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# In Check Dial: accuracy for Diskus and Turbuhaler

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**Abstract**

*Objective*: The In Check Dial was developed to evaluate whether a patient is able to generate an adequate peak inspiratory flow (PIF) through a certain inhalation device. The inhalation profile recorder (IPR) is a calibrated instrument that measures flows through Diskus and Turbuhaler in our research setting. The aim of this study was to compare the PIFs of patients when inhaling through a Diskus or Turbuhaler connected with the IPR (PIF_diskus and PIF_TH) to the flows through the corresponding orifices of the In Check Dial (Diskus_In Check and TH_In Check). *Methods*: Twenty-four stable asthma and twenty-one chronic obstructive pulmonary disease (COPD) patients inhaled, on two separate occasions, in randomised order, via the Diskus or Turbuhaler connected with the IPR. Subsequently, patients inhaled through the In Check Dial using the orifices of Diskus or Turbuhaler. *Results*: The difference between Diskus_In Check and PIF_diskus was 3.9 (11.9) l/min ($P = 0.038$). The difference between TH_In Check and PIF_TH was 3.5 (10.6) l/min (NS). All Diskus- and Turbuhaler-inhalations were performed with the minimum required flow of 30 l/min. However, four COPD patients inhaled with the non-optimal flow (<60 l/min) through the Turbuhaler. The In Check Dial did not indicate two of them. *Conclusion*: Measuring PIF through Diskus and Turbuhaler using the IPR and the In Check Dial, respectively shows a disagreement of 3.9 l/min. A disagreement of 3.5 l/min was found for the Turbuhaler. The In Check Dial did not identify two of four patients as 'non-optimal' users.


*Keywords:* Dry powder inhaler; Peak inspiratory flow; In Check Dial

## 1. Introduction

Hand-held inhalers such as dry powder inhalers (DPIs) are commonly used for the delivery of drugs into the airways of asthma and chronic obstructive pulmonary disease (COPD) patients.

Multiple factors such as the drug itself, the design of the device (resistivity) and the patient characteristics (Dekhuijzen, 1998; Ganderton, 1997) influence the therapeutic efficacy. Patients have to generate a sufficient inspiratory flow in order to release the powder and to deaggregate the drug into respirable particles. Some patients may be hampered in generating a sufficiently high inspiratory flow, due to pulmonary function, such as hyperinflation, respiratory muscle dysfunction or clinical status (e.g. during an exacerbation) (Madison and Irwin, 1998). Accordingly, some DPIs may be less suitable for certain patients or in certain conditions.

In order to assess such potential absence or loss of efficacy, a new easy to use, hand-held peak inspiratory flow meter, the In-Check Dial (Clement Clarke, UK)

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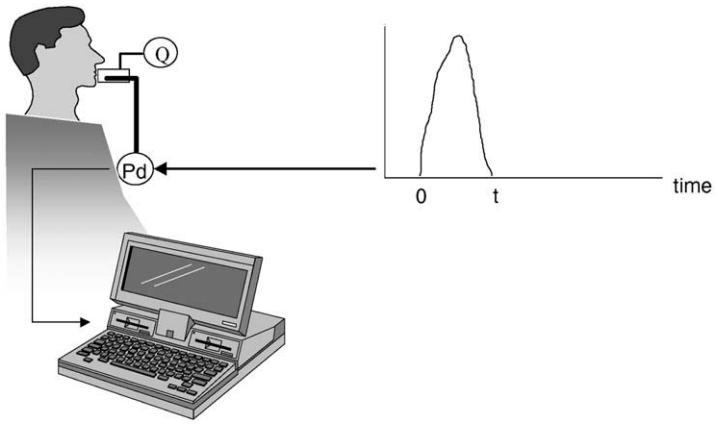


Fig. 1. Inhalation profile recorder.

was developed. The In Check Dial mimics the internal resistivities of Diskus® (GlaxoSmithKline, UK), Turbuhaler® (AstraZeneca, Sweden), Autohaler® (3 M Pharmaceuticals, USA) and Easi-Breathe® (Norton Healthcare, UK). This meter is intended to evaluate whether an individual patient is able to generate a sufficiently high peak inspiratory flow (PIF) through a certain type of inhalation device.

In the present study, the PIFs of two multidose DPI were compared: Turbuhaler and Diskus. Previous in vitro studies showed that the (higher resistivity) Turbuhaler can produce a therapeutic dose at a PIF of 30 l/min. However, for the Turbuhaler, a maximum fine particle mass and consistent dose delivery is reached at PIF_TH $>$ 60 l/min (Borgstrom et al., 1994; Engel et al., 1990; Hill and Slater, 1998). The Turbuhaler reached a higher level in terms of mass median aerodynamic diameter (MMAD) and fine particle mass at 60 l/min as compared to Diskus. So, for this study, PIF_TH $>$ 30 l/min is considered 'minimal' and PIF_TH $>$ 60 l/min as being 'optimal'. The Diskus has a lower internal resistivity and operates effectively at PIF_diskus $>$ 30 l/min (Hill and Slater, 1998; Nielsen et al., 1998). This device provides a consistent fraction of particles $<$6 μm, relatively independent of airflow (Brindley et al., 1995; Mortensen et al., 1991). For both DPIs, a PIF of 90 l/min is claimed as the maximal flow, because at higher flows the oropharyngeal deposition increases (Borgstrom, 2001).

The inspiratory effort produced by patients, inhaling through a device generates a pressure drop in the mouth. The mouth pressure versus time curve was defined as inhalation profile. The inhalation profiles were stored into the inhalation profile recorder (IPR, GlaxoSmithKline R&D, Ware, UK) (Bisgaard et al., 1998). The pressure profile can be converted into a flow profile when the resistivity of the device is known.

The aim of this study was to compare the PIFs of asthmatics and COPD patients when inhaling through a Diskus or Turbuhaler connected with the IPR (Fig. 1), to the flows when inhaling through the corresponding orifices of the In Check Dial.

## 2. Methods and measurements

Twenty-four stable asthma and twenty-one patients with COPD according to ATS (1987) criteria participated in the study. The patient characteristics are shown in Table 1.

They signed a consent form and the hospital ethics committee approved the study.

The study was performed as an open randomised comparison of the PIFs through Diskus and Turbuhaler measured with the IPR (PIF_diskus and PIF_TH) and the flow through the In Check Dial using the orifices of Diskus and Turbuhaler (Diskus_In Check and TH_In Check). The devices were tested on two separate occasions, within 1 week.

A flow volume curve was measured, airway resistance (Rrs6, Random Noise Oscillator, SensorMedics,

Table 1
Patient characteristics

| Parameter mean (S.D.) | Asthma ($n = 24$) | COPD ($n = 21$) |
|---|---|---|
| Gender (M/F) | 17/7 | 19/2 |
| Age (years) | 52.5 (7.7) | 61.1 (7.3) |
| Height (cm) | 175 (8.9) | 176 (5.9) |
| Weight (kg) | 82 (13.1) | 76 (11.9) |
| FEV1%pr (%) | 89 (7.7) | 41.6 (10.3) |
| FEV1 (l) | 3.0 (0.6) | 1.4 (0.4) |
| FEV1/VC (%) | 64 (5.8) | 39 (7.4) |
| FRC (l) | 3.5 (0.8) | 4.3 (1.1) |
| FIV1 (l) | 4.3 (0.9) | 3.3 (0.9) |
| Reversibility | 15 (7.7) | 12 (3.0) |
| MIP (kPa) | 9.2 (2.7) | 9.2 (2.9) |
| MIP%pr (%) | 107 (29.7) | 117 (35.5) |
| MEP (kPa) | 9.4 (3.2) | 10.3 (3.4) |
| MEP%pr (%) | 69 (28.8) | 86 (31.2) |
| Rrs6 (cm $H_2O$/l/s) | 2.4 (0.7) | 3.1 (1.5) |
| Smoking non/ex/current | 5/18/1 | 4/12/5 |
| Device: DPI/pMDI/spacer | 16/5/3 | 11/4/6 |

FEV1%pr: forced expiratory volume in 1 s as percentage of predicted; FEV1: forced expiratory volume in 1 s; FIV1: forced inspiratory volume in 1 s; FEV1/VC: FEV1/vital capacity; FRC: functional residual capacity; MIP and MEP: maximal in- and expiratory mouth pressure; MIP%pr and MEP%pr: MIP and MEP as percentage of predicted; Rrs6: airway resistance measured at 6 Hz; device used by the patients in daily life. Data given are mean (S.D.).

Bilthoven The Netherlands) and maximal in- and expiratory mouth pressures (MIP and MEP, MicroMedical Ltd., Rochester, UK) were also obtained. Patients were trained in the prescribed use of the Diskus or Turbuhaler according to manufacturer's leaflet.

Patients inhaled 200 μg salbutamol via the Diskus or Turbuhaler (two inhalations of 100 μg) connected with the IPR (Fig. 1). A pressure transducer measured pressures in the mouthpiece of the DPI during inhalation: the inhalation profile. The parameters of the inhalation profile are peak pressure drop, PIF, inhaled volume, inhalation time and slope. The flow profile can be calculated if the resistivity of the device is known. The flow signal was integrated in order to be able to calculate the inhaled volume. The pressure transducer was calibrated monthly and the IPR was checked daily with a 3.00 l syringe.

Subsequently, patients were asked to inhale three times, in the same way, through the In Check Dial. The best of these three flows was used for analysis.

### 2.1. Statistical analysis

SPSS for Windows version 9.0 was used for the statistical analysis. The means of PIF_diskus, PIF_TH, Diskus_In Check and TH_In Check were calculated. These values were compared using the Wilcoxon matched pairs signed-rank test. The relationship between PIF values measured with the In Check Dial and with the IPR, was plotted according to the Bland–Altman technique, for both Diskus and Turbuhaler (Bland and Altman, 1986).

Data is expressed as mean ± S.D. $P \leq 0.05$ was considered as the limit of significance.

## 3. Results

The results of the PIF_diskus and PIF_TH and the Diskus_In Check and TH_In Check are shown in Table 2. Figs. 2 and 3 show the differences of PIF_inhalation profile recorder and flows of the In Check Dial for Diskus and Turbuhaler, respectively. The significant difference between Diskus_In Check and PIF_diskus was 3.9 (−19.9 to 27.7) l/min ($P = 0.038$). The difference between TH_In Check and PIF_TH was 3.5 (−17.7 to 24.7) l/min (NS). (Data are expressed as mean ± 2 S.D.)

The Bland–Altman plots showed that for the Diskus the In Check Dial values may be 27.7 l/min above or 19.9 l/min below the PIF values of the IPR. For the Turbuhaler, the differences were 24.7 l/min above or 17.7 l/min below the IPR values.

All Diskus inhalations were optimally performed with PIF_diskus > 30 l/min. All inhalations through the Turbuhaler were performed with the minimum required flow (>30 l/min). Four patients were not able to inhale with the most optimum flow of more than

Table 2
Peak inspiratory flows measured with the inhalation profile recorder and In Check Dial

| | Inhalation profile recorder (l/min) | In Check Dial (l/min) |
|---|---|---|
| Diskus | 101.7 (20.7) [43–146] | 105.6 (15.7) [62–130]* |
| Turbuhaler | 79.3 (13.8) [43–107] | 82.8 (15.4) [40–110] |

Data were expressed as mean (S.D.) [range].
* Significant difference between flows In Check Dial and IPR $P < 0.05$.

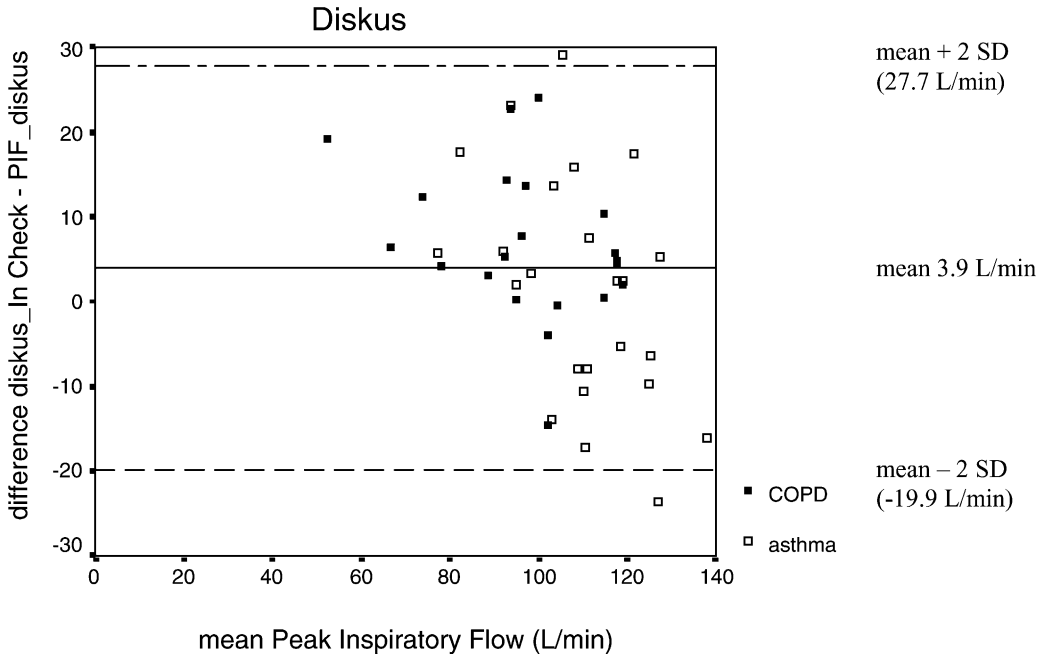


Fig. 2. Bland–Altman plot for Diskus. Flow In Check Dial and PIF inhalation profile recorder.

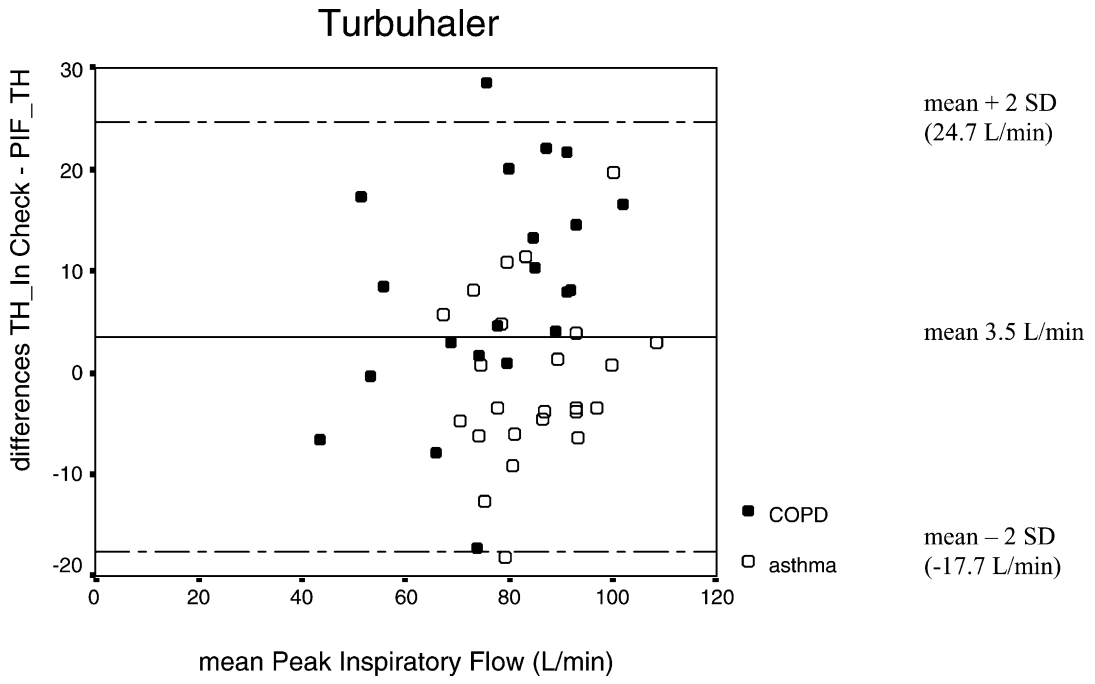


Fig. 3. Bland–Altman plot for Turbuhaler. Flow In Check Dial and PIF inhalation profile recorder.

60 l/min through the Turbuhaler. Two of them appeared to have an adequate inspiratory flow on the In Check Dial.

## 4. Discussion

Checking the actual PIF may be useful before prescribing DPI, because drug particle release from DPIs is determined by e.g. patient's effort.

The aim of present study was to assess whether the In Check Dial could be used to predict the PIF through Diskus and Turbuhaler measured with the calibrated IPR.

This study showed mean differences between the values of the In Check Dial and the IPR of 3.9 l/min for the Diskus and 3.5 l/min for the Turbuhaler. This is approximately 3–4% of the PIF value.

The Diskus_In Check were significantly higher compared to the PIF_diskus of the IPR. No significant difference between TH_In Check and PIF_TH were found ($P = 0.056$).

However, a plot of differences between the methods, displays a lack of agreement between the IPR and the In Check Dial, with discrepancies of up to 24 l/min in one patient.

Differences between the measurements can be due to instrument variability (orifices of devices and In Check Dial) or to patient variability in subsequent inhalations. There might have been a small difference in resistivity between the used Diskus inhaler and the resistivity of the In Check Dial. The resistivity of the Diskus is 0.02 kPa 0.5 l/min (Broeders et al., 2001), the resistivity of the Turbuhaler is 0.03 kPa 0.5 l/min (data on file GSK R&D Ware), respectively. We were not able to measure the resistivity of the In Check Dial. Since, the IPR was calibrated and daily checked, these values seem to be the most reliable. So, the IPR was used as 'the golden standard'.

It must be noted that patients inhaled with a fixed sequence through the IPR and then the In Check Dial. However, the within-day reproducibility of PIF is very high (coefficient of variation 4%). Therefore, it might be expected that they inhaled with the same reproducibility through both flow meters.

The Bland–Altman plot for Diskus shows an overestimation of the values of the In Check Dial in the PIF_diskus <100 l/min. An underestimation of the In Check Dial values was seen in the PIF_diskus >100 l/min.

It is important to know how far measurements can be apart without causing the risk that doctors prescribe erroneously a DPI. From this study it appears that for the Diskus this is not clinically relevant. All patients achieved more than the required minimum PIF for Diskus >30 l/min, both on IPR and In Check Dial. So, all patients, in the measured range were able to inhale adequately via the Diskus.

All inhalations through the Turbuhaler were performed with the minimum required flow (PIF_TH > 30 l/min). Four patients did not attain the optimal flow through the Turbuhaler (PIF_TH > 60 l/min). Two of them were not identified as such using the In Check Dial. Consequently, there is some risk that doctors will prescribe erroneously a Turbuhaler after checking the flow with an In Check Dial. However, all four patients inhaled with more than the minimum, (but less desirable) flow of 30 l/min. These patients were able to inhale a reduced, but still a therapeutically active amount of drugs.

In conclusion, measuring PIFs through Diskus and Turbuhaler by IPR and the In Check Dial shows a disagreement up to 24 l/min. This is not clinically relevant for the Diskus, because all patients achieved more than the recommended inspiratory flow of 30 l/min measured by both instruments. The In Check Dial must be used with caution to check the patient's ability to use a Turbuhaler. The In Check Dial did not identify two of four patients as 'non-optimal' users. When in their cases doctors would prescribe a Turbuhaler, these patients were not capable to use their inhalation device optimally.

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