Evaluation of the Importance of Capsule Transparency in Dry Powder Inhalation Devices

Rocío Reinoso Arija, MD[1]
Rosario Ruiz-Serrano de la Espada[1]
Mª Dolores Núñez Ollero[1]
Laura Carrasco Hernandez, MD[1,2]
Esther Quintana Gallego, MD[1,2]
Jose Luis López-Campos, MD[1,2]

[1]Unidad Médico-Quirúrgica de Enfermedades Respiratorias. Instituto de Biomedicina de Sevilla (IBiS). Hospital Universitario Virgen del Rocío/ Universidad de Sevilla, Seville, Spain

[2]Centro de Investigación Biomédica en Red de Enfermedades Respiratorias (CIBERES), Instituto de Salud Carlos III, Madrid, Spain

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Conflicts of interest: J.L.L-C. has received honoraria in the last 3 years for giving lectures, scientific advice, participation in clinical studies or writing publications for (alphabetical order): AstraZeneca, Bial, Boebringer, Chiesi, CSL Behring, Faes, Gebro, Grifols, GSK, Menarini and Zambon. Additionally, during his career, J.L.L-C. has received fees from all the companies that market these inhalers in Spain: Boebringer, Bial, Gebro Pharma, Menarini, Novartis, and Teva Pharmaceuticals. The remaining authors report none.

CORRESPONDING AUTHOR

Jose Luis López-Campos
Hospital Universitario Virgen del Rocío
Avda. Manuel Siurot, s/n
41013 Seville, Spain
lopezcampos@separ.es

ABSTRACT

The aim of this work is to test whether the use of a transparent capsule affects the residual capsule weight after inhalation as a surrogate of the inhaled delivered dose for patients with non-reversible chronic airway disease. Researchers conducted an observational cross-sectional study with patients using a single-dose dry powder inhaler. The weight of the capsule was measured with a precision microbalance before and after inhalation. Ninety-one patients were included, of whom 63 (69.2%) used a transparent capsule. Inhalation with a transparent capsule achieved a weight decrease of 30.1% vs 8.6% for devices with an opaque capsule ($P < 0.001$). These data reinforce the need to provide patients with mechanisms that verify the correct inhalation technique.

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INTRODUCTION

One of the factors considered most important by patients when using inhaled medications is the verification of the dose taken.[1] Additionally, critical errors in dose delivery have been associated with worse clinical outcomes.[2] Dose verification has been achieved in various ways, such as the perception of a noise or vibration, a particular taste, or some change in the configuration of the device after inhalation.[3] Additionally, for single-dose dry powder devices, the correct verification can also be checked when the empty capsule is viewed after inhalation,[4] which requires the capsule to be transparent.[5] To date, however, it has not been studied whether having a transparent capsule actually has any impact on the emitted dose. The present work is based on the hypothesis that, when using a transparent capsule, feedback is given to the patient about inhalation efficacy, ensuring a further reduction in the weight of the capsule.

METHODS

We conducted a cross-sectional observational study carried out in a tertiary university hospital located in an urban setting and including patients who were using long-acting bronchodilators with a single-dose dry powder inhaler (**Supplemental Figure 1**) for a non-reversible chronic airway disease. Patients were aged over 35 years and of both sexes. The exclusion criteria were patients with poor inhalation technique despite adequate training, and patients who did not bring their own inhalation device on the day of the visit. The patients were recruited between October 2020 to October 2022. Pre-chronic obstructive pulmonary disease (COPD) patients were mainly symptomatic with chronic bronchitis and smoking history without obstruction in spirometry at the time of inclusion.[6] We did not evaluate the conditions that motivated the prescription of the drugs at the time of prescription.

On the day of the evaluation, after signing the informed consent form, patients were given an on-site verbal plus demonstration reminder about correct inhalation technique with their inhalation device and the weight of the capsule was measured before the patient was asked to perform the inhalation. All inhalations were done under supervision. All the patients were left to perform as many inhalations as they felt necessary to be sure that the medication had been taken without the influence of the research team. Once inhalation was over, the capsule was weighed again. The capsules were weighed using a precision micro-balance (model MS105DU; Mettler Toledo, Inc). Functional severity of the airway disease was assessed by spirometry

according to the Global Initiative for Obstructive Lung Disease (GOLD) 2023 document.[6]

The study was approved by our institutional review board and complied with local regulations. The statistical studies were carried out using IBM SPSS Statistics, version 26.0 (IBM Corp). Data were summarized as median and interquartile range in brackets or absolute counts with relative frequencies in brackets. The changes in capsule weight after inhalation were expressed as percentages from baseline. Comparisons of capsule weight before and after inhalation were performed with the Wilcoxon signed-rank test. The comparative studies in the capsule weight between the 2 capsule types were evaluated by calculating the Mann-Whitney U or Fisher exact test. The significance level was set at 0.05.

RESULTS

Ninety-one patients were included in the study, of whom 63 (69.2%) used a transparent capsule; their characteristics are summarized in Table 1. The inhalers examined were 28 (30.8%) cases with HandiHaler (Boehringer Ingelheim Pharmaceuticals, Inc) (opaque capsule), 17 (18.7%) with Zonda (Teva UK Ltd) (transparent capsule), and 46 (50.5%) with Breezhaler (Novartis AG) (transparent capsule). The capsules' weights before inhalation are shown in the Supplemental Table and Supplemental Figure 2. Inhaler use time was significantly different between opaque and transparent capsules and between the 3 types of inhalers: HandiHaler 48.0 (82.0) months, Breezhaler 34.5 (72.0) months, and Zonda 6.0 (8.0) months. The weight of the capsule before inhalation was on average 67.5 (20.9) mg. Inhalation with a transparent capsule achieved a weight reduction of 30.1% compared with 8.6% for devices with an opaque capsule (P <0.001; Figure 1). Interestingly, we also found significant differences between the 2 transparent capsule inhalers (Zonda −24.1%; Breezhaler −32.3%; P <0.001). No differences were found in weight change according to functional severity in either absolute or relative values (Supplemental Figure 3), nor were there differences between patients with COPD and pre-COPD (Supplemental Figure 4).

DISCUSSION

The present study shows the differences in the residual weight of the capsules of the single-dose dry powder inhalers, indicating that the transparent capsules have a greater reduction in the weight of the capsule, suggesting a greater delivery of the medication. The benefits of inhaled therapy in the treatment of obstructive airway diseases are well recognized.[7] When using these devices, verification of medication intake is one of the factors to which patients attach most importance.[1] For this reason, inhalers should have mechanisms that inform the patient whether they are inhaling the drug correctly or not. Currently, the wide variety of devices allows us to personalize a patient's inhaled treatment. Not all inhalation devices, however, are suitable for all patients. It has been reported that between 4% to 94% of patients with a prescribed inhaler do not use it correctly and 25% have never received basic training in the outpatient clinic.[8] In inhaled therapy, ease of use and positive feedback are considered the most important factors by most patients. A dry powder device in capsule format has several positive feedback mechanisms. In addition, in devices with transparent capsules, an empty capsule is a sure sign that inhalation has been performed correctly with the possibility of repeating the inhalation if not empty.[9]

This study work has certain strengths, such as the use of a high-precision micro-balance to ensure the correct measurement of capsule weights and the fact that our patients were previously trained, thus avoiding confusing results due to incorrect technique. To correctly interpret the results, however, we must take into account the following considerations. First, patients diagnosed with COPD or pre-COPD

Table 1. Characteristics of Patients Included

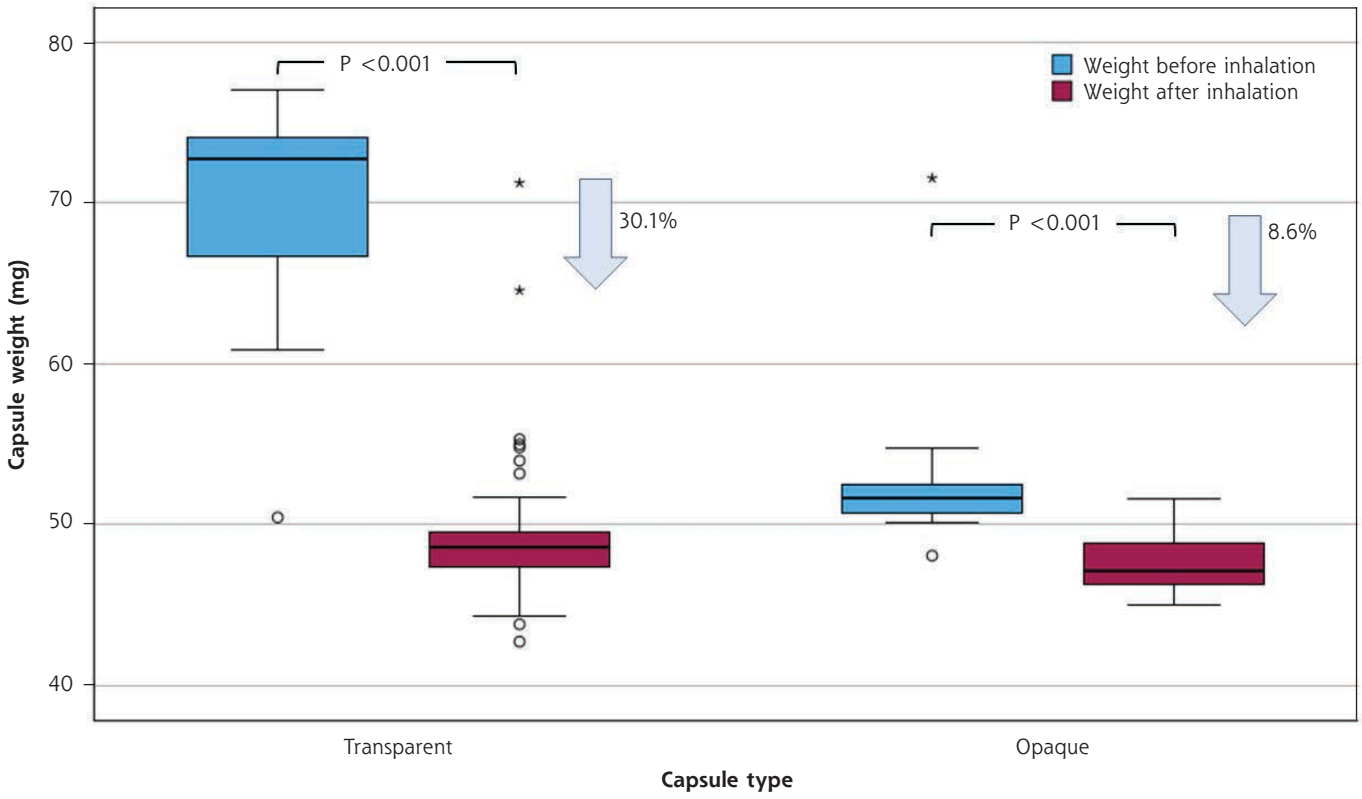
Variable	Total Sample (n = 91)	Opaque Capsule (n = 28)	Transparent Capsule (n = 63)	*P* Value[a]
Age, y	68.0 (15.0)	68.0 (13.0)	66.0 (15.0)	0.627
Sex, male	61 (67.0%)	19 (67.9%)	42 (66.7%)	0.556
Active smokers, n	25 (27.5%)	8 (28.6%)	17 (27.0%)	0.533
Tobacco history, pack-year	40.0 (25.0)	35.0 (21.0)	40.0 (24.0)	0.097
BMI, kg/m^2	27.0 (7.5)	27.0 (9.0)	27.0 (9.0)	0.986
FVC, %	82.0 (27.0)	82.0 (26.5)	82.0 (28.0)	0.452
FEV1, %	65.0 (34.0)	66.0 (37.2)	64.0 (33.0)	0.786
Time of inhaler use, mon	22.0 (73.0)	48.0 (82.0)	12.0 (61)	0.010
Diagnosis, (%)				0.054
Pre-COPD	21 (23.1)	11 (39.3)	10 (15.9)	
COPD	67 (73.6)	16 (57.1)	51 (81.0)	
Other	3 (3.3)	1 (3.6)	2 (3.2)	
COPD obstruction severity,[b] (%)				0.203
Mild	11 (16.4)	3 (18.8)	8 (15.7)	
Moderate	34 (50.7)	6 (37.5)	28 (54.9)	
Severe	17 (25.4)	7 (43.8)	10 (19.6)	
Very severe	5 (7.5)	0 (0.0)	5 (9.8)	

BMI = body mass index; COPD: chronic obstructive pulmonary disease; FEV1: forced expiratory volume in the first second; FVC: forced vital capacity.

Note: Values expressed as median (interquartile range) or as absolute frequencies (relative) depending on the nature of the variable. Relative frequencies referred to the total number of cases per group, unless otherwise specified. The other diagnoses included cases of interstitial involvement, thromboembolic disease, and sequelae of pneumonia.

[a] Calculated by the Mann-Whitney U or by the chi-square tests according to the variables.
[b] Percentages calculated on the total number of COPD patients in each group.

Figure 1. Differences in chamber weight before and after inhalation in the 2 types of capsules.



were included. The concept of pre-COPD is very new. The term has been coined only recently in the latest version of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2023 document[6] to identify subjects with previous toxic exposure and clinical, radiological, or functional alterations, but with non-obstructive spirometry. Second, inhaler use time was significantly different between the devices. This result is expected and is related to the marketing time of each one in our country. We estimate that the impact of these differences is small since all patients had been using the inhaler long enough to have overcome the learning curve and the inhalation technique was also reviewed before the measurement. Third, in this study we did not measure the residual powder, but the total weight of the capsule, assuming the weight of the capsule should vary slightly and that the change, therefore, should be due to differences in the amount of powder. Fourth, the study was unblinded since inhalations were done under supervision. Fifth, we included patients aged over 35 years because we were focusing on non-reversible chronic airway disease patients. Therefore, younger patients with other airway disease (eg, asthma) were not evaluated. Finally, this is a cross-sectional study that only evaluated changes in capsule weight, without prospectively evaluating the clinical or functional impact of the differences.

In conclusion, the present study analyzes a comparison of the weight after inhalation through single-dose dry powder devices, comparing those with transparent capsule vs opaque capsule. Despite the limitations commented, our results show the differences found between the 2 types of capsules with a benefit for transparent capsules. Further studies should evaluate the clinical impact of these differences in drug efficacy. These data reinforce the need to provide patients with mechanisms that verify the correct inhalation technique.

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Key words: chronic obstructive airway diseases; dry powder inhalers; dry powder capsules; clinical outcomes

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Author contributions: R.R.A. coordinated fieldwork, contributed to data analysis, and drafted the initial draft. R.R-S.D. and M.D.N.O. performed the fieldwork, carried out the complementary studies of the study, and collaborated in writing the manuscript. L.C.H. and E.Q.G. contributed to the recruitment of patients and writing the final version of the manuscript. J.L.L-C. designed the study, conducted the statistical study, and contributed to writing the results.

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Supplemental materials

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