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

Maria Luisa Brandi[1]
Dennis Black[2]

[1] Department of Surgery and Translational Medicine, University of Florence, Florence, Italy
[2] Department of Epidemiology and Biostatistics, University of California, San Francisco. San Francisco, California, USA

Address for correspondence:
Maria Luisa Brandi, MD, PhD
Department of Surgery and Translational Medicine
University of Florence
Viale Pieraccini, 6
50139 Florence, Italy
Phone: +39 337 685511
Fax: +39 055 2337867
E-mail: marialuisa.brandi@unifi.it

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 esophagous (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 bisphosphonates 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 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).

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

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.

References

1. Black DM, Cummings SR, Karpf DB, Cauley JA, Thompson DE, Nevitt MC, Bauer DC, Genant HK, Haskell WL, Marcus R, Ott SM, Torner JC, Quandt SA, Reiss TF, Ensrud KE. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. Lancet 1996;348:1535-1541.
2. Cummings SR, Black DM, Thompson DE, Applegate WB, Barrett-Connor E, Musliner TA, Palermo L, Prineas R, Rubin SM, Scott JC, Vogt T, Wal-

lace R, Yates AJ, LaCroix AZ. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. JAMA 1998;280:2077-2082.
3. Black DM, Thompson DE, Bauer DC, Ensrud K, Musliner T, Hochberg MC, Nevitt MC, Suryawanshi S, SR. C 2000 Fracture risk reduction with alendronate in women with osteoporosis: the Fracture Intervention Trial. FIT Research Group. J Clin Endocrinol Metab 2000;85:4118-4124.
4. Parfitt JR, Driman DK. Pathological effects of drugs on the gastrointestinal tract: A review. Hum Pathol 2007;38:527-536.
5. Graham DY, Malaty HM, Goodgame R. Primary amino-bisphosphonates: A new class of gastrotoxic drugs-Comparison of alendronate and aspirin. Am J Gastroenterol 1997;92:1322-1325.
6. Graham DY. Excess gastric ulcers are associated with alendronate therapy. Am J Gastroenterol 1998;93:1395-1396.
7. Graham DY, Malaty HM. Alendronate gastric ulcers. Aliment Pharmacol Ther 1999;13:515-519.
8. Watts N, Freedholm D, Daifotis A. The clinical tolerability profile of alendronate. Int J Clin Pract Suppl 1999;101:51-61.
9. Cryer B, Bauer DC. Oral bisphosphonates and upper gastrointestinal tract problems: What is the evidence? Mayo Clin Proc 2002;77:1031-1043.
10. Greenspan SL, Harris ST, Bone H, et al. Bisphosphonates: Safety and efficacy in the treatment and prevention of osteoporosis. Am Fam Physician 2000;61:2731-2736.
11. Watts NB. Treatment of osteoporosis with bisphosphonates. Rheum Dis Clin North Am 2001;27:197-214.
12. De Groen PC, Lubbe DF, Hirsch LJ, et al. Esophagitis associated with the use of alendronate. N Engl J Med 1996;335:1016-1021.
13. Kaye PS. Gastric hemorrhage and ulceration in hiatal hernia sac associated with alendronate (letter). Dig Dis Sci 1999;44:903-904.
14. Colby CJ, Levin TR, Boyko WL. Costs of acid related disorders associated with alendronate use for osteoporosis in a large managed care organization. Abstract presented at the Annual Meeting of the American Society for Bone and Mineral Research, St. Louis, MO, September 30-October 4, 1999.
15. Graham DY. What the gastroenterologist should know about the gastrointestinal safety profiles of bisphosphonates. Dig Dis Sci 2002;47:1665-1678.
16. Graham DY, Malaty HM. Alendronate and naproxen are synergistic for development of gastric ulcers. Arch Int Med 2001;161:107-110.
17. Pazianas M, Abrahamsen. Safety of bisphosphonates. Bone 2011;49:103-110.
18. Pazianas M, Cooper C, Ebetino FH, et al. Long-term treatment with bisphosphonates and their safety in postmenopausal osteoporosis. Ther Clin Risk Manag 2012;6:325-343.
19. Bauer DC, Black D, Ensrud K, Thompson D, Hochberg M, Nevitt M, Musliner T, Freedholm D. Upper gastrointestinal tract safety profile of alendronate: the fracture intervention trial. Arch Intern Med 2000; 160:517-525.
20. Tosteson AN, Grove MR, Hammond CS, et al. Early discontinuation of treatment for osteoporosis. Am J Med 2003;115:209-216.
21. Siris ES, Hris ST, Rosen CJ, et al. Adherence to bisphosphonate therapy and fracture rates in osteoporotic women: Relationship to vertebral and nonvertebral fractures from 2 US claims databases. Mayo Clin Proc 2006;81:1013-1022.
22. Curtis JR, Westfall AO, Chen H, et al. Benefit of adherence with bisphosphonates depends on age and fracture type: Results from an analysis of 101,038 new bisphosphonate users. J Bone Miner Res 2008;23:1435-1441.
23. Sampalis J, Adachi JD, Rampakakis E, et al. Long-term impact to adherence to oral bisphosphonates on osteoporotic fractures incidence. J Bone Miner Res 2011;27(1):202-10.
24. Piscitelli P, Marcucci G, Parri S, et al. Compliance to antifracture treatments in Tuscany: A regional survey based on institutional pharmaceutical dataste. Clin Cases Miner Bone Metab 2011;8:62-65.
25. Ringe JD, Moller G. Differences in persistence, safety and efficacy of generic and original branded once weekly bisphosphonates in patients with postmenopausal osteoporosis: 1-year results of a retrospective patient chart review analysis. Rheumatol Int 2009;30:213-221.
26. Grima DT, Papaioannou A, Airia P, et al. Adverse events, bone mineral density and discontinuation associated with generic alendronate among postmenopausal women previously tolerant to brand alendronate: A retrospective cohort study. BMC Musculoskel Disor 2010;11:68-75.
27. Kanis JA, Reginster JY, Kaufman JM, et al. A reappraisal of generic bisphosphonates in osteoporosis. Osteoporos Int 2012;23:213-221.
28. Danserau RJ, Crail DJ, Perkins AC. In vitro disintegration studies of weekly generic alendronate sodium tablets (70 mg) available in the US. Curr Med Res Opin 2009;25:449-452.
29. Danserau RJ, Crail DJ, Perkins AC. In vitro disintegration and dissolution studies of once weekly copies of alendronate sodium tablets (70 mg) and in vivo implications. Curr Med Res Opin 2008;24:1137-1146.
30. Epstein S, Geusens P, Fisher JE, et al. Disintegration and esophageal irritation profiles of alendronate formulations: Implications for clinical safety and efficacy. Journal of Applied Research 2005;5:253-265.
31. Epstein S, Cryer B, Ragi S, et al. Disintegration/dissolution profiles of copies of Fosamax (alendronate). Curr Med Res Opin 2003;19:781-789.
32. Roldan EJA, Quattrocchi O, Zanetti D, et al. In vitro and in vivo equivalence studies of alendronate monosodium tablets. Arzneimittelforschung 2005;55:93-101.
33. Portoles A, Prieto E, Calvo A, et al. Truncated area under the urinary excretion rate curve in the evaluation of alendronate bioequivalence after a single dose in healthy volunteers. Arzneimittelforschung 2009;59:397-402.
34. Thudi NR, Gagnon S, Hussain S, et al. Two-way crossover bioequivalence study of alendronate sodium tablets in healthy, non smoking male volunteers under fasted conditions. Arzneimittelforschung 2009;59:521-525.
35. Lahner E, Annibale B, Delle Fave G. Systematic review: Impaired drug absorptionb related to the co-administration of antisecretory therapy. Aliment Pharmacol Ther 2009;29:1219-1229.
36. Gertz BJ, Sherry DH, Kline WF, et al. Studies on the oral bioavailability of alendronate. Clin Pharmacol Ther 1995;58:288-298.
37. Peter CP, Handt LK, Smith SM. ESophageal irritation due to alendronate sodium tablets (possible mechanisms). Dig Dis Sci 1998;43:1998-2002.
38. Dobrucali A, Tobey NA, Awayda MS, et al. Physiological and morphological effects of alendronate on rabbit esophageal epithelium. Am J Physiol Gastrointest Liver Physiol 2002;283:G576-G586.
39. Schnitzer T, Bone HG, Crepaldi G, et al. Therapeutic equivalence of alendronate 70 mg once-weekly and alendronate 10 mg daily in the treatment of osteoporosis. Aging Clin Exp Res 2000;12:1-12.
40. Lanza F, Sahba B, Schwartz H, et al. The upper GI safety and tolerability of oral alendronate at a dose of 70 milligrams once weekly: A placebo-controlled endoscopy study. Am J Gastroenterol 2002;97:58-64.
41. Bonnick S, Saag KG, Kiel DP, McClung M, Hochberg M, Burnett SA, Sebba A, Kagan R, Chen E, Thompson DE, de Papp AE. Comparison of weekly treatment of postmenopausal osteoporosis with alendronate versus risedronate over two years. J Clin Endocrinol Metab 2006;91:2631-2637.
42. Black DM, Delmas PD, Eastell R, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. N Engl J Med 2007;356:1809-22.
43. Cruz L, Assumpcao E, Andrade SF, et al. Microencapsulation of sodium alendronate reduces drug mucosal damage in rats. Drug Deliv 2010;17:231-237.
44. Cryer B, Binkley N, Simonelli C, et al. A randomized, placebo-controlled, 6-month study of once-weekly alendronate oral solution for postmenopausal osteoporosis. Am J Geriatr Pharmacother 2005;3:127-136.
45. Hodges LA, Connolly SM, Winter J, et al. Modulation of gastric pH by a buffered soluble effervescent formulation: A possible means of improving gastric tolerability of alendronate. Int J Pharmaceut 2012;432:57-62.
46. Gomez Acotto C, Antonelli C, Flynn D, et al. Upper gastrointestinal tract transit times of tablet and drinkable solution formulations of alendronate: A bioequivalence and a quantitative, randomized study using video deglutition. Calcif Tissue Int 2012;91:325-334.
47. Vega D, Baggio R, Garland MT. Monosodium 4-amino-1-hydroxy-1,1-butanediyldiphosphonate tri-hydrate (alendronate). Acta Cryst C 1996;52:2198-2201.
48. Pellegrini R. Which water for alendronate administration? Osteoporos Int 2009;20:1451.
49. Bateman DN. Effects of meal temperature and volume on the emptying of liquid from the human stomach. J Physiol 1982;331:461-467.