Case Report

Increased Upper Airway Reactivity Associated with Placebo Inhaler

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Patient instruction on the proper administration technique for metered-dose inhalers (MDIs) is paramount in helping patients achieve adequate control of their asthma or chronic obstructive pulmonary disease and minimize adverse effects.[1-3] Teaching strategies employing placebo MDIs are often utilized in conjunction with verbal and written communication methods in order to ensure that patients understand the proper administration technique.[4-6]

Health care providers may lack proficiency in the use of MDIs and help contribute to the improper use of these devices by patients.[7] Placebo MDIs can be used to help these health care providers gain the expertise required in order to adequately educate patients. It was as a result of an instruction lecture to various members of the health care team on MDI technique that the following reaction occurred.

CASE

A 32 year-old female registered nurse with no chronic medical conditions and no prior exposure to MDIs, inhaled two puffs from a placebo MDI (Glaxo) as instructed in the inhaler lecture. Aside from a history of sneezing and throat irritation when using Pam® or no-name vegetable cooking sprays, she had no other documented history of allergic or adverse drug reactions. Despite no immediate reaction to the inhaled placebo, 30 to 60 minutes later the patient experienced repetitive sneezing episodes and rhinorrhea that lasted a total of three days. The patient did not contact or ingest any substance between inhaling the placebo and first experiencing the sneezing episodes. Although the sneezing spells did not prevent the patient from undertaking her normal daily activities, it was so intense that she reported her teeth hurt by the second day. Ice packs were applied over the jaw and face to alleviate the pain. In addition, approximately 15 hours after the onset of the reaction her throat felt tight and sore. Shortness of breath was not reported. All of her symptoms gradually improved and finally resolved by day four. The patient did not seek medical attention nor self-medicate but on day five reported her reaction to the pharmacist who conducted the lecture.

DISCUSSION

The placebo inhaler contained Freon 11 (trichloromonofluoromethane) and Freon 12 (dichlorodifluoromethane) as propellants and oleic acid as a preservative (written communication, Glaxo Canada). Most MDIs contain these propellants.[8] Either agent, Freons or oleic acid, could have potentially caused this reaction. The manufacturer does not record reactions reported from placebo inhalers, however, similar reports of sore throat/irritation from MDIs containing salbutamol have been noted (written communication, Glaxo Canada).

Freon-related adverse reactions have been reported in the literature.[8-11] A large proportion of reports are related to the occupational exposure to fluorocarbons or to the abuse of substances containing Freon propellants, including medicated MDIs.[8] Only one study and five case reports documenting Freon-related adverse effects with the therapeutic use of MDIs have been reported in the literature.[9-11] Three of these reports involved a placebo MDI.[9-11]

In one study involving 18 children it was found that Freons significantly decreased expiratory flow rates during the first two hours post aerosol inhalation.[9] However, the decreased lung function was of no clinical significance when the Freons were combined with bronchodilator medication.[9]

Three reports in three adult patients of increased breathlessness and wheezing within minutes of inhaling bronchodilator aerosols prompted an investigation into

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the probable cause of such adverse events.[10] The authors of these three reports found that while placebo aerosols (containing propellants 11 and 12) decreased the patients' forced expiratory volume in one second (FEV1) by greater than or equal to 20% from baseline, gaseous propellants 11 and 12 did not.[10] The authors concluded that the absence of reaction to gaseous Freons suggests that Freons were not the causative agents responsible for the reactions seen with the placebo aerosols.[10]

The final two case reports were presented by a single author.[11] Lip swelling in a male patient occurred within minutes following the use, on separate occasions, of two different bronchodilator MDIs (salbutamol and terbutaline) suggesting to the author that the formulation, not the drug itself, was responsible for the adverse effect.[11] In addition, while salbutamol and terbutaline both contained Freon 11 and Freon 12 propellants, they contained two different preservatives (oleic acid and sorbitan trioleate, respectively) further suggesting to the author that Freons may have been solely responsible for causing the adverse reaction.[11]

Lastly, a patient reported worsening of her asthma when she used a medicated MDI.[11] A comparison of the effects upon the administration of a placebo MDI, salbutamol MDI, salbutamol nebulization, and salbutamol breath activated device (Rotahaler), revealed that the patient's lung function deteriorated to a much greater extent when the placebo and salbutamol MDIs (i.e., those dosage forms containing Freon propellants) were administered versus the nebulization and powder inhalation.[11] Furthermore, this patient developed oral mucosal inflammation following two purposeful spray applications of a placebo MDI to her lower lip.[11]

Although the adverse effects in the case reports described above are dissimilar to our report, the time frame to onset of the adverse events following the use of the MDI and the amount (puffs) of MDI administered are generally similar to the case we describe.

The present case represents, to our knowledge, the first report of sneezing associated with the use of a placebo MDI. Based on an ADR probability scale[12], the likelihood that the contents of the placebo inhaler resulted in this patient's increased airway reactivity is "probable". While it is tempting to implicate Freons in this reaction it would appear that the patient had a non-specific response to an aerosol, based on previous events with a non-fluorocarbon aerosol. However, preservatives, such as oleic acid, can not be eliminated as a possible etiologic agent. Rechallenge and additional testing with other MDIs are needed to draw any further conclusions but were not performed. In addition, the patient's lgE levels were not evaluated but would have been helpful in determining whether the reaction was immune mediated.

While an infrequent occurrence, pharmacists should be aware of the potential for adverse effects from placebo MDI aerosols.

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