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Esophageal transit of the weekly film-coated risedronate (Actonel®) placebo tablet in subjects with Kyphosis

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Abstract

Risedronate sodium is a pyridinyl bisphosphonate of proven effectiveness for the treatment and prevention of osteoporosis and Paget's disease of the bone. The aim of this study was to compare the esophageal transit and gastric emptying of the placebo film-coated risedronate tablet when taken with 50 or 120 mL of water in subjects with Kyphosis. A total of 23 patients with radiologically documented osteoporosis participated in a single-center, open-label, crossover gamma scintigraphy study. The mean esophageal transit times were 15.6 s (50 mL) and 12.0 s (120 mL) and the mean gastric emptying half-times were 20.5 min (50 mL) and 14.3 min (120 mL). There was no relationship between the degree of Kyphosis measured from lateral standing radiographs and the esophageal transit time. This study demonstrated that even when taken with a minimal volume of water the esophageal transit and gastric emptying of the film-coated 35 mg weekly risedronate placebo tablet was similar in kyphotic subjects to previously obtained results from healthy control subjects.

Keywords: Risedronate; Esophageal transit; Scintigraphy; Kyphosis

1. Introduction

The major risk factors for "pill-induced esophagitis" (Kikendall et al., 1983; Kikendall, 1991) are patient age-related impairment of esophageal motility and the characteristics of the dosage form, including size, shape and coating (Spiller, 1986; Perkins et al., 1999; Ferriolli et al., 1996). As the population ages, the problems of osteoporosis and impaired esophageal peristalsis both increase. Impaired esophageal peristalsis in elderly subjects increases the likelihood that solid oral dosage forms (mainly tablets and capsules) will lodge in the esophagus or reflux back into the esophagus, where impaired clearance prolongs the contact time with esophageal mucosa. Risedronate (Actonel®, Optinate® Procter & Gamble, Cincinnati, OH), a pyridinyl bisphosphonate that inhibits bone resorption, is effective in the treatment of Paget's disease of bone (Miller et al., 1999; Brown et al., 1999), and in the prevention and treatment of glucocorticoid-induced (Cohen et al., 1999; Reid et al., 2000), and postmenopausal osteoporosis (Eriksen, 1986; Harris et al., 1999; McClung et al., 2001; Parfitt et al., 1987; Reginster et al., 2000). In women with postmenopausal osteoporosis, risedronate treatment can reduce the risk of vertebral fracture by up to 65% in the first year of treatment and sustained effects of continuing treatment have now been demonstrated over 5 years (Sorensen et al., 2003). The dose approved in the United States, Canada, and in many other countries for the prevention and treatment of postmenopausal osteoporosis is 5 mg daily or 35 mg once a week; 30 mg tablets are indicated for the treatment of Paget's disease of the bone.

Clinically, there have been reports of gastrointestinal adverse events including dysphagia, esophagitis and ulceration of the stomach and esophagus associated with oral bisphosphonate therapy (Lufkin et al., 1994; deGroen et al., 1996). In

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most cases, the esophageal problems fit the pattern of pill-induced esophagitis or reflux of partially dissolved tablets from the stomach. Administration of oral forms of aminobisphosphonates is contraindicated in patients with esophageal abnormalities.

To further reduce the likelihood of esophageal complications for risedronate sodium, a film-coated formulation was developed to facilitate rapid esophageal transit and minimize contact with the mucosa. In previous studies in healthy elderly subjects, the mean transit time of the film-coated risedronate placebo tablet was 3.3 s (range 1.5–7.0 s) when swallowed with 50 mL of water (Perkins et al., 1999). Similar results were obtained in a subsequent study in healthy, elderly subjects when the tablet was ingested with either 50 or 240 mL of water (Connor et al., 2001). When swallowed with 50 mL of water, the mean esophageal transit time was 4.6 s (range 0.8–10.4 s) and when ingested with 240 mL of water the mean esophageal transit time was 5.3 s (range 2.4–18.4 s). The esophageal transit time of a similar film-coated placebo tablet was also evaluated in subjects with gastroesophageal reflux disease (GERD) who are at risk for esophageal motility disorders and delayed gastric emptying (Perkins et al., 2001a). When swallowed with 240 mL of water the mean esophageal transit time in subjects with GERD was 4.4 s (range 1.0–14.5 s) and in the healthy control group the mean esophageal transit time was 3.1 s (range 0.5–6.0 s). The mean gastric emptying half-time in subjects with GERD was 15.9 min (range 11.0–26.0 min) and in the healthy control group the healthy mean gastric emptying half-time was 15.0 min (range 11.0–21.0 min).

The radiologic manifestation of Kyphosis was first described by Scheuermann (1920) with a prevalence which varies between 1% and 8%, however, only 1% of those affected seek medical treatment (Tribus, 1998). The age of onset is unknown but is rarely observed before 10 or 11 years of age. The appearance of the deformity is the most common complaint but approximately 50% of patients that seek medical attention have pain particularly if the lumbar spine is involved. Severe congenital Kyphosis may require surgical correction, while Kyphosis from osteoporosis may lead to significant height loss, change in shape, and disability. Compression of the abdominal contents due to approximation of the lower ribs and iliac crests may lead to a sensation of distension or discomfort.

The esophageal transit of the dosage forms used in clinical practice has not previously been evaluated in subjects with Kyphosis. The postural effects resulting from Kyphosis might be expected to cause impaired esophageal transit with adverse results for patients on long-term bisphosphonate therapy. Postural problems in osteoporotic kyphotic patients can be severe and this may also affect the swallowing of food and oral medication.

The purpose of this study was to determine if there is any difference between the esophageal transit and the gastric emptying time of the radiolabeled 35 mg placebo risedronate tablet when taken with either 50 or 120 mL in kyphotic osteoporotic patients who were on treatment with oral bisphosphonates. This method is noninvasive and involved minimal discomfort to the subjects (Ham et al., 1985; Klein and Wald, 1984).

2. Materials and methods

2.1. Formulations

Film-coated placebo weekly risedronate tablets were supplied by Procter and Gamble Pharmaceuticals (Physician's Desk Reference, 2004). The film-coated placebo tablets, identical to the commercial 5, 30 mg and weekly 35 mg tablet formulations, were oval shaped (5.7 mm × 11.5 mm), weighing 247 mg. Because the exterior surface and density of the dose form, rather than the presence of active drug, determine the esophageal transit properties, we were able to use a placebo formulation, thus simplifying the execution of the study. There is no evidence to suggest that the drug alters gastric emptying, therefore the placebo tablet is representative of the in vivo disintegration and gastric emptying of the active tablets.

2.2. Radiolabeling

Technetium-99m sodium pertechnetate was obtained by elution of a molybdenum-99/technetium-99m generator (Elumatic III, CIS Schering (UK) Ltd.). The ^{99m}Tc sodium pertechnetate was converted into the chelate ^{99m}Tc-labeled diethylenetriaminepentaacetic acid (^{99m}Tc-DTPA) at a high specific activity (approximately 500 MBq (13.5 mCi) per mL), using a standard commercial kit (Mallinckrodt Medical Ltd.). This material was dried onto powdered lactose using a warm air dryer to yield the modified dried fill to a final predetermined activity that ensured that each tablet contained between 3.8 and 6.2 MBq (103–168 uCi) ^{99m}Tc-DTPA/lactose at the scheduled time of dosing.

A single hole, 1.5 mm in diameter, was drilled into the edge face in line with the long axis of the tablet to facilitate radiolabeling with ^{99m}Tc-DTPA. After the hole was filled with the radioactive powder, the tablet edge was sealed with bone cement to ensure that the contact face was smooth and clean of material. Stability of labeling and the effect of incorporating the radiopharmaceutical on the disintegration properties of the formulation were evaluated and determined to be acceptable at the site prior to the clinical study. Previous in vitro dissolution studies undertaken with the radiolabeled film-coated placebo risedronate tablets have confirmed that the release of radioactivity into solution coincides with visual observations of tablet dispersion, thus validating the scintigraphic procedure. Validation of the radiolabeling and imaging methodology is an essential component of scintigraphic studies and has been addressed previously by our group (Perkins et al., 2001b).

2.3. Study population

Twenty-three patients (two male, 21 female) were recruited from the osteoporosis clinic at Nottingham City Hospital. To be eligible for entry into the study subjects had to be more than 50 years old, postmenopausal if female (surgical or natural), be on oral bisphosphonate therapy, and have clinical evidence of Kyphosis. The degree of Kyphosis deformity was graded radiologically according to previously published methodology

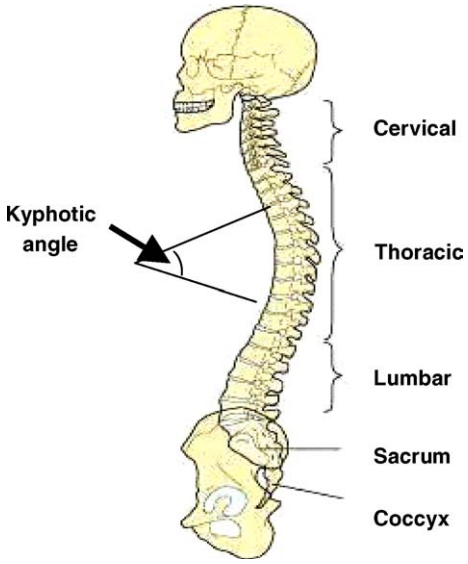

Fig. 1. Schematic of the degree of kyphotic curvature measured from the T5 and T12 projected lines on the standing lateral radiographs.

(Stokes, 2000). In each case a standing lateral radiograph was obtained as documented by Moe et al. (1978). This was carried out by measurement of the angle between the intersection of lines extending from the superior end plate of the fifth and the inferior end plate of the 12th thoracic vertebrae as shown in Fig. 1.

Subjects were excluded from the study if they: (a) had a history of alcohol or drug abuse, (b) had any investigational drug administered within the previous 8 weeks, (c) failed to satisfy the investigator's assessment of fitness to participate based on a complete medical history and physical examination, (d) consumed alcohol within 24 h of start of study, (e) participated in a similar study involving the use of radioisotopes in the previous 3 months such that radiation exposure from the current study would exceed the recommended yearly exposure limit (5 mSv), (f) taken any medication which may affect esophageal or gastric motility within the previous 8 weeks (such as atropine, propantheline, narcotic analgesics, amitriptyline, imipramide, loperamide, desipramine, and chlorpromazine), or (g) had a previous history of gastric surgery or active upper gastrointestinal diseases.

This was a single-center, open-label, crossover study. The study was approved by the Nottingham Hospital's Ethical Committee and the Administration of Radioactive Substances Advisory Committee (ARSAC) of the UK Department of Health. All subjects were fully informed of the procedure and gave written consent to participate. The effective dose to each subject from the radiolabeled formulation was 0.13 mSv giving a total effective dose of 0.26 mSv from the two parts of the study. Patients attended on two separate occasions within a 7 day period. The volume of water used at each visit (50 or 120 mL) was selected according to a randomized schedule. The subject arrived on the morning of the study having fasted from 22:00 h the previous evening, and did not consume alcohol within 24 h prior to dosing. In strict order commencing at 09:00 h, the subjects were seated in front of the gamma camera to facilitate anterior imaging of the esophagus extending from the oropharynx to the upper margin of the stomach. In each case, the subject received the Tc-99m-film-coated placebo risedronate tablet with 50 or 120 mL water taken in a continuous sequence of swallows. The images were recorded in a 64 × 64 cell matrix over a total imaging time of 10 min as 60 (0.5/s) dynamic frames, followed by 38 (15 s) dynamic frames. After 10 min, external radioactive markers were taped to the anterior and posterior abdomen to permit accurate alignment of the subsequent sequential static images. Anterior and posterior images (each of 30 s duration) of the stomach were recorded every 20 min until gastric emptying was completed.

2.4. Processing and displaying of scintigraphic data

All images were analyzed using a dedicated nuclear medicine computer (Nuclear Diagnostics Ltd., London/Stockholm) by one of two experienced operators who were blinded to the dosing schedule. The esophageal transit time and gastric emptying time of the radiolabeled placebo tablet were measured from the images. In each case, the individual frames in the study were first displayed to determine the time that activity was first seen in the oropharynx. The subsequent frames were displayed to show the time of arrival of the film-coated placebo tablet in the stomach. The difference in the time between these frames was used to give the esophageal transit time of the film-coated placebo tablet in seconds. Once the initial transit time was recorded, the software application was used to produce a condensed image display. The display was produced by adding the collected data across the 40 cm field of view of the gamma camera detector to form a single column of data for each frame. The condensed image was produced by placing all columns of data in sequence. Dynamic frames were analyzed by defining regions of interest over the oropharynx, esophagus, and stomach.

Anterior and posterior static images of the gastric activity were displayed and emptying was assessed after defining a region of interest over the stomach and recording counts from the images. All data were corrected for radioactive decay and background radioactivity, and a geometric mean value was calculated to account for anterior–posterior movement of activity in the images. The time at which at least 50% of the formulation had passed from the stomach was recorded.

2.5. Statistical analysis

Descriptive statistics, including the mean, standard error of the mean, median, and range, were provided for each outcome parameter (esophageal transit time and gastric emptying time). A one-way analysis of variance (ANOVA) model was fitted with the term of subject group, and a 95% confidence interval (CI) was constructed to quantify the difference in mean time between the 50 mL group and the 120 mL group. The normality assumption was examined in the above one-way ANOVA model. If the assumption was not satisfied, a 95% CI was constructed for each outcome parameter to quantify the difference in median time between the 50 mL group and the 120 mL control group by using the nonparametric Hodges–Lehman procedure with StatXact-3® (Cytel® Software, Cambridge, MA).

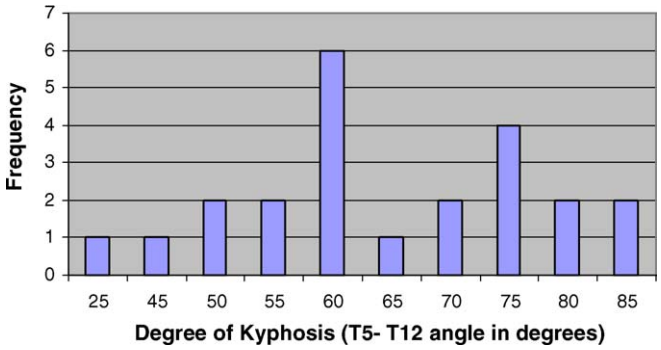

Fig. 2. Histogram of the kyphotic curvature recorded in 23 subjects.

3. Results

A total of 21 women and two men participated in the study. Twelve patients swallowed the formulations 2 days apart and 11 patients swallowed the formulations 5 days apart. The mean age of the subjects was 72 years (range 55–83). The median degree of kyphotic curvature measured from the T5 and T12 projected lines on the standing lateral radiographs was 60° with a range of 25–85°. A histogram of the degree of kyphotic curvature is shown in Fig. 2. The smaller the angle indicates a greater degree of curvature of Kyphosis.

Due to a computer failure, data on the esophageal transit time was lost for two subjects. The mean esophageal transit times of the placebo risedronate tablet was 15.6 s (range 4.0–116.0 s) when taken with 50 mL of water and 12.0 s (range 4.5–60.0 s) when taken with 120 mL of water. No subjects complained of dysmotility and there were no signs of esophageal stasis. Fig. 3 shows the esophageal transit time for each subject in relation to the severity of Kyphosis. Subjects with the longest transit time did not have the most severe Kyphosis. The difference between esophageal transit time means was found to be not statistically significant ($p = 0.58$). The sequence (which water volume each subject received first), carry-over, and period effects were also found to be not statistically significant, supporting the validity of the treatment mean difference. The longest esophageal transit time of 116 s was observed in a subject with a Kyphosis angle of 60° who swallowed the tablet with 50 mL of water, but when ingested with 120 mL of water the transit time was 4.5 s. The second longest transit time of 60 s was observed in a subject with a Kyphosis angle of 60° when swallowing the tablet with 120 mL of water, however when ingested with 50 mL of water the transit time was 20 s.

The mean gastric emptying half-time of the placebo risedronate tablets taken with 50 mL of water was 20.5 min (range 5.5–80.6 min) and 14.3 min (range 5.5–34.5 min), with 120 mL of water. These were consistent with data obtained previously (21). Fig. 4 shows the gastric emptying half-time for each subject. Within each sequence, mean gastric emptying half-times were longer with the 50 mL water compared to the 120 mL water. However, on average, gastric emptying half-times were longer in the subjects that received 50 mL water first (A) compared to those that received 120 mL water first (B). Due to these factors,

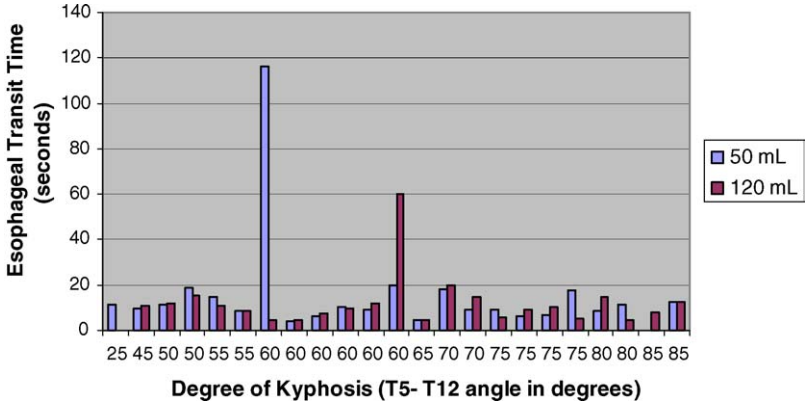

Fig. 3. Esophageal transit times for Kyphosis subjects following ingestion of a ^{99m}Tc-labeled, film-coated placebo risedronate tablet.

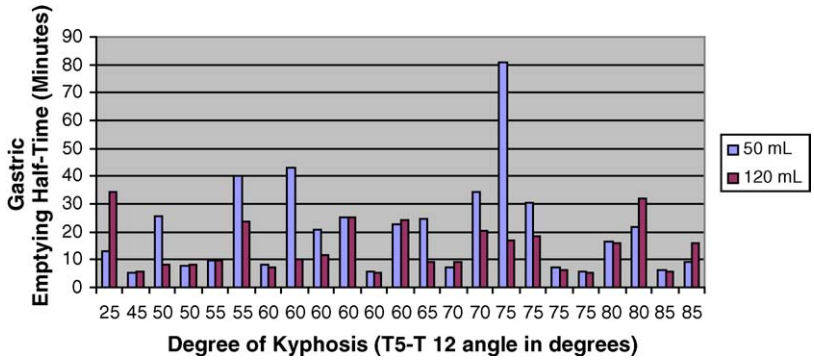

Fig. 4. Gastric emptying half-time for Kyphosis subjects following ingestion of a ^{99m}Tc-labeled, film-coated placebo risedronate tablet.

a firm conclusion could not be drawn with regard to difference in gastric emptying half-times between the 50 and 120 mL groups. Reasons for the sequence and sequence by treatment effects could be due to differences between subjects assigned to sequences A and B, despite randomization. Other possibilities are that something in the study procedures differed between the periods or that the subjects experienced a learnt response that affected the swallowing and emptying on the second occasion. However, this seems unlikely since the subjects did not complain of any swallowing difficulties and they were not aware of the swallowing times during the study procedures.

4. Discussion

There are limited data with regard to the esophageal transit and gastric emptying times of medication in subjects with Kyphosis. However given the advanced age of many patients with Kyphosis due to osteoporosis and the known deterioration of esophageal motility seen with age (Ferriolli et al., 1996) it was predictable that factors such as large size, circular outline, and surface muco-adherence of oral dose forms (Spiller, 1986) would all have an exaggerated effect. The risedronate formulation was designed to minimize these known effects being oval, film-coated, and as small as compatible with delivering the required amount of drug. Kyphosis is more prevalent in women because of the increased risk of widespread osteoporosis, but the sex of the patients was not an entry requirement of the present study and the proportion of women was a chance event. The volumes of water examined in the present study (50 and 120 mL) are less than recommended in the package insert in the United States which states that a minimum of 6–8 oz (180–240 mL) should be ingested with the tablet (Physicians' Desk Reference, 2004). Previous studies have shown the importance of the volume of water on esophageal transit (Perkins et al., 2001b). The volumes of water chosen for the present study, 50 and 120 mL of water, were selected as minimal volumes for detecting swallowing problems in these patients. The esophageal transit time in the current Kyphosis patients given 50 mL of water (mean 15.6 s, range 4.0–116.0 s) and 120 mL (mean 12.0 s, range 4.5–60.0 s) appear to be slightly longer than those obtained in healthy elderly subjects given a similar placebo tablet with 50 mL of water (mean 4.6 s, range 0.8–10.4 s) (15) but, this might be anticipated given the potential mechanical disadvantage of the esophagus in patients with Kyphosis. In a previous study, we defined esophageal stasis as a transit time of >20 s (Perkins et al., 2001b), but in the current study only two swallows out of the 44 measurements exceeded this value. The longest transit time was 116 s (with 50 mL) but the subject did not experience any sensation of esophageal obstruction and the film-coated placebo tablet entered the stomach without the ingestion of additional water. However, in this same subject when the tablet was administered with 120 mL of water the transit time was 4.5 s. Previously we evaluated the effect of 30 mL of water on the transit time of a similar film-coated placebo risedronate tablet (mean 3.2 s, range 0.5–6.5 s) compared to a round, uncoated placebo tablet (mean 65.2 s, range 1.5–596 s) in healthy elderly women (Perkins et al., 2001b). In three subjects, who swallowed the uncoated round tablet with 30 mL of water the transit time was 10 min which was the duration of imaging (Perkins et al., 2001b). Thus, tablet shape and the nature of the coating can have a significant impact on esophageal transit. The duration of gastric emptying (mean 50 mL, 15.9 min; controls, 15.0 min) was similar with the two ingestion volumes although the cause of the sequence effect is uncertain.

Table 1
Summary of esophageal transit and gastric emptying times in subjects with Kyphosis following ingestion of a film-coated placebo risedronate tablet

Outcome parameter	50 mL water ($N = 23$)	120 mL water ($N = 23$)	Difference (95% CI)[a] $p = 0.58$
Esophageal transit time (s)			
Mean (S.E.)	15.6 (4.88)	12.0 (2.46)	3.25 (−8.78,15.27)
Range	4.0–116.0	4.5–60.0	
Median	9.75	9.75	
Gastric emptying half-time (min)			
Mean (S.E.)	20.5 (3.64)	14.3 (1.81)	N/A[b]
Range	5.5–80.6	5.5–34.5	
Median	16.4	10	

[a] Difference and confidence interval calculated from crossover analysis.
[b] Treatment difference was not estimated due to the presence of statistically significant sequence and treatment by sequence effects.

To our knowledge this is the first study of gastric emptying of this type of tablet in patients with Kyphosis and it appears that gastric emptying is comparable to that seen with the same formulation in normal and GERD subjects (Connor et al., 2001; Perkins et al., 2001a,b) (Table 1).

In conclusion, the esophageal transit, and gastric emptying times of the placebo film-coated risedronate tablets were similar with both 50 and 120 mL of water in subjects with Kyphosis. The esophageal transit time did not correlate with the degree of kyphotic curvature. Although pill-induced esophagitis is rare, it is a potentially serious condition. It is therefore important that every effort is made to minimize the likelihood of this occurring in patients taking these forms of long-term medications. It should be noted that esophageal transit is unique to every formulation and this data does not apply to other commercially available oral formulations. All patients taking bisphosphonate tablets should always follow the dosing recommendation in the package insert. This study has further demonstrated the acceptable esophageal transit of the oval, film-coated placebo risedronate (Actonel®) tablet formulation.

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