Proton pump inhibitors (PPIs) are the best medical therapy for patients with gastro-oesophageal reflux disease (GORD), as they control symptoms and heal oesophagitis in about 80% of the cases [1]. Despite this high degree of efficacy, a substantial part of the patients remains symptomatic on once-daily PPI, and this is particularly true for those with non-erosive reflux disease (NERD). Although there is no universal agreement on the definition of PPI failure in terms of frequency and severity of symptoms, an incomplete or unsatisfactory response of them to a full course of PPIs can be empirically accepted as ‘refractory GORD’.

In this issue of Digestion, Sgouros and Mantides [2] review the underlying mechanisms of PPI failure and provide an algorithm to manage unresponsive patients. They subdivide the reasons for clinical non-response into two categories: patient- and therapy-related. Among the former group, poor compliance of patients with treatment is certainly the single most common cause. An early discontinuation of therapy has been documented in many patients [3], but a suboptimal PPI dosing in terms of timing and relation to meals has been also reported. Gunaratnam et al. [4] have recently shown that 54% of the patients treated with PPIs dose these drugs suboptimally, by taking PPIs >60 min before meals, after meals, or at bedtime. Conversely, it is well known that the maximal efficacy of PPIs is obtained when they are taken approximately 30 min before meals [5]. So, patients with refractory GORD symptoms should be first asked about their way to take PPIs, in particular, dose timing and frequency of dosing.

The presence of eosinophilic oesophagitis and motility abnormalities of the oesophago-gastric tract seem to have a limited clinical relevance. On the contrary, in our opinion, a neglected potential cause for PPI failure may be presence and size of a hiatal hernia which has been shown to be the most important factor in determining the best dosage of PPIs for effective intra-oesophageal acid suppression [6]. If so, it is reasonable to suppose that a hiatal hernia can be also responsible for a poor PPI response.

Non-acidic gastro-oesophageal reflux has been also implicated as a possible cause of symptoms refractory to PPIs, because it can induce the same typical symptoms as acid reflux [7]. It has been hypothesized that at least a part of NERD patients with normal oesophageal pH-metry and unresponsive to PPI therapy can be characterized by reflux of non-acid material [8]. Tack et al. [9] have also demonstrated that duodeno-gastro-oesophageal reflux can be an important underlying factor in GORD patients who do not respond to PPIs, but a clear cause-effect relationship between alkaline reflux and persistent GORD symptoms was lacking in their study.
Among the therapy-related reasons, the influence of *Helicobacter pylori* infection seems to have only a limited role, because dose adjustment of PPIs is not necessary to maintain therapeutic success in GORD patients who are or are not infected [10].

Much emphasis has been placed on the role of the genetic polymorphism of CYP2C19, which is the main enzyme responsible for the hepatic metabolism of PPIs. However, the poor metabolizer phenotype, which is associated with greater efficacy of PPIs, is much more common in Asian than in Caucasian populations. It is conceivable that a proportion as low as 5% of these subjects in Western countries [11] has only a marginal clinical impact.

Also, nocturnal acid breakthrough (NAB) has been overemphasized as a factor responsible for PPI failure. The clinical relevance of such episodes is controversial, because especially patients with Barrett’s oesophagus are more likely to have acid reflux during NAB [12]. Thus, NAB does not occur in most patients with uncomplicated GORD, and, moreover, a low correlation between NAB events and symptoms in patients who failed twice-daily PPIs has been reported [13].

As to the management of patients with PPI failure, if the intake of PPIs is acknowledged as correct after appropriate questioning, doubling their dosage and giving them in a fractionated manner (before breakfast and before dinner) is the simplest approach to try solving the problem. This attempt can be beneficial in many patients with both erosive oesophagitis and NERD, including those with a hypersensitive oesophagus [14].

Upper endoscopy is not useful, unless alarm symptoms are present. A recent study [15] has shown that this examination does not provide any advantage in the selection of the best dosing of PPIs in GORD patients. Oesophago-gastric pH testing on medication has a limited role in helping us to elucidate the reasons for PPI failure, because the majority of these patients have a normal test [16]. Also the Bravo wireless system, which records the oesophageal pH for 48 h, does not seem to provide better results [17], in that acid reflux is rarely responsible for non-response in patients treated with twice-daily PPIs.

Multichannel intraluminal impedance (MII) plus traditional oesophageal pH-metry has been recently introduced into clinical practice, in order to detect non-acid gastro-oesophageal reflux [18]. This technique has been briefly mentioned by Sgouros and Mantides, because of scarce data on its clinical application at that time. However, this novel examination is very promising, because a recent study [19] on a large group of patients unresponsive to PPIs has shown that the technique allows us to categorize them into three distinct subgroups: 11% had symptoms related to acid reflux, 37% had symptoms related to non-acid reflux, and 58% had symptoms related neither to acid reflux nor to non-acid reflux. This means that only few patients have persistent symptoms due to acid, whereas many of them have symptoms related to non-acid reflux. Most patients, however, have symptoms which are not related to any kind of reflux, and those with refractory heartburn can be better classified on the basis of MII plus pH-metry as affected by functional heartburn which is likely to generate many of the PPI failures in patients with NERD.

These results are also very important for choosing the best therapy for the various subgroups. For instance, anti-reflux surgery can be the optimal option in patients with both acid reflux and non-acid reflux not responding to twice-daily PPIs, and a recent study [20], although uncontrolled, has confirmed the excellent effect of this therapy in virtually all of these patients. The benefit of fundoplication in patients with PPI failure represents a revolutionary concept, because it is believed that the positive response to medical therapy is predictive of the surgical success [21]. Obviously, those patients with functional heartburn on the basis of absence of any reflux need to be treated with alternative therapies, such as tricyclics or other pain modulators.

If these results are confirmed in larger series, MII plus pH-metry will become the most useful tool to elucidate the reasons for PPI failure and to tailor the most appropriate therapy to the different subgroups it helps us to identify.
References


