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Esophageal transit of risedronate cellulose-coated tablet and gelatin capsule formulations

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Abstract

Risedronate sodium is an orally active antiresorptive agent and a member of the pyridinyl class of bisphosphonates. It has been approved for the treatment of Paget's disease of the bone and is under development as a chronic therapy for the treatment and prevention of osteoporosis. A novel cellulose film-coated tablet formulation was developed to optimize esophageal transit of this bisphosphonate. The aim of the present study was to compare the esophageal transit of the film-coated tablet formulation of risedronate with its original gelatin capsule dose form. A total of 25 elderly, healthy volunteers (mean 66 years), who were dysphagia-free, participated in this randomized cross-over study. On separate occasions, volunteers swallowed radiolabeled placebo formulations with 50 ml water. Dynamic images with participants in a sitting position were recorded for 10 min using a gamma camera. Scintigraphic imaging showed a delay in esophageal transit (greater than 15 s) in 28% of patients in the capsule group but in none of the tablet group ($P < 0.05$). The mean transit times of the capsules and tablets were 23.8 and 3.3 s, respectively. Esophageal transit of film-coated tablets was faster than gelatin capsules, suggesting that film-coated tablets would be the appropriate formulation for all pivotal trials with risedronate and for subsequent commercialization.

Keywords: Esophageal transit; Risedronate; Tablet formulations

1. Introduction

Erosive esophagitis can arise during long-term treatment with a wide range of oral medications, including tetracyclines, emerpronium bromide, slow-release potassium chloride and nonsteroidal anti-inflammatory drugs (Pemberton, 1970; Kikendall et al., 1983; Santucci et al., 1990; Eng and Sabanathan, 1991). Mucosal damage occurs when a formulation becomes lodged and starts to dissolve, creating a high local concentration of the

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drug on the mucosa. The mid-lower esophagus is the most common site of damage, possibly reflecting the reduction in peristaltic force in this area (Pemberton, 1970; Kahrilas et al., 1988; Eng and Sabanathan, 1991; Lufkin et al., 1994). The damage may result from high or low pH or from high osmolarity (Pemberton, 1970).

Risedronate sodium [1-hydroxy-2-(3-pyridinyl) ethylidene bisphosphonic acid monosodium salt] is a pyridinyl bisphosphonate drug approved for the treatment of Paget's disease of bone and is under development for the treatment of osteoporosis and other metabolic disorders. Risedronate is chemically distinct from the primary aminobisphosphonates. Proposed treatment regimens for risedronate range from 2 months of once-daily oral administration for the treatment of Paget's disease of bone to long-term daily oral administration for the treatment or prevention of osteoporosis.

Risedronate is well tolerated when taken orally as a gelatin capsule, its original clinical formulation. However, designing an optimal and robust solid oral formulation is desirable for chronic therapies. In general, gelatin capsules can be difficult to swallow and show a tendency to adhere to esophageal mucosa when they start to absorb water (Applegate et al., 1980; Bailey et al., 1987; Gallo et al., 1996). Pamidronate, another bisphosphonate in development, reported gastrointestinal intolerance with the capsule formulation (Coleman et al., 1991). As a proactive step, a novel cellulose film-coated tablet formulation of risedronate sodium, designed to have a rapid esophageal transit time, was developed to minimize the potential for gastrointestinal intolerance. In recent Phase III clinical trials in 3684 osteoporotic patients, treated for up to three years with oral risedronate sodium film-coated tablets, the upper gastrointestinal safety profile was comparable to placebo (Eastell et al., 1999; Watts et al., 1999). A pilot study suggested that the swallowing patterns of a tablet formulation were different from those of the gelatin capsules used in early clinical trials (Perkins et al., 1994). The aim of the present study was to compare the esophageal transit of the two formulations. Because the propensity for adhesion is determined primarily by the external properties of a formulation, placebo risedronate capsules and tablets were used in this study.

2. Materials and methods

Placebo risedronate film-coated tablets and no. 3 placebo risedronate hard gelatin capsules were supplied by Procter and Gamble Pharmaceuticals (Cincinnati, OH). The film-coated tablets (5.7×11.6 mm) were oval shaped with a cellulose-based film coating and weighed 247 mg. The gelatin capsules (5.8×15.9 mm) weighed 270 mg and contained a standard powder fill.

The tablets and capsules were radiolabeled at the clinical site with a small amount of ^{99m}Tc-Amberlite resin according to a standard operating procedure in a clean environment, as described previously (Perkins et al., 1994). Sterile ^{99m}Tc-sodium pertechnetate was added to approximately 150 mg of Amberlite ion exchange resin IRA 416 (Cl), particle size 0.3–1.2 mm (Merck, Lutterworth, UK). The mixture was dried in a glass beaker using a hot-air dryer before being incorporated into the dosage forms.

The radiolabeled resin was manually incorporated into the tablets and capsules. Briefly, film-coated tablets were clamped and drilled at one edge using a 1.5 mm diameter drill bit sterilized with alcohol and were inspected visually to ensure that surfaces were smooth and free from cracks. Approximately 5 mg radiolabeled resin was tamped into the interior of the tablet via the drill hole using a modified Eppendorf pipette tip. The tablets were then sealed with a small amount of sterile bone cement.

Capsules were placed upright in a Perspex® support and opened. Using a microspatula, approximately 5 mg of the contents was removed and replaced with 5 mg ^{99m}Tc-labeled Amberlite resin. The shell was firmly capped and the capsule inverted six times to mix the contents.

The radioactivity of ^{99m}Tc was calculated to give a dose of 3 MBq per tablet or capsule , accounting for the time delay between radiolabeling and administration. This resulted in an absorbed radiation dose of 0.15 mSv. The tablets

and capsules were assayed immediately after radiolabeling and immediately before administration using a Vinten Isocal ionization chamber dose calibrator (NE Technology, Weybridge, UK).

A total of 12 men and 13 women were recruited from the population surrounding Nottingham, UK. Their mean age was 66 years (range 56–80 years). All volunteers had a medical examination during the 2 weeks before the trial and immediately after completion. Volunteers received each dosage form according to a randomization schedule, with a minimum period of 3 days between investigations. The study was approved by the University of Nottingham Medical School Ethics Committee and the Administration of Radioactive Substances Advisory Committee of the UK Department of Health. All participants were fully informed of the procedure and gave written consent to participate in the study.

The study was undertaken in the Radionuclide Imaging Drug Evaluation and Research (RIDER) Unit, Department of Medical Physics, University Hospital, Nottingham. On each test day the volunteer ate a light breakfast of two slices of buttered toast and tea with milk at 08:00 h having fasted from 22:00 h on the previous evening. At 11:00 h (by which time the breakfast was expected to have emptied from the stomach), the volunteer was seated in front of the gamma camera for anterior imaging. The radiolabeled formulation was taken with 50 ml water in a continuous sequence of swallows. Scintigraphic images were recorded in a 64×64 digital cell matrix over a total time of 10 min using an IGE Maxicamera II (IGE Medical Systems, Slough, UK) interfaced with a Gamma 11/Hermes workstation (Nuclear Diagnostics, Gravesend, UK). A 20% symmetrical energy window was set, centered on the 140 keV gamma photon peak of ^{99m}Tc. Sixty dynamic frames were taken at a rate of 2 per second, followed by 38 dynamic frames taken at a rate of one every 15 s.

All images were analyzed by computer (Gamma 11, Nuclear Diagnostics) by one of two experienced operators who were blinded to the dosing schedule and analyzed the data using previously defined criteria (Perkins et al., 1994). For each study, the individual frames were displayed to determine the time that radioactivity was first observed in the oropharynx and the time of arrival of the dosage form in the stomach. The time difference between these frames was used to give the esophageal transit time (in seconds) of the formulation. A condensed image was then produced in which the distance between the oropharynx and the stomach was shown on the vertical axis as a function of time on the horizontal axis (Perkins et al., 1994).

Statistical analysis was used to quantify the degree of difference between the two formulations. For each formulation, participants were classified as having or not having prolonged esophageal stasis, which was defined as an esophageal transit time of greater than 15 s. This limit was selected on the basis of previous experience using scintigraphy, in which normal swallowing of the pharmaceutical dosage occurred within 15 s. Although McNemar's test is generally used in such situations, the small sample size in this study required the use of a conditional exact binomial test (Lehmann, 1959) in which the null hypothesis specifies the conditional probability associated with each of the two cells as 0.5. The statistical inferential procedure was performed at the 0.05 (nominal) significance level.

3. Results

A total of 50 esophageal transit studies were conducted, 25 with each formulation. All volunteers swallowed the units with the 50 ml water provided. None of the volunteers complained of discomfort or difficulty with swallowing the film-coated tablets or capsules, and additional water was not requested. There were no complaints of a delay in esophageal transit and no adverse reactions or events were reported.

The esophageal transit times for the two formulations in each volunteer are shown in Fig. 1. The mean transit time in the tablet group was 3.3 s, with a range of 1.5–7.0 s (sample standard deviation 1.4 s). The mean transit time in the capsule group was 23.8 s, with a range of 0.5–131.5 s (sample standard deviation 36.1 s). Prolonged stasis was defined as an esophageal transit time of

greater than 15 s, and this occurred in 28% of the capsule group but in none of the tablet group. This difference between the transit of the two formulations was found to be statistically significant ($P = 0.016$). Fig. 2 shows a condensed image display of data (subject number 8 from Fig. 1), which provides a useful method for visualizing a delay in esophageal transit. In the example shown, the transit time was 4.5 s for the tablet but 94 s for the capsule. Stasis of the formulation in the lower esophagus is clearly visible on the condensed image display.

4. Discussion

Scintigraphy was used in the present study to show that esophageal transit times were significantly shorter for cellulose film-coated tablets than for hard gelatin capsules prepared as placebo versions of risedronate sodium formulations. Prolonged stasis, defined as an esophageal transit time of greater than 15 s, occurred more frequently with the capsules than with the tablets ($P = 0.016$). This supports the findings of our pilot study (Perkins et al., 1994).

Scintigraphy is a powerful method for quantification of the transit of liquid and solids and a physiologic means of demonstrating esophageal spasm, status, and gastric reflux (Kazem, 1972; Tolin et al., 1979; Russell et al., 1981; Svedberg, 1982; Blackwell et al., 1983; Kjellen et al., 1984; Klein and Wald, 1984; Ham et al., 1985; Mughal et al., 1986; Sand et al., 1986; Holloway et al., 1989; Klein, 1995). Measurement of esophageal transit by scintigraphy is a routine clinical procedure; it is noninvasive and causes minimal discomfort to patients. Scintigraphy also provides a reliable method for observing the fate of a dosage form on swallowing, provided that radiolabeling does not have an adverse effect on the contact surface properties of the preparation (Channer and Virjee, 1986; Perkins et al., 1994). In the present study, great care was taken to ensure that radiolabeling procedures did not affect the disintegration characteristics of the formulation, particularly because the tablets had been drilled and sealed. The in vitro tablet disintegration time of the radiolabeled tablet was identical (data not shown) to the disintegration time of the unlabelled tablets.

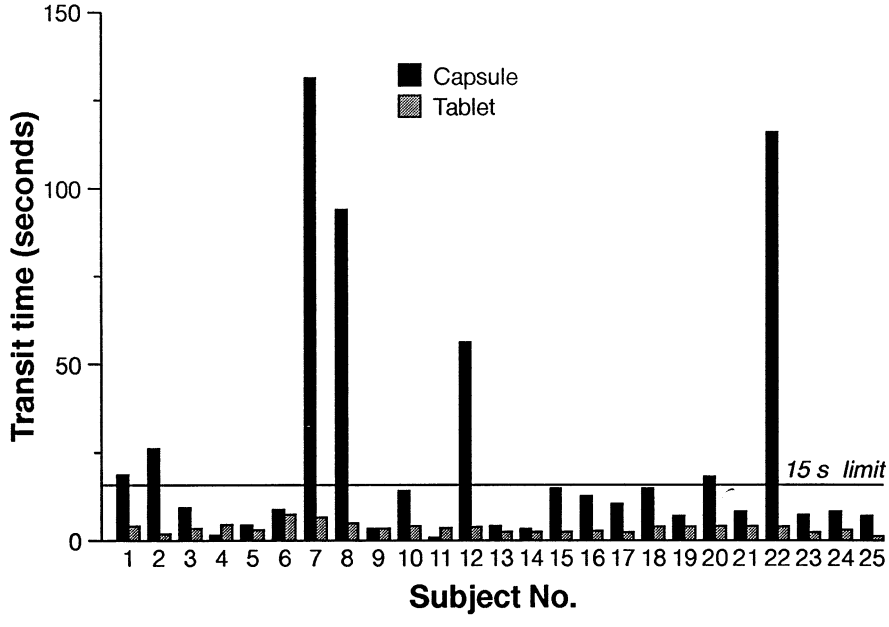

Fig. 1. Transit times of the paired esophageal transit studies in 25 healthy volunteers.

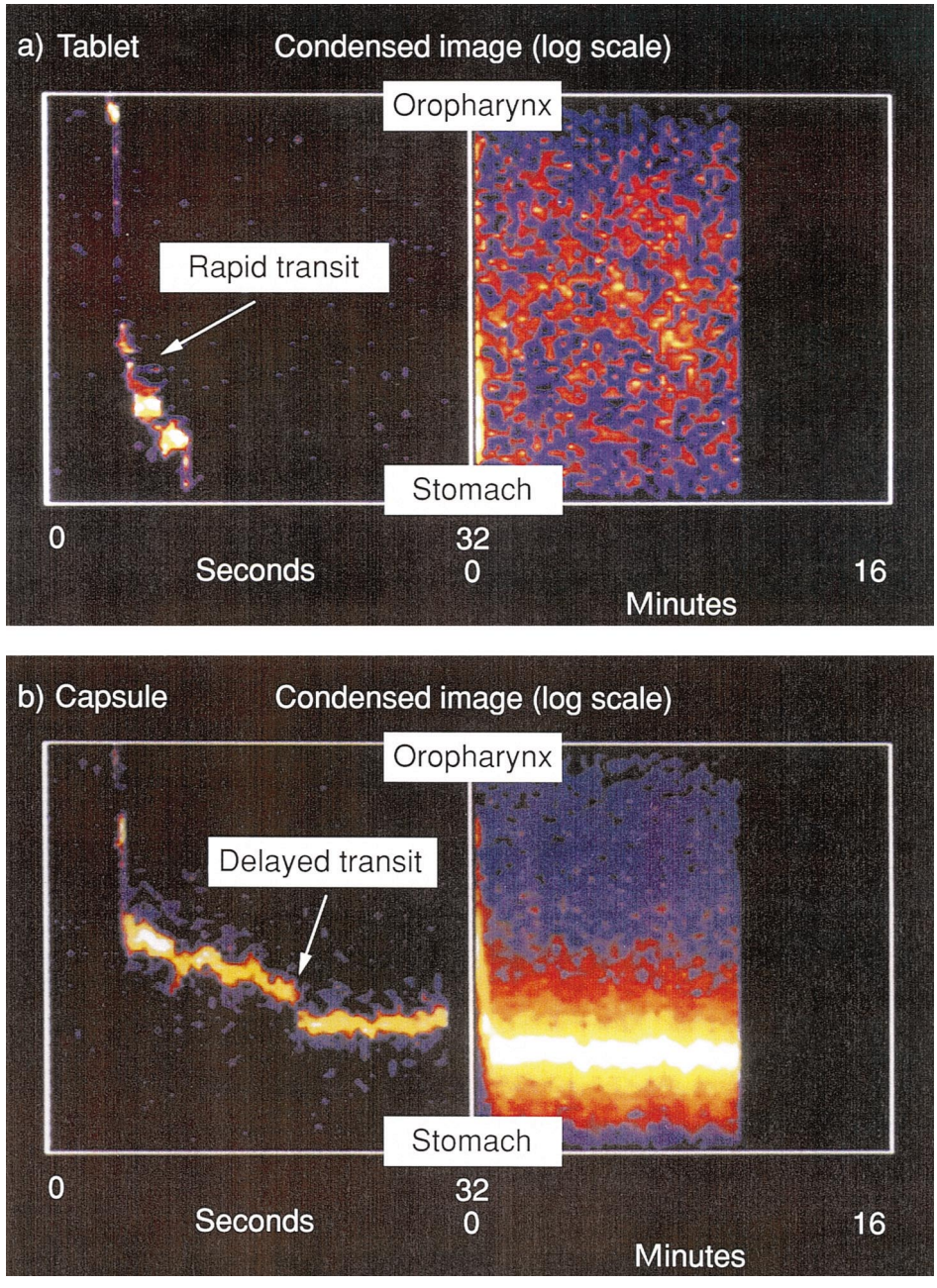

Fig. 2. Condensed image displays of the normal transit of the tablet and capsule formulations in subject number 8. (a) Rapid transit of the tablet formulation and (b) delayed transit of the capsule formulation. The vertical axis represents distance from the oropharynx (top) to the stomach (bottom); the horizontal axis represents time (left side: 0–32 s; right side: 0–16 min). Thus, the graph shows the speed of movement from the oropharynx to the stomach.

The transit of tablets and capsules through the gastrointestinal tract is influenced by various factors such as the size, shape, density, and surface characteristics of the dosage unit (Evans and Roberts, 1976; Channer and Virjee, 1986) and by physiologic factors such as posture and the volume of water taken with the units (Applegate et al., 1980; Bailey et al., 1987; Gallo et al., 1996). Pathophysiologic conditions associated with ageing, such as oropharyngeal dysphagia, esophageal dysphagia and, perhaps, gastrointestinal reflux, may adversely affect esophageal transport (Castell, 1990), and may increase the risk of esophageal retention and prolong the transit time when swallowing solid medications. Elderly individuals may have altered function without dysphagia (Ekberg and Feinberg, 1991) and are therefore more likely to have difficulty swallowing medication, perhaps because of changes in the viscoelastic properties of the esophagus associated with aging (Perlman et al., 1993). Healthy elderly volunteers were therefore selected as the cohort for the present study.

To standardize the experimental procedure, volunteers sat upright and took the capsule or film-coated tablets with water in a continuous sequence of swallows. Volunteers were asked to swallow the dosage forms with only 50 ml water, which is less than the volume of water recommended in the package insert for the treatment of Paget's disease (180–240 ml; Final Labeling, Actonel™; Procter and Gamble Pharmaceuticals, TM owner, Cincinnati, OH, USA). A previous study compared the esophageal transit time of a placebo delayed-release tablet and a placebo delayed-release capsule administered with 50 ml of water (Perkins et al., 1994). The esophageal transit time of the delayed-release tablet (mean 4.3 s) was five times faster than the delayed-release capsule (mean, 20.9 s). Thus, the 50 ml volume of water is a discriminatory volume and was selected as a reduced volume to compare the esophageal transit of the film-coated tablet and the gelatin capsule. In addition, the reduced volume of 50 ml is similar to volumes typically used in the study of esophageal transit (Wamberg et al., 1983; Channer and Virjee, 1985, 1986). The influence of water volume on the esophageal clearance of capsules was evaluated in a study by Bailey et al. (1987). Lodging of no. 00 capsules (8.5×22.9 mm) occurred in 61% of patients when taken with a 15 ml water bolus compared with only 17% of patients when taken with a water chaser of 120 ml. The 50 ml of water used in the present study was clearly adequate, because none of the volunteers required extra water or reported difficulty with swallowing the formulations.

The film-coated tablets and capsules used in the present study are of similar size; however, the capsules are less dense than the tablets and become tacky upon hydration, which may account, in part, for the difference in esophageal transit times between the two formulations. By contrast, the film-coated tablets are denser than the capsules and become slippery on hydration; this, in combination with the size and shape of the tablet, provides for a rapid esophageal transit.

A 15-s limit was used to define prolonged stasis. This limit is shorter than that used in other published studies, in which an upper limit of 90 s was used (Jorgensen et al., 1992). However, on the basis of our previous experience using scintigraphy, normal swallowing of pharmaceutical dosage forms occurs within 15 s (Perkins et al., 1994). Using this limit, the measured transit times of the film-coated tablets and hard gelatin capsules were significantly different, with a delay in esophageal transit occurring in 28% of capsule studies but in none of the film-coated tablet studies.

The cellulose film-coated tablet formulation described here had a rapid esophageal transit time, thus minimizing the contact time of the formulation with the mucosal tissue in the esophagus. These results suggested that the film-coated tablets would be the appropriate formulation for all pivotal trials with risedronate and for subsequent commercialization.

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