Exploration of Quality Control Testing Methods for a Novel Quantitative Assessment Instrument for Inhaled Medications (Postprint)

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Abstract

Background Inhalation drug delivery is a common route for chronic airway disease treatment. Patients' ability to use inhaler devices is a key factor affecting treatment efficacy. Recently, a novel quantitative assessment instrument for inhalation medication has been developed domestically, which can measure peak inspiratory flow (PIF) and inspiratory volume (VI) under conditions of multiple different built-in resistances of inhalers, accurately assessing patients' ability to use inhalers. However, currently there are no quality testing methods and acceptance standards for such inhalation assessment instruments domestically or internationally.

Objective To conduct quality testing on the quantitative assessment instrument for inhalation medication, evaluate its technical performance, and explore the application value of this method.

Methods The novel quantitative assessment instrument for inhalation medication PF810 was used to simulate different built-in resistances of dry powder inhalers, divided into 5 different levels (R1~R5), and a standard flow/volume simulator was used to test the flow, volume, and impedance performance of PF810. For inspiratory flow testing, a fixed volume (3.000 L) was used at different flow rates (within the 0~2.000 L/s range, with 0.250 L/s interval steps). For inspiratory volume testing, low (0.500 L/s), medium (1.000 L/s), and high (1.500 L/s) flow rates were used at different volumes (within the 1.000~4.000 L range with 1.000 L interval steps). GraphPad Prism 9.0 software' s Bland-Altman plot method was used to evaluate the consistency between PIF and VI measurements from the quantitative assessment instrument for inhalation medication and the actual values output by the simulator under different resistance levels.

Results Flow testing quality control evaluation results showed that the percentages meeting performance requirements for flow testing repeatability, accuracy, and linearity were 100.00% (40/40), 95.00% (38/40), and 94.29% (33/35), respectively. At the R5 level and flow rates of 1.500 L/s and above, PF810’ s accuracy and linearity did not meet performance testing requirements; all other levels and flow rates met the standards. Bland-Altman consistency test showed that the 95% limits of agreement (LOA) were (-0.271, 0.107) L/s, with 96.00% (192/200) of data points within the 95% LOA range. Volume testing quality control evaluation results showed that the performance testing pass rates for volume testing repeatability, accuracy, and linearity were all 100.00% (60/60, 60/60, 45/45). Bland-Altman consistency test showed that the 95% LOA were (-0.058, 0.017) L, with 100.00% (180/180) of data points within the 95% LOA range. Impedance testing quality control evaluation results showed that the absolute values of relative error between PF810 impedance values and corresponding inhaler built-in resistances were all <5%.

Conclusion This study used a standard flow/volume simulator to conduct quality testing on the quantitative assessment instrument for inhalation medication under conditions of different level built-in resistances of inhalers for inspiratory flow and volume. The method is simple and feasible, and can objectively and scientifically evaluate the performance and conduct regular testing and maintenance of this type of instrument, which is worthy of application and promotion.

Full Text

Discussion on the Quality Control Test Method for a New Inhalation Drug Quantitative Assessment Instrument

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Abstract

Background Inhalation therapy is a common route of administration for chronic airway diseases. The patient’ s ability to use inhaler devices is a critical factor affecting treatment efficacy. A novel quantitative assessment instrument for inhalation medication has recently been developed in China, capable of measuring peak inspiratory flow (PIF) and inspiratory volume (VI) under various internal resistance conditions of different inhalers to accurately evaluate patients’ inhaler use capability. However, there are currently no quality testing methods or acceptance standards for such inhalation assessment instruments either domestically or internationally.

Objective To conduct quality testing of the inhalation drug quantitative assessment instrument, evaluate its technical performance, and explore the application value of this method.

Methods The inhalation drug quantitative assessment instrument PF810 simulated various internal resistances of dry powder inhalers (DPIs) across five different gears (R1-R5). A standard flow/volume simulator was used to test the flow, volume, and impedance performance of the PF810. Flow testing was performed at a fixed volume (3.000 L) with different flow rates (ranging from 0 to 2.000 L/s in increments of 0.250 L/s). Volume testing was conducted at three flow rates—low (0.500 L/s), medium (1.000 L/s), and high (1.500 L/s)—with different volumes (ranging from 1.000 to 4.000 L in increments of 1.000 L). The Bland-Altman plot method in GraphPad Prism 9.0 software was used to evaluate the consistency between PIF and VI measurements from the inhalation drug quantitative assessment instrument and the actual values output by the simulator at different resistance gears.

Results Quality control evaluation of flow detection showed that the percentages meeting performance requirements for repeatability, accuracy, and linearity were 100.00% (40/40), 95.00% (38/40), and 94.29% (33/35), respectively. The accuracy and linearity of PF810 at the R5 gear with flow rates of 1.500 L/s and above did not meet performance testing requirements, while all other gears and flow rates met the standards. Bland-Altman consistency testing showed a 95% limit of agreement (LOA) of (−0.271, 0.107) L/s, with 96.00% (192/200) of data points falling within the 95% LOA range. Quality control evaluation of volume testing showed pass rates of 100.00% (60/60, 60/60, 45/45) for repeatability, accuracy, and linearity. Bland-Altman consistency testing showed a 95% LOA of (−0.058, 0.017) L, with 100.00% (180/180) of data points within the 95% LOA range. Impedance testing quality control evaluation showed that the absolute relative error between the impedance values of PF810 and the corresponding inhaler internal resistance was <5%.

Conclusion This study used a standard flow/volume simulator to conduct quality testing of inspiratory flow and volume for the inhalation drug quantitative assessment instrument under different DPI internal resistance conditions. The method is simple and feasible, enabling objective and scientific performance evaluation and regular testing and maintenance of this type of instrument, and is worthy of application and promotion.

Keywords: Pulmonary disease, chronic obstructive; Inhalation therapy; Dry powder inhalers; Quality control

Introduction

Chronic airway diseases such as chronic obstructive pulmonary disease and bronchial asthma have imposed a heavy disease burden and pose a major threat to global public health [1-2]. Inhalation therapy is the primary treatment for these diseases, requiring specific inhaler devices to assist drug delivery. Commonly used inhalers in clinical practice include pressurized metered-dose inhalers (pMDI), soft mist inhalers (SMI), and dry powder inhalers (DPI). DPIs have internal resistance that can be classified into five grades (R1–R5, from low to high) based on the inspiratory flow required to generate a 4 kPa pressure drop [3-6]. Patients must achieve a specific peak inspiratory flow (PIF) to overcome the DPI' s internal resistance and deliver the medication; this flow is referred to as the effective inspiratory flow. Either excessively high or low inspiratory flow can affect pulmonary drug deposition [8-10]. Patients with chronic airway diseases may fail to achieve the minimum flow required to use inhalers due to airflow limitation or insufficient respiratory muscle strength [11-13]. PIF is a key factor influencing inhalation efficacy [14-15], and literature also indicates that in addition to effective inspiratory flow, an ideal inhalation pattern requires an inspiratory volume (VI) of more than 1 L [16].

Measuring PIF under inhaler resistance conditions can assess patients' ability to use inhalers [17] and provide guidance for inhaler selection and inhalation technique training [16,18]. A novel quantitative assessment instrument for inhalation medication has recently been developed in China, capable of simulating the internal resistance of most clinical DPIs and simultaneously evaluating both PIF and VI, the two key indicators. Currently, there are few studies on quality testing methods and standards for inhalation drug quantitative assessment instruments domestically or internationally. Therefore, this study used a standard flow/volume simulator to test an instrument capable of simulating different inhaler internal resistances, aiming to explore quality testing methods and application value for this type of instrument.

1.1 Study Subjects

The study object was the novel inhalation drug quantitative assessment instrument (PF810, UBREATH®, Zhejiang Yilian Kang Company), with the measurement device being a standard flow/volume simulator (Model 1120, Hans Rudolph Company, USA). Commonly used DPI inhalers in domestic clinical practice include Accuhaler®/Diskus® (GlaxoSmithKline, UK), Turbuhaler® (AstraZeneca, UK), and HandiHaler® (Boehringer Ingelheim, Germany).

1.2 Research Methods

Before testing, all devices were powered on and preheated for at least 15 minutes and placed in the same environment for over 30 minutes. The PF810 was then connected to the standard flow/volume simulator interface, ensuring an airtight seal (Figure 1 [Figure 1: see original paper]). Flow and volume parameters were set through the simulator' s computer control terminal, and the PF810 was adjusted to apply resistance gears R1–R5. The standard flow/volume simulator was activated to generate a standard inspiratory air source for testing. The PIF and VI measurements from PF810 were recorded, and the air source values generated by the standard breathing simulator were used as reference values for analysis. Flow testing: A fixed inspiratory volume of 3.000 L was set, with inspiratory flow rates ranging from 0 to 2.000 L/s in increments of 0.250 L/s; each parameter group was tested five times, and the average was taken. Volume testing: Low (0.500 L/s), medium (1.000 L/s), and high (1.500 L/s) inspiratory flow rates were set, with VI ranging from 1.000 to 4.000 L in increments of 1.000 L; each parameter group was tested three times, and the average was taken. Impedance testing: Three inhalers—Accuhaler®/Diskus®, Turbuhaler®, and HandiHaler®—and the inhalation drug quantitative assessment instrument were connected to the standard flow/volume simulator (at position in Figure 1). The internal resistances of the three inhalers represented low, medium, and high resistance levels, respectively, while the inhalation drug quantitative assessment instrument was adjusted to resistance gears R2, R3, and R5 for comparison with the three inhaler resistances. Air source was generated according to the flow testing parameter settings, with five tests conducted for each parameter group. The flow values corresponding to 4 kPa pressure from the standard flow/volume simulator were read, and impedance values for the inhaler or inhalation drug quantitative assessment instrument were calculated using the formula: Impedance = Pressure/Flow.

Note: Inhalation drug quantitative assessment instrument (PF810, UBREATH®, Zhejiang Yilian Kang Company), Standard flow/volume simulator (Model 1120, Hans Rudolph Company, USA), PF810 tablet control terminal, Standard simulator computer control terminal.

Figure 1 Experimental equipment connection method

1.3 Performance Indicators

1.3.1 Repeatability The difference between the maximum and minimum values in multiple measurements. The absolute repeatability value for PIF should be ≤ 0.050 L/s; for VI, the absolute repeatability should be ≤ 3% or 0.050 L (whichever is larger).

1.3.2 Accuracy The difference between the mean of multiple measurements and the standard value from the standard flow/volume simulator, including absolute error and relative error. For PIF, the absolute error should be ≤ 0.167 L/s or the relative error ≤ 10% (whichever is larger); for VI, the relative error should be ≤ 3% or the absolute error ≤ 0.050 L (whichever is larger).

1.3.3 Linearity (1) Flow linearity: Formula (1) uses error (en) to calculate the linearity (n) of PIF (qn) values within the assessment measurement range, where en is the error of PIF at peak flow n, en+1 is the error of PIF at the next incremental peak flow, and qn+1 is the average of five PIF measurements at the reference flow one increment above the base flow n. The absolute linearity value should be ≤ 5%. (2) Volume linearity: Formula (2) uses mean error (Verr) to calculate the volume linearity between pairwise test parameters, where Verrn is the mean error of the nth measurement result and Vrefn is the reference value output by the standard flow/volume simulator for the nth measurement. The absolute linearity value for VI should be $\leq 3\%$.

$$\epsilon_n = \frac{(e_n - e_{n+1}) \times 100}{q_{n+1}} \quad (1)$$

$$\text{Linearity} = \frac{(V_{\text{err},n} - V_{\text{err},n+1}) \times 100}{0.5 \times (V_{\text{ref},n} + V_{\text{ref},n+1})} \quad (2)$$

1.3.4 Impedance Value The ratio of pressure to flow at 4 kPa pressure. The relative error compared to the inhaler’ s internal resistance should be <$±$5%.

1.4 Statistical Methods

Microsoft Excel 2016 was used for data statistics, and GraphPad Prism 9.0 software’ s Bland-Altman plot method was used to evaluate the consistency between PIF and VI measurements from the inhalation drug quantitative assessment instrument and the actual values output by the simulator at different resistance gears.

Results

2.1 Flow Testing Quality Control Evaluation Results

The percentages meeting performance requirements for flow testing repeatability, accuracy, and linearity were 100.00% (40/40), 95.00% (38/40), and 94.29% (33/35), respectively. At the R5 gear with flow rates of 1.500 L/s and above, the PF810’ s accuracy and linearity did not meet performance testing requirements, while all other gears and flow rates met the standards (Table 1). Bland-Altman consistency testing showed a 95% limit of agreement (LOA) of (−0.271, 0.107) L/s, with 96.00% (192/200) of data points falling within the 95% LOA range (Figure 2 [Figure 2: see original paper]).

2.2 Volume Testing Quality Control Evaluation Results

The pass rates for volume testing repeatability, accuracy, and linearity were all 100.00% (60/60, 60/60, 45/45) (Table 2). Bland-Altman consistency testing showed a 95% LOA of (−0.058, 0.017) L, with 100.00% (180/180) of data points falling within the 95% LOA range (Figure 3 [Figure 3: see original paper]).

2.3 Impedance Testing Quality Control Evaluation Results

The absolute relative error between the impedance values of the inhalation drug quantitative assessment instrument PF810 and the corresponding inhaler internal resistance was <5% (Table 3).

Table 3 Comparison of simulated resistance of PF810 and internal resistance of DPI inhaler for inhalation drug quantitative assessment instrument

Discussion

Accurately assessing patients' drug inhalation ability and selecting appropriate inhalers are important components of treatment and follow-up management for patients with chronic airway diseases. Inspiratory flow and VI are important factors affecting inhaled drug deposition. In conventional pulmonary function testing, inspiratory flow (such as PIF) or VI (such as forced inspiratory volume) is measured without resistance and shows weak correlation with flow and volume indicators measured under inhaler device resistance conditions [19-20], or even no correlation [21], making them unsuitable for measuring inspiratory levels under resistance conditions. Previously, the handheld inspiratory flow meter In-Check DIALTM (Clement Clarke, UK) was the primary tool used abroad to measure PIF under different inhaler resistance levels, providing guidance for assessing inhalation effort in patients [22]. Recently, China has developed a new quantitative assessment instrument for inhalation medication that can adjust resistance valve opening size to simulate various DPI internal resistances in clinical application and utilizes pulmonary function flow sensor technology to measure not only inspiratory flow under resistance conditions but also VI, providing more precise and quantitative assessment of patients' drug inhalation ability and offering objective evidence to guide patient medication use.

Instrument quality is essential for ensuring measurement data reliability. Industry standards for instruments are normative documents concerning instrument quality testing methods and standards. For example, for spirometers and peak flow meters—the most widely used pulmonary function measurement tools in clinical practice—relevant industry standards have been published both domestically and internationally [23-25], and professional organizations have established clear specifications for their quality testing methods and standards [26]. However, quality control methods and standards for the new inhalation drug quantitative assessment instrument discussed in this paper have not yet been established. This study is the first to explore quality testing methods and performance requirements for the new inhalation drug quantitative assessment instrument, primarily covering repeatability, accuracy (absolute/relative error), linearity, and impedance, providing a reference for establishing scientific, objective, and comprehensive quality control standards in the future.

Regarding repeatability, the study by BARNES et al. [27] required PIF repeatability <10 L/min when testing the Accuhaler inhaler (R2 gear) and <5 L/min when testing the HandiHaler inhaler (R5 gear). However, their subjects were patients with severe chronic obstructive pulmonary disease, where factors such as respiratory muscle weakness and airway obstruction may have affected test repeatability. Additionally, the mechanical inspiratory flow meter In-Check DIALTM used in their study had a minimum scale of 5 L/min, resulting in insufficient data precision that may have affected repeatability to some extent. This study used a standard flow/volume simulator that can generate a standard inspiratory air source with high data precision, eliminating bias from these factors and thus allowing for more stringent repeatability requirements. Based on our results, the instrument' s repeatability ranged from 0.000 to 0.050 L/s, making it reasonable to set the requirement for absolute inspiratory flow repeatability at $ $0.05 L/s. For volume repeatability, the national industry standard for spirometers requires ≤$±$3% or $±$0.05 L (whichever is larger) [24]. In this study, VI repeatability ranged from 0.000 to 0.030 L, fully meeting the above standard, making it reasonable to set the VI repeatability requirement at $ $3% or 0.05 L.

Regarding accuracy, the industry standard for expiratory peak flow meters proposes a maximum permissible error range for flow with an absolute value of 0.167 L/s or 10% [25]; the spirometer industry standard specifies a maximum permissible error range for volume with an absolute value of 3% or 0.05 L (whichever is larger) [24,28]. This study referenced these standards for accuracy analysis of inspiratory flow and volume. The results showed that the inhalation assessment instrument met all performance requirements under conventionally recommended inspiratory flow rates (the recommended inspiratory flow for clinical DPI use is 0.333–1.0 L/s [30-31], preferably not exceeding 1.5 L/s). Although accuracy and linearity did not meet performance testing requirements under high-resistance gear R5 at $ $1.5 L/s, this inspiratory flow exceeds the recommended range for DPI use. Furthermore, when the standard flow/volume simulator operates under certain impedance conditions, it achieves target flow through pressure regulation. When impedance is too high, the required pressure may exceed the device' s adjustable range, potentially causing instrument vibration and preventing achievement of target flow, thereby affecting performance evaluation at high flow rates. The performance evaluation methods and requirements for the tested instrument under high resistance and high flow conditions warrant further research and exploration. Based on this study' s results, quality testing of this type of instrument is feasible under appropriate inspiratory flow conditions (<1.5 L/s).

Regarding linearity, industry standards for expiratory peak flow meters and spirometers specify linearity standards of $ $5% and $ $3% for flow and volume measurements, respectively [29-30]. Except for the two highest flow rates at the R5 resistance gear, the inhalation drug quantitative assessment instrument PF810 passed the above standards for flow and volume linearity evaluation. These standards apply to expiratory flow and volume linearity without added resistance; whether they are suitable for evaluating inspiratory flow and volume linearity requires further investigation and verification.

During the experimental process, our research team identified several key points: (1) All measurement instruments should be placed in the same environment one hour in advance to reduce measurement bias caused by different environmental parameters; (2) All instruments should be powered on 30 minutes before the experiment to ensure stable performance; (3) The airtightness of the connection between the tested instrument and simulator must be ensured; (4) Three to five tests should be conducted under the same parameter conditions to avoid excessive error due to too few tests.

In summary, this study established a quality control testing method for a new inhalation drug quantitative assessment instrument, preliminarily proposed performance testing requirements for PIF and VI for this type of instrument, and confirmed that the flow and volume accuracy of the inhalation assessment instrument PF810 meets standards. We recommend that manufacturers of inhalation drug quantitative assessment instruments use standard validators for quality testing before instrument shipment, and that medical institutions regularly calibrate these instruments.

Author Contributions: PENG Yongyi was responsible for experiment implementation and manuscript writing; WU Zhongping was responsible for experimental design; ZHENG Jinping and GAO Yi provided guidance for the research and were responsible for manuscript revision; HUANG Jinhai, LIN Junfeng, and CHEN Shubing were responsible for data collection, organization, and analysis.

Conflict of Interest: The authors declare no conflict of interest.

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