

# Effects of sodium alendronate on body weight water and food intake in adult female Wistar rats

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## ABSTRACT

This study aimed to assess the body weight and food and water intake of alendronate-treated Wistar rats. Thirty rats were divided in 3 groups of 10. Group A (control group) received saline, and Groups B and C received alendronate 4mg and alendronate 0.033mg, respectively through gavage. Body weight and food and water intake were measured daily for 10 days. From the first to the last day, the mean body weight ranged from 188.2g (SD 7.3) to 183.2g (SD 5.7) in Group A, from 183.0g (SD 7.7) to 177.5g (SD 8.2) in Group B, and from 188.9g (SD 17.1) to 184.5 (SD 16.4) in Group C. Mean food intake ranged from 15.0g (SD 1.8) to 17.5g (SD 1.1) in Group A, from 14.0g (SD 2.2) to 15.4g (SD 2.6) in Group B, and from 23.3g (SD 2.0) to 14.9g (SD 2.6) in Group C. Mean water intake ranged from 17.0ml (SD 6.5) to 20.6ml (SD 5.6) in Group A, from 20.8ml (SD 1.3) to 22.1ml (SD 3.6) in Group B, and from 16.0ml (SD 5.7) to 19.3ml (SD 2.7) in Group C. Alendronate caused significant differences in body weight (the higher the dose the lower the weight) and water intake (the control group consumed less water). No difference regarding food intake was found.

Keywords: Alendronate. Rats. Weight gain. Diet.

## 1 INTRODUCTION

Bisphosphonates are a class of drugs effective in several conditions characterized by an increase in bone resorption and consequent brittle bones with higher fracture risk. Osteoporosis tops the list of such conditions, which has Paget's disease, malignancy-associated hypercalcemia and osteolytic bone metastases as other examples (FLEISCH, 1991, 2000). Sodium alendronate is the drug most widely studied and prescribed in clinical practice (PETER; KINDT; MAJKA, 1998).

As enzymatic lysis-resistant chemical analogues of inorganic pyrophosphate, bisphosphonates contain two phosphonate groups making up a P-C-P moiety, while in pyrophosphate an oxygen is substituted for carbon (RUSSEL et al., 1999).

Bisphosphonates are synthetic compounds not produced by human or animal organisms, with an unknown absorption site believed to be the stomach and small bowel (FLEISCH, 2000). Absorption is substantially reduced when they are taken along with food, calcium and iron, either through the formation of non-absorbable compounds or due to impairment of the absorptive process itself. Between 20% and 80% of the absorbed dose is deposited in the bones, the rest undergoing active tubular secretion (FLEISCH, 2000).

We aimed to study the effect of gavage-administered sodium alendronate on body weight and water and food intake of female Wistar rats.

## 2 METHODS

Thirty Female Wistar rats (*Rattus norvegicus*), aged between 5 and 7 months, were assigned to three groups (A, B, and C, with ten rats in each one) and kept in individual cages. Group A animals received 1ml saline, group B 4mg alendronate in 1 ml saline, and group C 0.033 mg alendronate in 1 ml saline.

The doses of 4mg and 0.033 mg were obtained by powdering 10mg tablets, so that 20mg were diluted in 5ml saline (4mg/ml), and 10mg diluted in 300ml saline (0.033mg/ml). The drug was administered for 10 days, through gastric feeding (gavage), at around 13:30, after a 6-hour fasting.

Each cage was loaded with 30g of food and 200ml of water daily. The leftovers were also measured daily, at 7:30, the difference between the loading quantities and the leftovers taken as the daily intake. Body weight was measured daily.

The study was conducted in the animal research facility of the federal University of Juiz de Fora, MG, Brazil, in an airy environment at an average temperature of 22°C and sequential 12-hour shifts of darkness and lighting. The cages were kept 10cm

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apart from one another, at a height of 73cm-112cm from the floor.

The results were statistically analyzed with the Statistical Package for Social Sciences (SPS), version 8.0, software.

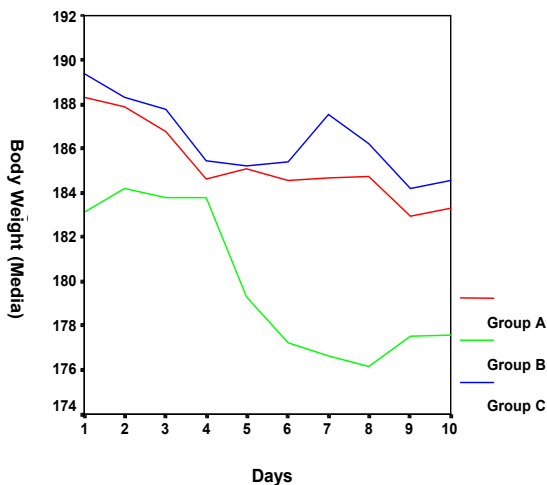
Anova ( $p < 0.05$ , two-tailed), and non-parametric Kruskal-Wallis ( $p < 0.05$ , two-tailed) tests were used to compare body weight, and food and water intake means among the three groups studied. t-test ( $p < 0.05$ , two-tailed), and non-parametric Mann-Whitney test ( $p < 0.05$ , two-tailed) were also used to compare these variables between two groups only.

This trial was submitted to the Animal Ethics Committee.

### 3 RESULTS

#### 3.1 Body weight

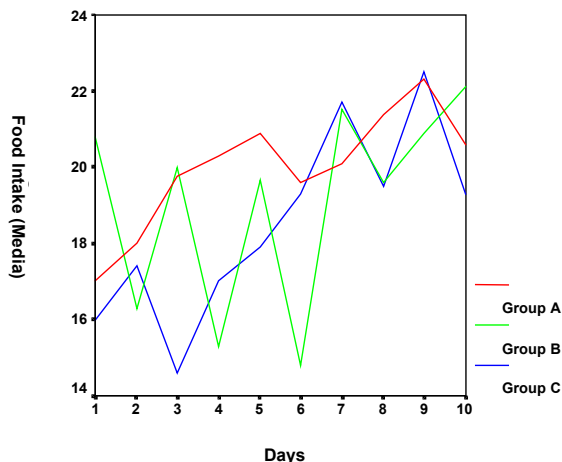
Mean body weight ranged from 188.2g (SD 7.3) on the first day to 183.2g (SD 5.7) on the last day in Group A; from 183.0g (SD 7.7) on the first day to 177.5g (SD 8.2) on the last day in Group B; and from 188.9g (SD 17.1) on the first day to 184.5g (SD 16.4) on the last day in Group C (Graphic 1).



Graphic 1: Body weight (media) during the experiment  
Font: Authors (2007)

#### 3.2 Food intake

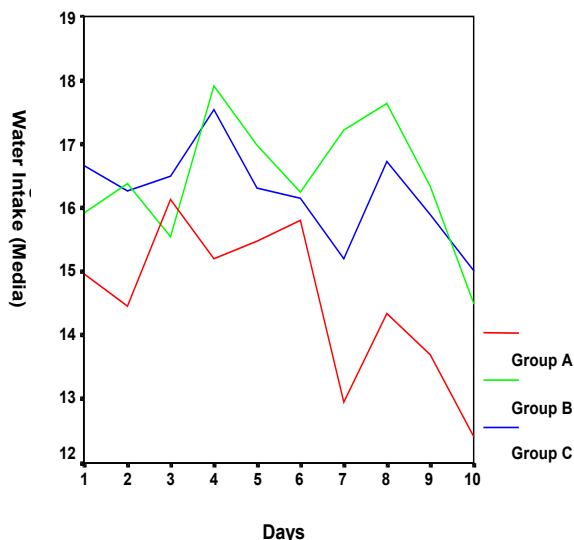
Mean food intake ranged from 15.0g (SD 1.8) on the first day to 17.5g (SD 1.1) on the last day in Group A; from 14.0g (SD 2.2) on the first day to 15.4g (SD 2.6) on the last day in Group B; and from 23.3g (SD 2.0) on the first day to 14.9g (SD 2.6) on the last day in Group C (Graphic 2).



Graphic 2: Food intake (media) during the experiment  
Font: Authors (2007)

#### 3.3 Water intake

Mean water intake ranged from 17.0ml (SD 6.5) on the first day and 20.6ml (SD 5.6) on the last day in Group A; from 20.8ml (SD 1.3) on the first day and 22.1ml (SD 3.6) on the last day in Group B; and from 16.0ml (SD 5.7) on the first day to 19.3ml (SD 2.7) on the last day in Group C (Graphic 3).



Graphic 3: Water intake (media) during the experiment  
Font: Authors (2007)

### 4 DISCUSSION

Alendronate has been widely used to treat a diversity of illnesses such as osteoporosis, Paget's disease, polyostic fibrous dysplasia, urinary calcium microlithiasis, and to prevent bone fractures (AKI et al., 2003; ATAMAZ et al., 2006; CRANNEY et al., 2002; KHAN et al., 1997; KITAGAWA;

TAMAI; ITO, 2004; SENZAKI et al., 2004; TSENG et al., 2006; UNAL et al., 2006). At the same time, some side effects have been reported, such as nausea, esophagitis, laryngitis, esophageal ulcers, oral ulcerations, gastric ulcers, and anterior uveitis, among others (AKI et al., 2003; BHUTA et al., 2005; GONZALES-MOLES; BAGAN-SEBASTIAN, 2000; GRAHAM; MALATY, 1999; KELLY; TAGGART, 1997; KHAPRA; ROSE, 2006; SALMEN et al., 2002; TOTH et al., 1998).

Changes in intake patterns and body weight may be surrogate markers for administered or ingested substances, little having been studied about the effects of alendronate on such physiological parameters in laboratory animals. Peter, Kindt e Majka (1998) reported the sudden death of a female rat on alendronate, 30mg/Kg/day, in the second week of the experiment. These authors also noticed a significant reduction in the body weight of the group receiving alendronate, 30mg/Kg/day, during 28 days.

In our study, body weight was assessed daily for 10 days. Body weight reduction was observed in the three groups. Similarly to what happened in the study of Peter, Kindt e Majka (1998) body weight reduction was statistically more significant in the group receiving the highest dose of alendronate (4mg).

Anova ( $F=20.397$ ;  $p=0.001$ ) and non-parametric Kruskal-Wallis ( $p=0.001$ ) tests were carried out and showed statistically significant differences among the three groups. t-test and non-parametric Mann-Whitney test were also carried out for comparison between two groups. Statistically significant differences in mean body weight between controls and the group receiving 4mg alendronate (Mann-Whitney :  $Z= -3.250$ ;  $p=0.001$ , and t-test :  $t=4.431$ ;  $p= 0.001$ ), and between the group receiving 0.033mg alendronate and the group receiving 4mg alendronate (Mann Whitney :  $Z= -3.743$ ;  $p= 0.001$ ; and t-test:  $t= -5.402$ ;  $p= 0.001$ ) were confirmed.

As body weight means in the groups were already different at baseline, the t test was chosen to compare the means on the first day, no significant difference being found ( $p>0.05$ ).

No literature reference regarding the relationship between food intake and alendronate use was found. When Anova ( $F= 1.081$ ;  $p= 0.354$ ) and non-parametric Kruskal-Wallis ( $p= 0.264$ ) were used, the three groups in this study showed no statistically

significant difference regarding food intake. In the doses used, alendronate did not influence food intake during the period of observation.

No literature reference concerning water intake of animals on alendronate was found either. The water intake of our controls was smaller than that of animals on alendronate.

Anova ( $F= 10.675$ ;  $p= 0.001$ ) and non-parametric Kruskal-Wallis ( $p= 0.001$ ) tests showed statistically significant differences. t-test and non-parametric Mann-Whitney test were used for comparisons between two groups. Significant differences were observed in mean water intake between controls and the group receiving 4mg alendronate (Mann-Whitney :  $Z= -3.175$ ;  $p= 0.001$ ; and t-test:  $t= -3.818$ ;  $p= 0.001$ ), and between controls and the group receiving 0.033mg alendronate (Mann-Whitney :  $Z= -3.099$ ;  $p= 0.001$ ; and t-test :  $t= -3.716$ ;  $p= 0.002$ ).

Our data show that the groups on alendronate had a higher water intake than controls, suggesting that the drug may lead to increased water needs.

Weight loss was observed in the three groups, those receiving 4mg alendronate showing the highest reduction, in spite of no reduction in food intake and a water intake similar to that of the group on the lower dose. Some physiological variables that might explain the weight reduction without corresponding reduction in food intake, such as physiological urinary and fecal losses, intestinal transit time, metabolic features, and nutrient absorption, were not assessed in this study. Female rats on 0.033mg alendronate, equivalent to the therapeutic dose used in humans, only showed an increase in their water intake. Animals receiving 4mg, 120 times the therapeutic dose for humans, showed remarkable weight loss and increased water intake. Although no straightforward extrapolation can be made, the observation period of 10 days in rats is roughly equivalent to 300 days in humans (WHEIHE, 1987).

## 5 CONCLUSION

Alendronate caused significant difference in body weight (the higher the dose the lower the weight) and water intake (control group consumed less water). No difference regarding food intake was observed.

# Effects of sodium alendronate on body weight, water and food intakes in adult female wistar rats

## ABSTRACT

Evaluate body weight, food and water intakes, of Wistar rats on alendronate. Thirty rats, divided in 3 groups of 10. The group A (control group) received saline, the B and C received alendronate 4mg and alendronate 0.033mg, respectively (gavage). Body weight and food and water intakes were measured daily for 10 days. From the first to the last day the mean body weight ranged from 188,2g (SD 7,3) to 183,2g (SD 5,7) in group A, from 183,0g (SD 7,7) to (177,5g (SD 8,2) in group B, and from 188,9g (SD 17,1) to 184,5 (SD 16,4) in group C. Mean food intake ranged from 15,0g (SD 1,8) to 17,5g (SD 1,1) in group A, from 14,0g (SD 2,2) to 15,4g (SD 2,6) in group B, and from 23,3g (SD 2,0) to 14,9g (SD 2,6) in group C. Mean water intake ranged from 17,0ml (SD 6,5) to 20,6ml (SD 5,6) in group A, from 20,8ml (SD 1,3) to 22,1ml (SD 3,6) in group B, and from 16,0ml (SD 5,7) to 19,3ml (SD 2,7) in group C. Alendronate caused significant difference in body weight (higher the dose lesser the weight) and water intake (control group consumed less water). No difference regarding food intake.

Keywords: Alendronate. Rats. Weight Gain. Diets.

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