

Atypical symptoms of GORD in Belgium : Epidemiological features, current management and open label treatment with 40 mg esomeprazole for one month

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For the Belgian study group of atypical GORD.

Abstract

Frequency of atypical symptoms in patients suffering from gastro-oesophageal reflux disease (GORD) is not well known, and the optimal management of such symptoms has not been well established. Our aims were to set up an observatory of these atypical symptoms of GORD in Belgium and to study the efficacy of one month treatment with esomeprazole 40 mg.

Patients and methods : Gastroenterologists participating in this observational survey were asked to register every new outpatient with symptoms of GORD during a period of 20 consecutive working days. All patients who reported predominant presence of atypical manifestations of GORD were documented and characterized more in detail. In patients with dominant chest pain or ENT symptoms, a treatment with esomeprazole 40 mg daily during 4 weeks was proposed.

Results : 90 gastroenterologists included 2864 patients consulting for symptoms suggestive of GORD, including 776 (27.1%) with dominant atypical symptoms. Endoscopy (performed in 2800 patients) showed significantly less oesophagitis in atypical than in typical GORD patients (68% vs. 81.1% ; $P < 0.0001$). Management of atypical GORD patients appeared to be very heterogeneous. Overall 516/776 patients were included in the open phase of treatment with esomeprazole 40 mg, but data for analysis are only available in 228 patients. After one month, symptoms had disappeared in 57.1% and significantly improved in 26.6%.

Conclusion : Atypical GORD represents a large number of consultations in gastroenterology in Belgium. It is associated with less endoscopic lesions than typical GORD. Its management is heterogeneous reflecting the lack of guidelines on this topic. Response rate after esomeprazole 40 mg for one month in this open uncontrolled trial was high. This result warrants confirmation in a placebo-controlled trial. (*Acta gastroenterol. belg.*, 2006, 69, 203-208).

Key words : GORD, atypical, ENT symptoms, unexplained chest pain, esomeprazole.

Introduction

Gastro-oesophageal reflux disease (GORD), defined as the presence of symptoms or lesions that can be attributed to the reflux of gastric contents into the oesophagus, is one of the most common disorders affecting the gastrointestinal tract (1,2). The most typical clinical symptoms of reflux disease are heartburn and regurgitation, but GORD may also manifest itself through atypical symptoms which include ear-nose and throat (ENT) symptoms (hoarseness, chronic non-productive cough, sore throat,...), unexplained chest pain and respiratory symptoms (asthma, chronic cough) (3,4). Some studies have shown a significant association, although sometimes weak, between these symptoms and GORD (5-8). However the prevalence of these atypical symp-

toms amongst patients with reflux disease is not well known. Furthermore, the optimal management of GORD with atypical manifestations, including number and type of diagnostic procedures and treatment, has not been established. The usefulness of diagnostic investigations in atypical GORD manifestations has been questioned (9-14). A few studies have shown that a prolonged treatment, at least two to three months with full dose or even double dose PPI, may be necessary to achieve significant improvement in patients presenting with atypical GORD symptoms (3,4,15,16). Therefore, attitudes of physicians towards these clinical entities are most likely based on personal experience and empiric approach. The aims of the present study were : 1) to assess the frequency of patients presenting with predominant atypical symptoms of GORD amongst all patients consulting Belgian gastroenterologists for suspected GORD, 2) to study the characteristics of this population in comparison to patients with predominant typical GORD symptoms and 3) to describe the management of these patients in every day practice. Finally, 4) we also evaluated the efficacy of open label treatment with esomeprazole 40 mg/day for one month in alleviating these symptoms.

Patients and methods

Survey design

This study was accepted by Liège University Ethical committee and all the patients gave their informed consent. Gastroenterologists participating in this observational survey were asked to register every new outpatient with symptoms of GORD during a period of 20 consecutive working days. Patient demographics, smoking habit (smokers were defined by more than 7 cigarettes a week), alcohol consumption (alcohol drinkers were defined by more than 7 units of alcohol a week), concomitant medications, the type of symptoms, the predominant symptom, and the overall results of gastroenterological investigations were recorded. This patient population is referred to as the "total population".

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All patients from the total population who reported predominant presence of atypical manifestations of GORD, including asthmatic symptoms, unexplained chest pain or ear-nose-throat (ENT) symptoms, were documented more in detail. Information was recorded about referral, previous and additional investigations, intensity and frequency of the atypical symptoms, and about previous and current therapeutic approaches. This patient population is referred to as the “*atypical population*”.

For the patients in the atypical population, the treating physician was asked what would be his usual choice of treatment. In case of a choice to treat with standard dose PPI in patients with dominant chest pain or ENT symptoms, a treatment with esomeprazole (Nexiam®) 40 mg daily during 4 weeks was initiated. Patients with asthmatic symptoms were not included in the treatment phase because of the difficulty to assess response to treatment with a simple short-term clinical evaluation in this population. Clinical response was assessed at the 4-week follow-up visit. A simple evaluation of the treatment was performed based on the dominant atypical symptom during the last week before the visit. This symptom was quoted as worse, unchanged, improved or disappeared. This patient population is referred to as the “*esomeprazole open phase population*”.

Data collection

Information was retrieved using a palmtop computerised data collection program with direct data entry control and warnings for missing input. Gastroenterologists recorded patient initials in order to identify and search patient records. At the end of the observation period, patient records were transferred for analysis, except for patient initials, which were filtered out. Persons involved in data analysis were by no means able to identify any patient.

Statistical analysis

Initial data analyses were based on descriptive statistics, including percentages, means, ranges and standard deviations. Percentages were calculated based on all values for that particular question (missing excluded). Comparison of parameters between subgroups was carried out using the Chi-square test for nominal data and the Wilcoxon statistic for ordinal and continuous data. All statistical tests were interpreted at the 5% significance level (two-tailed). The outcome of esomeprazole treatment was analysed according to intention-to-treat principles. Logistic regression was applied on the response rates to treatment.

Results

Frequency and characteristics of patients with dominant atypical symptoms of GORD

Over the study period, 90 gastroenterologists recruited 2864 patients. These consisted of 1341 patients

Table 1. — **Demographic and clinical characteristics in patients with dominant atypical or typical symptoms of GORD**

	Dominant typical GORD symptoms (n = 2088)	Dominant atypical GORD symptoms (n = 776)
Age (years ; median-range)	50 (8-95)	52 (14-89)
Male gender (%)	44.7	43.2
Referral		
– Spontaneous (%)	17.1	12.5
– General practit. (%)	67.5	51.9
– Other specialist (%)	15.4	35.6 **
Alcohol consumption (%)	11.2	11.2
Smoker (%)	24.4	19.7*
Concomitant medication (%)	24.4	26.5

* P < 0.05 ; ** P < 0.0001 (3X2 contingency table for various types of referrals).

(46.8%) with only typical GORD symptoms, 314 patients (11.0%) with only atypical GORD symptoms and 1209 patients (42.2%) with mixed typical and atypical symptoms. Atypical symptoms were dominant in 776 patients (27.1%), while 2088 patients (72.9%) had dominant typical symptoms. Demographic and clinical characteristics in these two subgroups of patients are shown in table 1. Some weak but statistically significant differences were observed, including a more frequent referral by other specialized physicians and a slightly lower frequency of smokers in dominant atypical GORD patients.

Patients with dominant atypical symptoms could be subdivided according to whether the reported predominant atypical symptoms were ENT symptoms (57.8%), asthmatic symptoms (3.2%) or chest pain (38.9%). The only statistically significant difference was that patients with ENT symptoms as presumed atypical GORD manifestation were more likely to be female compared to other symptoms (64.1% vs. 48.6% ; P < 0.0001).

Results of upper gastro-intestinal endoscopy

An upper GI endoscopy was performed in almost all patients, both with typical and atypical dominant GORD (98.0% and 97.0%, respectively). Results of the endoscopy in these two groups of patients are shown in table 2. The overall prevalence of oesophagitis was high, but was lower in patients with atypical GORD. This was particularly the case in isolated atypical GORD (56.4%). However, when present, the prevalence of different grades of oesophagitis was similar between groups, although some complications were less frequent in atypical GORD, including Barrett’s oesophagus, confirmed by histology (1.6% vs. 3.7% in typical GORD ; P = 0.0064). When comparing different types of atypical symptoms, oesophagitis was significantly less frequent in patients with ENT symptoms (63.0% vs. 72.5% in other atypical GORD ; P = 0.012).

Table 2. — Results of upper GI endoscopy in patients with dominant typical or atypical symptoms of GORD

	Dominant typical GORD symptoms (n = 2047)	Dominant atypical GORD symptoms (n = 753)
Oesophagitis (%)	81.1	68.0 **
– LA grade A (% of oesophagitis)	61.5	62.5
– LA grade B (% of oesophagitis)	29.5	29.7
– LA grade C (% of oesophagitis)	5.8	4.9
– LA grade D (% of oesophagitis)	3.2	2.9
Complications		
– Barrett (%)	3.7	1.6 *
– Stricture (%)	0.8	1.5
– Ulcer (%)	1.5	1.2
Hiatal hernia (%)	49.8	43.4 *
Gastroduodenal ulcer (%)	7.7	6.2
HP positivity (%) ^o	32.7	27.7

^o HP status was determined in 297 patients with typical GORD and 112 patients with atypical GORD. * P < 0.01 ; ** P < 0.0001.

Other investigations performed for atypical GORD patients

Type, duration, frequency and intensity of atypical GORD symptoms, as well as previous explorations and treatments in the 776 patients studied are summarized in table 3. The most frequent symptoms were unexplained chest pain, throat ache and non-productive cough. The majority of the patients had a long-standing history of symptoms from which they suffered daily, but that were mild in intensity.

After the upper GI endoscopy, additional examinations were performed in 241 (31.1%) patients, including cardiologic exploration in 7.6%, ENT exploration in 9.3%, pneumologic exploration in 5.3%, 24 hour oesophageal pH-monitoring in 10.2%, and oesophageal manometry in 4.7%. Among the patients in whom an additional examination was planned, significantly more patients had no oesophagitis compared to patients in whom no further exploration was planned (46.2% vs. 23.9% ; P < 0.0001). This proportion was particularly high in patients in whom additional pH-monitoring or oesophageal manometry was planned (73.0% without oesophagitis).

When analysing additional diagnostic investigations before and after referral to the gastroenterologist, 145/301 (48.2%) patients with unexplained chest pain had cardiac exploration, and 209/379 (55.1%) patients with either sore throat or chronic cough had ENT exploration.

Treatment of patients with predominant atypical GORD symptoms

Overall, the treatment strategy for these patients was quite heterogeneous, with the majority being planned to

Table 3. — Characteristics of the symptoms and previous explorations and treatments in patients referred to the gastroenterologist for dominant atypical GORD symptoms (n = 776)

Type of symptoms	
– Asthma : dominant (present) (%)	3.2 (10.7)
– Chest pain : dominant (present) (%)	38.9 (45.9)
– Halitosis : dominant (present) (%)	5.0 (10.4)
– Hoarseness : dominant (present) (%)	4.0 (22.8)
– Irritation cough : dominant (present) (%)	19.3 (40.7)
– Throat pain : dominant (present) (%)	29.5 (49.2)
Duration of symptoms	
– < 1 month (%)	18.3
– 2-6 months (%)	44.6
– > 6 months (%)	37.0
Frequency of symptoms	
– < once a week (%)	4.3
– Weekly (%)	25.2
– Daily (%)	70.6
Intensity of symptoms	
– Mild (%)	18.8
– Moderate (%)	63.5
– Severe (%)	17.7
Previous exploration (%)	31.2
– Cardiac (% of explorations)	24.5
– ENT (% of explorations)	29.9
– Pneumologic (% of explorations)	17.0
– Oesophageal manometry (% of explorations)	14.9
– pH-metry (% of exploration)	32.8
Previous treatment (%)	35.8
– H2-antagonist standard dose (% of treatments)	39.2
– H2-antagonist low dose (% of treatments)	17.9
– PPI half dose (% of treatments)	7.7
– PPI standard dose (% of treatments)	37.4
– PPI double dose (% of treatments)	1.8

be treated with standard dose PPI (69.4%), but also 14.2% with PPI double dose, 1.8% PPI half dose, 1.9% H2-antagonists standard dose, 0.3% H2-antagonists double dose, 1.2% prokinetics, 8.5% no treatment and 2.7% other treatments. The decision to treat with a standard dose of PPI, depended both on the type of symptoms and on the results of endoscopy. A decision to treat with full dose PPI was more often taken in patients with ENT symptoms compared to patients with chest pain (73.7% vs. 55% ; P < 0.0001), and in patients with oesophagitis compared to those without oesophagitis (70.8% vs. 59.8% ; P = 0.0039). A total of 516/776 patients were treated with esomeprazole 40 mg daily.

Results of the open label esomeprazole 40 mg treatment

Only 228/516 patients were evaluable for efficacy after the acute esomeprazole treatment phase. Out of the 516 patients, there were 20 protocol violations (patients with asthma symptoms who should not have been included in the treatment phase) and 268 patients lost to follow up. The characteristics of the 228 evaluable patients are shown in table 4. The response of atypical symptoms to treatment with esomeprazole 40 mg daily in these 228 patients is shown in figure 1. The large majority of the patients improved. The atypical symptoms disappeared in 57.1% of cases while the non-dominant typical

Table 4. — Characteristics of the evaluable patients treated with esomeprazole 40 mg/day in the open label trial (n = 228)

Age (years, median-range)	52 (14-81)
Male gender (%)	43.9
Smokers (%)	13.3
Alcohol consumption (%)	9.5
Concomitant treatment (%)	23.2
Type of dominant symptom	
– Chest pain (%)	23.2
– Halitosis (%)	6.1
– Hoarseness (%)	6.6
– Irritation cough (%)	27.2
– Throat pain (%)	36.8
Result of endoscopy	
– Oesophagitis (%)	68.2
– Barrett (%)	0.4
– Gastroduodenal ulcer (%)	8.5
Intensity of the symptoms	
– Mild (%)	10.5
– Moderate (%)	67.5
– Severe (%)	21.9
Frequency of symptoms	
– < once a week (%)	1.3
– Weekly (%)	21.9
– Daily (%)	76.8

symptoms of these patients (present at baseline in only 154/228 patients) disappeared in 91.3% of cases.

We looked for predictors of a favourable response to the treatment. Among the parameters studied in the multivariate analysis, only smoking habit had a slightly significant impact on complete response to treatment: smokers were less likely to respond to treatment, than non-smokers (40% vs. 65%; $P = 0.009$). Other variables, particularly type, intensity or duration of symptoms as well as results of upper GI endoscopy and previous treatment had no prognostic value on response to esomeprazole 40 mg for one month.

Discussion

In this study, we found that more than half of the patients consulting Belgian gastroenterologists for suspected GORD, experience atypical symptoms, and these symptoms are dominant in more than a quarter of them. The study represents a large group of patients in current gastroenterological practice. The most frequent symptoms in our population with putative atypical GORD manifestations were unexplained chest pain, chronic cough and throat pain, representing more than 80% of cases.

Several case-control studies have shown a significant association between a series of ENT, respiratory and chest symptoms and GORD (7,17,18). However, the prevalence of these symptoms has actually rarely been studied in population-based studies. Such data is available from the Olmsted County, Minnesota, USA (8). It

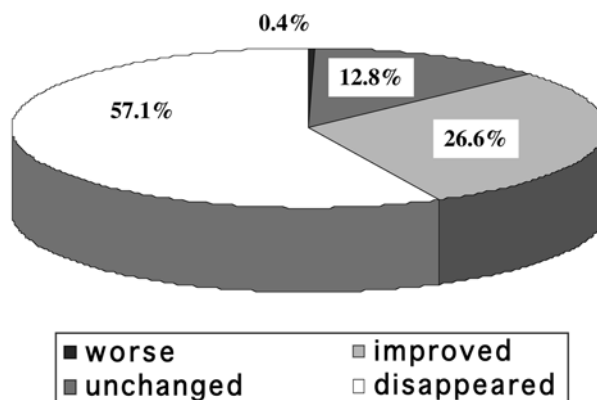


Fig. 1. — Response to 4 weeks of treatment with esomeprazole 40 mg/day in 228 patients with dominant atypical GORD symptoms. Assessment of the dominant atypical symptom over the last week of treatment was performed.

shows prevalence similar to what we observed in our gastroenterology outpatient clinics, for several symptoms including non cardiac chest pain (30-37%), asthma (9-12%), or hoarseness (15-23%). Throat pain and irritation cough, which were amongst the most frequent symptoms in our study were not studied in that population-based study. Furthermore, in that study, no information was given on the proportion of patients presenting with these symptoms as dominant symptoms but our data indicate that it may be close to 50%.

In our study, most demographic and clinical aspects of the population with dominant atypical GORD were similar to the one with dominant typical GORD. Quite logically however, patients with dominant atypical symptoms were more often referred by other specialists including ENT physicians, chest physicians and cardiologists. Even in this group of patients however, almost two thirds of the patients were referred by general practitioners or consulted on their own initiative. We also found a slightly but significantly lower proportion of smokers among patients with dominant atypical GORD symptoms: this is a rather unexpected finding for which we have no clear explanation. However, it is conceivable that symptoms like irritation cough, throat ache and hoarseness are readily attributed to the use of tobacco in smokers, who therefore do not seek medical attention for such symptoms.

Upper GI endoscopy revealed significantly less oesophagitis, Barrett's oesophagus and hiatal hernia among dominant atypical GORD symptoms. This may reflect a less severe GORD, or a greater proportion of patients who do not really have GORD, and the data of the present study do not allow answering this question, since only a small minority of the endoscopy-negative atypical GORD patients underwent pH-monitoring. Alternatively, it may suggest a different type of reflux disease, with more proximal reflux or better

oesophageal mucosal resistance and a lower trend to develop distal oesophageal lesions. According to this, several studies have shown a low rate of oesophagitis in patients with suspected GORD-related ENT symptoms or lesions. Using barium oesophagography, a method that would now be considered insufficiently sensitive, Koufman found oesophagitis in only 18% of 182 ENT patients (10). Using endoscopy, the same group reported only a 19% prevalence of oesophagitis in 58 patients with abnormal pharyngeal pH monitoring (19). A similarly low prevalence of endoscopic oesophagitis was reported in two relatively small studies. An oesophagitis prevalence of approximately 10% was found in 63 ENT patients with chronic unexplained throat symptoms (20), and a prevalence of approximately 27% was reported in 11 patients with laryngoscopic findings suggestive of reflux disease (21). Our percentages are much higher than these but it is also the case for patients with typical GORD. The diagnostic of erosive oesophagitis thus seems higher in Belgium than in other countries. This could be related to a particular pathology of GORD in Belgium but this is unlikely since Belgian genetic background and environmental factors are similar to those of surrounding European countries. More probably, it is explained by the particular reimbursement system of PPI by the national health system in Belgium that has long been conditioned by the existence of erosive oesophagitis. One can thus speculate on the fact that more erosive lesions are recognized by Belgian gastroenterologist because they are more actively looking for them.

As far as additional examinations and general management of these patients with dominant atypical GORD symptoms are concerned, our data indicate a profound heterogeneity. This heterogeneity may be directly linked to the various types of atypical symptoms and the various differential diagnoses they could potentially generate. Within each particular type of symptom however, management revealed also considerable heterogeneity. The referral to gastroenterologist and other concerned specialist occurred in variable order and was not systematic. For unexplained chest pain for example, more than a half of the patients were not referred in first or second instance to the cardiologist. The same was true for more than 40% of the patients with ENT symptoms and ENT referral. Along the same line, only one third of patients had first line empirical treatment and these treatments varied in nature and dose, although the majority was standard dose PPI or H₂-antagonist. Even after the consultation by the gastroenterologist, the strategy remained variable and difficult to standardize. The decision to perform a complementary GI tract functional study (either oesophageal manometry or pH-metry) for example, was more frequently made in patients without oesophagitis, but still was not performed systematically in endoscopy negative patients, and was also performed in a significant proportion of patients in which oesophagitis was present. Likewise, the decision to treat with standard dose PPI, was more frequent in patients

with signs of reflux disease at endoscopy, but still a significant proportion of patients with such signs were not treated. Overall, while typical GORD is more uniformly managed (22), atypical symptoms of GORD represent a complex clinical situation, with variable type of symptoms, various types of concomitant pathologies, and various differential diagnoses. Therefore, the management is often based on empirical approach and particular to each specific case, many features being integrated in the choice of the best estimated management.

Finally, a decision to start standard dose PPI treatment was made for 516/776 patients. These patients mainly represent a subgroup of patients for which the treating gastroenterologist had sufficient conviction of implication of GORD in the symptoms. Accordingly, there were more patients with endoscopic signs of reflux in this subgroup compared to the others. The proportion of patients with ENT symptoms was also greater than those with chest pain. This may reflect either less arguments in this last group to treat with anti-reflux treatment or a more careful approach in patients who always may be affected by potentially life-threatening diseases such as cardiac ischemia. Unfortunately, less than the half of the patients included were available for a one-month follow up visit. This is linked to the open label and real-life character of our study. We used small portable computers with programs not allowing skipping data to ensure a complete and strict recording by the gastroenterologists. Nevertheless, this did not prevent such a high rate of patients lost to follow up. The incompleteness of follow-up data most likely represents the routine in Belgian clinical practice to assign the evaluation of outcome of a therapeutic intervention to the patient's general practitioner. However, the global characteristics of the evaluable patients were the same as the included patients and we may therefore assume that they are representative of the whole population. The response rate after one month esomeprazole 40 mg was rather high. Such a high response rate has been described mainly in patients with non-cardiac chest pain. In these patients, one week of omeprazole 40 mg in the morning and 20 mg in the evening gave 78% of improvement and 53% of complete resolution (23). In chronic cough and other ENT symptoms a few, mainly uncontrolled and small, studies have shown significant improvements, but usually after prolonged periods of treatment, up to six months (24,25). Therefore, for chronic cough and other ENT symptoms it is usually recommended to treat with high dose PPI, administered twice a day and for a long period of time, up to 3 months, before considering the patient has failed medical therapy (4). Importantly, in our study, the response rate was similar in all subgroups of patients depending on demographic and clinical characteristics, including the type of symptoms, showing that such treatment with esomeprazole 40 mg for one month may be effective and fruitful in many clinical settings. The only factor that had a significant impact on the outcome of treatment was smoking, which was

associated with a slightly lower response rate. This may be explained by a specific role of smoking in the most frequent atypical symptoms encountered in our population : chest pain, chronic cough and throat pain.

In conclusion, atypical symptoms of presumed GORD are a frequent cause of consultation in gastroenterology routine practice. The management of such patients is heterogeneous, probably due to the lack of clear guidelines regarding the optimal management of these symptoms. The response rate to one month treatment with esomeprazole 40 mg was high in this open trial and should be confirmed in controlled studies.

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