Esophageal Transit and In Vivo Disintegration of Branded Risedronate Sodium Tablets and Two Generic Formulations of Alendronic Acid Tablets: A Single-Center, Single-Blind, Six-Period Crossover Study in Healthy Female Subjects

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ABSTRACT

Background: Delayed esophageal transit or disintegration of oral bisphosphonate tablets before they enter the stomach may be of concern with respect to iatrogenic complications among patients receiving long-term treatment. Different formulations of generic bisphosphonate tablets meeting regulatory requirements may have substantial differences in pharmaceutical attributes from the branded product that may result in different characteristics during esophageal transit.

Objective: The primary objective of this study was to evaluate and compare esophageal transit times and in vivo disintegration of 3 bisphosphonate formulations, one branded and the others generic, that are commercially available in Canada and the United Kingdom.

Methods: This was a single-center, randomized, single-blind, 6-period crossover study in healthy postmenopausal women aged >50 years. Each subject received a single oral dose of a branded risedronate sodium 35-mg tablet and 2 generic formulations of alendronic acid 70-mg tablets (Novopharm Limited, Toronto, Canada, and Teva UK Limited, Morley, United Kingdom) in both the erect and semisupine (45°) positions. Although the products are labeled to be taken in the erect position, the semisupine position was included to simulate dosing in bedridden patients. Subjects took tablets with 30 mL of water in the morning after an overnight fast. The tablets were radiolabeled with technetium-99m ion-exchange resins to enable visualization and measurement of esophageal transit time and disintegration using a gamma camera. Dynamic scintigraphic images were obtained for a total of 10 minutes: 2 images per second for the first 30 seconds and 1 image every 15 seconds for 9.5 minutes. This was a mechanistic study and tolerability was not assessed.

Results: The study was conducted in 20 healthy white female subjects with a mean age of 62 years (range, 51–77 years). The effect of body position was statistically significant ($P = 0.043$), with the estimated hazard ratio (HR) of 0.74 indicating longer transit time in the semisupine position relative to the erect position. There was a statistically significant difference in transit time among the 3 types of tablets ($P = 0.007$), with the Novopharm tablet (HR = 0.59; $P < 0.001$) and Teva tablet (HR = 0.71; $P = 0.042$) having longer transit times compared with the risedronate tablet. In 4 instances, the Novopharm tablet disintegrated and dispersed in the esophagus, once in the erect position and 3 times in the semisupine position.

Conclusions: In these healthy female subjects, esophageal transit was delayed when the tablets were given in the semisupine position. The branded risedronate tablet had a significantly faster transit time than the 2 generic formulations of alendronate tested. (*Clin Ther*. 2008;30:834–844) © 2008 Excerpta Medica Inc.

Key words: generic alendronate, esophagus, in vivo disintegration, transit time, risedronate sodium.

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INTRODUCTION

The major risk factors for pill-induced esophagitis[1,2] are age-related impairment of esophageal motility and the characteristics of the dosage form, including size, shape, and coating.[3–5] As the population ages, increases in both osteoporosis and impaired esophageal peristalsis can be expected. Impaired esophageal peristalsis in elderly subjects increases the likelihood that solid oral dosage forms (mainly tablets and capsules) may lodge in the esophagus or undergo retrograde movement due to esophageal dysmotility.[6,7] Such impaired clearance prolongs the contact time of the formulation with the esophageal mucosa. In addition to the characteristics of the dosage form, the esophageal transport of solid dosage forms depends on body position, swallowing volume, and pharyngeal propulsion velocity.[6]

There have been reports of gastrointestinal adverse events, including dysphagia, esophagitis, and ulceration of the stomach and esophagus, associated with oral bisphosphonate therapy in clinical practice.[7,8] In most cases, the esophageal problems fit the pattern of pill-induced esophagitis or reflux of partially dissolved tablets from the stomach. As a result, it was recognized that administration of oral bisphosphonates in patients with esophageal abnormalities was potentially hazardous, and that efforts should be made to avoid prolonged drug contact with the esophagus.[7,8]

To reduce the risk of esophageal complications with risedronate sodium,* a film-coated formulation was developed to facilitate rapid esophageal transit and minimize contact with the mucosa. In a previous esophageal-transit study in 25 healthy male and female subjects aged >56 years,[4] the mean transit time of a film-coated risedronate placebo tablet swallowed with 50 mL of water was 3.3 seconds (range, 1.5–7.0 seconds; sample SD, 1.4 seconds), and the mean transit time of a hard-gelatin risedronate capsule swallowed with the same amount of water was 23.8 seconds (range, 0.5–131.5 seconds; sample SD, 36.1 seconds) (P = 0.016), indicating the faster transit time of the film-coated tablet. In a subsequent study in 14 healthy female subjects aged >55 years,[9] the film-coated risedronate tablet swallowed with 50 mL of water had a median esophageal transit time of 4.0 seconds (range, 0.8–10.4 seconds); when the tablet was swallowed with 240 mL of water, the median esophageal transit time was 4.0 seconds (range, 2.4–18.4 seconds). The transit times with the 2 volumes of water were considered equivalent because the 90% CI was within the equivalence range of ±8.0 seconds.

A branded form of the bisphosphonate alendronate sodium† is currently available worldwide, including Canada and countries in Latin America and Europe. The once-weekly formulation is an uncoated, oval-shaped tablet containing the sodium salt of alendronate. In the United States, generic versions of this tablet are required to contain the same active ingredients as the branded drug (inactive ingredients may vary); to be identical in strength, dosage form, and route of administration; to have the same indications as the branded drug; to be bioequivalent; to meet the same batch requirements for identity, strength, purity, and quality; and to be manufactured under the strict standards of the US Food and Drug Administration's good manufacturing practice regulations for branded products.[10] However, generic products are approved based on the results of single-dose bioavailability studies and are not required to have disintegration characteristics or esophageal transit times equivalent to those of the branded product.[10] A potential concern is that differences in the pharmaceutical attributes (eg, film-coating, size, shape, disintegration time) of generic alendronic acid formulations may affect the local-irritation and tolerability profiles of the drug, particularly in the upper gastrointestinal tract. Epstein et al[11] reported a greater irritant response to a 10-mg generic alendronate tablet (Novopharm Limited, Toronto, Canada) in a rabbit injection study and to another 10-mg generic alendronate tablet (Teva Pharmaceutical Industries Ltd., Petah Tikva, Israel) in a dog esophageal study compared with the 10-mg branded product. Because the active ingredient and dose were the same in the generic alendronic acid tablets and the branded tablets, the differences in irritant response were attributed to differences in the pharmaceutical preparations.

The present study evaluated and compared esophageal transit times and disintegration of 3 bisphosphonate formulations, the branded film-coated risedronate sodium tablet and 2 generic alendronic acid products that are commercially available in Canada and the United Kingdom. The particular generic tablets stud-

*Trademark: Actonel® (Procter & Gamble Pharmaceuticals, Inc., Cincinnati, Ohio).

†Trademark: Fosamax® (Merck & Co., Inc., West Point, Pennsylvania).

ied were chosen because they are made by established manufacturers of generic products and because, at the time the study was conducted, generic alendronic acid tablets were not available in the United States. The branded alendronate sodium tablet was not used because this dosage form has been extensively studied in the course of clinical trials.[12] The film-coated risedronate sodium tablet was included as a control because its esophageal transit time has been reported previously.[4,9] It was not necessary to adjust the doses of the risedronate sodium and alendronic acid tablets, because transit time and disintegration are functions of the properties of the dosage form and not of the active ingredient, and study comparisons were between the weekly doses of each (35 and 70 mg, respectively).

The approved labeling for the branded alendronate sodium tablet states that to facilitate delivery to the stomach and thus reduce the potential for esophageal irritation, the tablet should be swallowed with a full glass of plain water (6–8 fluid ounces); furthermore, patients are not to lie down for at least 30 minutes after swallowing the tablet and not until after they have consumed the first food of the day.[12] A 30-mL volume of water was used in this study, as this volume has been found sufficient to differentiate between the transit times of pharmaceutical preparations,[13] and subjects aged >50 years may have difficulty following the dosing instructions for bisphosphonate tablets with respect to water volume. The transit of the bisphosphonate formulations was studied with the subject in both the erect and semisupine (45°) positions, as a literature review found that no such studies have been conducted with bisphosphonate formulations. Although the products are labeled to be taken in the erect position, a 45° angle was chosen to simulate dosing in bedridden patients.[14]

SUBJECTS AND METHODS

Study Population

Healthy white female volunteers were recruited from Queen's Medical Centre, Nottingham, United Kingdom, and the surrounding area. Eligible subjects had to be aged >50 years, be postmenopausal (surgical or natural), be able to give consent, and be willing to abstain from alcohol from 24 hours before each dose through the end of each study day. Subjects were excluded if they had a history of alcohol or drug abuse; had received any investigational drug within the previous 3 months; in the investigator's opinion, were not sufficiently fit to participate based on a complete medical history and physical examination; had consumed alcohol within 24 hours of the start of the study; or had participated in a similar study involving the use of radioisotopes in the previous 3 months, such that radiation exposure from the present study would exceed the recommended threshold for yearly exposure (5 millisievert [mSv]).[15] (The Sv is a measure of the effective dose. A member of the general public is exposed to ~2.5 mSv per year from background radiation.[16]) Additional exclusions were use within the previous 8 weeks of any medication that may affect esophageal or gastric motility (eg, atropine, propantheline, narcotic analgesics, amitriptyline, imipramide, loperamide, desipramine, chlorpromazine); a history of gastric surgery or active upper gastrointestinal disease; and milk intolerance or other inability to drink milk.

The study was approved by the Ethical Committee of Nottingham Hospital and the Administration of Radioactive Substances Advisory Committee of the UK Department of Health. All subjects were fully informed of the study procedures and gave their written consent to participate.

Study Design

This was a mechanistic, randomized, single-blind, 6-period crossover study conducted at a single center. Double-blinding was not possible because the tablets differed in size, shape, and coating, qualities that are known to affect esophageal transit.

Each of the 6 treatment periods was separated by a minimum of 40 hours and a maximum of 14 days. To explore treatment effects and position effects simultaneously, the study was conceptually divided into 2 phases consisting of the first and second 3 treatment periods. In the first phase, half of the subjects were randomly assigned to receive the 3 treatments in the erect position and the other half received the 3 treatments in the semisupine position; in the second phase, the position assignments were reversed. Within each phase, dosing was organized as a 3-period crossover, with subjects receiving the 3 tablet types in 1 of 6 possible sequences. The randomization list was further structured so that each tablet type was administered to between 6 and 8 subjects in each period.

Study Drugs

Three varieties of bisphosphonate tablets were used in this study: branded risedronate sodium 35-mg tablets

(Actonel, lot 0000417436, expiration March 2008) and 2 generic formulations of alendronic acid 70-mg tablets (lot A34009, expiration August 2008, Novopharm Limited, Toronto, Canada; lot A18028, expiration February 2009, Teva UK Limited, Morley, United Kingdom). The branded risedronate sodium tablets are film coated and oval shaped, weighing 247 mg and measuring 11.7 × 5.8 mm. The Novopharm alendronic acid tablets are uncoated and oval shaped, weighing 200 mg and measuring 10.8 × 6.2 mm. The Teva alendronic acid tablets are uncoated, round, and flat, weighing 200 mg and measuring 8 mm in diameter.

Radiolabeling

Technetium-99m (^{99m}Tc) sodium pertechnetate was obtained by elution of a ^{99}molybdenum/^{99m}Tc generator (Elumatic III, Cisbio, Sandhurst, United Kingdom). The ^{99m}Tc sodium pertechnetate at a high specific activity (~500 MBq [13.5 mCi] per mL) was adsorbed onto ion-exchange resin (Amberlite IRA402[Cl], Alfa Aesar, Ward Hill, Massachusetts). This material was prepared to a final predetermined activity that ensured that each tablet contained ~5 MBq ^{99m}Tc at the scheduled administration time.

A single hole measuring 1.5 mm in diameter was drilled into the edge face of the tablets in line with the long axis to facilitate radiolabeling. After the hole was filled with radioactive resin, the tablet edge was sealed with bone cement to ensure that the contact face was smooth and clean of material. Previous in vitro dissolution studies undertaken using radiolabeled film-coated risedronate placebo tablets indicated that the release of radioactivity into solution coincided with visual observations of tablet dispersion, validating the scintigraphic procedure.[13] Validation of the radiolabeling and imaging methodology, which is an essential component of scintigraphic studies, has been addressed previously.[13] The in vitro disintegration time of the tablets was similar before and after radiolabeling,[13] confirming that the radiolabeling process did not alter the physical integrity of the tablets.[17]

The effective dose of radiation from the radiolabeled formulation was 0.13 mSv per subject, for a total effective dose of 0.75 mSv over the 6 periods of the study.

Study Procedures

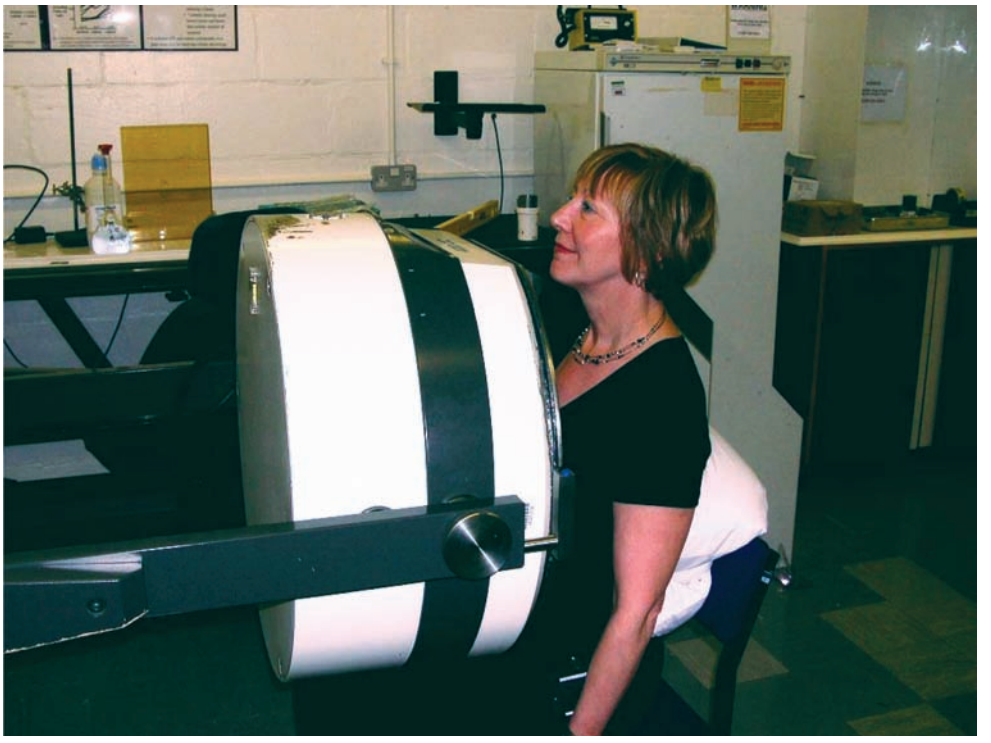
Scintigraphic data were obtained using a gamma camera (Maxicamera II, GE Healthcare Ltd., Chalfont St. Giles, United Kingdom) fitted with a low-energy collimator and peaked at 140 keV for ^{99m}Tc. The 128 × 128 pixel matrix images were stored on a dedicated Hermes nuclear medicine computer (Nuclear Diagnostics Ltd., Gravesend, United Kingdom).

Oral dosing took place between 7:30 AM and 12:00 noon on each study day. Subjects received each dose after an overnight fast; they could drink plain water as needed up to the time of dosing. Subjects were positioned in the erect or semisupine (45°) position in front of the gamma camera (**Figure 1**) and were asked to swallow the tablet with 30 mL of water from a spouted drinking beaker and to remain still during the imaging period. The 45° position was checked using a large angle measure placed alongside the subject's body while she lay on the chair with her head supported by a headrest. The subject was asked to adjust her position in the chair to achieve the correct angle.

The dynamic-imaging sequence was initiated at the start of swallowing and was stopped when the tablet was observed to enter the stomach. Esophageal transit was captured by dynamic acquisitions of 10 minutes' maximum duration. Transit times of ≥600 seconds were censored. The dynamic-imaging protocol was composed of 2 frame groups: 2 frames per second for 30 seconds (total of 60 frames), followed by 1 frame per 15 seconds for 9.5 minutes (total of 38 frames). After dynamic imaging was completed, subjects received 240 mL of half-fat milk to reduce absorption of the drug, followed by a light meal of tea or coffee and a toasted teacake with butter.

All image analysis was carried out in a blinded fashion by 2 experienced independent observers (A.C.P. and P.D.H.) working to standardized criteria for determining swallowing times and tablet disintegration. The observers reached a final decision after reviewing the data independently. The dynamic images were viewed on the computer monitor and the time of the frame in which the tablet was seen in the oropharynx was noted. The images were then displayed in turn to identify the time of any stasis in the esophagus and the time at which the tablet entered the stomach. For tablet swallowing, the series of images showed the tablet passing along the esophagus and moving laterally through the cardiac orifice into the stomach, features that could be identified by an experienced observer without the need for administration of a second radioactive marker. The spread and separation of tablet activity from a single defined spot to an extended trace or multiple discrete sites of activity, as

A



B

Figure 1. Subject in front of the gamma camera for monitoring of tablet swallowing in (A) the erect position and (B) the semisupine (45°) position.

seen on the image, were taken as evidence of tablet disintegration.

Sample Size and Statistical Analysis

A previous study of the coated risedronate tablet taken in the erect position with 30 mL of water reported a mean (SD) transit time of 3.2 (1.6) seconds in a group of 28 postmenopausal women.[13] In the present study, assuming that the within-subject variation would have an SD of ≤1.6 seconds, 18 subjects would provide >90% power to detect a treatment difference of 2 seconds in either the erect or semisupine position. By design, each subject was to contribute 2 observations per treatment and 3 observations per position; thus, the power to detect differences of ≥2 seconds in association with treatment or position (main effects) was also expected to be >90%.

The disintegration data were summarized as counts by tablet type, and the transit-time data were summarized as medians and ranges. The plan for statistical analysis of transit times was to use a linear mixed-effects model. However, because of the occurrence of several transit times >15 seconds (a time previously defined as representing prolonged stasis[4]) and 2 transit times that were censored at 600 seconds, stratified Cox proportional-hazards regression models were used for statistical analysis of transit times. Explanatory variables were coded in such a way that hazard ratios (HRs) <1.0 indicated longer transit times. The estimation of HRs and tests of statistical significance conducted with the Cox regression modeling included an adjustment for repeated measures on each subject. Kaplan-Meier plots of transit times were also prepared. All statistical analyses used SAS versions 8.2 and 9.1.3 (SAS Institute Inc., Cary, North Carolina).

RESULTS

Twenty women participated in the study, all of whom completed the 6 study periods. The mean age of the subjects was 62 years (range, 51–77 years).

Esophageal Transit Times

The median transit times for the 3 bisphosphonate formulations swallowed in the erect and semisupine positions are shown in the **table.** In the erect position, the median transit times were 3.0 seconds (range, 1.0–5.5 seconds) for risedronate sodium tablets, 3.3 seconds (range, 0.5–13.5 seconds) for Novopharm alendronic acid tablets, and 3.8 seconds (range, 1.5–8.5 seconds) for Teva alendronic acid tablets. In the semisupine position, the corresponding median transit times were 3.0 seconds (range, 1.0–27.0 seconds), 4.5 seconds (range, 1.0–600 seconds), and 4.0 seconds (range, 1.0–98 seconds). Three subjects had prolonged esophageal transit times of 98, 593, and 600 seconds; the first of these prolonged transit times involved a Teva

Table. Transit times for the 3 types of bisphosphonate tablets in the erect and semisupine (45°) positions.

	Transit Time, Median (Range), Seconds	
Formulation	Erect	Semisupine
Risedronate sodium 35-mg tablets*	3.0 (1.0–5.5)	3.0 (1.0–27.0)
Alendronic acid 70-mg tablets†	3.3 (0.5–13.5) 1 Tablet disintegrated in the esophagus	4.5 (1.0–600‡) 3 Tablets disintegrated in the esophagus
Alendronic acid 70-mg tablets§	3.8 (1.5–8.5)	4.0 (1.0–98)

*Actonel® (Procter & Gamble Pharmaceuticals, Inc., Cincinnati, Ohio).
†Novopharm Limited, Toronto, Canada.
‡The duration of imaging was 600 seconds, beyond which observations were censored.
§Teva UK Limited, Morley, United Kingdom.

tablet, and the others involved Novopharm tablets. The 2 longest transit times were associated with tablet disintegration throughout the esophagus; there were no other observed systematic factors to explain these results.

Seven transit times of ≥15 seconds were observed during the study: 2 with risedronate sodium tablets (15.0 and 27.0 seconds), 4 with Novopharm alendronic acid tablets (15.5, 57.0, >593, and >600 seconds), and 1 with a Teva alendronic acid tablet (98 seconds). All 7 of these transit times were recorded while subjects were in the semisupine position and during the first period of the study, when the first 3 tablets were taken. The model term for position-by-period interaction was statistically significant ($P < 0.05$).

Further analyses to elucidate the effects of position and tablet were conducted in a stratified manner to provide conclusions that would be as robust as possible in the presence of the interaction cited. **Figure 2** presents the transit-time data in the form of Kaplan-Meier plots for the erect and semisupine positions. Because of the 6-period crossover design, each subject contributed a transit-time value for each tablet type in each panel. All transit times in the erect position were <15 seconds, 67% of them ≤5 seconds. In contrast, 7 transit times in the semisupine position were ≥15 seconds, including 2 that were censored at the maximum observation time of 600 seconds.

For a fuller examination of the effect of position, the data were separated into 6 sets, one for each combination of tablet type (risedronate, Teva, and Novopharm tablets) and position order (semisupine in the first or second period). Each set consisted of 2 values from each of 10 subjects, one for the semisupine position and one for the erect position. In 5 of the 6 sets, more subjects had a longer transit time in the semisupine position than in the erect position. The exception was the first set of data for risedronate in the semisupine position, in which 5 subjects had a longer transit time in the erect position and 5 had a longer transit time in the semisupine position.

In light of the consistency in direction of the position differences, a stratified Cox model was fitted to estimate an average position effect. The position effect was statistically significant ($P = 0.043$). The estimated HR was 0.74, indicating longer transit times in the semisupine position. Differences in transit times by tablet type also were explored in a stratified manner. Data were separated into 4 sets defined by combinations of position (erect or semisupine) and period (first or second). Each set consisted of 3 values from each of 10 subjects, one for each tablet type. Although the ordering with respect to tablet type was not as consistent as the ordering for position, transit times for the risedronate sodium tablets were shortest for 50% of subjects when the 3 tablet types were administered in the erect position and shortest for 60% of subjects when the tablets were administered in the semisupine position (**Figure 2**).

In light of the consistent direction of the HRs for the Novopharm and Teva tablets versus the risedronate tablet, a stratified Cox model was fitted to estimate average tablet effects. The Cox model indicated a statistically significant difference in transit times among the 3 types of tablets ($P = 0.007$), with significantly longer transit times compared with the risedronate tablet for the Novopharm tablet (HR = 0.59; $P < 0.001$) and the Teva tablet (HR = 0.71; $P = 0.042$).

Disintegration

In the erect position, the Novopharm alendronic acid tablet disintegrated in the mouth of 1 subject during swallowing, causing her to cough excessively. She was given 20 mL of water 1 minute after imaging, and the tablet was seen to disintegrate in the esophagus. A further 150 mL of water was given at the end of the 10-minute scintigraphic study to clear the disintegrated tablet from the esophagus. Gamma camera images from this subject are shown in **Figure 3**. In the semisupine position, the Novopharm tablet disintegrated in the esophagus during swallowing in 3 subjects, one of whom still had the disintegrated tablet in the esophagus at the end of the 10-minute period of scintigraphy.

Figure 4 contains images of esophageal transit after dosing with the risedronate sodium tablet (part A), the Novopharm alendronic acid tablet (part B), and the Teva alendronic acid tablet (part C) in the semisupine position in a single subject. The Novopharm tablet disintegrated along the length of the esophagus and had not reached the stomach after 300 seconds (5 minutes).

DISCUSSION

This study provided information on the in vivo swallowing and disintegration of oral bisphosphonate tablets. Some patients, particularly the elderly, have difficulty swallowing oral dosage forms, and this difficulty may be increased if the surface properties of

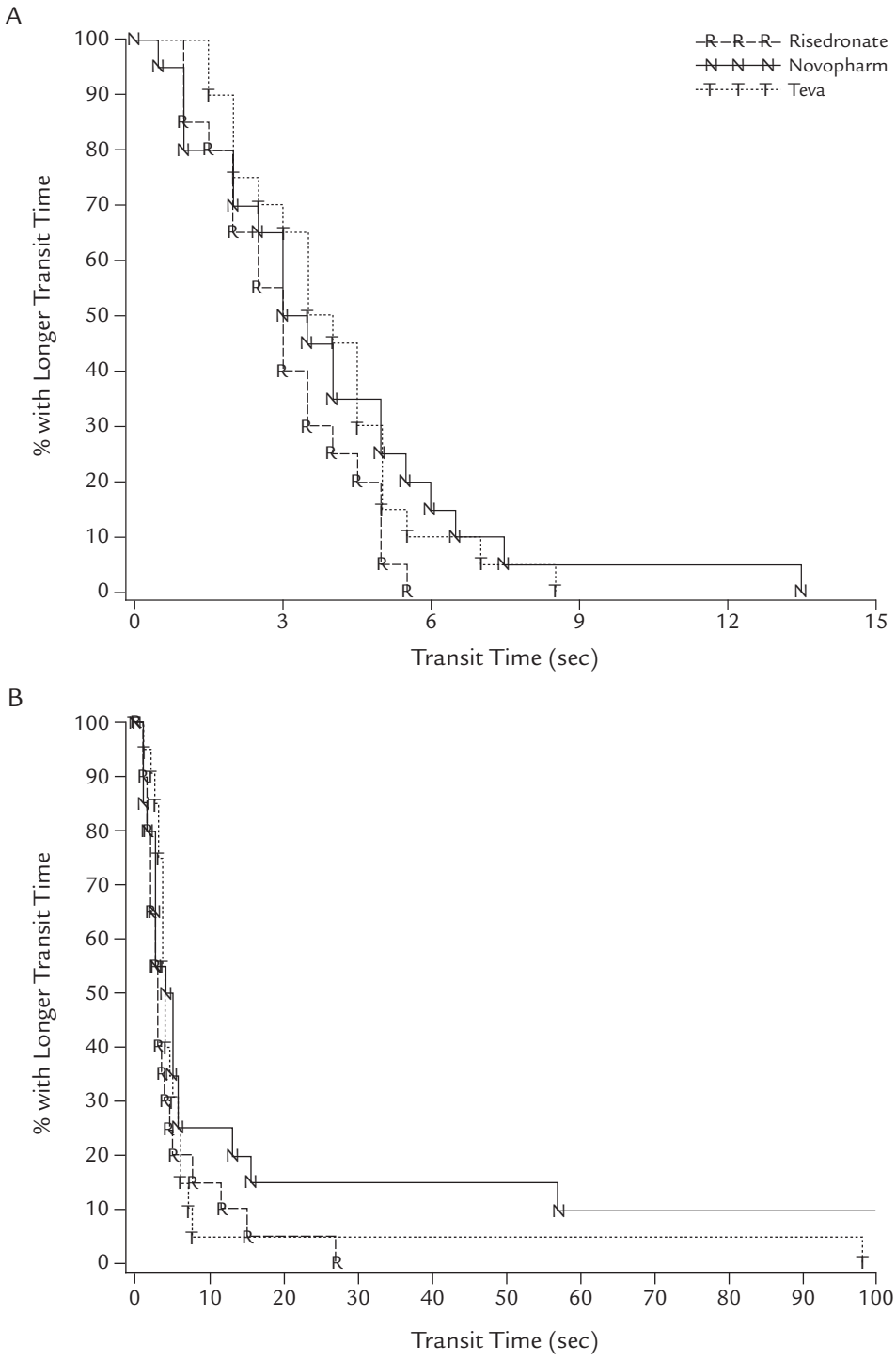


Figure 2. Kaplan-Meier plots for esophageal transit in (A) the erect position and (B) the semisupine (45°) position. In part B, 2 transit times for the Novopharm tablets were censored at 600 seconds. R = branded risedronate sodium 35-mg tablets (Actonel®, Procter & Gamble Pharmaceuticals, Inc., Cincinnati, Ohio); N = Novopharm generic alendronic acid 70-mg tablets (Novopharm Limited, Toronto, Canada); T = Teva generic alendronic acid 70-mg tablets (Teva UK Limited, Morley, United Kingdom).

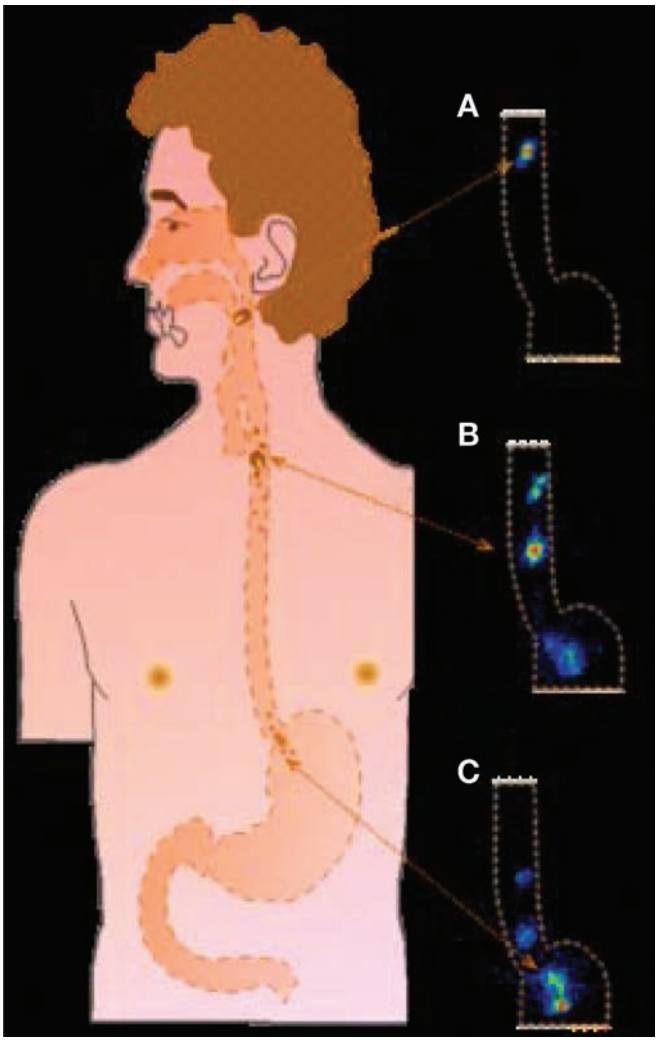


Figure 3. Gamma camera images from the subject in whom a generic alendronic acid 70-mg tablet (Novopharm Limited, Toronto, Canada) disintegrated in the mouth during swallowing in the erect position. (A) Tablet in the mouth after 1 minute. (B) Break-up of tablet at 2 minutes after subject was given 20 mL of water. (C) Dispersion of tablet in esophagus and stomach after 10 minutes. The areas of greatest activity are shown in red and yellow, and the areas of lowest activity in blue.

the formulation cause the pill or tablet to become sticky once it comes in contact with moisture. Comparative in vitro studies have reported different degrees of adhesiveness of various commercial formulations containing alendronate, suggesting the potential for differences in esophageal tolerance.[18] In the present study, a tablet of one of the generic formulations disintegrated in the subject's mouth during swallowing, and she had to be given an additional 20 mL of water 1 minute after imaging to suppress coughing; the tablet then disintegrated in the esophagus. Use of a rapidly disintegrating formulation in such an instance would increase mucosal exposure to drug. It should be noted that because the radiolabel in this study was inserted into the center of the tablet, disintegration could not be observed until the tablet had essentially disintegrated completely. Thus, it was not possible to determine the onset of in vivo disintegration (which would occur before the time of complete disintegration). The Novopharm tablets used in this

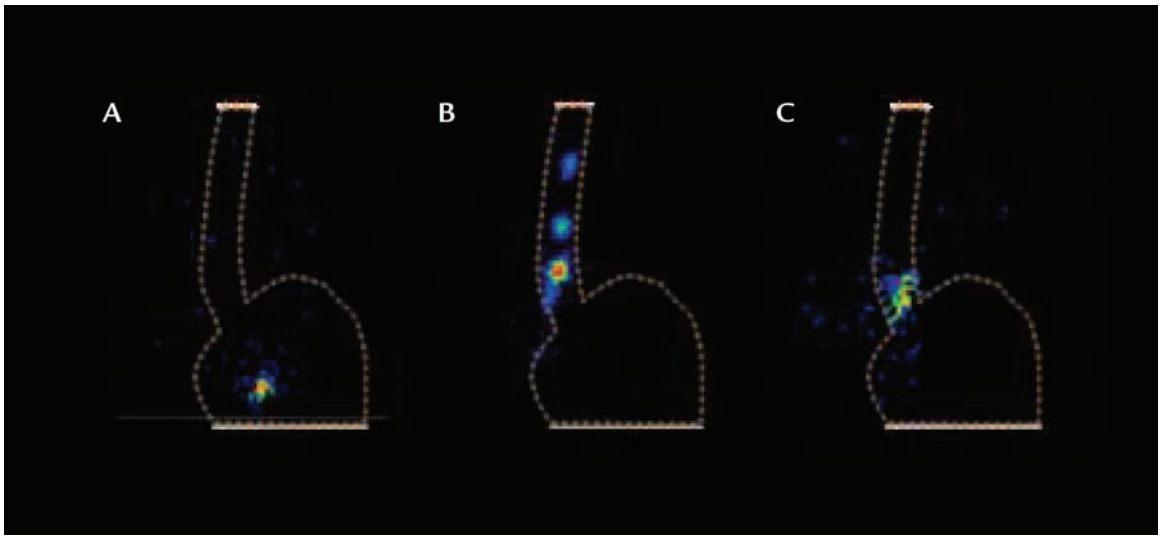


Figure 4. Scintigraphic gamma camera images illustrating the transit of the 3 types of bisphosphonate tablets during swallowing in the semisupine (45°) position in the same subject. (A) Branded risedronate sodium 35-mg tablet (Actonel®, Procter & Gamble Pharmaceuticals, Inc., Cincinnati, Ohio) arriving intact in the stomach after 6 seconds. (B) Novopharm generic alendronic acid 70-mg tablet (Novopharm Limited, Toronto, Canada) dispersed along the length of the esophagus. (C) Teva generic alendronic acid 70-mg tablet (Teva UK Limited, Morley, United Kingdom) beginning to break up as it enters the stomach after 6 seconds. The areas of greatest activity are shown in red and yellow, and the areas of lowest activity in blue.

study can readily disintegrate in the mouth or the esophagus during swallowing if not taken according to the dosing instructions.[12]

The model term for position-by-period interaction in this study was statistically significant ($P < 0.05$). Despite careful design, any study of this nature involves the possibility of a learning effect. However, this would not negate the findings of a genuine effect of posture and premature tablet disintegration. In general, Cox regression modeling indicated that esophageal transit times were shorter in the erect position than in the semisupine position and were shorter for the risedronate tablet than for the other 2 tablet types. However, the survivor functions presented in the Kaplan-Meier plots crossed at some points, and these general findings did not hold uniformly at the individual level. These departures from the general findings may be the result of interactions between tablet characteristics (eg, shape, coating) and individual factors (eg, physiology, swallowing behavior), leading to variation in observed transit times and disintegration.

A potential limitation of this study is that the tablets could not be blinded, as this would have altered esophageal transit times. The observers who read the scintigraphic images were blinded to treatment, which is a standard procedure in scintigraphic studies of commercial dosage forms. Another potential limitation was that the tablets were dosed with 30 mL of water and not with the 6 to 8 fluid ounces (180–240 mL) recommended in the product labeling for alendronate sodium.[12] However, a previous habits-and-practices study in 108 female subjects aged >60 years found that if subjects were not instructed about the volume of water to ingest, the median volume of water ingested with the film-coated placebo risedronate tablet was 124 mL (4.2 fluid ounces) and ranged from 7 to 385 mL.[13] Thus, a volume of 30 mL of water was used in the present study because the previous study found it to be the minimal volume of water that could be swallowed and adequately allow differentiation between formulations.[13] A final limitation is that the tolerability of the tablets was not determined, as this was a mechanistic study.

CONCLUSIONS

In this study of 3 formulations of bisphosphonate tablets in healthy female volunteers, the effect of body position was statistically significant, indicating longer transit times in the semisupine position. There was a statistically significant difference in transit times among the 3 types of tablets, with both generic formulations of alendronic acid 70-mg tablets having longer transit times compared with the branded risedronate sodium 35-mg tablet. In a single case, a generic alendronic acid tablet disintegrated in the mouth and during esophageal transit, exposing the entire length of the esophagus to drug. The findings of this study indicate that the pharmaceutical attributes of various formulations can affect esophageal exposure. Given the low frequency of tablet disintegration in the esophagus, a larger blinded, controlled study is needed to determine whether this is a consistent feature of generic alendronic acid tablets.

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