Combined Inhalation of Cromolyn Sodium and Metaproterenol Sulfate in Life-Threatening Asthma

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After its introduction over ten years ago, the use of cromolyn sodium was often reserved for asthmatics who were uncontrolled on conventional therapy of bronchodilators and steroids. Most of these patients were steroid-dependent, and cromolyn was promoted as a steroid-sparing intervention.[1] Recent studies, however, indicate no additive or steroid-sparing effect of cromolyn, and frequently report worsening of asthma in some patients after reducing beclomethasone dipropionate aerosol.[2,3] It has been suggested that cromolyn has little value once asthma has progressed to the point of being steroid-dependent.[3] On the other hand, the use of cromolyn as a first-line drug and as adjunct therapy in non–steroid-dependent asthmatics is well supported.[4–7] Although cromolyn is currently recommended for mild or moderate asthma, the dilemma persists of what nonsteroidal therapy to use for steroid-dependent asthmatics who continue to have life-threatening episodes of status asthmaticus. A case of a dramatic response to simultaneous inhalation of nebulized cromolyn sodium and metaproterenol sulfate is presented as a possible solution to this serious clinical problem.

CASE REPORT

The patient was a 37-year-old woman who has had asthma and allergic rhinitis for approximately 14 years. Skin tests revealed positive response to house dust, molds, pollen, animal danders, and several foods. During the first five years of illness, the patient had mild episodes of asthma, which were treated with intermittent oral theophylline and aerosolized bronchodilators. During these first five years, the patient had one hospitalization and two emergency room visits. During the next five years, the patient began taking oral theophylline and aerosolized bronchodilators on a daily basis in an attempt to control the symptoms. The patient had two hospitalizations and five emergency room visits during this period. Near the end of the second phase of the patient's illness, oral β_2-agonists were added to the regimen of theophylline and aerosolized bronchodilators.

The next phase of the illness began four years ago (1983) with progressive deterioration of the patient's status. To improve control of the symptoms, aerosolized bronchodilators were replaced with nebulized bronchodilators, and at-home administration of epinephrine was initiated. The patient also began continuous use of aerosolized steroids in addition to the occasional bursts of oral steroids for acute attacks. Despite this maximal therapy, the patient's condition continued to deteriorate and the most severe stage began in the summer of 1984. From August 1984 until August 1985, the patient had five hospital admissions and 12 emergency room visits, as well as multiple episodes at home requiring one to two epinephrine injections. When admitted to the hospital, the patient was usually cyanotic with hypoxemia, hypercarbia, and mild acidosis.

After the fifth admission, the patient was discharged on her standard therapy of theophylline, oral albuterol, aerosolized beclomethasone, nebulized metaproterenol, and a tapered dose of oral steroids. Cromolyn sodium was added to the therapeutic regimen by mixing the cromolyn-sodium-nebulized solution with the metaproterenol-inhalation solution (individual dose packages of one ampule of cromolyn sodium, 20 mg in 2 mL, and one vial of 2.5 mL of 0.6 percent metaproterenol, equivalent to 0.3 mL of 5.0 percent metaproterenol in 2.2 mL of normal saline). Since adding cromolyn to the therapeutic regimen in this combined solution, the patient has had no emergency room visits or hospitalizations until a hospitalization in May 1987. When not in status asthmaticus, peak-flow rates

Submitted, revised, November 10, 1987.

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ranged from 200 to 310 L/min before beginning cromolyn and 375 to 450 L/min since instituting the cromolyn.

DISCUSSION

Deaths from asthma reached their lowest rates (0.8 per 100,000 population) in 1977 and 1978. Since that time there has been a steady increase in the death rate to 1.5 per 100,000 in 1983.[8] The characteristics of high-risk patients include chronic disease with more frequent hospitalization; discharged recently from the hospital and recovering from status asthmaticus; cyanosis, hypercarbia, dehydration, concurrent severe respiratory infection, mechanical ventilation, and persistent symptoms while in the hospital; concurrent chronic bronchitis; airflow-obstruction pattern indicating gradual deterioration over time, significant early morning obstruction, and labile and inconsistent obstruction; and emotional factors, such as depression, denial of severity of asthma, and dependence or abuse of sympathomimetic aerosol-inhaler substances.[9] The patient in this case report had several of these features and was at high risk for death from asthma.

Although a variety of contributing factors have been identified, the pathophysiologic mechanism of asthma death is asphyxia due to severe airflow limitation resulting from the three stages of bronchoconstriction: (1) rapid spasmogenic phase, (2) later sustained phase, and (3) persistent or chronic inflammatory phase.[10] The patient in this case had been receiving the conventional therapies, which are directed at bronchial smooth-muscle spasm, mucosal edema, and hypersecretion of mucus, but continued to have life-threatening episodes. The addition of nebulized cromolyn and the inhibition of mast-cell mediators[11,12] led to near elimination of the life-threatening episodes, perhaps through a reduction of excessive bronchial lability and airway hyperreactivity.[13] In the 20 months following the introduction of this combined nebulized therapy, the patient had no emergency room visits or any hospitalizations.

Although the physical and chemical compatibility of cromolyn and bronchodilator mixtures has been reported,[14] there have been no reports of their use in adults.[15] When cromolyn has been used by the spinhaler or aerosol method, it typically has been preceded by an aerosolized bronchodilator. This standard clinical practice is supported by evidence of the additive effect of combination therapy over the use of individual agents.[16] This additive effect may be caused by an improved delivery of cromolyn to its site of action or to its intrinsic properties as a bronchodilator.[17,18] The simultaneous inhalation of both drugs may potentiate bronchodilatation and delivery of cromolyn to the lower respiratory tract.

A question remains, however, whether nebulization of a combined solution of cromolyn and metaproterenol provides any advantage over sequential inhalations of these same drugs. Effective delivery of aerosolized drugs to the lower respiratory track depends on the size of the aerosol particles and respiratory functions such as inspiratory flow rate, tidal volume, breath-holding time, and airway caliber. The three ways of delivering cromolyn, through spinhaler, nebulizer, and metered-dose inhaler, all generate particles of appropriate size.[19] These methods of administration do, however, influence the delivery of the aerosolized particles by virtue of different inspiratory flow rates (less than 1 L/sec is optimal). Based on pulmonary-function testing, the spinhaler and nebulizer delivery systems are equally effective,[20] but the spinhaler is superior to the metered-dose inhaler.[21] There is no reported direct comparison of the nebulizer to the metered-dose inhaler. Whether adoption of alternative techniques[22–24] of administering metered-dose cromolyn would make it comparable to the other two formulations is unknown.

The exact mechanisms of action of this combined therapy, its potential abuses and complications, and its comparison to other methods of delivering the same pharmacologic agents must be studied prior to widespread adoption of this new treatment. The simultaneous delivery of two inhalation drugs has obvious implications for patient compliance, which may be a major contributor to the success of this therapeutic intervention.

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