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CASE REPORT

Beneficial effect of omeprazole in a patient with severe bronchial asthma and gastro-oesophageal reflux

A.C. Depla*, J.F. Bartelsman**, C.M. Roos***, G. N. Tytgat**, H.M. Jansen***

Beneficial effect of omeprazole in a patient with severe bronchial asthma and gastro-oesophageal reflux. A.C. Depla, J.F. Bartelsman, C.M. Roos, G.N. Tytgat, H.M. Jansen.

ABSTRACT: A 25-yr-old man suffered from severe nocturnal asthma, which was shown to be provoked by pathological gastro-oesophageal reflux. A dramatic, immediate improvement of his pulmonary condition was achieved by treatment with omeprazole after failure of other therapeutic measures, including high doses of ranitidine.

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Depts of Internal Medicine*, Gastroenterology and Hepatology** and Pulmonology***, Academic Medical Center, University of Amsterdam, The Netherlands.

Correspondence: A.C. Depla, Dept of Gastroenterology and Hepatology, St.Antonius Hospital, Kookoekslaan 1, 3430 EM Nieuwegein, The Netherlands.

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An association between gastro-oesophageal reflux (GOR) and respiratory disease is well documented [1], although the mechanisms triggering the respiratory problems are still hypothetical [2]. Surgical treatment of GOR has been reported to improve pulmonary symptoms in some patients with both asthma and GOR [3, 4]. Other reports deal with the beneficial effects of conservative management of GOR in asthmatic patients [5–7].

We report a patient with well documented nocturnal asthma and severe pathological GOR who showed dramatic improvement after treatment with omeprazole, a very powerful inhibitor of gastric acid secretion [8].

Case Report

A 25-yr-old male patient with a 2-yr history of asthma was admitted to the emergency room with progressive shortness of breath and wheezing. He required three further hospitalizations during the next three months for the same reason. The values of arterial oxygen tension (Pao_2) on admission varied between 7.1–9.1 kPa. He had no history of pulmonary infection and sputum analysis was negative. Allergic causes were excluded by skin tests and serological examination (IgE-RAST). Institution of therapy, including systemic corticosteroids, intravenous aminophylline and inhalation of β_2-sympathomimetics and anticholinergics, resulted in a rapid clinical improvement of day-time symptoms. However, at night dyspnoea was so intense that the patient was forced to remain upright in a chair. He finally admitted to frequent episodes of heartburn, ructus, regurgitation and nausea without a clear relationship to dyspnoea or wheezing.

Upper gastro-intestinal tract endoscopy showed no evidence of oesophagitis or hiatus hernia. Twenty-four hour oesophageal pH-monitoring 5 cm above the lower oesophageal sphincter was strikingly abnormal [9], showing a pH below 4 27% of the time, with the longest reflux episode lasting 89 min at the beginning of the night. No nocturnal aspiration could be demonstrated by pulmonary scanning on the morning after consumption of a ^{99m}Tc sulphur colloid labelled meal [10]. Assessment of pulmonary function revealed a remarkably variable forced expiratory volume in one second (FEV_1), ranging from 2.85–3.81 *l* (predicted normal value 3.87 *l* [11]), on consecutive days under comparable clinical circumstances and with unchanged therapy. Bronchial hyperresponsiveness to histamine was not tested because of spirometer-induced bronchospasm. The diurnal variation was determined from the peak expiratory flow rate at 1 and 2-hour intervals (fig. 1). All observations were performed during hospitalization, where the patient remained stable. Maintenance treatment including salbutamol rotacaps, aerosolized ipratropium bromide, oral slow-release terbutaline sulphate and beclomethasone diproprionate rotacaps was continued. No theophylline was given because of its known effects on lower oesophageal sphincter tone.

In this patient a relationship was assumed between asthma and pathological GOR. High doses of ranitidine, an H_2-receptor antagonist, and domperidone, a prokinetic to facilitate oesophageal clearance, were added to medication. Although slight subjective improvement was noted, daily peak flow measurements and conventional spirometry failed to show any change (fig. 1 and table 1). Twenty-four hour pH-recording in the oesophagus

was repeated and showed continued pathological GOR (table 1). The anti-reflux medication was then changed to omeprazole 40 mg daily for 3 days. Within one day our patient showed a remarkable improvement (fig.2). For the first time in two years he slept the whole night without requiring $ß_2$-sympathomimetics. Twenty-four hour monitoring of his pulmonary function confirmed his clinical improvement and showed a definite decrease in night-time bronchospasm (fig. 1). During days 2 and 3 of the omeprazole treatment, oesophageal pH was in the normal range (table 1).

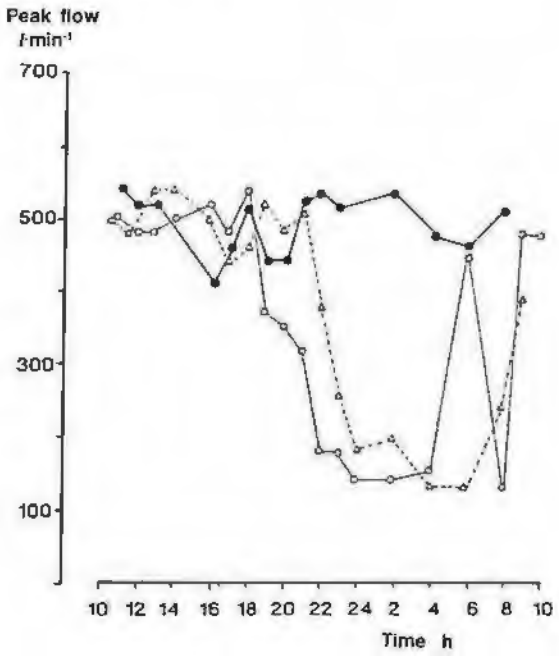

Fig. 1. – Values of peak flow measurements over 24 h. ○: without anti-reflux therapy; Δ: with ranitidine and domperidone; ▲: with omeprazole.

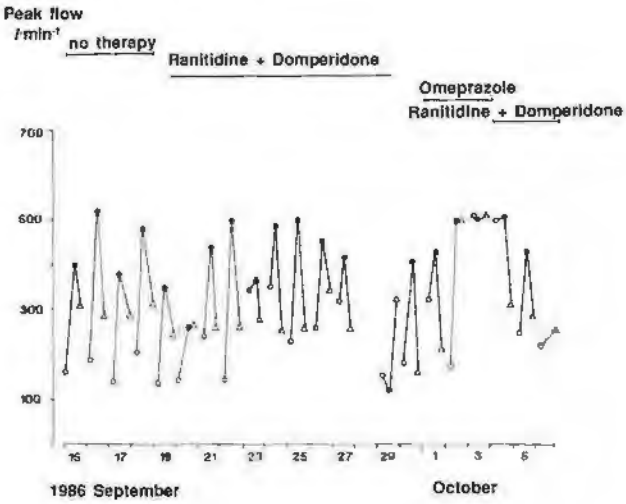

Fig. 2. – Daily pattern in peak flow without anti-reflux therapy; with ranitidine 750 mg daily and domperidone 20 mg *q.i.d.*; with omeprazole 40 mg daily. No change in bronchospasmolytic medication. ○: registration in the morning; ●: in the afternoon; Δ: in the evening.

Subsequently anti-reflux therapy with ranitidine and domperidone was restarted. The beneficial effect of omeprazole was maintained for 24 h only (fig. 2). Repeated measurement of pulmonary function and 24-hour pH-recording in the oesophagus showed the same picture as before (table 1).

The patient was then given omeprazole 20 mg daily for 3 months. The effect of omeprazole was maintained, as assessed by daily peak flow measurements at home (data not shown) and oesophageal pH measurement (table 1). No side effects of omeprazole were noticed except for a slight elevation of plasma gastrin to 220 U·l^{-1} (normal value <150 U·l^{-1}).

Table 1. – Results of 24 hour pH-recordings in the distal oesophagus and pulmonary function tests under variable therapeutic regimens

	Normal▲ values Δ	No therapy	Ranitidine+ Domperidone*	Omeprazole** 2nd day	Omeprazole** 3rd	Ranitidine+ Domperidone*	Omeprazole***
number of reflux episodes	<50	96	43	12	30	76	50
number of reflux episodes >5 min	≤3	16	16	0	2	13	1
longest episode min	≤9	89	62	4	9	86	8
% time pH<4 %	<4	27	19	<1	2	18	4
upright %	<6	28	26	<1	3	27	56
supine %	<1.2	27	11	3	<1	9	<1
FEV_1 *l*	3.87	2.85–3.81	4.08	4.04		3.78	3.88
VC *l*	4.43	4.10–4.02	4.51	4.70		4.63	4.66
FEV_1/VC	0.79	0.70–0.92	0.90	0.86		0.82	0.83

Δ: normal values for 24 hour pH-recording according to the criteria of JOHNSON and DEMEESTER [9]; ▲: normal values for pulmonary function according to the criteria of the European Coal and Steel Community [11]; *: ranitidine total dose 750 mg daily and domperidone 4x20 mg daily; **: Omeprazole 40 mg daily for 3 days, results of 2nd and 3rd day; ***: Omeprazole 20 mg daily after 3 months; FEV_1: forced expiratory volume in one second; VC: vital capacity.

Discussion

This case illustrates a close association between acid GOR and severe and disabling asthmatic symptoms. Although this relationship is assumed, it is remarkable that this patient showed evidence of bronchospasm restricted mainly to the evening and night, whereas pH-recording in the oesophagus also revealed prolonged episodes of acid pH during the day (data not shown). Davis *et al.* [12], observed nine children with asthma and GOR and showed that they were more susceptible to the triggering of bronchoconstriction due to the presence of acid in the oesophagus from 4 to 5 am than at midnight. From these observations we may conclude that a lower threshold for bronchoconstrictive stimuli may occur at night, due to normal circadian variation in bronchial hyperresponsiveness [13]. Alternatively, at night the volume of acid reflux may be larger and/or the distribution of the acid in the oesophagus may involve a larger surface area than in the upright position.

Therapy for GOR in this patient unequivocally showed improvement in pulmonary function. According to the literature, advice on diet and lifestyle [5], cimetidine [6] and ranitidine [7] may result in amelioration of pulmonary symptoms. Objective improvement, showed by pulmonary function tests, varied [5–7]. To ascertain the role of pathological GOR as a trigger for bronchospasm in these patients, the efficacy of anti-reflux therapy on the quantity of acid reflux should be evaluated by 24-hour pH measurements. This has not been carried out in any of the previously mentioned studies. In our patient it proved to be impossible to fully eradicate acid reflux in the oesophagus with conventional anti-reflux therapy, including H_2-receptor antagonists. Omeprazole inhibits the terminal stage of the acid secreting pathway by inhibiting the proton pump (H^+/K^+-ATPase) located in the secretory membrane of the parietal cell [8]. With 40 mg of omeprazole daily, an almost complete inhibition of gastric acid secretion can be obtained [14]. Omeprazole has been shown to be highly effective in peptic oesophagitis [15]. Improvement of our patient's clinical condition could be noted within 24 h after the first dose, and disappeared within 24 h after the last dose of omeprazole 40 mg, correlating directly with effective control of acid reflux. Thus, even in the absence of endoscopically detectable oesophagitis, omeprazole appears to be highly efficacious. It would appear from this case report that complete suppression of acid secretion is necessary to abolish the GOR-induced bronchospasm. A possible direct bronchospasmolytic effect of omeprazole was not studied, but is unlikely.

To our knowledge this is the first report of the documented beneficial effects of omeprazole in a patient with nocturnal asthma and pathological GOR without oesophagitis.

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Effet bénéfique de l'oméprazole chez un patient atteint d'asthme bronchique sévère avec reflux gastro-oesophagien.. A.C. Delpa, J.F. Bartelsman**, C.M. Roos***, G.N. Tytgat**, H.M. Jansen***.*

RÉSUMÉ: Un homme de 25 ans souffre d'asthme bronchique sévère dont l'étiologie réside en un reflux gastro-oesophagien pathologique. Une amélioration dramatique et immédiate de son état pulmonaire a été obtenue par traitement au moyen d'oméprazole, après échec des autres mesures thérapeutiques, ayant inclu de fortes doses de ranitidine.

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