

## IMPROVEMENT OF RESPIRATORY SYMPTOMS BY LONG-TERM LOW-DOSE ERYTHROMYCIN IN SULFUR MUSTARD EXPOSED CASES: A PILOT STUDY

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### ABSTRACT

**Background:** Patients with chronic pulmonary complications due to sulfur mustard (SM) exposure suffer from symptoms such as chest pain, cough, sputum production, hemoptysis and dyspnea. Erythromycin (EM) has been found to be effective in some chronic inflammatory lung diseases such as diffuse panbronchiolitis (DPB), bronchiectasis and chronic obstructive pulmonary disease (COPD). This study evaluates its efficacy in symptomatic improvement of SM exposed patients.

**Methods:** Low-dose EM (400-600 mg/day) has been administered in 43 patients with documented history of SM exposure for 6 months. All the patients were refractory to the bronchodilators and corticosteroids. Dyspnea, sleep disturbance, cough and hemoptysis were evaluated by a questionnaire at the beginning and at the end of the study period.

**Results:** The intensity and frequency of dyspnea, sleep disturbance due to dyspnea, cough and hemoptysis were all reduced significantly after the treatment ( $p < 0.05$ ).

**Conclusion:** The results of this preliminary study show that low-dose EM may improve respiratory symptoms in SM injured patients, and randomized double-blinded, placebo-controlled clinical trials are indicated to prove it. Given the suggestive diagnosis of Bronchiolitis Obliterans (BO) in SM exposed patients, the results imply that EM might be helpful in management of BO.

### KEYWORDS

Sulfur mustard, respiratory symptoms, erythromycin

## INTRODUCTION

Macrolide antibiotics have been reported to have some anti-inflammatory effects apart from their antibacterial effects (Culic et al, 2001). It has been shown that macrolides can change the spectrum of inflammatory mediators released by damaged or inflamed tissue. Erythromycin (EM) has been used successfully to treat some pulmonary diseases such as diffuse panbronchiolitis (DPB) and bronchiectasis (Kudoh, 1998; Tsang, 1999; Kudoh, 1987; Tamaoki 2004). The mechanisms of the action of EM on these diseases include anti-inflammatory effects (Umeki, 1993) and the inhibition of secretory actions (Tamaoki, 1992; Goswami, 1990). The anti-inflammatory mechanism of EM includes the downregulation of inflammatory cytokines: TNF $\alpha$ , IL-8, IL-4 and IL-1 (Oishi, 1994), and chemotaxis of polymorphonuclear cells (PMN) (Kadota, 1993), lymphocytes and histiocytes (Keicho, 1993; Keicho, 1994).

Thousands of Iranians who were exposed to sulfur mustard (SM) during the Iraq-Iran war (1980-1988) suffer from chronic respiratory symptoms. In fact, pulmonary complications are one of the most important complications of this chemical warfare agent (Wormser, 1991; Somani, 1989; Perrotta, 1996). Many of these SM victims complain of chronic cough, dyspnea and hemoptysis. The main findings of bronchoalveolar lavage (BAL) of these patients are inflammation and neutrophil excess (Emad, 1997). Neutrophil dominated diseases, such as bronchitis, COPD, bronchiectasis and emphysema, are the most common pulmonary complications of SM exposure (Emad, 1999). Inflammation and tissue damage due to neutrophil-derived enzymes have a major role in such diseases. In addition, recent studies have shown that Bronchiolitis Obliterans (BO) is another complication of this group (Thomason, 2003; Ghanei, 2004). As in post-lung transplant patients (Laohaburanakit, 2003; Chan & Allen, 2004), conventional treatments such as immunosuppression and corticosteroid therapy are usually disappointing for BO in SM exposed cases (Thomason, 2003).

In this pilot study, we evaluated the efficacy of long-term low-dose EM in symptomatic improvement of the patients with chronic respiratory symptoms and complaints due to SM exposure.

## MATERIALS AND METHODS

### *Study design*

An open labeled clinical trial study was performed on a group of patients complaining of respiratory symptoms, in Tehran, Iran, 2003. All of these cases were patients who had been exposed to a single, high-dose of SM from 1985 to 1987 during the Iraq-Iran war. Documentation of SM exposure was based on official certification from the veteran (Janbazan) organization, which is the official center for compensation of war disabled victims. Written consent was taken from all enrolled cases in this study. The study was approved by the ethical committee of Baqiyatallah University on 12 February 2001.

### *Inclusion Criteria*

Patients that complied with the following criteria were included in our study:

1. Availability of documented chemical exposure data based on official certification from the veteran (Janbazan) organization. Exposure in this study is defined as a single, high-dose exposure to a chemical agent that causes transient or permanent disability in exposed people.
2. Availability of medical records documenting the treatments the patient received for chemical exposure. According to their records, all injured victims had been transferred to local military hospitals, where the types of chemical agents were determined, based on signs and symptoms and through the use of special kits. The physicians treated these patients using standard protocols determined by military health services.
3. Patients complaining of any of the following: chronic cough, dyspnea or hemoptysis.
4. Evidence of air trapping in chest high resolution computerized tomography (HRCT), equal to or more than 25% of the cross-sectional area of an affected lung on at least one scan level, and within the previous three months prior to the study.
5. Normal spirometry findings compatible with the stage 0 of BO (Estenne, 2002).

Some of the included cases did not respond to high doses of bronchodilator (Salmeterol/ 2 puffs BD) and inhaled corticosteroid (Flixotide 125 mg/ 2 puffs BD), at least during the three month period prior to the study. These patients were still included, and administration of bronchodilator and inhaled corticosteroid were continued during the study.

#### ***Exclusion Criteria:***

Patients were excluded from the study if any of the following conditions were met:

Radiographic evidence of pneumonia, active tuberculosis, lung carcinoma, or an infection that necessitated the use of a concomitant antibiotic.

History of cigarette smoking and occupational exposure to toxic agents.

History of hypersensitivity to beta-lactam or to macrolide antibiotics;

History of treatment with a systemic antibiotic within seven days prior to the start of the study, or with any investigational medicine within four weeks of the study, or with a long-acting injectable antibiotic within six weeks of the study; and the use of concomitant theophylline or carbamazepine, unless their serum concentrations were regularly monitored.

Patients were in the exacerbation phase of their respiratory complications.

#### ***Data collection:***

Demographic characteristics of each patient including age, sex and age at time of exposure to SM were recorded.

A scaling questionnaire, consisting of three subscales, was designed to evaluate the intensity of dyspnea and cough, and the frequency of sleep disturbance due to nocturnal dyspnea.

Patients were asked to evaluate each symptom/subscale on a 5-point Likert-type scale, ranging from 0 to 4, with higher score indicating a more severe manifestation of the symptom- once before and once after treatment (table 1).

Furthermore, an open question was considered to evaluate the frequency of hemoptysis. Eligible patients were asked to take a daily single dose of oral EM (400 – 600 mg) for 6 months. There were no routine follow-up visits during the course of treatment, but any patient with any type of adverse drug reaction was examined by a licensed physician.

### ***Statistical analysis:***

Numeric data were expressed as mean values  $\pm$  standard deviation. SPSS software was used to calculate the differences between the study and control groups. The differences were considered statistically significant ( $p < 0.05$ ). The Wilcoxon signed ranks test was used to compare dyspnea, cough, and sleep disturbance and hemoptysis mean scaling before and after treatment.

## **RESULTS**

In total, 43 male patients with a mean age of 37.6 yr ( $\pm 3.45$  D) were included in the study. Six patients were excluded from final analysis due to irregular administration of the drug. Sixteen patients had experienced some type of adverse side effects. However, none of these were so significant as to stop treatment (10 with abdominal pain, 1 with nausea and vomiting, 1 with diarrhea and 4 with abdominal pain, nausea and diarrhea).

Table 2 illustrates the changes in the severity of the symptom after the course of EM administration. A considerable number of patients showed improvement for each of the studied symptoms. The mean dyspnea scale score was reduced significantly after treatment ( $P < 0.05$ ). Sleep disturbance due to dyspnea was also reduced significantly ( $P < 0.05$ ). The decrease in mean cough scale score was statistically significant as well ( $P < 0.05$ ). In total ten patients stated that frequency of hemoptysis was reduced after treatment; no patient complained of exacerbation of hemoptysis with the treatment.

## **DISCUSSION**

Sulfur mustard (SM) is capable of producing severe chemical injuries in lungs. Victims usually suffer from chronic respiratory symptoms such as chronic cough, hemoptysis and dyspnea (Wormser, 1991; Somani & Babu, 1989; Perrotta, 1996). Conventional treatment for these patients includes bronchodilators, corticosteroids, immunosuppressant and mucolytics, but their effects are not as desirable as expected. Moreover, long-term administration of these drugs may cause significant adverse effects, which limits their usage. For instance, long-term administration of corticosteroids may cause adrenal suppression, growth inhibition, diabetes and osteoporosis (Buchman, 2001).

The main findings in Bronchoalveolar lavage (BAL) studies in patients with SM exposure are inflammation and neutrophil excess. It has also been indicated that TGF- $\beta$ , an anti-inflammatory factor, is increased in these patients (Aghanouri, 2004).

Macrolide antibiotics have been reported to have anti-inflammatory effects in some diseases. Low-dose, long-term erythromycin, e.g., has been used effectively in treating patients with diffuse panbronchiolitis or bronchiectasis via mechanism other than antibacterial activity, such as mimicking the effect of vasointestinal hormone, anti-inflammatory effects and the inhibition of secretory actions (Culic et al, 2001; Kudoh, 1998; Tsang, 1999). Erythromycin therapy also proved to have beneficial effects on prevention of exacerbation in COPD patients (Suzuki, 2001). In line with these studies, we anticipated that low doses of EM would work to alleviate the symptoms in SM exposed patients.

In this pilot study, we showed that low-dose long-term erythromycin treatment may improve the chronic respiratory symptoms of patients with a history of SM exposure. The cases enrolled in this study were deliberately chosen from the symptomatic cases with normal spirometry (pulmonary function test), which implies that the respiratory system involvement is mild. The rationale for this selection is to avoid the possible confounding factors caused by severity and complications of the disease; if EM is effective on SM exposed cases, its efficacy should be detected in mild and uncomplicated cases.

The anti-inflammatory effects of EM include the downregulation of inflammatory cytokines:  $TNF\alpha$ , IL-8, IL-6, IL-4 and IL-1 (Oishi, 1994; Kadota, 1993; Khair, 1995), and chemotaxis of polymorphonuclear cells (PMN), lymphocytes and histiocytes (Keicho, 1993; Keicho, 1994). It is therefore possible that EM may reduce the chronic respiratory symptoms by suppressing inflammatory cytokines in patients with a history of SM exposure.

Fifteen years after being exposed to SM as a chemical warfare agent, these patients are suffering from chronic, and often disabling, respiratory symptoms such as shortness of breath, cough and chest tightness. The overwhelming findings of bronchiectasis, air trapping in expiration and inspiratory mosaic parenchymal attenuation lead us to the diagnosis of BO in this patient population. The majority of these patients have normal plain chest roentgenograms. However, their chest HRCT findings are highly suggestive of BO (Ghanei, 2004). Two recent case-report studies showed that BO is the main lung pathology following exposure to SM (Thomason, 2003; Dompeling, 2004), in which the lung function abnormalities were not reversed by treatment with corticosteroids or bronchodilators (Thomason, 2003). Also, in our current study, the selected patients had more than 25% air trapping in chest HRCT. They did not respond to bronchodilators and corticosteroids, both of which are highly suggestive of the diagnosis of BO as the underlying pathology of the respiratory symptoms. The fact that long-term, low dose administration of EM alleviated the symptoms remarkably, suggests that similar EM treatment maybe effective in the treatment of BO. This has been shown earlier for newer agents from the macrolide family, such as tacrolimus, which have mainly immuno-suppressant effects, and has been used in the management of the BO following lung transplantation (Cairn, 2003).

Given the lower cost of EM in comparison with bronchodilators, and the much lower incidence of complications compared to corticosteroids, it can be considered as a treatment for SM exposed patients. However, this study evaluated only symptomatic improvement of the patients with normal pulmonary function test, spirometry, findings. In this group, the clinical symptoms are the only indices available to be evaluated before and after EM

administration. Further research is needed to assess the efficacy of this treatment in cases with different degrees of involvement and severity, by considering the spirometry and other paraclinical measures in a randomized, double-blinded, placebo-controlled clinical trial.

## TABLES

**Table 1. The scaling questionnaire which was used for evaluating symptomatic improvement in subjects**

| Score \ Symptom | Dyspnea  | Cough   | Sleep Disturbance due to Cough           |
|-----------------|--|---|--|
| 0               | None   | None: unaware of coughing                                       | None                                     |
| 1               | Mild: noticeable during strenuous activity                           | Mild: rarely caused problem                                     | Rare: less than monthly                  |
| 2               | Moderate: noticeable during routine daily activity                   | Moderate: noticeable as a problem                               | Occasional: less than weekly             |
| 3               | Marked: noticeable during lighter than daily activity                | Marked: frequently interferes with daily activity               | Frequent: almost weekly                  |
| 4               | Severe: almost constant, present even when resting took out coughing | Severe: almost always, interferes with daily activity and sleep | Almost always: two or more nights a week |

**Table 2. Changes Patient Symptoms after Erythromycin Administration**

| Change \ Symptom | Dyspnea    | Cough      | Sleep Disturbance due to Cough |
|------------------|------------|------------|--------------------------------|
| Improved         | 11 (29.7%) | 16 (43.2%) | 19 (51/3%),                    |
| Not changed      | 24 (64.4%) | 21 (56.75) | 17 (45.9%)                     |
| Deteriorated     | 2 (5.4%)   | 0          | 1 (2.7%)                       |

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