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The use of scintigraphy to demonstrate the rapid esophageal transit of the oval film-coated placebo risedronate tablet compared to a round uncoated placebo tablet when administered with minimal volumes of water

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Abstract

As our population ages, and the consumption of pharmaceutical products rises, the incidence of solid oral dosage forms lodging in the esophagus is likely to increase and may be formulation dependent. The aim of this study was to compare the esophageal transit of the commercial film-coated risedronate tablet and a round uncoated tablet resembling the alendronate 10 mg tablet which is reported to cause esophagitis if ingested with little to no water. Water volumes of 30 ml and 50 ml were selected as these volumes can detect formulations prone to esophageal adhesion and a habits and practice study showed that these volumes are within the range preferred by women (7–385 ml). A total of 28 healthy postmenopausal women completed the four-way crossover scintigraphy study. For both volumes of water, the film-coated placebo risedronate tablet had a statistically significant faster esophageal transit time than the uncoated placebo tablet ($P = 0.002$ for 30 ml water and $P < 0.001$ for 50 ml water). Among those taking the round, flat, uncoated tablet, five subjects had esophageal stasis (transit > 20 s) and in three subjects the tablet remained in the esophagus at the end of the 10-min imaging period. No stasis was observed for the oval film-coated placebo risedronate tablet. This study demonstrates that tablet size, shape and coating are pharmaceutical parameters which can be controlled to minimize esophageal contact of a dosage form with esophageal tissue.

Keywords: Risedronate; Esophageal transit; Scintigraphy; Film-coating; Tablet

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1. Introduction

The major risk factors for 'pill-induced esophagitis' are patient age-related impairment of esophageal motility and dosage form characteristics. Impaired esophageal peristalsis in elderly subjects will increase the likelihood that solid oral dosage forms (mainly tablets and capsules) will lodge in the esophagus or reflux back into the gullet, where impaired clearance prolongs the period of contact with the esophageal mucosa. The volume of swallowed water, the position of the body when swallowing, and the size, shape and surface characteristics of the pharmaceutical dose form are important determinants of esophageal transit time (Applegate et al., 1980; Bonavina et al., 1987).

Bisphosphonates are a class of synthetic compounds used in the treatment of various metabolic bone diseases, including osteoporosis and Paget's disease of bone. Clinically, there have been reports of gastrointestinal adverse events including dysphagia, esophagitis and ulceration of the stomach and esophagus associated with primary aminobisphosphonate (pamidronate and alendronate) therapy (Lufkin et al., 1994; deGroen et al., 1999). In most cases, the esophageal problems fit the pattern of pill induced esophagitis or reflux of partially dissolved tablets from the stomach (Kikendall, 1999). The incidence of gastrointestinal side effects due to alendronate is reported to be higher in clinical practice than observed in the clinical trials (Ettinger et al., 1998). The esophageal irritation problems observed postmarketing for the round alendronate 10 mg tablets appear to be especially problematic if the tablet was ingested with little to no water or ingested lying down during or after ingestion of the tablet (deGroen et al., 1999).

Risedronate, a potent pyridinyl bisphosphonate, is chemically distinct from the primary aminobisphosphonates. The nitrogen in risedronate is in the pyridinyl ring structure, whereas the aminobisphosphonates (alendronate and pamidronate) contain the nitrogen as a primary amine. To further reduce the likelihood of esophageal complications, a film-coated oval formulation of risedronate was developed to facilitate rapid esophageal transit and minimize contact with the mucosa. In healthy, elderly subjects, the esophageal transit of the film-coated risedronate tablet ingested with 50 ml of water had a more rapid transit (mean time of 3.3 s) than that of a gelatin capsule form (mean time of 23.8 s) (Perkins et al., 1999). In a comparative endoscopy study, risedronate treatment resulted in significantly fewer gastric ulcers than alendronate treatment (Lanza et al., 2000).

Product labeling for risedronate sodium tablets in the United States instructs patients to take the tablet with a full glass of plain water (6–8 oz) to facilitate delivery to the stomach, and in Europe a water volume of at least 120 ml (4 oz) is recommended. In practice, patients may not comply with these dosing instructions and may take less than the recommended volume of water. A habits and practice study (section 2.1) showed that women prefer to ingest film-coated placebo risedronate tablets with a wide range of water volumes (7–385 ml). Thus, in designing an optimal risedronate tablet formulation, it was important to study the esophageal transit under these non-ideal conditions (minimal volumes of water).

This scintigraphy study compared the esophageal transit time of the film-coated placebo risedronate tablet and a round, flat uncoated placebo tablet that resembled the round alendronate 10 mg tablet in size and shape, as this formulation is prone to esophageal adhesion if swallowed with little or no water (deGroen et al., 1999). Water volumes of 30 and 50 ml were selected, as these volumes can detect formulations prone to esophageal adhesion and also represent minimal volumes of water that patients may ingest with the risedronate tablet (Perkins et al., 1999).

2. Materials and methods

2.1. Habits and practice study

One hundred and eight female subjects 60 years and older participated in a habits and practice study. The participants were required to appear at a local research facility and bring with them a

drinking glass or utensil that they normally use to ingest water with their medications. The participants were provided with a film-coated placebo risedronate tablet and a pitcher of water. The moderator stepped away and asked the participant to use their normal habits and fill their glass or utensil with water and swallow the tablet. The volume of ingested water was determined by reconciliation and recorded for each participant.

2.2. Scintigraphy study

2.2.1. Formulations

Film-coated placebo risedronate tablets and placebo uncoated round tablets were supplied by Procter and Gamble Pharmaceuticals. The placebo film-coated tablets, identical to the intended commercial 5 and 30 mg tablet formulations, were oval shaped (5.7 × 11.5 mm), weighing 247 mg. The placebo uncoated tablets, identical to the alendronate 10 mg tablet formulation (except for engraving), were round shallow convex shaped (9.5 mm), weighing 200 mg. The compositions of both placebo tablets were designed to match those of the corresponding commercial formulation. Because the exterior surface and density of the dose form, rather than the presence of active drug, determine its properties, we were able to use a placebo formulation, simplifying the execution of the study. The in vitro disintegration properties of the placebo tablets were measured and shown to be identical to those of the active tablets (data not shown).

2.2.2. Radiolabeling

The test formulations were manufactured to contain 5 mg of samarium (Sm) oxide and placed in a nuclear reactor approximately 48 h prior to dosing. This process converted the Sm oxide to ^{153}Sm, which is a gamma-ray-emitting isotope with a 47-h half-life. Neutron activation was performed by the Imperial College of Science Technology and Medicine (Ascot, Berks SL5 7TE). Stability of labeling and the effect of incorporating the radioisotope in the formulations were evaluated prior to the clinical study. The tablets were assayed for radioactive content to ensure that each tablet contained up to a maximum of 1.0 megabecquerel (MBq) ^{153}Sm at the scheduled time of dosing. This equated to an effective single dose of 0.7 mSv and a total subject dose of 2.8 mSv over the dosing period. The acceptable yearly exposure limit was 5 mSv.

2.2.3. Study design

This was a randomized, single-center, evaluator-blinded, four-way crossover study. A total of 31 healthy postmenopausal women (at least 55 years old and at least 1 year postmenopausal) were enrolled to ensure that a minimum of 28 subjects completed the study. Subjects were randomly assigned to dosing sequences using a 2×2 factorial combination of formulations (film-coated placebo risedronate or uncoated placebo) and volumes of water (30 or 50 ml) laid out in 4×4 Latin squares balanced for first-order carryover effects. The four combinations of formulation and volume of water were administered to each subject sequentially over the course of the dosing period. There was a washout period of at least 48 h between each visit to clear the radioactivity from the gastrointestinal (GI) tract. The study was approved by the hospital 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.

2.2.4. Scintigraphic procedures

The scintigraphic procedure took place on the morning of each visit and lasted about 2 h. Subjects were asked to fast prior to each visit and refrain from smoking from 22:00 h on the evening before dosing until the end of the 2-h procedure. No water, other than the assigned volume taken with the radiolabeled tablet, was permitted from 1 h before dosing until the end of the 10-min dynamic sequence of images. In the event that the tablet adhered and lodged in the esophagus during the 10-min dynamic sequence, the subject was asked to drink additional amounts of water at the end of the 10-min period to dislodge the tablet and flush it into the stomach. At the time of the procedure, each subject was given full instructions and positioned, while seated in front of the

gamma camera, to provide an anterior view of the esophagus extending from the oropharynx to the upper margin of the stomach.

Scintigraphic imaging was performed using a gamma camera with a 40-cm field of view (Maxicamera II, IGE Slough, UK). Data were recorded by computer (Sun/Spark, Hermes workstation, Nuclear Diagnostics, Gravesend UK). A continuous dynamic sequence of images of the esophagus was recorded over a 10-min period in a 64×64 matrix. A note of the frame marker was made at the time the subject was instructed to swallow the radiolabeled tablet.

2.2.5. Esophageal transit

The primary outcome measurement was the esophageal transit time of the tablets taken with either 30 or 50 ml of water. Individual scintigraphic images for each subject at each visit were taken to determine the time the activity of the radiolabeled tablet was first seen in the oropharynx. Subsequent images were then taken to show the time of arrival of the tablet in the stomach. The difference (in seconds) between these times was the measure of esophageal transit.

In addition to the total transit time, a novel technique was developed to characterize the transit pattern of the dose form in the esophagus. This technique is based on measurement of the plateau phase associated with the esophageal transit time to identify stationary periods during transit of the dose form in the esophagus. This parameter better reflects the likelihood of prolonged contact with esophageal mucosa and hence damage to the esophagus than the transit time.

A grading system for the esophageal plateau phase was developed in corroboration with four scintigraphy observers (Prof. Clive Wilson at the University of Strathclyde, Prof. Alan Perkins at Queen's Medical Centre, Dr Michael Jay at the University of Kentucky, and Dr Jeffrey Cooper at Albany Medical Center). The observers graded 13 condensed images from a previous scintigraphy study (Perkins et al., 1999). The results of the scores from each observer were comparable and ensured the relevance and consistency of the grading system.

2.2.5.1. Grading system for the esophageal plateau phase. The following grading system was used by a single, blinded evaluator at Queen's Medical Centre to score the condensed esophageal transit images:

Grade 0: no observable stationary periods.

Grade 1: short stationary periods (single or multiple stationary periods) each less than 5 s.

Grade 2: longer stationary periods (single or multiple stationary periods) each between 5 and 20 s.

Grade 3: prolonged stationary periods (single or multiple stationary periods) each greater than 20 s.

NB: Each stationary period was graded and recorded for each condensed image, then an overall grade was recorded. If multiple stationary periods were observed in a condensed image, the highest grade was reported as the overall grade. For example, if Grades 2 and 3 were both observed at Visit 1, Grade 3 was reported as the overall grade. Retrograde transit was defined as stasis.

2.2.5.2. Rationale for the grading system. The grading system used to define the plateau phase was based on the results of previous esophageal transit studies using placebo risedronate dose forms and published data (Perkins et al., 1999; Perkins et al., 2000; Ham et al., 1985).

Grade 0: no stationary periods. This grade represented very rapid esophageal transit with no observable stationary periods. This grade also included cases where esophageal transit was a slow, gradual process, but with no observable stationary periods.

Grade 1: short stationary periods. In a study by Ham, five subjects swallowed a 5 ml krypton-81 m solution as a single swallow (Ham et al., 1985). The esophageal transit was very rapid, and all of the swallowed activity reached the stomach within 5 s. In another study, the mean esophageal transit time of a film-coated placebo risedronate tablet was 3.3 s (range 1.5 to 7 s) (Perkins et al., 1999). Therefore, the esophageal transit time of a solution bolus or film-coated placebo risedronate tablet should occur within approximately 5 s, which was the basis for selecting the 5-s cut-off time for Grade 1.

Grade 2: longer stationary periods. An esophageal transit time of greater than 20 s was defined as esophageal adhesion (hereafter referred to as esophageal stasis) in a previous study (Perkins et al., 2000), which showed that stationary periods rarely exceed 5 s and should be less than 20 s in normal subjects.

Grade 3: prolonged stationary periods. This was recorded when the stationary period exceeded 20 s.

Esophageal stasis. Esophageal stasis was defined as an overall esophageal transit time of >20 s which has been used in previous scintigraphy studies (Perkins et al., 2000).

2.2.6. Statistical analysis

Data from a previous study revealed that the mean esophageal transit time of a film-coated placebo risedronate tablet was approximately 4.0 s, and the common between-subject standard deviation was 4.0 s (Perkins et al., 2000). Assuming that the within-subject correlation was 0.5, 28 completed subjects provided at least 90% power to detect a difference of 8.0 s in the esophageal transit time between oval, film-coated placebo risedronate tablets and round, flat, uncoated placebo tablets for each volume of water evaluated.

An analysis of variance (ANOVA) model for the crossover design was used to compare the esophageal transit time between the two formulations for each volume of water. When the normality assumption in the ANOVA model was not satisfied, nonparametric methods such as the Wilcoxon signed-rank test were used to compare the esophageal transit time between the two formulations. A 95% confidence interval (CI) for the median difference was constructed, based on the Hodges–Lehmann method, to quantify the difference in esophageal transit time for each volume of water. The number and percentage of subjects in each grade of the esophageal plateau phase were provided for each combination of formulation and volume of water. The number of subjects having esophageal stasis (transit time of the tablet was >20 s) was summarized.

3. Results

3.1. Habits and practice study

The median volume of water taken with the film-coated placebo risedronate tablet was 124 ml (4.2 oz) with a range of 7 to 385 ml. A histogram of the water volume distribution is shown in Fig. 1. The results indicate that 50 ml is at the low end (13th percentile) of the range of typical volumes voluntarily consumed by postmenopausal women. The 50 ml volume was selected because it is a volume shown to differentiate between the esophageal transit time of the placebo risedronate tablet and capsule, and represents a volume that subjects may ingest with the film-coated risedronate tablet. Additionally, subjects at the 5th percentile consumed 33 ml of water with the tablet and were considered to be at highest risk for delayed transit. Therefore, 30 ml was selected as the lowest volume of water to test in this study.

3.2. Scintigraphy study

Out of 34 screened subjects, 31 subjects were randomized to participate in the study. Three subjects were withdrawn during the study, therefore 28 subjects completed the study. The mean age of the subjects was 63 years (range 55 to 74 years).

3.2.1. Esophageal transit

Table 1 summarizes the esophageal transit time of each formulation and volume of water. For each volume of water, only 28 of the 31 subjects had transit times for both formulations and were, therefore, included in the comparison between the two formulations. For both volumes of water, the film-coated placebo risedronate tablet had a statistically significant shorter esophageal transit time than the uncoated placebo tablet. The median difference in esophageal transit time between the film-coated placebo risedronate tablet and the uncoated placebo tablet was -2.5 s (95% CI $=-18.5$ to -1.0 s; $P=0.002$) for 30 ml of water and -1.0 s (95% CI $=-1.8$ to -0.5 s; $P<0.001$) for 50 ml of water.

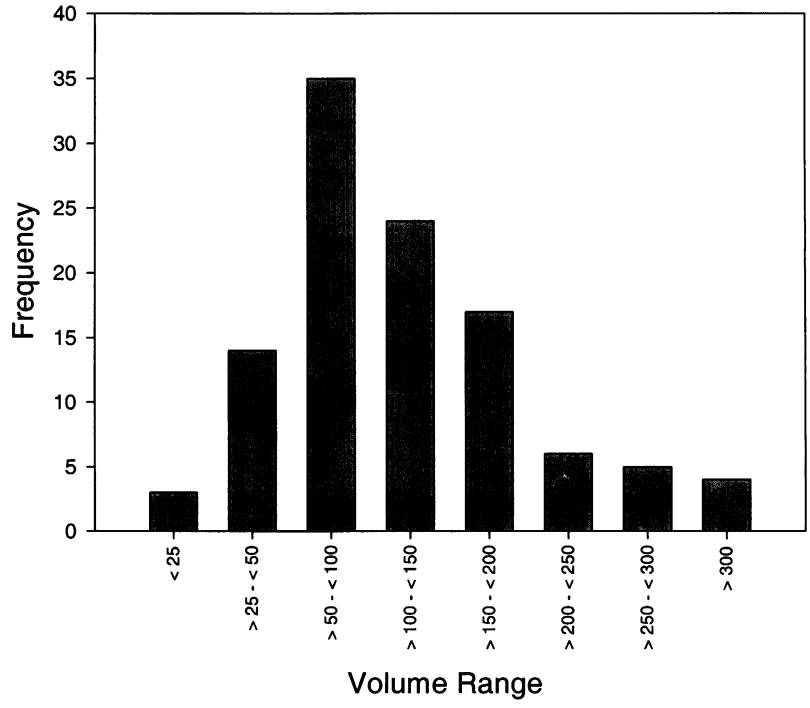

Fig. 1. Water volume distribution for participants ingesting the film-coated placebo risedronate tablet

Table 1
Summary of esophageal transit time (all randomized subjects)

Parameter	30 ml water		50 ml water	
	Placebo risedronate ($N = 28$)	Uncoated placebo ($N = 30$)	Placebo risedronate ($N = 29$)	Uncoated placebo ($N = 30$)
Total esophageal transit time (s)				
Mean ± SEM	3.2 ± 0.31	65.2 ± 32.8	2.3 ± 0.18	3.4 ± 0.36
Median	2.8	3.8	2.0	2.8
Min, Max	0.5, 6.5	1.5, 596	1.0, 5.5	1.0, 10.0
Placebo risedronate-uncoated placebo				
Difference	−2.5		−1.0	
95% CI[a]	(−18.5, −1.0)		(−1.8, −0.5)	
p value	0.002		<0.001	

[a] Confidence interval estimates of the median difference between the two formulations were based on the nonparametric Hodges–Lehmann method.
N = number of randomized subjects who received formulation and volume of water; n = number of randomized subjects who received formulation and volume of water and had a esophageal transit time measurement; SEM = standard error of the mean.

Table 2
Summary of the overall grade for esophageal plateau phase (all randomized subjects)

Grading system[a]	30 ml		50 ml	
	Placebo risedronate ($N = 28$) n (%)	Uncoated placebo ($N = 30$) n (%)	Placebo risedronate ($N = 29$) n (%)	Uncoated placebo ($N = 30$) n (%)
Grade 0	9 (32%)	11 (37%)	19 (66%)	12 (40%)
Grade 1	17 (61%)	11 (37%)	10 (34%)	17 (57%)
Grade 2	2 (7%)	3 (10%)	0 (0%)	1 (3%)
Grade 3 (Esophageal stasis)	0 (0%)	5 (17%)	0 (0%)	0 (0%)

N = number of randomized subjects who received formulation and volume of water; n (%) = number and percentage of subjects.
[a] Each stationary period was graded and if multiple stationary periods were observed, then the highest grade was reported as the overall grade. Grade 0 = no observable stationary periods; Grade 1 = short stationary periods (single or multiple stationary periods) each less than 5 s; Grade 2 = longer stationary periods (single or multiple stationary periods) each between 5 and 20 s; Grade 3 = prolonged stationary periods (single or multiple stationary periods) each greater than 20 s.

Three subjects taking the round, flat, uncoated, placebo tablet with 30 ml of water had an esophageal transit time at a single visit over 500 s, and the tablet was still in the esophagus after the end of the 10-min imaging period; one subject had an esophageal transit time of 596 s, one had a time of 591 s and one had a time of 595 s.

3.2.2. Esophageal plateau phase

Table 2 summarizes the overall grade for the esophageal plateau phase of each formulation and volume of water. For the 30 ml volume of water, two of 28 subjects (7%) receiving the oval, film-coated placebo risedronate tablet had a stationary period greater than 5 s (zero of 28 had a stationary period greater than 20 s) and eight of 30 subjects (27%) receiving the round, flat, uncoated placebo tablet had a stationary period greater than 5 s (five of eight had a stationary period greater than 20 s). For the 50 ml volume of water, zero of 29 (0%) subjects receiving the oval, film-coated placebo risedronate tablet had a stationary period greater than 5 s and only one of 30 subjects (3%) receiving the round, flat, uncoated placebo tablet had a stationary period greater than 5 s but less than 20 s.

3.2.3. Esophageal stasis

As shown in Fig. 2 esophageal stasis (defined as an esophageal transit time of > 20 s) was seen in 17% (5/30) of subjects, but only in those subjects who received the round, flat, uncoated placebo tablet with 30 ml of water.

4. Discussion

The aim of this study was to compare the esophageal transit time of a round, flat, uncoated placebo tablet with an oval, film-coated placebo risedronate tablet. The data indicate that the oval, film-coated placebo risedronate tablet had a statistically significant shorter esophageal transit time than the round, flat, uncoated placebo tablet when taken with either 30 or 50 ml of water. No esophageal stasis (transit time > 20 s) was observed with the oval, film-coated placebo risedronate tablet with either volume of water. In comparison, five of 30 subjects had esophageal stasis (transit > 20 s), including three subjects (10%) with an esophageal transit time greater than 10 min, the duration of imaging, when the round, flat, uncoated placebo tablet was ingested with 30 ml of water. It was interesting to note that no subjects were aware that the tablet was lodged in their esophagus. The 10-min adhesion was of no safety concern since all subjects received placebo tablets. If the round, uncoated tablet contained alendronate, then the prolonged contact of the dissolving tablet may create high local

drug concentration on the esophagus and possibly increase the risk of esophageal irritation, e.g. inflammation or even penetration of the mucosa. The adhesion of the uncoated round tablet, similar in size and shape to the alendronate 10 mg tablet, observed in this scintigraphy study is consistent with reported cases of esophagitis if the alendronate tablet is taken with little to no water (deGroen et al., 1999). The alendronate 10 mg tablet was a round shallow convex uncoated tablet with a diameter of 9.5 mm. The flat surface of the tablet presents a high surface area and may contribute to the esophageal adhesion of the tablet when swallowed with little to no water.

The habits and practice showed that women prefer to ingest the film-coated risedronate tablet with a wide range of water volumes (7–385 ml) and 30 ml is at the low end (< 5th percentile) of the distribution and represents subjects at high risk for delayed transit. Even at this minimal water volume, the contact time of the film-coated risedronate tablet with the esophagus is minimal, as the longest transit time was 6.5 s with a single stationary period of 5 s.

A previous in vitro test system in an isolated pig esophagus was used to measure the detachment force of the film-coated risedronate tablet (Actonel® 30 mg) and an uncoated placebo tablet of the same size and shape (Gibson et al., 1999). The results showed that the film-coated risedronate tablet had a statistically significant higher detachment force than the uncoated tablet. This present scintigraphic study demonstrated the faster transit of the placebo film-coated risedronate tablet compared to the placebo uncoated round tablet. As a consequence, we would suggest that the in vitro mucoadhesion model should not be used to predict dosage form transit in humans.

This scintigraphy study confirms our in-depth examination of esophageal transit and supports

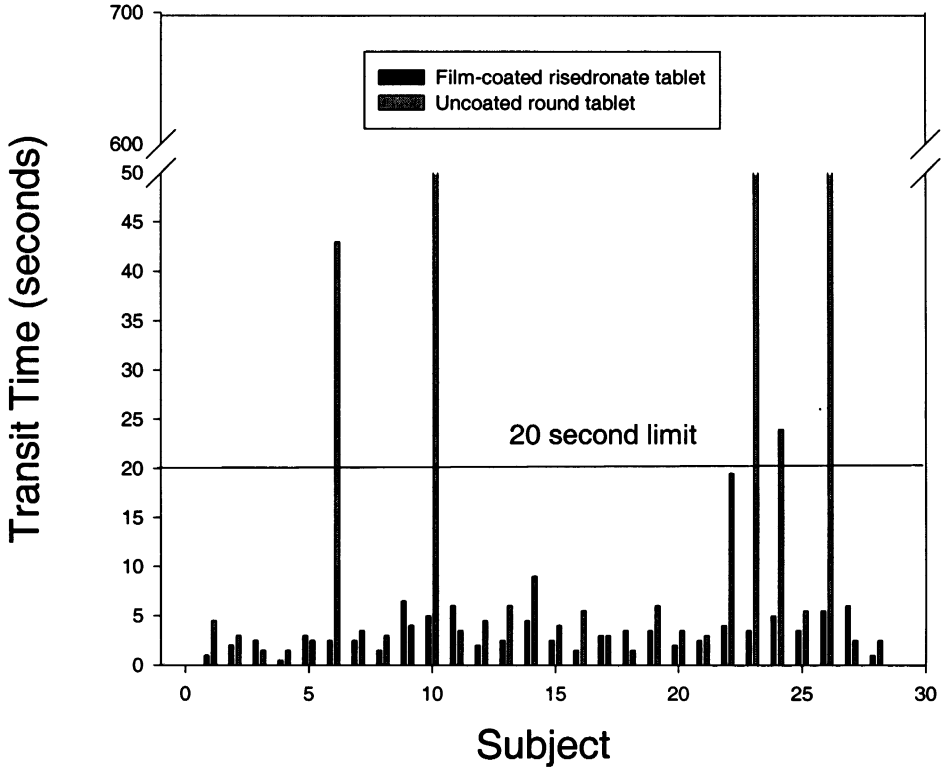

Fig. 2. Esophageal transit times for subjects following ingestion of the film-coated placebo risedronate tablet and the placebo round uncoated tablet with 30 ml of water

the design and optimization of the risedronate tablet for use in elderly subjects (Perkins et al., 1999, 2000). This study demonstrates that tablet size, shape and coating are pharmaceutical parameters which can be controlled to minimize esophageal contact of a dosage form with esophageal tissue. The esophageal safety of risedronate is supported by clinical trials with the rapidly disintegrating film-coated risedronate sodium tablets (2.5 and 5.0 mg) in postmenopausal women, which showed an overall safety profile of risedronate sodium, including gastrointestinal safety, was similar to that of placebo (Reginster et al., 2000; Harris et al., 1999, McClung et al., 2001). Since oral tablet formulations are not identical in terms of size, shape and coating material, scintigraphy studies should be conducted to establish the esophageal transit for bisphosphonate formulations intended for use by elderly patients. A volume of 30 ml of water is suggested because it can differentiate between formulations and represents a minimal volume of water which may be swallowed with the formulation.

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References

Applegate, G.R., Malmud, L.S., Rock, E., Reilley, J.R., Fisher, R.S., 1980. "It's a hard pill to swallow" or "don't take it lying down". Gastroenterology 78, 1132.

Bonavina, L., DeMeester, T.R., McChesney, L., Schwizer, W., Albertucci, M., Bailey, R.T., 1987. Drug-induced esophageal strictures. Ann. Surg. 206, 173–183.

deGroen, P.C., Lubbe, D.F., Hirsch, L.J., Daifotis, A., Stephenson, W., Freedholm, D., Pryor-Tillostson, S., Seleznick, M.J., Pinkas, H., Wang, K.K., 1999. Esophagitis associated with the use of alendronate. N. Engl. J. Med. 335, 1016–1021.

Ettinger, B., Pressman, A., Schein, J., Chan, J., Silver, P., Connolly, N., 1998. Alendronate use among 812 women: prevalence of gastrointestinal complaints, non-compliance with patient instructions and discontinuation. J. Managed Care. 4 (5), 488–492.

Gibson, T.M., Ikeda, C.B., Senderak, E., Chen, T-S., Rose, J.M., Novak, L.B., Hua, J., Yates, A.J., 1999. Effects of film coating on adhesion to the esophagus. ASBMR Abstract SA417.

Ham, H.R., Georges, B., Froideville, J.L., Piepsz, A., 1985. Oesophageal transit of liquid: effects of single or multiple swallows. Nucl. Med. Comm. 6, 263–267.

Harris, S.T., Watts, N.B., Genant, H.K., McKeever, C.D., Hangartner, T., Keller, M., Chesnut, C.H. III, Brown, J., Eriksen, E.F., Hoseyni, M.S., Axelrod, D.W., Miller, P.D., 1999. The effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis. JAMA 282 (14), 1344–1352.

Kikendall, J.W., 1999. Pill-induced esophageal injury. In: Castell, D.O., Richter, J.E. (Eds.), The Esophagus, third ed. Lippincott Williams & Wilkins, Philadelphia, pp. 527–537.

Lanza, F.L., Hunt, R.H., Thomson, A.B.R., Provenza, J.M., Blank, M.A., 2000. Endoscopic comparison of esophageal and gastroduodenal effects of risedronate and alendronate in postmenopausal women. Gastroenterology 119, 631–638.

Lufkin, E.G., Argueta, R., Whitaker, M.D., Cameron, A.L., Wong, V.H., Egan, K.S., O'Fallon, W.M., Riggs, B.L., 1994. Pamidronate: an unrecognized problem in gastrointestinal tolerability. Osteoporos. Int. 4, 320–322.

McClung, M.R., Geusens, P., Miller, P.D., 2001. Effect of risedronate on hip fracture risk in elderly women. N. Engl. J. Med. 334, 333–340.

Perkins, A.C., Wilson, C., Frier, M., Vincent, R.M., Blackshaw, P.E., Dansereau, R.J., Juhlin, K.D., Bekker, P.J., Spiller, R.C., 1999. Esophageal transit of risedronate cellulose-coated tablet and gelatin capsule formulations. Int. J. Pharm. 186, 169–175.

Perkins, A.C., Vincent, R.M., Wilson, C., Frier, M., Blacshaw, P.E., Spiller, R.C., Wenderoth, D., Li, Z., Dansereau, R.J., 2000. Esophageal transit, disintegration and gastric emptying of a risedronate placebo tablet in gastroesophageal reflux disease and normal subjects. Osteoporos. Int. 11 (1), 89.

Reginster, J.Y., Minne, H.W., Sorensen, O.H., Hooper, M., Roux, C., Brandi, M.L., Lund, B., Ethgen, D., Pack, S., Roumagnac, I., Eastell, R., 2000. Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. Osteoporos. Int. 11, 83–91.