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Supra-oesophageal Manifestations of Gastro-oesophageal Reflux Disease

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Abstract

The extra-oesophageal signs that are most commonly related to gastro-oesophageal reflux include chest pain, asthma, chronic cough, posterior laryngitis and dental erosions. It is characteristic to find in such patients a poor presence of symptoms and endoscopic and pH-metric findings that are common in typical reflux. The therapeutic response to antisecretory drugs has become the most cost-effective tool for the diagnosis and treatment of this condition. Both the evidence available and expert agreement in consensus conferences support the use of proton pump inhibitors with doubled standard doses for at least 12 weeks in most cases. While an acceptable response is achieved with this significant acid inhibition, there are still questions to be answered in these and other aspects, such as the true prevalence, path physiology and diagnosis of this condition. It is therefore necessary and increasingly useful to create multidisciplinary teams with the aim to improve and promote understanding and the care of patients suffering from these supra-oesophageal symptoms caused by gastro-oesophageal reflux.

1. Introduction

A number of extra-oesophageal conditions and diseases have been described that are suspected to be related to gastro-oesophageal reflux (table I). In this multifarious and globally assessed group, less than one-half of the patients will complain of typical gastro-oesophageal reflux disease (GORD)-related symptoms (heartburn and acid regurgitation). This, together with the fact that there are no absolutely reliable study methods or procedures that may be able to detect small quantities of supra-oesophageal acid or to identify the role of gastro-oesophageal reflux on neuronal reflexes, renders it difficult to definitely establish the supposedly direct cause–effect relationship between supra-oesophageal manifestations and GORD. Yet there are data, and not at all scarce, that show how the symptoms and lesions of these complications improve after inhibition of gastric acid secretion. These data have, over the past decade, been the main responsible factors for the increased interest awakened among gastroenterologists, but also among other specialists [ear, nose and throat (ENT) specialists, pneumologists, allergologists, cardiologists, paediatricians and even stomatologists and dentists].

As in all the other articles in this issue, the scientific evidence will be categorised according to the proposals of the Centre for Evidence-Based Medicine (Oxford, UK) that have been adopted by the Ibero-American Cochrane Centre (see Introduction — Potent Acid Inhibition, by Ponce and Mearín).

2. State of the Art in the Management of Supra-oesophageal Manifestations of GORD

In this group of conditions we do find ourselves, to a greater or lesser degree, faced with difficulties

Table I. Extra-oesophageal conditions related to gastro-oesophageal reflux

Non-cardiac chest pain	Pulmonary conditions	Laryngeal conditions	Oral cavity conditions	Other
	Bronchial asthma	Pharyngitis	Dental erosions	Otalgia
	Lung fibrosis	Dysphonia	Oral burning	Otitis media
	Stridor/croup	Chronic cough	Oral ulcers (aphthae)	Chronic sinusitis
	Chronic bronchitis	Hoarseness	Dysgeusia/ageusia	Postnasal drip
	Bronchiectasis	Chronic laryngitis		
	Chronic obstructive pulmonary disease	Globus sensation		
	Pneumonia	Vocal chord ulcerations		
		Granulomata		
		Laryngospasm		
		Laryngeal stenosis		
		Tracheal stenosis		
		Laryngeal cancer		
		Torticollis (Sandifer's syndrome)		

in interpreting therapy trials. The number of patients in the various studies is generally rather small, and the therapy periods — and most particularly the follow-up periods — are not altogether long. Furthermore, and this in our eyes is a serious qualitative aspect, the patient inclusion criteria are (to say the least) debatable, as there are no precise diagnostic procedures available and the various studies thus include mostly 'patients with suspected supra-oesophageal suspected manifestations of suspected GORD'. Well, all those thrice-repeated '*suspected*s' have been the cause for the meeting of multidisciplinary working groups with the task of putting forward recommendations, general recommendations, regarding mostly and above all the therapy of these conditions. Even though most (practically all) of the relevant studies and trials have been carried out with omeprazole, ever since the first meeting that occurred in the 1990s[1] it has been clearly established that any proton pump inhibitor (PPI), at double the standard dose and for a period of not less than 3 months, is the recommended therapeutic approach in supra-oesophageal reflux manifestations. Even though a standard dose of esomeprazole is more effective than the same dose of omeprazole in the treatment of oesophagitis,[2] recommending a double dose of omeprazole does also seem to be reasonable. This requirement for a more profound acid inhibition during a longer period for achieving relief of symptoms or healing of the lesions as compared with patients with heartburn and/or oesophagitis has been confirmed in other multidisciplinary meetings in the USA[3,4] and in a national meeting in December 2003 in Seville (unpublished data). Thus, recent literature does not contain studies using standard doses of PPIs or other drugs such as the histamine H_2 receptor antagonists for treating these conditions.

2.1 Non-cardiac Chest Pain

Non-cardiac chest pain evidences some peculiarities as compared with the other supra-oesophageal manifestations of GORD. First, it is conceptually an extra-oesophageal rather than a supra-oesophageal manifestation, as the possible pathogenic factor of micro-aspiration is not involved. Second, it has been demonstrated that up to two-thirds of the patients may have documented GORD. Although chest pain is addressed in another article of this issue, it can be stated that it is the extra-oesophageal condition that has the greatest body of evidence (from randomised, placebo-controlled studies) about the therapeutic efficacy of double-dose PPIs; response rates of up to 81% have been recorded in the active therapy group *versus* 6% in the control group[5] (level of evidence 1b).

2.2 Bronchial Asthma

Recently, and after reviewing 171 papers published in English between 1966 and 1999 on reflux-induced supra-oesophageal manifestations, 12 of them were critically analysed in order to assess the efficacy of anti-reflux therapy in patients with asthma (eight placebo-controlled studies, three open studies, and one study with an untreated control group).[6] The medications used were H_2 receptor antagonist, cisapride and PPIs. It was concluded that the asthma symptoms improved with anti-reflux therapy in most patients (69%) and that the requirements for anti-asthmatic medication diminished (62%) (level of evidence 1a). However, only 26% of the patients evidenced improvement in the lung function parameters. Another systematic review[7] found no results favouring anti-reflux therapy either in the clinical parameters or in the functional parameters (level of evidence 1a). The duration of therapy in the 12 studies reviewed, however, ranged from 1 week (too short) to 6 months; nine of them were cross-over trials and three were of parallel group design, and in no less than four studies were H_2 receptor antagonists used as medication. The best results were seen with high-dose PPIs, usually given b.i.d. for 2–3 months. Table II summarises the most relevant studies on patients with asthma treated with PPIs.[8–14] Further efforts are warranted for identifying those subgroups of patients who may benefit from PPI therapy, and for this reason future studies should aim at identifying response predictors.

2.3 Chronic Cough

Only two controlled studies have been published to date assessing the efficacy of gastric acid inhibition in patients with chronic cough after having ruled out asthma or postnasal drip as the cause. In the study by Ours et al.[15] the cough improved significantly in 35% of the patients treated with omeprazole 40 mg b.i.d. for 12 weeks, all of them with abnormal pH-metry. The authors suggest that analysis of the response to 2 weeks of empiric PPI therapy is the best diagnostic and therapeutic attitude in patients with chronic cough (level of evidence 1b). The other controlled study[16] showed omeprazole 40 mg/day for 8 weeks to be superior to placebo in cough relief (level of evidence 1b). Nevertheless, the controlled studies do not reproduce the results of other non-controlled ones, in which symptom relief was achieved in up to 100% of the cases even with drugs different from PPIs (H_2 receptor antagonist, etc.), but with treatment for up to 6 months[17–19]

Table II. Proton pump inhibitor therapy in gastro-oesophageal reflux disease-associated asthma

Reference	n	Study design	Therapy	Results regarding asthma
Meier et al.[8]	15	Placebo-controlled, cross-over	Omeprazole 20 mg b.i.d. for 6 weeks	Lung function test improvement in 27%
Ford et al.[9]	11	Placebo-controlled, cross-over	Omeprazole 20 mg b.i.d. for 4 weeks	No differences
Teichtahl et al.[10]	20	Placebo-controlled, cross-over	Omeprazole 40 mg/day for 4 weeks	Slight improvement in night-time expiratory peak-flow rate
Harding et al.[11]	30	No control group	Omeprazole 20–60 mg/day for 3 months	Lung function test and symptom improvement in 73%
Levin et al.[12]	9	Placebo-controlled, cross-over	Omeprazole 20 mg/day for 8 weeks	Significant improvement in expiratory peak flow rate and quality of life
Boeree et al.[13]	36	Placebo-controlled, parallel groups	Omeprazole 40 mg b.i.d. for 3 months	No differences
Kiljander et al.[14]	52	Double-blind placebo-controlled, cross-over	Omeprazole 40 mg/day for 8 weeks	Symptom relief and improvement in forced expiratory volume in 35%

(level of evidence 3b). While awaiting further studies that may better define the duration and dosage of therapy, the currently recommendable attitude would be to give a PPI at double the standard dosage for at least 12 weeks.

2.4 ENT Manifestations

At present, at least in Spain, there is a focus of interest on the study and discussion of reflux-induced ENT manifestations as compared with other supra-oesophageal manifestations. The main disease entity in this group is chronic idiopathic posterior laryngitis with possible association to GORD, which will hereinafter be termed 'peptic laryngitis'. There are other ENT manifestations that have been related to GORD (sinusitis, otitis media, subglottic stenosis, laryngomalacia, paroxystic laryngospasm, histeric globus) but the therapeutic trials are scarce, the reports are mostly of single cases or short series, and the therapies used are not comparable. Current therapeutic recommendations have been extrapolated from those for peptic laryngitis. This group of entities has a considerable potential for future study and research.

Even though the diagnosis of peptic laryngitis is not the subject here addressed, it should be stressed that demonstration of the existence of GORD is not a prerequisite for treating peptic laryngitis with acid secretion-inhibiting drugs. The selection of patients in the known studies was based on laryngeal symptoms and — mostly non-specific — laryngoscopic signs of chronic laryngitis. Table III presents the major published non-controlled therapeutic trials.[20–30] The clinical response rate ranges from 60% to 98% (level of evidence 3b–4). The drug most often used is omeprazole; the dosing and duration of therapy are not homogeneous, although the mean duration is 3 months and most studies have used twice the standard dose. Some trials have increased the duration of therapy to up to 6 months and achieved an important increase of the final response rate.[28] Increasing the dose of omeprazole beyond 40 mg has not brought forward any added benefit,[24] and neither has the addition of H_2 receptor antagonist.[26] In the only published study using esomeprazole[29] eight out of the 30 patients (27%) initially treated with 40 mg/day responded at week 4, and 19 patients (63%) did so at week 8. Among 10 non-responders to the 40 mg dose (one of them was a protocol infraction), four responded to the dose of 80 mg/day, increasing the response rate to 77% (23 out of 30) (level of evidence 3b). This study would put into question the general recommendation of 'double-standard-dose PPIs as initial therapy' for esomeprazole and this dosage would be reserved for non-responders, although this must be confirmed in controlled studies. However, few studies have addressed laryngeal symptom recurrence some time after withdrawing medication. This has been done, however, by the only two Spanish studies to have so far published

Table III. Therapeutic management of peptic laryngitis: non-controlled trials

Reference	n	Therapy	Duration (months)	Symptomatic response (%)	Laryngoscopic response (%)
Koufman[20]	33	Anti-H_2	6	85	85
Kamel et al.[21]	16	Omeprazole 40 mg/day	1–6	92	56
Hanson et al.[22]	182	Anti-H_2, omeprazole	1–3	98	98
Shaw et al.[23]	68	Omeprazole 20 mg b.i.d.	3	60	–
Wo et al.[24]	21	Omeprazole 40 mg/day	2	67	50
Metz et al.[25]	10	Omeprazole 40 mg b.i.d.	1	60	–
Vaezi et al.[26]	45	Omeprazole 20 mg b.i.d.	4	67	62
Rodríguez-Téllez et al.[27]	21	Omeprazole 20 mg b.i.d.	3	90	80
Garrigues et al.[28]	73	Omeprazole 20 mg b.i.d.	6	65	83
DelGaudio and Waring[29]	30	Esomeprazole 40 mg/day	2	63	–
Williams et al.[30]	70	Omeprazole 20 mg t.i.d.	3	63	–

their results: the 'La Fe' group (Valencia) observed 46% recurrences after 6 months,[28] and the 'Virgen Macarena' University Hospital (Seville) records 25% after 3 months.[27] In the latter study the symptom recurrence rate was non-significant, but the reoccurrence of lesions on laryngoscopy 3 months after treatment withdrawal was significant. Wo et al.[24] observed a 38% clinical recurrence rate after 2 months, and DelGaudio and Waring[29] describe worsening of the symptoms 1 month after withdrawal of esomeprazole therapy. This group of previously responding patients might be amenable to maintenance therapy with the minimum effective dose.

Rather less optimistic as to clinical and laryngoscopic response are the placebo-controlled trials hitherto published.[31–34] There is only one trial (with lansoprazole 30 mg b.i.d.) that shows a 50% response rate in the active therapy group *versus* 10% in the placebo group, with a significant difference for PPI active treatment *versus* control[32] (level of evidence 1b). In the other three studies, all of them with small numbers of patients, no significant differences were observed between the therapy groups, although PPIs are most often effective in the initial control of symptoms.[34] At the last American Gastroenterological Associaton meeting the results were reported of a US multicentre study with 145 patients who were randomised to receive esomeprazole 40 mg b.i.d. or placebo, without significant differences in either clinical or laryngoscopic response.[35] Considerations against this (as yet unpublished) study are the exclusion of patients with moderate-to-severe heartburn (most previous studies include such patients, and some of them record up to 60% of patients with typical GORD), and the non-application of absolutely objective criteria such as, for instance, pathognomonic laryngoscopic signs if present, for selecting patients with peptic laryngitis. It should be most desirable to define one criterion with as large a specific weight as, for instance, oesophagitis in typical GORD. This one controlled study should be followed by further similar ones. Besides confirming (or not) its results, further studies must be carried out with the aim of identifying response-predictive factors. In this context, the study of Garrigues et al.,[28] even though it does not define consistent predictor factors, does observe a better response in younger patients and in those with a shorter evolution over time of peptic laryngitis prior to the institution of therapy.

3. Clinical Experience and Problems in the Therapeutic Approach

According to the aforementioned, all those patients who evidence supra-oesophageal manifestations and also report typical symptoms of GORD should be treated; this combination, however, will be present in less than one-half of the cases. pH-metry may be useful, but in these conditions its sensitivity, specificity, reproducibility and predictability are all reduced; thus, what will (or will not) dictate the institution of therapy in these cases will be the physician's suspicion index. No 'most effective' therapeutic approach has as yet been definitely established, but the recommendations derived from expert panel meetings suggest that therapy should be begun with PPIs at double the standard dose (figure 1), as slightly over two-thirds of the patients will improve with this approach. This therapy achieves something that is considered important in reflux-induced supra-oesophageal manifestations, to wit an adequate control of oesophageal acid. The cause of a possible lack

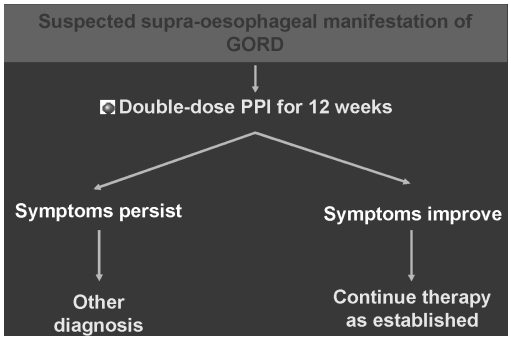

Fig. 1. Management algorithm for supra-oesophageal manifestations of gastro-oesophageal reflux disease (GORD). **PPI** = proton pump inhibitor.

of response to 'double-dose PPIs' may be found in lack of patient compliance, in an inefficacious or therapeutically suboptimal dosage, or in an incorrect presumptive diagnosis. In any case, patient clinical response variability supports the empirical attitude based on the experience of physicians treating these conditions; that is, to enforce and ensure for a protracted period, of at least 3 months, the therapeutic approach with double-dose PPIs. It has been often and long discussed, and some experts still advocate it, to carry out pharyngo-oesophageal pH-metry, so as to have available (or not) objective data for GORD. In the large majority of the cases, even before carrying out this examination, the non-responding patient will most probably already belong to the 'incorrect presumptive diagnosis' group. However, if a patient with a suspected supra-oesophageal manifestation responds to double-dose PPIs (regardless of his/her evidencing criteria for GORD), the follow-up will be more satisfactory. Responding patients will have their PPI dose adjusted to the optimally effective dose for control of their symptoms. An incomplete response warrants prolongation of therapy for up to 6 months.

The negative results of the placebo-controlled trials, some of them as yet unpublished, should not discourage gastroenterologists (and particularly Spanish gastroenterologists) from performing further studies in their own country, and this requires close collaboration of other specialists concerned with gastro-oesophageal reflux (ENT specialists, pneumonologists, etc.), who will represent a great help in selecting patients with supra-oesophageal manifestations of GORD.

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