

Long-term management of GERD in the elderly with pantoprazole

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Abstract: The prevalence of gastroesophageal reflux disease (GERD) increases with age and elderly are more likely to develop severe disease. Older patients often complain of less severe or frequent heartburn than younger patients and they may present with atypical symptoms such as dysphagia, weight loss, or extraesophageal symptoms. Proton pump inhibitors (PPIs) are central in the management of GERD and are unchallenged with regards to their efficacy. They are considered safe and more effective than histamine receptor antagonists for healing esophagitis and for preventing its recurrence using a long term maintenance treatment. PPI have minimal side effects and few slight drug interactions and are considered safe for long term treatment. Pantoprazole is significantly effective both for acute and long-term treatment with excellent control of relapse and symptoms. It is well tolerated even for long-term therapy and its tolerability is optimal. Pantoprazole shows to have minimal interactions with other drugs because of a lower affinity for cytochrome P450 than older PPIs. Although the majority of elderly has concomitant illnesses and receive other drugs, this does not adversely effect the efficacy of pantoprazole because of its pharmacokinetics, which are independent of patient age. Clinical practice suggests that a low dose maintenance of PPIs should be used in older patients with GERD.

Keywords: GERD, long-term management, pantoprazole, safety, efficacy, tolerability

Introduction

The reflux of gastric contents from the stomach into esophagus is well recognized to play a major role in the pathogenesis of gastroesophageal reflux disease (GERD).

Significant information has accumulated over the past decade to support the position that the proton pump inhibitors (PPIs) represent powerful drugs that are especially effective in the treatment of GERD. These drugs inhibit the final common pathway to acid secretion, the H⁺/K⁺ ATPase located in the secretory canalicular membrane of the gastric parietal cell (Sachs et al 1993). In addition a long acting inhibition of gastric acid secretion occurs because of the covalent bonds formed by PPIs with the H⁺/K⁺ ATPase (Shin and Sachs 2002). As a consequence of their ability to significantly suppress acid secretion, PPIs are the preferred class of therapeutic agents for the treatment of GERD.

Symptom relief and acute healing of esophageal lesions can be achieved with short-term treatment. It has been demonstrated that healing regards not only erosive esophagitis but also negative endoscopy esophagitis (NERD) at the ultrastructural view of the mucosa (Calabrese, Bortolotti, et al 2005).

Otherwise, GERD is a chronic relapsing disease requiring long-term therapy in most patients. The high prevalence of chronic discomfort, which may or may not be associated with macroscopic esophagitis or related complications, decreases the patient's quality of life, increases the need for physician of visits and hospitalizations, and is costly for society. Most GERD patients require long term treatment to remain

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asymptomatic and/or sustain esophageal healing (Earnest and Robinson 1999; Katz 1999). The proportion of patients remaining in remission is very low at only 10%–25%, after six months of therapy (Dent et al 1999). Patients with NERD experience relapse over 6 months, and in more severe cases of erosive esophagitis (particularly Los Angeles classification grades C and D), relapse rate has been calculated between 80%–90% (Ollyo et al 1993; Lieberman 1987; Venables et al 1997b; Hetzel et al 1998; Sandmark et al 1998; Richter et al 2004). Due to this marked tendency towards relapse, almost all patients with GERD, regardless of endoscopic status, need an effective long-term management strategy for adequate symptom control, maintenance of mucosal healing, prevention of complications, and improvement of quality of life. Particularly, a maintenance therapy on a daily basis has been advocated in patients with severe esophagitis. Reports indicate that long-term therapy with appropriate PPI maintenance doses can be effective in as many as 100% of GERD patients (Katz 1999).

Recently acid-suppressive therapy ‘on demand’ has been proposed as an alternative to maintenance therapy; the patients decide when to start and to stop treatment. In this way the therapeutic strategy is likely to be more cost-effective than day by day maintenance therapy. Otherwise, the few data published to date regards only patients with grades A–B esophagitis (Bardan et al 1999; Kaspari et al 2005; Scholten et al 2005). Johnsson and colleagues (2002) suggested that it is the patient’s habits more than symptoms that determine the frequency and interval of medication intake since the patient could not find any correlation between the severity of the disease and medication intake. Several studies, and in particular, Venables and colleagues (1997a) who evaluated nearly 1000 patients (32% with erosive esophagitis), report that neither the physician evaluation nor a validated questionnaire that segregated patients into mild, moderate, or severe symptoms were predictive of erosive esophagitis (Venables et al 1997a; Devault 2006). ‘On demand therapy’ can be inadequate if the severity of the disease is not well documented because of the unpredictability of its course.

There is no consensus or agreed definition on what constitutes long term PPIs prescription. The definition has varied: from one repeated prescription over 12 months to continuous therapy for periods ranging from 4 to >12 months (Table 1) (Ryder et al 1994; Roberts and Bateman 1995; Rubin et al 1995; Goudie et al 1996; Ahnfeldt-Mollerup et al 1997; Boutet et al 1999; Hungin et al 1999; Prach et al 1999; Vetvik and Straand 2001; Hurenkamp et al 2002; Chen et al

2003; Jacobson et al 2003; Majumdar et al 2003; Lassen et al 2004; Raghunath and Hungin 2004; Tsai et al 2004; Raghunath et al 2005).

GERD is a very common complaint when considering the management of treatment with PPIs in the population over 65 years of age. GERD is usually more severe in the elderly than in younger patients and is frequently under-diagnosed and under-treated. Although there are a number of published articles reviewing the relative merits and limitations of the various therapy options for relapsing GERD, relatively few of them have specifically considered the elderly. In particular, there has been concern about the effects of different PPIs when coadministered with other drugs, such as benzodiazepin, warfarin, and digoxin, which are frequently used by older subjects.

Efficacy, safety, and tolerability of pantoprazole

Pantoprazole is a PPI that has been evaluated in more than 100 clinical trials (van Zyl et al 2004). It is a substituted benzimidazole derivative. Pantoprazole has a higher chemical stability at neutral and moderately acidic pH compared with other PPIs, which makes it less likely to become activated in moderately acidic compartments of the body. Most importantly, it has a low potential for metabolic interactions with cytochrome P450-dependent oxidase system and so it is particularly suitable for patients in co-medications (Stupnicki et al 2004).

Orally administered pantoprazole is very effective in GERD and achieves high healing rates as well as successful relief of symptoms (van Zyl et al 2004). Bardhan and colleagues (2005) reported that most patients need only the standard dose of 40 mg and healing occurs within 4 weeks in the vast majority. Otherwise, a maintenance treatment is advocated because of the high incidence of relapse of esophagitis. Prolonged pantoprazole therapy, also lasting up to 5 years, is also effective for the long term management of severe ulcers and reflux disease (Bardhan et al 2005). A particular concern regards GERD and its association with extra-esophageal complications and in particular with intrinsic asthma. In this case a high-dose long-term PPI treatment has been advocated. A recent study (Calabrese, Fabbri, et al 2005) showed that mild persistent asthma, besides having a highly prevalent relation with GERD, improves till a complete regression with 80 mg/daily for 6 months of pantoprazole. Twelve months follow up was carried out in this work. A possible occurring of a relapse

Table I Rates of long-term PPIs use

References	Country	Definition	Population size
Ryder et al 1994	UK	Six months or more	60 148
Chen et al 2003			
Roberts and Bateman 1995	UK	All PPI prescribing in a defined period	41 GP practices
Rubin et al 1995	UK	>12 months	24 400
Goudie et al 1996	UK	Repeat prescribing register	15 495
Boutet et al 1999	Sicily, UK	Repeat prescribing register	42 GP practices
Hungin et al 1999	UK	6 months or more	46 650
Prach et al 1999	UK	More than 56 days/year	35 000
Roberts and Bateman 1995			
Vetvick and Straand 2001	Norway	ddu	17 105
Jacobson et al 2003			
Ahnfeldt-Mollerup et al 1997	Denmark	Constant treatment	7160
Hurenkamp et al 2002	Holland	More than 12 weeks	46 813
Tsai et al 2004			
Chen et al 2003	Taiwan	Prescription items and ddu	/
Jacobson et al 2003	USA	More than 90 days	168 727
Raghunath and Hungin 2004	UK	Six months or more	46 933
Lassen et al 2004	Denmark	>180 ddu/year	470 000
Majumdar et al 2003	USA	Equal to or more one year	216 720

Abbreviations: ddu, daily defined units; GP, general practitioner; PPIs, proton pump inhibitors.

of GERD and asthma after discontinuation of treatment is not known.

PPIs, and among them pantoprazole, produce superior symptomatic remission rates and clinical efficacy compared with H₂ antagonist (such as ranitidine). Moreover pharmacokinetic considerations suggest that H₂ antagonist present a progressive phenomena of tolerance with continuous administration, leading to a consequent shortening of the clinical efficacy (Jalving et al 2006). For example, in a study of comparison with ranitidine, (Richter et al 2004) reports that pantoprazole provided the greatest degree and the most consistent effect for all efficacy parameters compared with the ranitidine throughout the 12 months of evaluation (van Zyl et al 2004).

Maintenance dosage is not well established. Patients with moderate to severe symptoms of esophagitis, whose disease has been initially controlled with PPIs, frequently, require PPI maintenance dosages similar to those used for initial esophageal healing (Donnellan et al 2005; Berardi 2006). A dissimilar result was found in a recent European trial (Escourrou et al 1999), which indicated that pantoprazole 20 mg/day was at least as effective as 40 mg/day with respect to prevent symptomatic and endoscopic recurrence in patients with grade B and C esophagitis who were initially healed with either pantoprazole (40 mg/day) or omeprazole (20 mg/day).

Data on the safety of prolonged therapy with PPI and pantoprazole are relatively sparse. In early days there was particular concern about hypergastrinemia in response to profound acid inhibition with resultant endocrine cell hyperplasia and possible tumor formation. Endocrine cell hyperplasia has been looked for in Man but is rarely found in the few reported studies. The development of frank carcinoid tumors is described to be exceptional (Laine et al 2000; Bardhan et al 2005; Jalving et al 2006). There is inadequate evidence to support the association between PPIs and colonic polyps and no data has been reported on pantoprazole and an association with gastric or colorectal neoplasia in humans (Berardi 2006). Other concerns are about the possible bacterial overgrowth with consequent nitrosamine formation induced by the suppression of gastric acid in patients treated with PPIs. *Helicobacter pylori* and many other urease positive gastric bacteria can be advocated at this point (Brandt et al 2006). A causal relationship between intragastric nitrosamine and gastric development of neoplasia in patients taking PPIs has never been established (Freston 1997; Garnett 1998). The influence of *H. pylori* infection during prolonged PPIs therapy is still in doubt. Reductions in chronic antral gastritis and corresponding increases in chronic corpus gastritis in those with *H. pylori* infection have been observed; in contrast, there is little change in the uninfected. A corpus gland atrophy has been also observed and it develops in some

H. pylori-infected patients. This observation could raise a theoretical risk of tumor development, but other studies have not been able to confirm this progression. Hence, there is no agreement on whether to eradicate *H. pylori* before commencing long-term PPIs therapy (Bardhan et al 2005).

Digestion of protein and the absorption of calcium and iron are normal in patients treated with PPIs (Garnett 1998). Only a slight decrease of B₁₂ serum concentration has been reported in a small number of patients on long term therapy (longer than 3 years) but only with omeprazole and this appeared to not be a major clinical concern (Garnett 1998).

Less is known about safety of pantoprazole during pregnancy. Data reported are only for omeprazole and they suggest that, until it is possible to rule out an association between PPIs and an increased risk of fetal malformations or preterm birth, the benefit of using a PPI during pregnancy must be weighted against the potential risk for the fetus (Berardi 2006).

Pantoprazole is overall a well tolerated drug. Most recurrent short-term adverse effects are headache, diarrhea, nausea, and abdominal pain. These events are uncommon (approximately 1%) and rarely lead to withdrawal of treatment. Data from numerous clinical trials and clinical experience confirm the short-term adverse effects of PPIs and also of pantoprazole (Fitton and Wiseman 1996; Dupas et al 1998; Richardson et al 1998; Vicari et al 1998).

Data from long-term studies with pantoprazole suggest a similar tolerability to that reported with their short-term use (Fitton and Wiseman 1996; Moosner et al 1997; Richardson et al 1998; Escourrou et al 1999).

Quality of life, patient's satisfaction/acceptability, adherence, and reuptake

Since impairment of normal life consequent upon GERD symptoms (health-related quality of life [HRQoL]) is generally the primary motive of the patient to seek therapy, the relief of typical GERD symptoms is of considerable interest for patients. From the perspective of the patient, symptom relief is the most critical component in determining the success of treatment. Numerous previous data clearly indicate that the frequency and severity of common GERD-related symptoms correlate with an impairment of normal functioning and general well-being (Dupas et al 1998; Kaplan-Machlis et al 1999). An adequate control of symptoms and a sustained reduction of symptoms to a level that does not significantly impair HRQoL is the end-point

of treatment (Dimenas et al 1996). The speed of the change in HRQoL during therapy may influence the choice of the treatment drug.

Tools to assess how symptoms of GERD relate to and impair HRQoL are important for a better understanding of diagnosis and treatment.

In contrast to the obsolete assessment of heartburn as a single outcome criterion, a recently validated symptom assessment scale (ReQuest) (Monnikes et al 2005) reliably covers a broad range of GERD-related symptoms on a daily basis by its dimension-orientated structure. An evaluation study using ReQuest demonstrated that even individuals without evidence of GERD experienced mild symptoms that are commonly related to GERD.

In the study by Monnikes and colleagues (2005), the rapid and sustained relief of a wide range of symptoms is documented in patients with NERD treated with 20 mg pantoprazole. The median time to first symptom relief was 2 days. This study is in accordance with the literature that treatment can achieve effect in a matter of days (Dent et al 1999; Kovacs et al 2002; Moretzsohn et al 2002). Moreover, the data indicates that pantoprazole is well tolerated, safe and provide efficacy in time to both first and sustained symptom relief in patients with NERD. Pantoprazole is strictly related to a rapid and sustained relief with the minor short term adverse effects with regards to patient satisfaction and acceptability. PPIs and pantoprazole reflect this end-point.

Adherence and uptake is another point of interest. Compliance with continuous PPIs therapy is poor: only a minority of patients regularly requests their prescriptions. The main factors determining whether or not patients take their PPI is the presence or severity of symptoms, the desire to remain in personal control, ignorance about the drugs, and a fear of side effects (Hungin et al 1999) despite PPIs being a well tolerated class of drugs.

Special considerations in the elderly

The goals of treatment of GERD in the elderly are essentially the same as those for other age groups: to alleviate symptoms; to heal esophagitis; to manage complications; and to maintain remission.

GERD is a widespread problem in the elderly, but the incidence of GERD in older patients is difficult to define because of the limited number of studies addressing the population age >65 years. In addition, co-morbidity with increasing age and the use of concomitant therapies complicate both diagnosis and management. In the primary

care setting in the US, as many as 20% of older patients report acid reflux (Mold et al 1991). In a Japanese study, the prevalence of reflux esophagitis in patients aged >70 years was more than triple the prevalence in patients younger than 39 years (Maekava et al 1998).

Interestingly, there are significant differences between elderly and younger patients in the presentation of GERD. Older subjects with GERD are less likely to report frequent or severe heartburn and the majority do not experience acid regurgitation (Raiha et al 1991). Dysphagia usually occurs in the setting of long standing heartburn with slow progressive dysphagia for solid and rarely for liquids. Weight loss is infrequent because appetite is unchanged, which helps distinguish this usually benign dysphagia. This symptom is usually correlated to a peptic stricture, severe peristaltic dysfunction, and sometimes the first presentation of Barrett's esophagus with cancer (Raiha et al 1992). Extraesophageal presentation of GERD are more common in the elderly (Raiha et al 1992). The chest pain produced by acid reflux may be identical in quality to angina, making an appropriate diagnosis a difficult problem. Because of this different symptom profile of GERD in the elderly, the disease, particularly in the milder form, may remain undiagnosed and untreated for a long period of time.

The management of GERD in the older patient poses special challenges. GERD among older people shows a higher incidence of severe esophagitis and of its complications, ie, bleeding, stenosis, and Barrett's esophagus. The disease presentation is more severe despite milder symptoms because of the cumulative injury of acid reflux over many years. A large epidemiological study from the US reported that age was an important risk factor for the development of severe forms of GERD, together with male gender, white ethnicity, and hiatus hernia (el-Serag and Sonnenberg 1997). Collen and colleagues (1995) noted that 81% of GERD patients aged 60 years or older developed erosive esophagitis compared with 47% of those younger than 60 years with GERD.

Some other factors related to the development of GERD in the older patient are: a greater degree of nocturnal and supine reflux; the increased prevalence of hiatus hernia; reduced patient mobility and increased recumbence; altered gastrointestinal mobility; decreased saliva volume and bicarbonate secretion; and increased prevalence of co-morbid conditions affecting esophageal tone (ie, diabetes, cerebrovascular accident, Parkinson's disease, and increased usage of concomitant medication) (Mold et al 1991; Hungin et al 1999).

The management of long-term treatment is a major point of interest because of the high occurrence of relapse after cessation of therapy. In fact, symptoms and esophagitis recur quickly if therapy is not continuative and long-term treatment appears to be the key to effective management. The intermittent use of antacids, alginic acid, or H₂ receptor antagonists are usually helpful in relieving mild symptoms, if present, but do not heal esophagitis. Continuous PPI therapy is particularly useful in elderly patients with GERD to obtain a profound acid inhibition and to maintain complete symptom relief and healing of esophagitis. A placebo-controlled clinical trial demonstrates that maintenance therapy with pantoprazole 20 mg daily is an effective measure for minimizing the occurrence of relapse in patients over 65 years of age (Maekava et al 1998). In the maintenance period of the study, 80% of patients treated with placebo had an esophagitis relapse compared with 30% of patients who continued active treatment. Moreover, the study reports an intention-to-treat healing of 80% after 12 months of treatment with 20 mg of pantoprazole, which confirms that this low dosage is sufficient to reduce relapse. Interestingly, 76% of patients were affected by concomitant diseases and 65% were taking other drugs concomitantly with pantoprazole in this population. The low adverse reactions and relapse rates confirmed that pantoprazole interacted minimally with other drugs and suggested that it could be used successfully in patients with multiple therapies.

Another study indicates that esophagitis relapse rates in elderly who were not treated with maintenance therapy were constant during three years of follow up (relapse rates of 65.5%, 63.6%, and 57.1% after 1, 2, and 3 years respectively) (el-Serag and Sonnenberg 1997).

A recent study focused on the managing of GERD in the elderly and posed the question about the better dosage to prevent relapse of heartburn compared with placebo (Hungin et al 1999). The study suggests that the most effective therapy is a full dose PPI than a low dose (average relapse rate with low dose was 28% and 13% with full dose). Instead, a study by Escourrou and colleagues (1999) suggests a maintenance therapy with pantoprazole 20 mg daily for six months to prevent relapse of reflux esophagitis and shows that it is at least equivalent to the 40 mg dose. It is without doubt that besides the necessity of a long-term treatment in the elderly with GERD, there is no general consensus on the optimal dosage.

An important problem is the interaction of PPIs with other drugs. It is known that the interaction occurs through

the cytochrome P450 systems potentiating other drugs. The drugs most cited are benzodiazepines, theophylline, and the calcium-channel blockers, but their effects seem to be slight (Raiha et al 1991) (Table 2). The most significant interaction is suggested to be between PPIs and warfarin. Also in this case it has been shown that 16% of patients on warfarin, taking an acid suppressive drug, presented fluctuations in international normalized ratio (INR) but only in those in intermittent PPIs (Raiha et al 1992). Pantoprazole has shown to have fewer drug interactions than older PPIs because of a lower affinity for cytochrome P450 (Stupnicki et al 2004). Moreover a pharmacokinetics evaluation of pantoprazole shows that it may be a good choice for the treatment of the older patient with GERD because it is also independent of the patient's age (Pilotto et al 2005).

Dosage adjustments for PPIs are not necessary in elderly patients experiencing renal failure and mild hepatic impairment. Pantoprazole should be used with caution in patients with severe hepatic impairment (Raiha et al 2005).

There is concern regarding the use of nonsteroidal anti-inflammatory drugs (NSAIDs) that elderly widely use to provide effective pain relief in chronic arthritic, inflammatory conditions, and prophylaxis against cardiovascular events. However, despite the great benefits associated with NSAIDs use, up to 25% of patients taking NSAIDs experience chronic upper gastrointestinal adverse effects (Singh and Triadaphilopoulos 1999). Among adverse effects, severe complications of the gastro-intestinal tract are included, and it has been estimated a 4% of major accidents in the older subject (Armstrong and Blower 1997).

PPIs such as pantoprazole are emerging as effective agents that protect the stomach and the duodenum during NSAID administration (Cheer et al 2003).

Table 2 Effects of pantoprazole when co-administered with other drugs

Drug	Pantoprazole
Carbamazepine (Tegretol)	None
Clarithromycin (Biaxin)	Unknown
Diazepam (Valium)	None
Digoxin	> Absorption
Ketoconazole (Nizoral)	Unknown
Methotrexate	Unknown
Nifedipine (Procardia)	> Absorption
Oral contraceptives	None
Phenytoin (Dilantin)	None
Warfarin (Coumadin)	None
Theophylline	None

A study in healthy volunteers has shown that even a low dose of aspirin causes significant injury to the stomach whereas coadministration with pantoprazole offers protection against such damage (Muller and Simon 1998). This gastroprotective effect of pantoprazole translates into clinical benefits by reducing the damage in long-term users.

Pantoprazole has also been shown to be superior to placebo in the prevention of NSAIDs-associated peptic ulcers (Bianchi Porro et al 2000). In this study pantoprazole 40 mg once daily or placebo was administered for 12 weeks to patients requiring long-term NSAIDs. At baseline about half of patients had endoscopically detected gastroduodenal lesions while the other half had normal or hyperaemic mucosa at baseline. After 12 weeks the probability of remaining free of gastric or duodenal ulcers was 72% in the pantoprazole group compared with 59% in the placebo group.

An other study focused on the prevention of NSAIDs-associated lesions and it concluded that for patients taking NSAIDs continually, pantoprazole 20 mg once daily or omeprazole 20 mg once daily provided effective and well-tolerated prophylaxis against gastrointestinal lesions (Regula and Butruk 2006). Regarding the use of misoprostol in the prevention of gastrointestinal lesions, a interesting study shows that pantoprazole 20 mg once daily is superior to misoprostol 200 µg twice daily in the prevention of lesions and symptoms in patients on continuous long-term treatment with NSAID and at risk to develop such lesions or symptoms (Stupnicki et al 2003).

Conclusions

This review shows that PPIs are highly effective drugs that have revolutionized the management of GERD. Pantoprazole is significantly efficacious both for acute esophageal healing both for long-term treatment with excellent control of relapse of esophagitis and symptoms. This report also confirms that pantoprazole is a well tolerated treatment even for long-term therapy with optimal tolerability. It is perfectly suited for use in patients taking concomitant therapies and in particular in the elderly.

There is a limited body of evidence advocating the optimal dosage for long-term treatment. Clinical practice suggests that at least a low dose maintenance should be carefully taken in consideration especially in the elderly as they are more exposed to severe complications.

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