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Editorial

COPD: Will There Be Room for Nebulisers After the Current COVID-19 Pandemic?

EPOC: ¿habrá lugar para los nebulizadores tras la actual pandemia de COVID-19?

Inhaled medication is the mainstay of chronic obstructive pulmonary disease (COPD) management and therapeutic success depends on the maintenance of a correct inhalation technique. However, there is a growing evidence concerning misuse of handheld inhalers as a common clinical problem worldwide.[1] In clinical practice, up to 94% of patients can present inhalers' mishandling. In the largest study assessing the use of inhalers in real-life,[2] 49–76% of patients presented at least one error, depending on the type of inhalers they used, and, in a more recent study, handling errors were observed in more than 50% of demonstrations.[3] In previous published papers, a significant inhalers' misuse was also confirmed in a Portuguese cohort of COPD patients.[4,5] Moreover, the functional progression of COPD and the ageing process, reducing inspiratory muscle function, decreases the patient's ability to generate sufficient inspiratory flow, limiting at least the use of dry-powder inhalers properly. In patients with severe COPD and limited inspiratory capacity it is often necessary to introduce metered dose inhalers with or without a spacer in order to provide the necessary treatment to the patient. This has several limitations as many of the more recent COPD treatment drugs are not available in such devices.

Nebulisers are the oldest devices developed to produce aerosols and deliver inhaled medication, and they are regularly used at home, when elderly people are unable to handle portable inhalers correctly. They are known to present significant disadvantages: lack of portability, lack of chemical stability of some drugs, lengthy administration time, significant waste of medication, health care professionals and caregivers' exposure to aerosolised medication, and the lack of the definition regarding the optimal doses required. Their high costs and the need for daily cleaning are other usual drawbacks. They are not regularly recommended for chronic disease management in COPD, because there is no evidence of superiority of nebulisers in patients who are able to use portable inhaler devices properly.[6] However, when prescribed, patients are usually satisfied with nebulised therapy, and it is often preferred by those who have been recently hospitalised.[6]

In recent years, nebulised drug delivery has significantly evolved. Nebulisers became more portable, lighter and battery-powered, and more silent in operation. Breath-enhanced and breath-actuated technologies improved the efficiency of jet nebulisers by reducing the loss of medication to the environment and the exposure of caregivers. Recent developments, the vibrating mesh and the adaptive aerosol delivery technologies provide precise and reproducible doses, reduces the losses of aerosol, during expiration, and allows a deeper aerosol deposition in the lungs, together with a shorter treatment duration. They can also give feed-back to the patient and to the caregiver that the prescribed dose was delivered. However, they are even more expensive, their cleaning more difficult, and they need a more complex initial learning period.

Another common limitation for the use of nebulisers has always been the reduced availability of drugs, or their associations, that can be used in these devices. Currently, the most frequently used are short-acting β_2-agonists, short-acting muscarinic antagonists and budesonide. Twice-daily nebulised formoterol fumarate, a long-acting β_2-agonist (LABA), was proven to be effective and well-tolerated in COPD treatment, and arformoterol, another LABA, can also be useful as a nebulised maintenance therapy for COPD.[7] Two different long-acting muscarinic antagonists, a soluble glycopyrrolate bromile formulation and revefenacin, are nebulised therapies already approved by the US Foods and Drugs Administration, respectively for twice- and once-daily maintenance therapy of COPD. In the future, a dual inhibitor of phosphodiesterase 3 and phosphodiesterase 4 enzymes, developed for use as nebulisation, could be used as maintenance therapy for COPD patients, because of the bronchodilator and anti-inflammatory related effects.[8]

In a recent systematic review and meta-analysis, high doses of nebulised budesonide during hospitalisation, seemed to be non-inferior to systemic corticosteroids, in the treatment of COPD acute exacerbations.[9] Nebulised corticosteroids can also be preferable versus oral prednisolone in patients with diabetes mellitus or with heart failure, because of the mineralocorticoid effects and fluid retention related to systemic corticosteroids. A subgroup of COPD patients is known to present chronic bronchial infection, and the use of antibiotics can be associated with reduction of bacterial load.[10] Low doses of nebulised antibiotics can provide higher tissue concentration with fewer bacterial-resistance related issues. However, a possible bronchial hyperesponsiveness can occur. COPD patients suffering from severe α1-antitrypsin (AAT) deficiency commonly present an emphysema phenotype, and accelerated disease progression. Intravenous AAT can be administered to protect the lungs from inflammatory destruction and to reduce the development of emphysema. More recently, nebulised AAT can be delivered directly to the lungs, leading to AAT levels three times higher than those reached by intravenous administration.[11]

Because the increased risk of infection transmission via aerosols during treatment with nebulisers, there has been a progressive

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shift from the use of nebulisers to metered-dose inhalers with valved holding chambers. However, nebulisers remain widely used in hospital setting and in ambulatory clinics. The current COVID-19 pandemic demands greater infection control precautions, and many national and international guidelines recommend against the use of nebulised therapies, as an infection control measure. Some authors advise that nebuliser treatments should be performed only if absolutely necessary, and in negative pressure environments.[12] Although there is no evidence regarding whether nebulisations are related to SARS-CoV-2 transmission,[13] it was previously associated with the risk of transmission of SARS in a Honk-Kong hospital. In a systematic review of articles published in all languages from 01/01/1990 to 22/10/2010, Tran et al. found two studies describing an association between nebulisations and risk of SARS transmission.[14] Because it is not clear how significant is the role of nebulisers in the spread of SARS-CoV-2, and there are no reviews or trials investigating this association, recommendations were established based on general principles and previous case reports, related to other viruses.

Probably in the future, inhaled medication delivered by portable devices will continue to be largely preferred. Due to the current awareness that nebulisations may potentially aerosolise respiratory pathogens, nebulisers will be significantly deprescribed, and relief medication will preferably be administered using metered-dose inhalers with valved holding chambers. However, in face of the recent developments related both to nebulisers and new drugs developed to be administered by nebulisation, there will probably be a room for the use of nebulisers in the future, both for COPD exacerbations and maintenance therapy.

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References

1. Chrystyn H, van der Palen J, Sharma R, Barnes N, Delafont B, Mahajan A, et al. Device errors in asthma and COPD: systematic literature review and meta-analysis. NPJ Prim Care Resp Med. 2017;27:22, http://dx.doi.org/10.1038/s41533-017-0016-z.
2. Molimard M, Raherison C, Depont F, Abouelfath A, Moore N. Assessment of handling of inhaler devices in real life: an observational study on 3811 patients in primary care. J. Aerosol Med. 2003;16:249–54.
3. Molimard M, Raherison L, Lignot S, Balestra A, Lamarque S, Chartier A, et al. Chronic obstructive pulmonary disease exacerbation and inhaler device handling: real-life assessment of 2935 patients. Eur Resp J. 2017;49:1601794.
4. Duarte-de-Araújo A, Teixeira P, Hespanhol V, Correia-de-Sousa J. COPD: analysing factors associated with a successful treatment. Pulmonology. 2020;26:66–72.
5. Duarte-de-Araújo A, Teixeira P, Hespanhol V, Correia-de-Sousa J. COPD: misuse of inhaler devices in clinical practice. Int J COPD. 2019;14:1209–17.
6. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2019 Report. Available from: https://goldcopd.org/wp-content/uploads/2019/11/GOLD-2020-REPORT-ver1.0wms.pdf.
7. Tashkin D. A review of nebulized drug delivery in COPD. Int J COPD. 2016;11:2585–96.
8. Franciosi L, Diamant Z, Banner H, Zuiker R, Morelli N, Kamerling M, et al. Efficacy and safety of RPL554, a dual PDE3 and PDE4 inhibitor, in healthy volunteers and in patients with asthma or chronic obstructive pulmonary disease: findings from four clinical trials. Lancet Resp Med. 2013;1:714–37.
9. Pleasants R, Wang T, Xu X, Beiko T, Bei H, Zhai S, et al. Nebulized corticosteroids in the treatment of COPD exacerbations: systematic review, meta-analysis and clinical perspective. Resp Care. 2018;63:1302–10.
10. Miravitlles M, Anzueto A. Chronic respiratory infection in patients with chronic obstructive pulmonary disease: what is the role of antibiotics? Int. J. Mol. Sci. 2017;18:1344.
11. Stolk J, Tov N, Chapman K, Fernandez P, MacNee W, Hopkinson N, et al. Efficacy and safety of inhaled α1-antitrypsin in patients with severe α1-antitrypsin deficiency and frequent exacerbations of COPD. Eur Resp J. 2019;54:1900673.
12. Whittle J, Pavlov I, Sacchetti A, Atwood C, Rosenberg M. Respiratory support for adult patients with COVID-10. JACEP Open. 2020;1:95–101.
13. Harding H, Broom A, Broom J. Aerosol generating procedures and infective risk to healthcare workers: SARS-CoV-2 – the limits of the evidence. J. Hosp. Infect. 2020, http://dx.doi.org/10.1016/j.jhin.2020.05.037.
14. Tran K, Cimon K, Severn 1, Pessoa-Silva C, Conly J. Aerosol generating procedures and risk of transmission of acute respiratory infections to healthcare workers: a systematic review. PLoS ONE. 2020;7:e35797, http://dx.doi.org/10.1371/journal.pone.0035797.

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