Medical treatment of gastro-oesophageal reflux disease

Terapia medica della malattia da reflusso gastroesofageo

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Key words

Gastro-oesophageal reflux disease • Treatment • Proton pump inhibitors

Parole chiave

Malattia da reflusso gastroesofageo • Terapia • Inibitori della pompa protonica

Summary

The introduction, in the last two decades, of strongly effective acid suppressant drugs, such as proton pump inhibitors has radically modified the way of treating gastro-oesophageal reflux disease. In clinical trials, these agents have constantly been demonostrated to be more effective than other acid-suppressant agents such as H_2-receptor antagonists in relief of symptoms and healing of oesophagitis, the two main goals of gastro-oesophageal reflux disease treatment. They provide a prompt clinical benefit to most patients and can be safely used in long-term gastro-oesophageal reflux disease management for maintenance of clinical and endoscopic remission, because of their negligible adverse-events profile. Therapeutic protocols vary depending on the severity of symptoms and the degree of oesophageal injury. In patients with mild symptoms and with minimal lesions at endoscopy, a "step-down" therapy, in the short-term, is considered the best medical strategy, while in the long-term the therapy "on-demand" appears to be a reasonable approach. Patients with non-erosive disease seem to have a lower response rate to proton pump inhibitor treatment. More severe grades of oesophagitis must be treated with full-dose proton pump inhibitors without withdrawal. Data on the treatment of extra-oesophageal manifestations of gastro-oesophageal reflux disease are few and controversial. Overall, it appears that patients with extra-oesophageal symptoms of gastro-oesophageal reflux disease must be treated with higher doses of pharmacological treatment, principally with proton pump inhibitors, and with longer periods of treatment to achieve complete relief of symptoms, as compared with patients with typical symptoms of gastro-oesophageal reflux disease and erosive oesophagitis.

Riassunto

L'introduzione negli ultimi vent'anni di farmaci inibenti la secrezione acida gastrica e altamente efficaci, come gli inibitori di pompa protonica (IPP), ha radicalmente modificato le modalità di trattamento della malattia da reflusso gastroesofageo (MRGE). Nei diversi trials clinici, questi farmaci si sono rivelati costantemente più efficaci di altri agenti acido-soppressivi, come gli antagonisti dei recettori H_2 dell'istamina, nella remissione dei sintomi e la guarigione dell'esofagite che rappresentano i due obiettivi principali della terapia della MRGE. Essi garantiscono un immediato beneficio clinico nella maggior parte dei pazienti e possono essere usati con sicurezza nel trattamento a lungo termine della MRGE per il mantenimento della remissione clinica ed endoscopica, grazie agli effetti collaterali trascurabili. I protocolli terapeutici variano in base alla severità dei sintomi ed al grado di esofagite. In pazienti con sintomi lievi e lesioni minime all'endoscopia, la terapia "step-down" è considerata la migliore strategia terapeutica nel breve termine, mentre la terapia "on-demand" nel lungo termine sembra rappresentare un ragionevole approccio. I pazienti sintomatici ma senza esofagite erosiva sembrano rispondere in maniera meno soddisfacente agli IPP. Gradi più severi di esofagite richiedono un trattamento con IPP a pieno dosaggio per lungo termine, senza sospensione. I dati sul trattamento dei sintomi extraesofagei della MRGE sono pochi e non univoci. In generale, si ritiene che i pazienti con sintomi extraesofagei, per ottenere la completa remissione dei sintomi, debbano essere trattati con terapia farmacologica, principalmente IPP, a dosaggi maggiori e per periodi di tempo superiori rispetto ai pazienti con sintomi tipici.

Introduction

Substantial progress has been made in the last two decades in the understanding and treatment of gastro-oesophageal reflux disease (GERD), prompted, in part, by the development and wider application of endoscopy and pH monitoring, and the availability of effective acid-suppressant drugs. Pharmacotherapy is considered the first-line treatment in GERD patients. Although some guidelines recommend instituting lifestyle changes at the same time as an initial trial of empiric medical therapy [1], others report that diet and lifestyle changes are of little therapeutic benefit and recommend medical therapy as initial treatment [2].

The choice of a medical therapy centres around several factors, including the efficacy and safety of the agent and the severity of the patient's symptoms and complications. Although the efficacy of antacids and

alginic acid has not been definitively proven in clinical trials, these agents are effective against mild GERD symptoms, in clinical practice. Prokinetic agents may be helpful in GERD treatment by increasing lower oesophageal sphincter (LES) pressure, accelerating gastric clearance and stimulating oesophageal peristalsis. However, the efficacy of these agents in improving GERD symptoms and healing oesophagitis come from small, sometimes poorly designed studies, often without a placebo control. Also, the adverse-event profile of these agents must be weighed against any clinical benefit of GERD treatment. Indeed, the withdrawal of cisapride from the market because of inducing lethal cardiac arrhythmias, has substantially lessened the role of prokinetic agents in the treatment of GERD.

Acid-suppressive agents have become the drugs of choice for GERD. Both proton pump inhibitors (PPIs) and histamine H_2-receptor antagonists (H_2-RA) are effective and can be safely used to treat GERD. PPIs have been shown, however, to provide the highest levels of symptom relief and oesophageal healing to most GERD patients, in the shortest time, and with the fewest side-effects.

Acid suppression in the management of GERD

Oesophageal 24-h pH monitoring suggests a direct relationship between the degree and duration of acid exposure and the extent of mucosal injury [3 4]. An intra-oesophageal pH of 4 is generally accepted as the threshold between pathological and normal, and, indeed, the proportion of the 24-h period with intra-oesophageal pH < 4 increases progressively from endoscopy-negative GERD through the more severe grades of oesophagitis [4-6]. Conversely, the ability to heal mucosal injury correlates directly with the ability to maintain an intra-gastric and intra-oesophageal pH > 4 throughout most of each 24-h period [3].

H_2-RAs have a relatively short duration of action and, depending on the individual agent and whether the patient is in a fed or fasting state, suppress acid for approximately 4-8 h [7]. Consequently, multiple daily doses of these agents are likely to be required. Furthermore, H_2-RAs produce incomplete inhibition of postprandial gastric acid secretion. Overall, these agents inhibit acid secretion by up to 70% over a 24-h period [7]. A further limitation is the development of tolerance to standard H_2-RAs within 2 weeks of repeated administration, resulting in a decline in acid suppression [8 9]. This can be explained by a gastrin-induced increase in entero-chromaffin-like cell-derived histamine concentrations at the H_2-receptor on the parietal cell [10].

In contrast, PPIs control both basal and food-stimulated acid secretion and produce more complete and long-lasting acid suppression than H_2-RAs. This acid inhibition virtually abolishes the damaging peptic activity of the gastric refluxate. In addition, tolerance to PPIs has not been observed, presumably because they act at the final site of acid production, thereby blocking the effects of any compensatory mechanisms promoting acid secretion [10].

PPIs *vs.* H_2-RAs: clinical evidence

PPIs have been shown to be more effective than H_2-RAs in relieving reflux symptoms and healing erosive oesophagitis. Results from 33 randomized trials with over 3000 patients showed that relief of symptoms could be anticipated in 83% of PPI-treated patients compared with 60% of patients treated with H_2-RAs, while oesophagitis healed in 78% and 50% of patients, respectively [11].

GERD is usually a chronic relapsing condition and withdrawal of treatment results in relapse of symptoms within 6 months in approximately 90% of patients with oesophagitis and 75% of patients with endoscopy-negative GERD [12]. H_2-RAs are less effective than PPIs in maintaining remission of GERD. A trial has shown that a significantly higher percentage of patients remained in remission after 12 months' treatment with omeprazole (72%) than with ranitidine (45%) [13].

Treatment strategies

In the short-term management of GERD, the primary goal is prompt and effective symptom relief; secondary goals include the healing of erosions or ulcerations and the prevention of complications [14]. International guidelines endorse "step-down therapy" as the best medical strategy for patients with oesophagitis [2]. This starts with the most powerful agent (i.e., a PPI) then gradually reduces the intensity of treatment to maintain the patient in remission [2]. Potential advantages of the step-down approach include faster ulcer healing, maximum symptom relief and a more rapid improvement in the patient's quality of life [15].

In the long-term management of GERD, the goals are symptom control (rather than complete abolition of symptoms) and maintenance of oesophageal healing [16]. In a meta-analysis of long-term trials including over l000 patients, symptom relief was found to be highly predictive for the maintenance of healing [17]. Maintenance therapy of oesophagitis should be stepped down to the lowest dose that allows symptom control [17].

Obviously, choice of treatment depends on the severity of symptoms and the degree of oesophageal mucosal injury.

In non-endoscoped, endoscopy-negative or low-grade oesophagitis patients, initial treatment with a PPI is recommended [2]. Step-down treatment is favoured as a cost-containment measure and the use of a half-dose PPI therapy is seen as an attractive long-term therapeutic option. Non-erosive reflux disease (NERD) patients seem to have a lower response rate to PPI therapy than patients with erosive oesophagitis. A systematic review combining data from 7 trials found response rates, after 4 weeks of PPI treatment, of 56% in patients with erosive oesophagitis and 37% in NERD patients [18]. This could be due to one of several factors. It is possible that the symptoms, in these patients, are unrelated to GERD, but associated with other factors. An alternative hypothesis suggests that post-prandial gastric acid secretion is actually more difficult to control in NERD patients, but the causes for this are unknown [19]. The long-term management of GERD should consider patient preference and opinion. "On-demand" therapy – episodic use to treat relapse of symptoms – may be a reasonable approach in patients with mild infrequent symptoms and/or low grade reflux disease at endoscopy [20]. Evidence suggests that "on-demand" therapy may be a valid long-term management option in NERD patients [21].

In more severe GERD, healing rates with H_2-RAs are inadequate and dramatically inferior to those achieved with PPIs [7]. PPIs are, therefore, the mainstay of treatment in higher grade oesophagitis. Insufficient response can be managed by a gradual increase in dose. A step-down approach to long-term therapy is inappropriate since any medical treatment other than full-dose PPI is unlikely to prevent relapse of oesophagitis or strictures in patients with severe oesophagitis [2]. Since moderate or severe oesophagitis almost always relapses, maintenance therapy, without a trial of treatment withdrawal, may be appropriate [22].

Treatment of extra-oesophageal symptoms

There have been few clinical trials of treatment involving patients with extra-oesophageal manifestations of GERD, specifically asthma, cough, and voice changes. The majority are uncontrolled and do not address long-term maintenance. Treatment is based on the principles advocated for treating patients with heartburn and erosive oesophagitis, observations from available clinical trials, and clinical experience. It appears that patients with extra-oesophageal manifestations of GERD must be treated with higher doses of pharmacologic agents, principally PPIs, and for longer periods of treatment to achieve complete relief of symptoms, compared with patients with heartburn and erosive oesophagitis.

Treatment trials in patients with pulmonary manifestations and suspected GERD have provided little insight into a causal relationship for these two conditions. An extensive review of eight randomized, placebo-controlled clinical trials revealed that treatment of GERD symptoms was associated with an improvement in asthma symptoms in over 60% of patients, with a reduced need for asthma medications [23]. A more recent Cochrane Review of 12 randomized-controlled trials failed, on the other hand, to find any overall improvement in asthma following treatment for GERD [24].

The data for treating possible GERD-related cough continues to be characterized by over enthusiasm based on uncontrolled trials and a few less convincing placebo-controlled studies. For example, in a placebo-controlled trial, 35% of coughers with positive pH tests were reported to have achieved resolution of their complaints after 2 weeks of omeprazole 40 mg b.d. compared with 0% response in the placebo group [25].

Nearly 10% of patients presenting to ear, nose and throat (ENT) doctors may have symptoms attributed to GERD. Uncontrolled studies suggest that 40-100% of patients who have suspected acid-related ENT symptoms improve on aggressive anti-reflux therapy [26]. In these studies, the drug regimen was usually a single- or double-dose PPI for 6-24 weeks. Placebo-controlled studies, in contrast, do not share this enthusiasm [27 28]. The data accumulating on patients with suspected acid-related ENT symptoms casts serious doubts that either the ENT examination or pH testing can accurately define the subset of patients who will improve with PPI therapy. Furthermore, the concept that most patients with this syndrome have silent reflux is no longer tenable [28].

Ahmad and Batch [29], in studies on a group of 303 patients with ENT disorders and GERD symptoms submitted to oesophagogastroscopy, showed 98% of cases with abnormal oesophagoscopy *vs.* 13% with posterior laryngeal lesions. Surprisingly, the same study revealed that globus and dysphony symptoms are predictable of a positive response to PPI.

In the present volume, results of a multicentric study are reported in which out of 220 patients with symptoms or signs indicative of reflux, 182 (82.72%) were responders to PPI; the prevalent manifestations, in responders, were cough, globus and dysphony.

One approach to treatment of GERD with extra-oesophageal manifestations, in clinical practice, is to begin with full-dosage PPI therapy given twice daily for 2 to 3 months [30]. Clinical experience suggests that 70% of patients will respond to this therapy, although many will require longer treatment periods to achieve optimal results. Patients who have a good initial, but incomplete, response to this therapeutic trial, should continue with the same dose for an addi-

tional 4- to 8-week period to assess continued improvement. If complete symptom relief and/or mucosal healing is not achieved at this point, it is useful to evaluate the patient with prolonged ambulatory pH monitoring studies while continuing treatment with a PPI to assess the adequacy of intra-gastric acid suppression and elimination of distal and proximal oesophageal acid exposure. If acid suppression is incomplete, additional medical treatment is indicated before assuming that the patient is a medical failure. If the patient has a poor response to the initial therapeutic trial, prolonged ambulatory pH monitoring should be performed while on therapy to evaluate drug efficacy.

Clinical experience suggests that most patients with extra-oesophageal GERD will have chronic GERD and thus require long-term medical treatment and/or anti-reflux surgery should possibly be considered for long-term control. Current evidence suggests that long-term medical treatment is safe, and tolerance, or tachyphylaxis, extremely rare. Patients who choose long-term medical treatment can be confident of excellent long-term control of acid-induced mucosal injury without worry of serious complications.

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