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A drinkable formulation of alendronate: potential to increase compliance and decrease upper GI irritation

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Summary

Osteoporosis is a growing public health problem and several drugs have been developed in the past two decades to offer pharmacological solutions both in prevention and in therapy. Alendronate was the first compound registered as an anti-fracture agent and also the most prescribed drug worldwide for osteoporosis. Patient compliance is a major problem with alendronate, with studies demonstrating that 50-60% of patients discontinue treatment within one year. Dysphagia and swallowing difficulties are common especially among elderly people and the perceived potential for upper GI problems is a barrier to good long-term adherence. As non-persistence and non-compliance are linked to increased risk of fractures, efforts have been made to develop forms of alendronate which are more acceptable to patients. Among these, the drinkable formulations have the potential great convenience, simplicity of administration and reduction in gastro-intestinal side effects. In addition these novel soluble products are equivalent in cost to generic alendronate tablets. The approaches to improve adherence to an old and effective medication for osteoporotic patients will be reviewed in this report, with a special focus on the recently marketed product Bonasol 70 mg oral solution.

KEY WORDS: alendronate; drinkable formulations; amino-bisphosphonates; drug-induced gastric damage; adherence to pharmacological treatments.

Background

Alendronate, the most prescribed drug for osteoporosis worldwide, is a second-generation amino-bisphosphonate with proven efficacy to reduce risk of vertebral, hip and other types

of fractures (1, 2). It has been shown to be particularly effective in those with osteoporosis defined by DXA and/or fracture history (3). However, alendronate, along with other oral bisphosphonates may cause dyspepsia, dysphagia, nausea, upper abdominal pain and discomfort and is included among commonly used drugs well characterized with respect to their ability to induce typical gastro-esophageal (GE) injury patterns (4), particularly if not taken according to dosing instructions.

In large phase III placebo-controlled clinical trials, alendronate did not increase the risk of upper gastro-intestinal (GI) irritation or increase upper GI problems. However, postmarketing data and case reports have documented cases where undesirable upper GI effects were associated with oral alendronate, even in patients who claimed to closely follow recommended dosing (5-7). In some of the case reports, the symptoms resolved upon cessation of the alendronate administration. Other case reports suggest that these effects may be more common among those who do not closely adhere to dosing instructions which taking the tablet upon arising with a full glass of water, at least 30 min before the first food, beverage, or medication of the day without lying down for at least 30 min (8, 9). Therefore, educating physicians and patients as to the proper method of administration has the potential to minimize risks of upper GI problems (10, 11).

Some of these adverse effects, such as GE inflammation and ulceration, may be serious, with even gastrointestinal bleeding being reported (12-14). These findings soon after alendronate approval created concerns among the gastroenterology community, with consequent reports describing what the gastroenterologist should know about the gastrointestinal safety profiles of amino-bisphosphonates (15). In this sense the experience with oral amino-bisphosphonates provided a paradigm for the critical role of endoscopists in evaluating the gastrointestinal profile of new drugs.

Recommendations were consequently made on the non simultaneous use of alendronate and non-steroidal anti-inflammatory drugs (NSAIDs), as their combination appears synergistic in inducing gastric ulcers (16). Oral amino-bisphosphonates are also contraindicated in patients with a history of Barrett's esophagus (17, 18). Typical osteoporosis patients are older and may be frail and in such patients upper GI problems are common, with or without bisphosphonates. These early case reports sensitized prescribing physicians and also patients to the possibility of upper GI irritation with oral bisphosphonates. Therefore, patient awareness of the possibility of GI irritation makes it much more likely that a patient experiencing an upper GI problem will ascribe it to the bisphosphonate and will not continue with its use. Interestingly, in a large placebo controlled trial in which patients were counselled about possible upper GI effects of alendronate and specifically queried about upper GI problems, such problems were quite common occurring in about 30% of patients. However, these reports were equally common in those on alendronate and those on placebo suggesting that whether or not the drug caused the problem, the patient will believe it does and will stop usage (19). This

has been shown to be an important contributor to the overall low compliance with bisphosphonates.

Consequences of alendronate-induced gastric damage

In a normal clinical setting, where patients are not often offered frequent follow-up visits and regular reminders on how to take the medication, GI adverse events are among the most common reasons for giving up oral amino-bisphosphonate therapy (20).

Analyses of administrative databases has suggested that compliance of at least 80% is necessary for full anti-fracture efficacy, with increasing refill compliance being associated with progressively lower fracture rates (21). A similar linear effect was observed by Curtis JR et al. by evaluating adherence in a time varying manner over 2.5 years (22). Even though it is clear that compliance to anti-fracture therapies is an important factor influencing epidemiological analyses have shown suboptimal adherence to osteoporosis treatments, with significantly decreasing rates with longer therapy duration (23, 24).

Generic formulations which have been recently introduced might worsen this scenario. Introduction of generic alendronate tablets was shown to be associated with an increase in upper gastrointestinal adverse events, leading to therapy discontinuation (25-27). One possible explanation of these findings is that the longer *in vitro* disintegration time of the generic alendronate tablets when compared to branded solid alendronate (28-31), a factor not easily appreciated in the bioequivalence studies where young volunteers are well trained to follow all dosing instructions (i.e. drink 200 ml of water) (32-34). As multiple factors contribute to the development of clinical GE adverse events in patients who are prescribed alendronate for prevention and therapy of osteoporosis, length of contact of the tablet, reflux, gastric acid conditions or the chemical formula of the molecule (free acid or sodium conjugated) should always be taken into consideration when an increase in the number of undesirable effects is reported.

Potential approaches to increase adherence

A number of different approaches have been attempted to increase adherence to alendronate and other oral bisphosphonates.

Antisecretory agents, including proton pump inhibitors (PPI) and histamine H2 receptor antagonists (H2RAs) are frequently prescribed in the prophylaxis of GI adverse effects in chronic alendronate users. Interestingly, differently than what was observed with other frequently prescribed drugs, whose absorption is impaired by the use of inhibitors of gastric acid secretion (35), the bioavailability of alendronate is increased in hypochlorhydria (36). Indeed, preclinical evidence suggests that gastric lesions were less severe under acid control (37, 38).

In order to maximize adherence compared to daily use, a 70-mg once weekly dosing regimen for alendronate was developed and is now universally used (39). Alendronate 70-mg once weekly was not associated with any increase in endoscopic GI tract relative to placebo (40). Compared with daily 10 mg, 70 mg once-weekly did not increase upper GI irritation and may have improved it (19, 41). Other oral bisphosphonates including ibandronate and risedronate have developed monthly formulations. However, all fracture trials for oral bis-

phosphonates used daily doses and thus the extrapolation to less frequent dosage requires equivalence of surrogate markers. A once per year IV with zoledronic acid is also available as an alternative to oral bisphosphonates (42).

Development of new oral formulations

More recently, efforts were made to develop alternative formulations for the oral administration of alendronate, with a goal of decreasing GI adverse events and possibly increasing compliance. Microencapsulation of sodium alendronate reduced drug mucosal damage in rats, with polymeric microparticles representing a promising platform to deliver alendronate for the oral route (43). However, this method could affect absorption and therefore efficacy studies would need to be done to assure equal efficacy.

In order to reduce the lodging of an alendronate tablet in the GI tract, recent efforts have been made to develop water-soluble alendronate delivery systems. Potential advantages of a drinkable formulation of alendronate are avoiding adherence of the tablet to the gastric mucosa, overcoming motility obstacles (i.e. hernia, spasm, the body position of the patient during transit), eliminating the variability in the tablet disintegration rate with consequent irritation or reflux of particles, and controlling the pH of the gastric fluid.

The first description of an alendronate oral drinkable solution dates back over 10 years ago (Original New Drug Application 21-575 for the once-weekly alendronate 70 mg buffered solution, Merck & Company, Inc., West Point, Pennsylvania, filed November 15, 2002). It is a clear, colorless liquid and is available in 75 ml single-dose bottles. Each bottle contains 70 mg of alendronate, as well as citrate buffer, artificially raspberry flavour, paraben preservatives, and saccharin as a sweetener. In a 6-month placebo-controlled clinical study involving 392 postmenopausal women treated with this alendronate formulation plus extra water, the drinkable alendronate was bioequivalent to 70 mg tablets and adverse events were generally mild to moderate and did not result in treatment discontinuation, with the majority of patients considering the flavour of the drink to be acceptable (44).

An effervescent buffered soluble alendronate formulation, named EX101, was described in 2012 (UK licence no: PL31752/0027) and developed to be palatable, to minimize the contact of solid alendronate to the GI mucosae and to buffer the stomach acid with its high pH (approximately pH 5) (45).

In the same year, another formulation (EP1372669B1) was developed. The active ingredient of this formulation has already been described (46). The excipients are xanthan gum, methyl parahydroxybenzoate, propyl parahydroxybenzoate, sodium cyclamate, sucralose, sunset yellow (E110), orange flavour (containing ethanol and butylated hydroxyanisole), and purified water. The formulation was added with synthetic viscosity agents, that confer to the solution syrup-like properties. The caloric content of the formulation is negligible.

A study to evaluate the bioequivalence and upper digestive tract transit time of this drinkable solution of 70 mg/100 ml (below 1%) alendronate was performed in 104 young male volunteers (47). The results showed that the drinkable alendronate formulation is bioequivalent in terms of absorbed alendronate (the results being within the acceptance limits of 80 to 125%) to the tablets and may be advantageous in patients in whom the transit or disintegration of the tablets is impaired (47).

In 2013 TAGI Pharma Inc., a specialty pharmaceutical company and subsidiary of Precision Dose, Inc., announced the signing of an exclusive marketing rights agreement to market and sell the approved ANDA product, Alendronate Sodium Oral Solution, 70 mg/75 ml in the US and its territories, possessions and protectorates. The ANDA solution contains 91.35 mg of alendronate monosodium salt trihydrate, which is the molar equivalent to 70 mg of free acid.

The extent of the activity in the development and marketing of liquid alendronate solutions indicates the interest of investigators and clinicians in alternative oral formulations of this medication. Future studies and marketing efforts will contribute data allowing for better information as to the differences and similarities among the various formulations developed in different countries and by different companies.

Bonasol: a commercially available drinkable alendronate

In 2013 Bruno Farmaceutici S.p.A. announced the marketing in Italy of an alendronate once weekly 70 mg oral solution, commercialized as Bonasol 70 mg oral solution, that corresponded to the EP1372669B1 original formulation (47). The product, approved in EU via Decentralized Procedure in 21 EU countries, has a goal to be a more patient-friendly form of alendronate which will result in higher compliance. Bonasol entered the osteoporosis market at approximately the same cost as generic alendronate tablets.

Bonasol is an orange flavoured opalescent solution in a single-dose 100-ml container (Figure 1). The solution should be



Figure 1 - The Bonasol container compared to a small mineral water bottle.

taken by adults once weekly at least 30 min before first food, other drug or drink of day with plain water only. This solution, unlike alendronate tablets, does not require the patient to remain upright for at least 30 min, but it should be taken with 30 ml added tap water, in order to avoid interactions with minerals present in calcic waters (48).

The compound is contraindicated in patients with abnormalities of the esophagus or other factors that delay esophageal emptying (such as stricture or achalasia). Special precautions should include upper gastrointestinal problems, recent history of major gastrointestinal diseases, active gastrointestinal bleeding, surgery of upper gastrointestinal tract other than pyloroplasty, and Barrett's esophagus.

The potential advantages of this formulation are: appearance and flavour that reinforces the pre-breakfast aspect of the product, greater convenience, simple administration regimen, reduced potential for administration errors, and an equivalent price to other generic alendronate formulations.

According to CHMP and FDA guidelines Bonasol, evaluated in healthy male adults (age range 39-68 years), was bioequivalent (evaluated by measuring 36 hr-urinary alendronate excretion) to weekly alendronate tablets and also is well tolerated at the gastric level (47). Through video-deglutition analyses, in young male healthy subjects, Bonasol produced a fast accessibility to the duodenum (average time <3 min, with the longest time <10 min), with a formulation already soluble and therefore ready and fast for absorption (47). Hence, the recommended minimum 30 min postdosing fast is a prudent period to enable further absorption of alendronate in the first portion of the intestine.

The syrup-like properties of Bonasol make it possible for the viscous mass to stay for a longer time in the first portion of the intestine and if administered after cooling in the refrigerator may improve palatability and reduce the transit time (49).

Interestingly, in older subjects administering Bonasol induced fewer variations in the access to the intestine when compared to solid alendronate (47). However, as subjects older than 70 years, with greater difficulties in swallowing, were excluded from this study, these results cannot be immediately extrapolated to this age group. The postmarketing experience will, therefore, become very important for collection of any relevant information related to the acceptability of this novel formulation by elderly patients. An active pharmacovigilance program will help to build a database to collect any potential adverse event.

In conclusion Bonasol solution has a rapid access to the gastrointestinal mucosae, with lower transit times than the tablet formulation, mitigating the potential for tablet gastroesophagitis that can result from contact of solid alendronate with the GE mucosae. The oral solution may be advantageous in patients in whom the transit or disintegration of the tablets is impaired. Altogether the results obtained suggest that Bonasol has the potential to improve gastric tolerability of orally administered alendronate.

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