LETTER TO THE EDITOR

PPIs for upper digestive symptoms: EBM does not support empirical practice

Dear Editor,

The possibility of prescribing medicines, before submitting patients to exploratory tests has fascinated physicians over centuries. Common complaints, like upper digestive symptoms, could represent an indication and would assist reductions in the national healthcare budget and save patients' time. Therefore, several studies have aimed to establish the benefit of such a strategy (1). A recent approach is that of Diculescu *et al* published in the previous issue of your journal (2). In this open trial, over 700 patients with symptoms likely due to gastroesophageal reflux and to nonulcer-dyspepsia received esomeprazole for 4 weeks (half of the cost being supported by the producing company). The drug improved the intensity and the frequency of the upper digestive symptoms. It is one of the first studies in this country involving so many dyspeptic patients. We would like to comment on this paper.

The study included patients with both esophageal and gastroduodenal symptoms. The patients with esophageal symptoms presented with heartburn and acid regurgitation. It is not very easy to make a differentiation between these two symptoms, not only for the patient but also for the physician. Some patients presented upper digestive symptoms that were altogether described either as pain or as discomfort. However, discomfort is defined as a symptom, which the patient would not define as pain (3) and therefore it is difficult to assess the homogeneity of this study group.

Depending on the precise clinical complaints: esophageal and gastroduodenal, there are different indications regarding the treatment of upper digestive symptoms with PPIs. Their response to therapy should be analyzed differently. No doubt, gastroesophageal reflux symptoms should be treated with PPIs. There is evidence showing the advantage of treating heartburn without endoscopy in the absence of alarm signs requiring laboratory tests and endoscopy before starting antisecretory therapy (4). But the problem of treating upper abdominal discomfort with PPIs does not remain straightforward. Despite the simplicity of such an approach, the effect is only good in part (5). PPIs decidedly work in cases presenting ulcer like symptoms. But unexplored dyspepsia, mainly including also cases of non-ulcer dyspepsia (even this term seems to have become obsolete) is a composite term comprising cases having a different pathogenic background (6). Those patients who suffer from non-ulcer dyspepsia, due to delayed gastric emptying or to visceral hypersensitivity, would mildly benefit from the administration of PPIs. In a meta-analysis of the use of PPIs in non-ulcer dyspepsia, a number of 8 trials including over 3000 patients were identified (1). The systematic review of those data showed that PPIs reduced the symptoms of dyspepsia by 14% and that 9 patients have to be treated in order to get the healing of one. Due to the high cost of such a strategy, the cost-effectiveness analysis showed that only the use of generic drugs as PPIs is convenient. In the study by Diculescu et al (2), a pharmaceutical company covered half the cost of the drugs and made it highly desirable. But the rare opportunity to have PPIs available at low cost limits the value of such an approach. On the other hand it has been suggested that the use of therapy in unexplored dyspepsia is not able to prevent endoscopy in the future, meaning that chronic symptoms remain constant (7).

Therefore it is my opinion that PPIs should be given in unexplored patients with GERD symptoms but not in unexplored dyspepsia, i.e. in patients where discomfort rather than ulcer-like pain is the main symptom. Despite the good empirical evidence of the benefit of PPIs in unexplored upper digestive symptoms, when reflux symptoms are excluded, PPIs alone are cost-effective in dyspeptic patients only when they are not expensive, according to the paradigm of EBM (evidence-based medicine).

Dan L. Dumitrascu
3rd Medical Dept., Cluj, Romania
ddumitrascu@cluj.astral.ro

Romanian Journal of Gastroenterology
June 2005 Vol.14 No.2, 203-205

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Reply,

We note with great interest the letter from Dr. Dan Dumitraşcu, and we are pleased to have the opportunity to respond, as the issue is of great interest for the medical community.

In this letter, the author makes a definite distinction between patients with esophageal and gastroduodenal symptoms stating that, depending on the precise clinical complaints - esophageal or gastroduodenal, there are different indications regarding the treatment of upper digestive symptoms with proton pump inhibitors (PPIs). In accordance with evidence based medicine, the author concludes that PPIs should be given in unexplored patients with gastroesophageal reflux disease (GERD) symptoms but not in unexplored dyspepsia, i.e. in patients where discomfort rather than ulcer-like pain is the main symptom.

From the very beginning, as stated repeatedly in our paper, we must emphasize that our study group included ONLY patients with KNOWN reflux disease, under follow-up by primary care physicians or internal medicine specialists. Furthermore, we must emphasize that our paper presented the results of an IPEP (In Practice Evaluation Program) and not those of a clinical trial. Within the design of an IPEP, the aim is not to employ restrictive inclusion/exclusion criteria, such as in controlled trials, but to test a specific hypothesis in day-to-day clinical practice conditions. The present IPEP aimed to test the efficacy of a well validated, medical treatment of GERD - PPI therapy using esomeprazole - in day-to-day clinical practice GERD patients, whose symptoms were not well controlled by the current medication prescribed by the treating physician. The aim of the present IPEP was not to identify patients with reflux disease or to differentiate them from dyspeptic patients, this being the job of the treating physician, but to test the efficacy of the specified drug in clinical practice setting, considering that the diagnosis of GERD is well established.

It is recognized that, in clinical practice, there is a large overlap between symptoms of dyspepsia and those of GERD, which often makes clinical distinction difficult. Among patients with upper GI symptoms, one third have heartburn (retrosternal burning sensation) with or without other dyspeptic symptoms (1-3). Although heartburn and regurgitation are commonly viewed as the typical symptoms, over half of patients with proven GERD have dyspepsia in addition to heartburn, and up to 20% have dyspepsia alone *without* heartburn or regurgitation (4). This is why the IPEP included among the clinical variables, upper abdominal pain along with the other two more specific complaints of GERD patients.

The results of the current IPEP, conducted in patients with known reflux disease, further supports this symptom overlap theory. In our study group, 83.2% of the patients presented moderate to very-severe heartburn episodes prior to esomeprazole treatment, 74.7% presented moderate to very severe acid regurgitations and 73.5% presented moderate to very severe episodes of upper abdominal pain. Nevertheless, all patients presented at least one of the main reflux symptoms, which is either heartburn or acid regurgitation.

In the letter, the author is citing an important meta-analysis (5), which proves that those patients who suffer from non-ulcer dyspepsia, due to delayed gastric emptying or to visceral hypersensitivity, would mildly benefit from the administration of PPIs. We totally agree with the results of the cited paper, but if our study group had contained a large number of such patients, we would not have noticed the excellent efficacy of the IPP treatment as supported by our results. Furthermore, the efficacy of the esomeprazole regimen was similar for all three symptoms considered. All these support the idea of an overlap between symptoms of GERD and dyspepsia in GERD patients and clearly exclude our patients from the non-ulcer dyspepsia category. Indeed, the Rome II consensus group excluded reflux-like dyspepsia (i.e., both dyspepsia and heartburn are present, but heartburn is the dominant symptom) from the dyspepsia classification system and recommended that such patients be treated as having GERD (6).

In fact, our study has found another and rather unexpected explanation for the lack of responsiveness to medical treatment in the patients prior to the inclusion in the IPEP. An extremely high number of patients (64.2%) were identified which had, prior to enrolment, other medication than PPIs as the treatment for reflux disease. This suggests

that, in Romania, the primary care physicians still use the step-up approach in the treatment of GERD, despite the evidence-based step-down strategy, which can rapidly control the reflux symptoms with a direct implication on the QOL of the treated GERD patient (7). We must also note that prior to the inclusion in our IPEP, at the indication of the general practitioner, 53% of patients had been subjected to upper digestive endoscopy only to diagnose, in 72% of them, erosive esophagitis. This can be easily explained by the usage of other "non-expensive" PPIs or other drugs as antiacids, H2 Blockers or prokinetics in the absence of PPIs in these patients. So, the conclusion of our paper is that, once the physician has a well documented GERD diagnosis, from the very beginning he should employ a potent PPI therapy, as this can easily control the reflux symptoms, heal the esophagitis and spare the additional costs of unnecessary upper digestive endoscopy.

Mircea Diculescu
Gastroenterology and
Hepatology Center
Fundeni Clinical Institute
Bucharest

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