the difference in proportion of patients requiring anti-inflammatory medication. We will also compare the difference in anti-inflammatory dosage between the two groups. Finally, we will assess for interactions between these outcomes and participant age.
4. **STATISTICAL CONSIDERATIONS**

7.1 Power

In a previous study, a mean temperature increase of approximately 0.85oC within 34 hours was observed following zoledronic acid infusion, compared to a mean temperature increase of 0.20oC in individuals receiving placebo. Mean difference in temperature change between the groups was 0.65 oC [[7](#_ENREF_7)]. A sample size of 40 (20 participants per group) will provide >80% power to detect a temperature difference of at least 0.65oC between treatment groups, at a significance threshold of 5% [[13](#_ENREF_13), [14](#_ENREF_14)], allowing for 10% loss to follow-up (Pass 2002, WWW.NCSS.COM, Kaysville, Utah).

7.2 Data-analysis

Change from baseline in mean temperature prior to infusion to morning, noon and night for three successive days will be modelled using a mixed effect model approach to repeated measures. The main effects of treatment allocation and time and their interaction will be modelled in the analysis of covariance (ANCOVA) which will include baseline mean temperature a covariate. Significant main or interaction effects will be further explored using the method of Tukey to preserve an overall pairwise error rate of 5%. In the unlikely event that change in temperature is not normally distributed, an appropriate normalizing transformation will be applied.

The analysis will be undertaken on an intention to treat basis with no data excluded from analysis and initially assuming an unstructured covariance. In secondary analysis, any missing temperatures will be imputed using standard imputation procedures (Proc Impute, SAS).

Should the distribution of change in symptom scores over time be normally distributed the same analysis method as will be used for change in temperature will be used, else repeated measures categorical modelling will be employed.

In sensitivity analysis, the potentially confounding effect of eGFR will be examined by repeating the primary analysis excluding those with impaired renal function (eGFR <60 mL/min/1.73m2). The influence of age will be explored by plotting the change in temperature at midday two days following the intervention (the anticipated maximum temperature [7]) by age for each treatment arm and comparing the slopes.

In secondary analysis, differences in the proportion of patients with a significant increase in oral temperature (i.e. a rise of > 1 degrees C) or a significant increase in symptom severity (i.e. an increase of 3 or more in the sum of symptom severities) will be assessed using Fisher’s exact test, and presented as relative risks. Differences in the proportion of patients who require anti-inflammatory medication will be assessed using Fisher’s exact test. Participants will also be classified into groups based on the dose of anti-inflammatory medication that they take over the 72 hours following the intervention (i.e. none, low dose, high dose), and differences in the proportion of patients in each dosage group will be compared between those who received dexamethasone and those who received placebo using the Chi-squared test.

These analyses will be performed on data from the first 3 days following the intervention. Two additional analyses will be performed, comparing firstly the proportion of people in each arm who have a significant increase in symptom severity reported at the phone call 15 days after the intervention and secondly the proportion in each arm who have a significant increase in symptom severity 15 days following intervention OR 0-3 days following intervention. The frequency of each symptom score 15 days following the intervention will be compared between treatment arms using the Chi-square test.

 All tests will be two-tailed, and p <0.05 will be considered statistically significant.

1. **ETHICAL APPROVAL**

An application for ethical approval from the Health and Disability Ethics Committee (HDEC) will be made.

1. **REFERENCES**

1. Black, D.M., et al., *Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis.* N Engl J Med, 2007. **356**(18): p. 1809-22.

2. Reid, I.R., et al., *A single infusion of zoledronic acid produces sustained remissions in Paget disease: data to 6.5 years.* J Bone Miner Res, 2011. **26**(9): p. 2261-70.

3. Major, P., et al., *Zoledronic acid is superior to pamidronate in the treatment of hypercalcemia of malignancy: A pooled analysis of two randomized, controlled clinical trials.* Journal of Clinical Oncology, 2001. **19**(2): p. 558-567.

4. Grey, A., et al., *Prolonged antiresorptive activity of zoledronate: a randomized, controlled trial.* J Bone Miner Res, 2010. **25**(10): p. 2251-5.

5. Wade, S.W., et al., *Medication adherence and fracture risk among patients on bisphosphonate therapy in a large United States health plan.* Bone, 2012. **50**(4): p. 870-5.

6. Reid, I.R., et al., *Characterization of and risk factors for the acute-phase response after zoledronic acid.* J Clin Endocrinol Metab, 2010. **95**(9): p. 4380-7.

7. Wark, J.D., et al., *Treatment with acetaminophen/paracetamol or ibuprofen alleviates post-dose symptoms related to intravenous infusion with zoledronic acid 5 mg.* Osteoporos Int, 2012. **23**(2): p. 503-12.

8. Chen CH, et al., *Prevention of acute phase reaction of intravenous bisphosphonates.* Osteoporosis International, 2013. **24**(S4): p. S589.

9. Melby, J.C., *Clinical pharmacology of systemic corticosteroids.* Annu Rev Pharmacol Toxicol, 1977. **17**: p. 511-27.

10. Triadafilopoulus, G., *Glucocorticoid therapy for gastrointestinal diseases.* Expert Opin. Drug Saf., 2014. **13**(5): p. 563-572.

11. Lindholm, J., *Cushing's disease, pseudo-Cushing states and the dexamethasone test: a historical and critical review.* Pituitary, 2014. **17**(4): p. 374-80.

12. Dichek, H.L., et al., *A comparison of the standard high dose dexamethasone suppression test and the overnight 8-mg dexamethasone suppression test for the differential diagnosis of adrenocorticotropin-dependent Cushing's syndrome.* J Clin Endocrinol Metab, 1994. **78**(2): p. 418-22.

13. Machin, D., et al., *Sample Size Tables for Clinical Studies, 2nd Edition*. 1997, Malden, MA: Blackwell Science.

14. Zar, J., *Biostatistical Analysis (Second Edition)*. 1984, Englewood Cliffs, New Jersey: Prentice-Hall.

**APPENDIX 1**

**Table 1:** Data Collection Schedule

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Investigation** | **Screening Visit\*** | **Day 0****(Baseline)** | **Day 0****(Post-treatment)** | **Day 1** | **Day 2** | **Day 3** | **Day 4** | **Day 15** |
| Inclusion/Exclusion | X |  |  |  |  |  |  |  |
| Medical history | X |  |  |  |  |  |  |  |
| Medication review | X |  |  |  |  |  |  |  |
| Review of blood work | X |  |  |  |  |  |  |  |
| Capillary blood glucose (if required) | X |  |  |  |  |  |  |  |
| Height and weight | X |  |  |  |  |  |  |  |
| Blood Pressure | X |  |  |  |  |  |  |  |
| Consent |  | X |  |  |  |  |  |  |
| Randomization |  | X |  |  |  |  |  |  |
| Oral temperature |  | X | Xa | Xb  | Xb  | Xb  |  |  |
| APR symptom questionnaire |  | X | Xa | Xa | Xa | X a |  |  |
| Follow-up telephone call |  |  |  | X |  |  | X | X |

\*Screening and Day 0 may occur at the same visit. APR = acute phase response

Day 0 = day of intervention, Day 1=1 day after intervention, Day 2=2 days after intervention, Day 3=3 days after intervention, Day 4=4 days after intervention, Day 15=15 days after intervention

aTo be done at bedtime

bTo be measured three times: before breakfast, mid-afternoon, bedtime

**APPENDIX 2**

**Symptom Questionnaire**

Please indicate whether you experienced one of the following complaints during the last **24** hours and rate symptoms using the scale below.

**0** = Complaint not present

**1** = Mild: complaint causes mild distress or discomfort, but no impairment in daily functioning

**2** = Moderate: complaint causes moderate distress or discomfort or at least some impairment in daily functioning

**3** = Severe: complaint causes severe distress and discomfort, severe impairment in daily functioning, or acute danger to health

 **In the past 24 hours, I had the following symptoms:**

|  |  |
| --- | --- |
| **Symptom** | **Intensity**0 not present 1 mild2 moderate3 severe |
| Headache | 0 1 2 3 |
| Nausea | 0 1 2 3 |
| Muscle or joint pain | 0 1 2 3 |
| Feverishness | 0 1 2 3 |
| Further symptoms: (please name)\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ | 0 1 2 30 1 2 30 1 2 3 |

**APPENDIX 3:** **Script for telephone symptom enquiry**

The following questions are to be asked to assess for the presence of late or residual symptoms. The investigator who completes the telephone call will fill out the symptom questionnaire, shown at the bottom of the page:

**Initial Questions:**

1. “Have you had any headaches since you last filled out the questionnaire?”
2. “Have you had any nausea since you last filled out the questionnaire?”
3. “Have you had muscle or joint soreness since you last filled out the questionnaire?”
4. “Have you had any feverishness since you last filled out the questionnaire?”
5. “Have you had any additional symptoms since you last filled out the questionnaire?”
	1. *If the participant indicates “Yes” to this question, then they will be asked to list these symptoms.*

*For questions answered “No”, a severity score of 0 will be assigned to the symptom in question.*

*For questions answered “Yes”, additional questions will be asked to ascertain severity and duration.*

**Follow-up Questions:**

1. “What day did \_\_\_\_\_\_\_\_\_\_\_\_ (name symptom) start?”
2. “At its worst, was \_\_\_\_\_\_\_\_\_ (name symptom) mild, moderate, or severe?”
	1. *Mild = score of 1, moderate=a score of 2, and severe = score of 3.*
3. “Has \_\_\_\_\_\_\_\_ (name symptom) now resolved?”
	1. *If the symptom has not resolved, then date of resolution will be listed as “ongoing”.*
	2. *If the symptom has resolved, then the participant will be asked to provide the day of resolution, and this will be recorded.*

Name:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_Allocation Number:\_\_\_\_\_\_\_\_\_\_\_

**Symptom Questionnaire (15 days after intervention)**

|  |  |  |  |
| --- | --- | --- | --- |
| **Symptom** | **Intensity** | **Onset** | **Status** |
| Headache | 0 1 2 3 | Start date:\_\_\_\_\_\_\_\_\_\_\_ | Date resolved:\_\_\_\_\_\_\_\_\_\_ |
| Nausea | 0 1 2 3 | Start date:\_\_\_\_\_\_\_\_\_\_\_ | Date resolved:\_\_\_\_\_\_\_\_\_\_ |
| Muscle or joint pain | 0 1 2 3 | Start date:\_\_\_\_\_\_\_\_\_\_\_ | Date resolved:\_\_\_\_\_\_\_\_\_\_ |
| Feverishness | 0 1 2 3 | Start date:\_\_\_\_\_\_\_\_\_\_\_ | Date resolved:\_\_\_\_\_\_\_\_\_\_ |
| Further symptoms: (please name)\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ | 0 1 2 30 1 2 30 1 2 3 | Start date:\_\_\_\_\_\_\_\_\_\_\_Start date:\_\_\_\_\_\_\_\_\_\_\_Start date:\_\_\_\_\_\_\_\_\_\_\_ | Date resolved:\_\_\_\_\_\_\_\_\_\_Date resolved:\_\_\_\_\_\_\_\_\_\_Date resolved:\_\_\_\_\_\_\_\_\_\_ |