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Otolaryngologic Effects of Inhaled Medications Used in Pulmonary Medicine: A Review

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ABSTRACT

Inhaled medications are rapidly emerging therapies for many pulmonary diseases such as asthma, chronic obstructive pulmonary disease, cystic fibrosis, non-cystic fibrosis bronchiectasis, mycobacterial lung disease, and pulmonary hypertension across the globe. Specifically, these have become widely used in Europe and are now being adopted in the United States. These include inhaled corticosteroids, long-acting beta-agonists, long-acting muscarinic antagonists, mucolytic agents, prostacyclins, and antibiotics.

The goal of such therapies is to achieve optimized airway and bronchial targeting while minimizing systemic side effects seen with alternative delivery methods. However, in many instances significant oropharyngeal and laryngeal drug deposition may cause unintended local mucosal effects resulting in otolaryngologic adverse effects that impair quality of life and treatment adherence. Dysphonia, xerostomia, local irritation, oral candidiasis, and vestibulotoxicity are some of the challenging obstacles to continued adherence of treatment that patients may encounter. Evidence-based and patient-centered prevention strategies, including modification of inhaler techniques, device adaptation and emphasizing oral mouth rinsing techniques after treatment, have helped mitigate some of these adverse effects.

This review evaluates the epidemiology, mechanisms, and mitigation strategies for otolaryngologic complications of inhaled medications used in pulmonary medicine. Additionally, it highlights the need for robust patient engagement, increased clinical surveillance, and multi-disciplinary patient care coordination between specialists in pulmonology and otolaryngology to produce better overall outcomes.

Introduction

Inhaled and nebulized medications play an important role in the management of various pulmonary conditions, offering direct delivery of therapeutic agents to the respiratory system. These routes of administration enhance drug efficacy while minimizing systemic side effects. In some ways, these medications can also be beneficial in the pharynx and larynx to decrease inflammation, eradicate pathogens, increase hydration, and more. However, the use of these medications can also result in otolaryngological adverse effects that call for closer examination.

Inhaled medications must pass through the upper respiratory tract on their way to the lower respiratory tract. This may inadvertently influence structures along the way, including the nasal passages, sinuses, oral cavity, pharynx, and larynx. Aerosol particles can deposit in these areas, causing a range of local responses. Additionally, when inhalers are used improperly and without certain precautions, some medications can cause injury, inflammation, and infection. Nasal effects such as dryness, irritation, and bleeding may be due to the use of propellants. Steroids can affect mucosal integrity of the larynx leading to dysphonia as well as oral thrush due to localized immunosuppression. Other commonly reported otolaryngological effects associated with certain inhaled and nebulized therapies include throat discomfort, infection, cough, ototoxicity, and dysgeusia. These may arise from the formulation of the medication, the delivery technique, or the volume of the aerosolized particles.

Mitigation strategies to minimize these complications have been proposed with variable success. Some of these include the use of spacer devices, oral hygiene measures, and vocal therapies. A clinical balance should therefore be considered, as physicians must weigh the upper airway adverse effects against the indications of inhalation therapy and necessity of treatment. This forms the cornerstone of management in these patients and requires close collaboration between pulmonologists and otolaryngologists.

Discussion

Inhaled Steroids

One of the most common indications for nebulized and inhalation therapy is obstructive lung disease, including patients with asthma and chronic obstructive pulmonary disease (COPD). Asthma is a reversible obstructive lung disease characterized by airway inflammation and hyperresponsiveness that responds well to inhaled bronchodilator therapy. Treatment for asthma follows a stepwise approach in which the first-line treatment is inhaled corticosteroids (ICS). In these cases, budesonide is one of the most frequently used steroid medications.[1]

Delivering budesonide and other steroid medications by aerosolization aims to lower systemic delivery and subsequent systemic side effects such as osteoporosis, diabetes mellitus, Cushing's syndrome, acne, skin thinning, and bruising.[2] However, more localized adverse effects along the airway passages may arise. One of the most common side effects reported after long-term use of a corticosteroid-containing inhaler is dysphonia (Table 1). Recently, a case-control study retrospectively evaluated ICS exposure in patients with a diagnosis of dysphonia made by an otolaryngologist. Other causes of dysphonia, such as malignant neoplasm of the glottis, vocal fold nodules or polyps, and laryngeal stenosis, were excluded. The study found that ICS use was a significant risk factor for dysphonia development, with an odds ratio of 5.11 (95% CI: 4.23–6.17). On average, the diagnosis of dysphonia was made 86.2 days after the ICS was prescribed. The most common steroid medications prescribed to these patients were fluticasone and budesonide.[3]

Table 1: Otolaryngologic Adverse Events of Aerosolized Medications and Their Management

Medication	Indication(s)	Adverse Effects	Mitigation Strategies
Inhaled Corticosteroids	Obstructive Lung Disease	Dysphonia[3,4] TVF Congestion/Edema[4] TVF Bowing[4] Cough[5] Oral thrush[4,6] Mucosal Inflammation[7]	Oral thrush: use of spacer device, pMDI may decrease risk compared to DPI[8] Dysphonia: use of a spacer device[3,4]
Combination Inhalers	Obstructive Lung Disease	Oral thrush[8] LAMA: Xerostomia[9,10]	Xerostomia: proper inhaler technique, rinsing the mouth with water immediately post-treatment[10]
Nebulized Hypertonic Saline	Cystic Fibrosis ± Non- CF Bronchiectasis	Burning/Irritation Cough[13,16]	Irritation/Cough: supervised test dose, pretreat with bronchodilator[17]
Inhaled Prostacyclins	Pulmonary Hypertension	Dizziness[19] Throat Irritation[19] Oropharyngeal Pain[19] Cough[18,19]	Cough: adjusting technique, changing device position, swallowing throat-soothing foods or drinks prior to treatment, pre-treating with short-acting bronchodilator or throat analgesic spray[19] Longer duration of therapy decreased throat irritation and cough over time[18]
Inhaled Aminoglycosides	Respiratory Infection in Patients with Airway Disease	With Preservative: Airway Irritation[20] Without Preservative: Voice Alteration[20] Tinnitus[20] Hearing Loss[20] Cough[20] Vestibulotoxicity[21]	Airway Irritation: pretreat with bronchodilator in CF patients[20] Voice alteration: improved during off-drug cycles and as exposure to inhaled medication increased over time[20] Vestibulotoxicity: monitoring, vestibular rehabilitation[21]
Amikacin Liposome Inhalation Suspension	Non-Tuberculous *Mycobacterium avium complex* (MAC)	Dysphonia[22,24] TVF Hyperemia[22] Mucosal Sloughing/ Ulceration[22] Increased Sputum[24] Cough[24]	Dysphonia: conservative measures[23] ± lozenges, antitussives, gargle warm water or glycerin, rinse the mouth after use, administration in the evening, temporarily decreasing frequency, briefly interrupting treatment[24] Sputum production resolved without intervention in most patients[24] Cough: bronchodilator use, temporary decrease in frequency, briefly interrupting treatment[24]
Dry Powder Inhaled Antibiotics	Respiratory Infection in Patients with Airway Disease	Cough[25] Pharyngeal Irritation[25] Dysgeusia[25]	Cough: education on proper inhaler technique and symptomatic management[25]

Some theories have been proposed to explain this pathophysiology. These include steroid particle deposition on the mucosa leading to plaque-like buildup, microhemorrhages, mucosal irritation and atrophy, inhibition of local immunity, and muscle myopathy. A single-center prospective case-control study sought to investigate potential changes to the voice profile and vocal fold structure experienced by patients who had chronically used either fluticasone–salmeterol or budesonide–formoterol for asthma or asthma-COPD overlap. All patients were evaluated by two otolaryngologists and one speech-language pathologist who were blinded to patient status. Videostroboscopy revealed that patients who had used these inhalers for six months or longer had significant decreases in vocal fold amplitude, frequency of vibration, and mucosal wave pattern. Chronic ICS users also had a higher prevalence of structural changes, with 40.8% of cases showing congestion or edema of the true vocal folds (TVFs) and 7.2% of cases notable for candidiasis. Additionally, these patients had adduction deficits resulting in bowing of the TVFs and incomplete glottic closure. These findings exponentially increased as the duration of therapy increased. Voice analysis was completed by scoring patients on grades of hoarseness, roughness, breathiness, asthenia, and strain, also known as the GRBAS scale. GRBAS scores for chronic ICS use showed significantly higher grades of dysphonia (62.2%) compared to controls (27.6%) as well as increased prevalence in "mild disturbance of voice."[4]

Another common concern for patients chronically using inhaled steroid medications is local immunosuppression and the development of new respiratory infections (Table 1). In a study to examine the effects of treating young asthmatic patients with nebulized budesonide, respiratory infections were described as the most common adverse event, occurring in 13.50% of patients receiving the 500-µg dose and 18.13% of patients receiving the 250-µg dose. The patients in this study also reported cough and hoarseness as side effects, which improved without additional intervention.[5] Another study utilized the Food and Drug Administration (FDA) Adverse Event Reporting System database to compare the infection risk of different inhaled steroid medications. The study discovered that patients using inhaled budesonide had less cases of oral fungal infections such as Candidiasis (0.10%) than patients using inhaled fluticasone (0.22%). Budesonide users also had a lower risk of pneumonia (0.86%) compared to fluticasone users (1.24%).[6] This is believed to be due to an ability of budesonide to counteract reductions in bacterial recognition receptors on macrophages carried out by both *Haemophilus influenzae* and *Streptococcus pneumoniae*. Fluticasone has only been shown to counteract a portion of the bacterial recognition receptor reductions completed by *Streptococcus pneumoniae*.[2] However, patients receiving budesonide did report the highest amount of mycobacterium infections compared to any other inhaled corticosteroid at 3.29%.[6]

Combination Inhaled Medications in Asthma and COPD

Steroids are often combined with a long-acting beta-agonist (LABA) in the treatment of asthma and COPD. Examples of commonly used combination inhalers include fluticasone–vilanterol, fluticasone–salmeterol, mometasone–formoterol, and budesonide–formoterol.[1] These medications are effective in treating obstructive lung diseases due to their role as bronchodilators and anti-inflammatory agents. However, these effects have not been thoroughly investigated on a cellular level at the laryngeal mucosa. One prospective, controlled, randomized study done to evaluate the histological effects of inhaled LABA and ICS medications in various combinations on the supraglottic and subglottic mucosa using an allergic rat model showed multiple changes at mucosal and submucosal levels. Microscopic evaluation was performed to assess inflammatory cell counts, epithelial thickness, submucosal gland hypertrophy, mucous production, mast cell counts,

and mast cell degranulation. Following exposure to the allergen, this assessment showed a severe inflammatory cell infiltrate and an increase in both granulated and degranulated mast cell counts compared to the unsensitized group. Similar findings were discovered in the sensitized rats who received ICS alone therapy, but these rats additionally displayed epithelial desquamation, epithelial thinning, and mucosal bleeding. In contrast, sensitized rats who received ICS+LABA combination therapy showed only a mild inflammatory cell infiltrate, decreased mast cell count, and decreased mast cell degranulation. Therefore, combining a LABA with ICS therapy was found to significantly decrease inflammation, mast cell count, and mast cell degranulation in the supraglottic mucosa. This is likely due to the process in which corticosteroids induce β-2-receptor expression on inflammatory cells, producing a more robust anti-inflammatory effect. However, the results of this study also show that ICS alone therapy can significantly increase inflammation in the supraglottic mucosa, which likely has a complex and multifactorial etiology. One possible explanation is that deposition of ICS on the laryngeal mucosa enhances intrinsic inflammation already present after allergen sensitization. This could explain ICS-associated laryngitis, which is characterized by mucosal edema, erythema, and thickening, similarly to laryngopharyngeal reflux. However, the exact mechanism is still unknown currently.[7]

Another well-documented concern for patients with asthma and COPD who are using combination inhalers is an increased risk of Candida infection along the upper respiratory tract. A cohort study sought to determine the specific incidence of oral thrush in this patient population by comparing how often it occurred in patients using a LABA alone versus those using ICS+LABA combination therapy. They found that patients whose therapy included an ICS had a higher incidence of oral thrush (5.5%) compared to those whose therapy did not contain any steroids (2.7%) with an odds ratio of 2.18 (95% CI: 1.84–2.59). In addition, the study wanted to assess if the incidence of oral candidiasis is affected by specific steroid ingredient or medication dose. After comparing budesonide–formoterol (BUD+FOR) and fluticasone–salmeterol (FP+SAL), they initially found that patients receiving BUD+FOR had significantly less oral candidiasis infections (5.7%) than those on FP+SAL (7.0%) with an odds ratio of 0.77 (95% CI: 0.63–0.94). However, most patients on FP+SAL were on a higher dose of steroid medication than the patients on BUD+FOR. Adjusting for the intended ICS daily dose produced data with no statistically significant difference.[8]

If symptoms of obstructive lung disease remain uncontrolled with ICS+LABA combination therapy, triple therapy may be indicated. This consists of the addition of a long-acting muscarinic antagonist (LAMA) inhaler. A systematic review and meta-analysis compared the effects of dual therapy (ICS+LABA) and triple therapy (ICS+LABA+LAMA) on patient outcomes in those with moderate to severe asthma. Increasing to triple therapy significantly reduced patient exacerbation risk from 27.4% to 22.7% (risk ratio 0.83, 95% CI: 0.77–0.90). Additionally, triple therapy improved overall asthma control (standardized mean difference [SMD] of –0.06 units on asthma questionnaires, 95% CI: –0.10 to –0.02 units). While serious adverse events were not significantly different between the two groups, specific adverse events of dry mouth and dysphonia were reported more often in the triple therapy group (3.0%) than in the dual therapy group (1.8%) (risk ratio 1.65, 95% CI: 1.14–2.38).[9] Dry mouth, also known as xerostomia, is one of the most frequently reported adverse effects of LAMA inhaler use. In a study utilizing the FDA Adverse Event Reporting System database to review medications associated with dry mouth, the most frequently reported drug was a LAMA named tiotropium bromide (2080 patients, 6.06% of cases). This is likely due to some of the medication depositing in the mouth and pharynx during

inhalation, where it can exert a local anticholinergic effect on the salivary glands, reducing saliva production. Over time, this may lead to histological changes and eventual atrophy of the glandular tissue. Therefore, it is important to verify proper inhaler technique and encourage rinsing the mouth with water immediately after inhaler use in these patients (Table 1).[10]

Influence of Device-Related Factors

Some studies have been performed to investigate if the type of inhaler device used or the addition of a spacer device could mitigate some of these reported adverse effects. The devices have been compared in simulated environments to assess if there are differences in the amount of medication deposited in the upper and lower airways. An Advanced Integrated Respiratory (AIR) model and the Next Generation Impactor (NGI) were both used in a recent study to evaluate salbutamol particle deposition by pressurized metered-dose inhalers (pMDIs), dry powder inhalers (DPIs), and jet nebulizers. DPIs produced the highest percentage of oropharyngeal deposition in both the AIR model (94.32 ± 3.52) and the NGI (87.31 ± 0.49). A smaller percentage of oropharyngeal deposition was produced by the pMDI inhalers at 67.44 ± 13.97 in the AIR model and 48.22 ± 4.90 in the NGI. Finally, jet nebulization produced significantly lower oropharyngeal deposition of 19.44 ± 10.47 and 10.19 ± 7.83 with the AIR model and the NGI, respectively.[11]

Since different inhalers may deposit varying amounts of medication in the upper airway on its way to the lungs, they may produce different rates of adverse effects. A recent systematic review and meta-analysis was performed including 44 randomized controlled trials to compare pMDIs, DPIs, and soft mist inhalers (SMIs) being used for the treatment of asthma and COPD. The study concluded that there was no significant difference between inhaler devices for both clinical benefits and unfavorable effects.[12] Other investigations have been done to evaluate if there are differences in rates for specific adverse events. For example, one study compared the incidence of oral thrush in patients on FP+SAL based on whether a DPI or pMDI inhaler device was used. Significantly less patients developed oral thrush when using a pMDI (5.5%) than those using a DPI (7.3%) with an odds ratio of 0.67 (95% CI: 0.55–0.82). This study also examined the impact of using a spacer device, concluding that patients who used a spacer had a lower incidence of oral thrush. However, this data was not statistically significant.[8] The effects of different inhalers in causing ICS-associated dysphonia has also been examined by various studies. While these generally did not find a significant difference in patient outcomes based on the type of medication or the type of inhaler used, subgroup analyses did demonstrate that the use of a spacer device could decrease the risk of dysphonia to an amount comparable to the control group (odds ratio of 1.08).[3,4]

Nebulized Hypertonic Saline

Nebulized hypertonic saline has many uses in clinical practice. In pulmonary medicine, it is widely used in cystic fibrosis (CF) patients older than six years to improve mucociliary clearance (MCC),[13] while its benefit in non-CF bronchiectasis patients (NCFB) has become a current focus of research. A recent randomized trial including 288 bronchiectasis patients compared the mean number of pulmonary exacerbations over a period of 52 weeks in patients receiving standard care alone (0.98, 95% CI: 0.78 to 1.19) to those receiving both standard care and 6% hypertonic saline (0.76, 95% CI: 0.58 to 0.95). The study found that adding hypertonic saline to standard care did not significantly reduce pulmonary exacerbations.[14] This conclusion was supported by a systematic review and meta-analysis including four randomized, controlled clinical trials totaling 386 NCFB patients. In this analysis, the SMD was calculated for various pulmonary measures in patients receiving either hypertonic or isotonic saline. The results showed that hypertonic saline did not significantly improve forced expiratory

volume in one second (SMD 0.03, 95% CI: –0.07 to 0.13), forced vital capacity (SMD 0.10, 95% CI: –0.06 to 0.25), or pulmonary exacerbation rates (SMD –0.02, 95% CI: –0.48 to 0.45) compared to isotonic saline.[15] Therefore, inhaled hypertonic saline improves airway clearance only in specific instances.

When using hypertonic saline nebulizers for any condition, adverse effects should always be considered. The solution is known for causing symptoms of burning and irritation, and its potentially irritating properties lead to many patients commonly reporting increased cough as a side effect (Table 1). One multicenter, double-blind, placebo-controlled trial evaluating the efficacy of inhaled hypertonic saline on CF patients younger than 6 years found cough or increased cough to be the most common adverse event. This occurred in 8% of patients in the hypertonic saline group and 10% of patients in the isotonic saline group. However, there was no significant difference in the proportion of adverse events between the two groups.[13] Cough was also found to be the most frequent side effect in a multicenter, double-blind, randomized clinical trial comparing hypertonic saline to normal saline nebulization for the treatment of acute bronchiolitis in infants. In this study, mild adverse events occurred more often in children receiving hypertonic saline (8.9%) than in those receiving normal saline (3.9%).[16] Therefore, the objective data supporting cough as a significant adverse effect of hypertonic saline nebulization is variable. Some methods have been suggested to mitigate the airway irritation that causes cough and bronchospasm after hypertonic saline nebulization. These include a supervised test dose and pre-treatment with a bronchodilator.[17]

Inhaled Prostacyclins

Prostacyclins are frequently prescribed to patients with pulmonary hypertension (PH) caused by interstitial lung disease. Inhaled solutions, such as inhaled treprostinil (iTRE) therapy, have been developed to decrease complications such as long-term invasive intravenous access, systemic vasodilation, and ventilation-perfusion mismatch.[18]

During the INCREASE study, the effects of iTRE were evaluated for 326 patients with Group 3 PH according to the World Health Organization's classification. While iTRE significantly improved patient exercise capacity and six-minute walk distance, it caused multiple adverse effects that should be considered for future patients. Dyspnea was reported by 25.2% of patients receiving iTRE, however this side effect also occurred in 31.3% of patients in the placebo group. Dizziness was reported by 18.4% of patients who received iTRE therapy. Some patients receiving iTRE therapy also reported throat irritation (12.3%) and oropharyngeal pain (11.0%). Finally, the most common side effect was cough, occurring in 43.6% of iTRE-treated patients. It is worth noting that many PH patients have a baseline cough, so it is possible that this baseline cough was exacerbated by the inhalation. In addition, the cough only occurred around the time the patient received treatment and did not persist throughout the day. Therefore, the study made recommendations to try to mitigate adverse effects such as cough, including adjusting the patient's breathing technique, changing the position of the inhaler device, swallowing throat-soothing foods or drinks prior to treatment, and pre-treating with relaxing agents such as a short-acting bronchodilator or throat analgesic spray (Table 1).[19]

Another study that sought to investigate the safety and tolerability of iTRE therapy was designed as a retrospective cohort study of 80 patients with PH. The study found that throat irritation decreased over time as patients remained on iTRE (7.5%, then 2.0%, and finally 0.0%). Cough was again reported as a frequent adverse event, occurring in 39% of patients. This also decreased as the patient was continued on iTRE over time to around 10% then 7% at later follow-up visits. Therefore, the study concluded that iTRE is overall safe and generally well-tolerated.[18]

Aerosolized Antibiotics

Aerosolizing antibiotics as a method of medication delivery has proven to be beneficial for treating infections in patients with airway disease, such as those with CF, NCFB, and ventilator-associated pneumonia. However, changing the method of delivery does not completely eradicate adverse effects caused by these medications. The most reported general side effects of inhaled antibiotics include cough, wheezing, hemoptysis, and dyspnea.[20] Of course, the side effect profile varies considerably based on the specific antibiotic used (Table 1).

Aminoglycoside antibiotics are bactericidal with effects against Gram-negative organisms, including *Pseudomonas aeruginosa*.[20] The use of medications from this class has previously been limited by systemic adverse effects such as ototoxicity and nephrotoxicity. As a result, inhaled preparations were developed to investigate if reduced systemic accumulation of the drugs could decrease the toxic effects experienced by the patient. While multiple studies initially showed reassuring safety profiles, some adverse effects have been reported over the years.[21] For example, the original formulation of inhaled tobramycin included a preservative that irritated the airway and caused bronchospasm. This issue could be mitigated by pre-treating CF patients with a bronchodilator. While the current FDA-approved prescription is preservative-free and causes less bronchospasm, its new formulation has been shown to cause tinnitus without hearing loss as well as mild to moderate voice alteration. These changes in voice usually improve during off-drug cycles and over time as the patient gains increased exposure to the inhaled solution.[20] Another possible side effect of inhaled aminoglycosides is vestibulotoxicity. One published case report describes a patient receiving inhaled tobramycin 300 mg twice a day who developed profound vestibulotoxicity without evidence of concurrent nephrotoxicity or renal insufficiency. The patient presented with progressive imbalance necessitating a new requirement of a cane for ambulation. Other presenting symptoms included a wide-based gait, bilateral catch-up saccades after rapid head thrust in the horizontal plane, and caloric testing significant for severe bilateral vestibulopathy. In this specific case, vestibular rehabilitation resolved the patient's symptoms over a three-year period. However, routine monitoring may be useful in patients with risk factors such as a positive family history to prevent the initial development of toxicity.[21] Some case reports have also linked inhaled aminoglycosides to acute renal failure as well as hearing loss. Additionally, adverse events appear to be worse in patients with severe NCFB compared to CF patients. One pilot study reported 10 out of 41 patients with NCFB withdrew due to adverse effects including cough, wheezing, and dyspnea.[20]

Amikacin liposome inhalation suspension (ALIS) was approved in 2018 to treat refractory non-tuberculous *Mycobacterium avium complex* (MAC) infections. While ALIS was shown by the CONVERT trial to achieve a higher rate of culture conversion than guideline-based therapy alone, it caused dysphonia in 45.7% of patients. However, the direct laryngeal effects of ALIS have not been extensively investigated. A case report published in 2020 describes a patient that had been taking once daily ALIS who experienced progressive dysphonia. She presented to a laryngologist with a severely raspy, rough, and strained voice as well as impaired projection. Videostroboscopy revealed hyperemia of the TVFs; sessile, plaque-like lesions suggesting mucosal sloughing or ulceration; fibrinous exudate; and absent TVF vibration. The patient's recovery process included a prolonged period of vocal fatigue.[22] It is important to note that most patients (85%) who experience dysphonia due to ALIS therapy improve with conservative measures alone during the continued course of treatment. Therefore, they do not require permanent discontinuation of treatment.[23] Further investigations into the side effect profile of ALIS have involved surveying patients on the incidence,

frequency, and resolution of specific adverse events they experienced while receiving the medication. Survey results from 26 patients on ALIS for refractory MAC lung disease showed that 73.1% endorsed dysphonia. Of these patients, 84.6% received interventions that improved their dysphonia, including lozenges, antitussive agents, gargling warm water or glycerin, rinsing the mouth after nebulizer use, changing ALIS administration to the evening, and temporarily reducing dosing frequency or briefly interrupting treatment. Additionally, 69.2% of patients endorsed increased sputum production. This resolved without any intervention in most patients. Increased cough was reported by 69.2% of patients, and interventions such as pretreatment with a bronchodilator, temporary reduction in frequency of treatment, or a brief interruption in therapy lead to symptomatic improvement in 72.7% of cases. Finally, dyspnea occurred in 57.7% of patients and resolved in 73.3% of those who implemented an intervention.[24]

While nebulized antibiotics have become widely used in bronchiectasis patients, there is another delivery method that is more limited in medical practice known as dry powder inhaled antibiotics (DPIA). The antibiotics available in this form include ciprofloxacin, vancomycin, tobramycin, and colistin. This new formulation was produced for several advantages, one of which is faster administration of medicine.[25] For example, dry powder tobramycin has a treatment time of 2-3 minutes, while the nebulized form takes 10-15 minutes twice daily.[20] Other advantages include greater pulmonary deposition as well as devices that are smaller, more transportable, easier to use and clean, and similar to ICS and LABA inhalers. However, it has been suggested that DPIA can produce more local adverse effects, such as cough, dyspnea, hemoptysis, and pharyngeal irritation. A multi-center cohort study collected data to analyze the clinical efficacy and safety profiles for various DPIA and found that at least one adverse effect was seen in 54.2% of cases. Side effects included cough, chest discomfort, dyspnea, hemoptysis, and dysgeusia. It has been recommended that cough management can be individualized to the patient if it arises. However, these side effects emphasize the overall importance of educating patients on proper inhaler technique, as this can be extremely impactful in mitigating adverse symptoms.[25]

Conclusions

Inhaled medications can be extremely beneficial for patients with pulmonary diseases such as asthma, COPD, bronchiectasis, and pulmonary hypertension. However, on their way to the lower airway, these medicines may deposit in the upper airway and cause unintended adverse effects. Management of otolaryngological side effects requires a combination of increased awareness, prevention, and treatment in a multi-disciplinary and multi-faceted manner. Measures such as dose reduction, local mouth hygiene, use of spacer devices, and monitoring inhaler techniques all play an important part in mitigating these side effects. Balancing adverse effect management with the benefits of treatment can improve adherence to this modality and may result in overall better patient outcomes.

Conflicts of Interest Statement

Dr. Juzar Ali has been a consultant and a speaker for Insmed and Euroimmun. The other authors have no conflicts of interest to declare.

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