GASTROPROTECTIVE EFFECTS OF EFFERVESCENT ALENDRONATE FORMULATION SHOWN BY SCINTIGRAPHIC AND GASTRIC pH MONITORING

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INTRODUCTION AND OBJECTIVES

It is postulated that an effervescent form of orally administered alendronate (ALN) may exit the stomach more rapidly than a solid form. Furthermore the buffering capacity of an effervescent form may lead to a lower incidence of gastrointestinal adverse events in the population at large.

ALN is administered with a large volume of water and the patient is instructed to wait in a vertical position for 30 minutes before ingesting food. The Fosamax® NDA states that *"under acidic conditions (pH <3) alendronate exists in the free acid form (>67%) which is more irritating than the sodium salt form"* and *"most of the clinical cases of oesophagitis are associated with deviations from proper dosing. Irritation can be minimized by proper dosing and avoidance of conditions known to exacerbate gastric acid reflux*".

This study aimed to evaluate the dosing advantages of two different soluble effervescent ALN dosage forms when compared to each other and a conventional ALN tablet, Fosamax®. Scintigraphic imaging enabled determination of the differences between gastric emptying (GE) of the three formulations. Simultaneous gastric pH monitoring was also conducted to determine the effects of the three formulations on gastric pH after dosing.

EXPERIMENTAL METHODS

Radiolabelling of study treatments

Effervescent formulations (EX101 and M-K blend) were manufactured by SwissCo Development AG, Switzerland; Fosamax® was manufactured by Merck Sharpe and Dohme Ltd, Germany. The effervescent tablet was dissolved in 100 mL Volvic water labelled with 4.0 MBq ^{99m}Tc-DTPA. Fosamax® tablets were radiolabelled with 4.0 MBq ^{99m}Tc-DTPA-lactose using a 'drill and fill' method.

Clinical study

This was a single centre, open label, randomised, three-way crossover study in twelve fasted healthy female volunteers. pH probes were inserted via the nasogastric route to monitor pH from 2 hours pre-dose to 4 hours post-dose. Fosamax® was administered with 240 mL Volvic water and the effervescent dosage forms with 100 mL Volvic water followed by an additional 20 mL of Volvic water that was added to the glass, swirled and swallowed. Anterior and posterior static acquisitions were taken with the subject in a standing position using a Siemens E-Cam gamma camera fitted with a low-energy, high-resolution collimator. Imaging was stopped when complete gastric emptying was observed.

Scintigraphic data analysis

The scintigraphic images were analysed to quantitatively assess GE of the labelled formulations. The GE descriptors ($T_{50\%}$ and $T_{90\%}$ - time to half and 90% emptying of the formulation) were determined. Gastric pH monitoring traces were also evaluated to determine the pH at $T_{50\%}$ and $T_{90\%}$.

RESULTS AND DISCUSSION

10 subjects completed all arms of the study; one subject dropped out after Arm 1, and another subject only completed two arms. All dosage forms administered were tolerated well by the subjects and completely reached the stomach without oesophageal adhesion on all dosing occasions.

There was considerable variability in gastric emptying after ingestion of all three formulations, and no clear trend was observed across the treatments. Surprisingly, neither effervescent formulation triggered a consistent and rapid emptying event compared to the Fosamax® tablets.

The time taken for the gastric pH to fall below pH 3 after dosing was determined for each dosing occasion. This time was then subtracted from the corresponding $T_{50\%}$ and $T_{90\%}$ to obtain the parameters, Exposure Time$_{T50}$ and Exposure Time$_{T90}$ respectively. These values are shown in Table 1.

Table 1: Mean values for pH parameters.

Parameter	Mean ± S.D.		
	Fosamax®	EX101	M-K Blend
pH at T_{50} -	1.9±0.5	3.5±1.2	4.6±2.2
pH at T_{90}	1.3±0.3	1.8±0.8	1.4±0.3
Time of crossing pH 3 threshold (min post-dose)	3.9±3.0	56.0±56.0	23.8±15.7
Exposure Time$_{T50}$ (min)	26.9±27.8	-21.6±42.4	-0.6±17.2
Exposure Time$_{T90}$ (min)	61.7±36.1	15.7±42.2	33.1±32.4

When considering the Exposure Time$_{T50}$ and Exposure Time$_{T90}$, EX101 provided the greatest level of protection. Based on Exposure Time$_{T50}$, EX101 and the M-K Blend were significantly more protective than Fosamax® (p=0.014 and 0.014 respectively). A similar trend was observed with Exposure Time$_{T90}$, with EX101 proving superior to the other two formulations with a mean value of 15.7 min, compared to 33.1 min (M-K Blend) and 61.7 min (Fosamax®).

GE was associated with a decrease in stomach pH in both effervescent formulations. To account for this, the stomach pH at 30 min in subjects which did not achieve $T_{50\%}$ within 30 min was determined and is shown in Table 2. Despite the small sample size, it is clear that both Fosamax® subjects for which pH data is available have acidic ALN in their stomachs at 30 min.

Conversely, all EX101 subjects in this subgroup maintained an elevated pH at 30 min. Of the two M-K Blend subjects in this subgroup, one maintained an elevated pH at 30min but the other had an acidic stomach pH at that time, thereby placing the subject at risk.

Table 2: pH at 30 min post-dose in subjects where $T_{50\%}$ > 30 min.

Fosamax® (n=2)			EX101 (n=4)			M-K Blend (n=2)		
Subject	T_{50}	pH at 30 min	Subject	T_{50}	pH at 30 min	Subject	T_{50}	pH at 30 min
003	87.6	2.07	003	75.0	4.16	003	67.2	0.91
006	30.6	Device malfunction	004	51.0	5.22	004	55.2	7.49
009	64.8	1.20	005	47.4	4.80			
			006	72.6	3.49			

Figure 1 shows the overlays of gastric pH traces on scintigraphic gastric emptying curves in Subject 003. Gastric pH rapidly returned to basal levels after Fosamax ® dosing. The M-K blend displayed an increase of pH at dosing which also quickly decreased to pH 1-2. In both these treatments, ALN was present in the stomach for more than 3.5 h. However, EX101 maintained pH>3 for approximately 4 h by which the ALN formulation was more than 80% emptied.

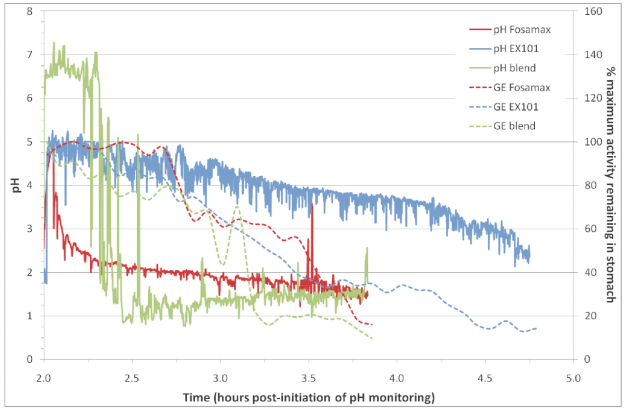

Figure 1: Collated gastric emptying and gastric pH overlays (Subject 003).

CONCLUSION

For the various parameters defined to indicate gastroprotection, there were highly significant differences between the effervescent formulations and Fosamax®. Generally, Fosamax® provided no pH protective effects, while EX101 was superior in providing pH protection. EX101 was also superior to the M-K Blend in certain parameters. The data clearly demonstrate that ingestion of Fosamax® resulted in ALN being present in the stomach at a pH below 3 within minutes of dosing. EX101 minimises the possibility of exposing the stomach and oesophageal (in case of reflux) mucosa to acidified ALN, as in no subject are the stomach contents below pH 3 during the crucial 30 minute post-dose fasting period.