

Application and efficacy of the multi-dose powder inhaler, Easyhaler[®], in children with asthma

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With powder inhalers, optimal performance is dependent on the inspiratory flow produced by the patient through the devices. The objective of this open, non-randomized study was to evaluate the suitability of a new, multi-dose, dry powder inhaler, the Easyhaler[®], for children with asthma. The peak inspiratory flow (PIF) through the Easyhaler (PIF_{EH}) was measured with a pneumotachograph in 120 asthmatic children aged 4–16 yr. The bronchodilatory effect of 0.2 mg salbutamol through the Easyhaler was compared with that of 0.2 mg salbutamol through a metered dose inhaler (MDI) with a spacer, in 15 children with obstruction. The mean PIF_{EH} was 56 l/min (range 22–83 l/min). The PIF_{EH} correlated significantly with age, height, and absolute peak expiratory flow (PEF), but not with the level of obstruction (PEF percentage of predicted, range 45–146%). Only four children (aged 5, 6, 10, and 16 yr) had PIF_{EH} values below 28 l/min, which has been shown in *in vitro* studies to be the threshold for effective use of the Easyhaler. In 15 children with PEF, < 85% of predicted bronchodilatory effects of 0.2 mg salbutamol through the Easyhaler and from an MDI-cum-spacer were equal. Most children aged 6–16 yr produce PIF values sufficient for the use of the Easyhaler. The gain of 0.2 mg salbutamol from the Easyhaler was equal to that from a new, unprimed, MDI with a spacer in children with asthma.

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In the treatment of bronchial asthma, multi-dose dry powder inhalers (DPIs) are widely used for the delivery of bronchodilators and anti-inflammatory medication in children and adults. DPIs have several advantages over metered dose inhalers (MDIs). In children, in particular, the co-ordination necessary for simultaneous inspiration and delivery of the drug from an MDI may be poor, necessitating the use of a spacer. The smaller size of DPIs makes them more convenient than MDIs with spacers. In addition, DPIs do not contain chlorinated hydrocarbon propellants, which makes them more environmentally friendly.

Delivery of the drug from DPIs requires a crucial minimal inspiratory flow. Previous studies have demonstrated that the peak inspiratory flow (PIF; l/min) through a DPI is dependent on the type of device, the age of the patient, and the level of bronchial obstruction (1–4). The effects of an

equal amount of salbutamol from the Easyhaler[®] (Orion Pharma, Espoo, Finland) and from more conventional systems – an MDI (5–7) or an MDI with a spacer (8) – have been shown to be equal in both clinical and deposition studies in adults.

There are no previously published studies on the use of the Easyhaler in children. In this pilot study we evaluated the PIF through the Easyhaler (PIF_{EH}) vs. age, height, and peak expiratory flow (PEF) and compared, non-randomly, the bronchodilatory effect of 0.2 mg salbutamol from an Easyhaler and from an MDI with a spacer.

Patients and methods

Patients

We studied 120 consecutive patients (50 girls, 70 boys), with bronchial asthma, at the out-patient

clinic of the Department of Allergology, University Central Hospital, Helsinki. The children were 4–16 yr old (mean age: 9.1 yr). The children had regular or periodic treatment with inhaled anti-inflammatory drugs (nedocromil, sodium chromoglycate or glucocorticoids) through an MDI or a DPI, and beta-sympathomimetics through an MDI or a DPI, as needed. None of the children used any long-acting beta-sympathomimetics. The patients and their parents gave informed consent for participation in this study. The protocol was approved by the Ethics Committee of the hospital.

Methods

Spirometry was performed by using a pneumotachograph (Vitalograph, Compact, Birmingham, UK), and PEF was assessed. No bronchodilator was used for 12 h prior to the visit. In order to evaluate the maximum inspiratory flow through an Easyhaler, the children were taught to inhale as fast and as long as possible through a lactose-placebo-loaded Easyhaler connected to the pneumotachograph (Fig. 1). The children were allowed to practice inhaling five times before the recordings were made. The inspiratory curves were then recorded and the best of three measurements was analyzed. The PIF_{EH} values were related to age, height, gender, and PEF values.

The bronchodilation test was carried out in children with obstruction ($PEF < 85\%$ of the mean level for healthy children of the same height and gender). Spirometry was performed before and 15 min after inhalation of 0.2 mg salbutamol aerosol with a non-primed spacer (one puff of Ventoline[®], 0.1 mg/dose, actuated separately with a 1-min interval into Volumatic[®]; Glaxo, Greenford, Middlesex, UK) and the best of three measurements was analyzed. The children were taught to inhale five times, deeply and slowly. If the test showed that PEF or forced expiratory volume in 1 s (FEV_1) were increased by $> 12\%$, a new test was carried out with 0.2 mg salbutamol through the Easyhaler (Buventol Easyhaler;

200 µg/dose) the following day. For analysis of the bronchodilation produced, PEF, FEV_1 , and maximal expiratory flow at 50% of the vital capacity (MEF_{50}), were recorded by the spirometer. The sum of PEF, FEV_1 , and MEF_{50} was calculated for each measurement and the best result was chosen for further analysis.

Statistical analysis of data

Pearson's test was used for calculation of the significances of the correlation coefficients. Variance analysis was used for analysing the variability of inspiratory flows through the Easyhaler. Wilcoxon's matched signed paired *t*-test was used to compare the effects of the bronchodilation test.

Results

The mean PIF_{EH} was 56 ± 15 l/min (range 22–83 l/min). It was positively correlated with age ($r = 0.6$; $p < 0.001$), height ($r = 0.6$; $p < 0.001$), and the absolute PEF ($r = 0.6$; $p < 0.001$) values, similarly in the two sexes (Fig 2a,b,c). The PEF values as percentages of the predicted values (mean $86 \pm 21\%$, range 45–146%) did not correlate with the PIF_{EH} ($r = 0.04$) (Fig. 2d). The intra-patient variance of three inspiratory flows through the Easyhaler was 6.2 l/min, and the inter-patient variance of three inspiratory flows through the Easyhaler was 14.9 l/min.

The bronchodilation study was carried out on 15 children (aged 5–12 yr). The individual lung function values before and after bronchodilation are shown in Table 1. There was no significant difference between the baseline FEV_1 (1.5 ± 0.3 l vs. 1.5 ± 0.3 l), PEF (184 ± 48 l vs. 184 ± 39 l) or MEF_{50} (1.6 ± 0.4 l vs. 1.6 ± 0.4 l) values on consecutive days ($p = ns$, respectively). The PIF_{EH} ranged from 16 to 80 l/min. The bronchodilatory effects of 0.2 mg salbutamol as powder and as aerosol were equal when calculated from the absolute values of FEV_1 (1.7 ± 0.4 l vs. 1.7 ± 0.4 l; $p = ns$), PEF

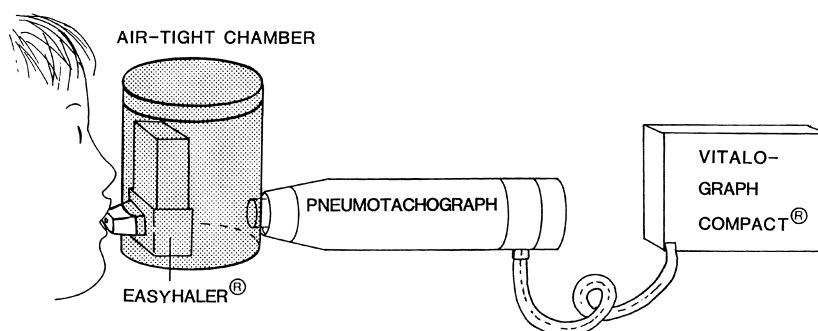


Fig. 1. A loaded Easyhaler[®] connected in series to a pneumotachograph.

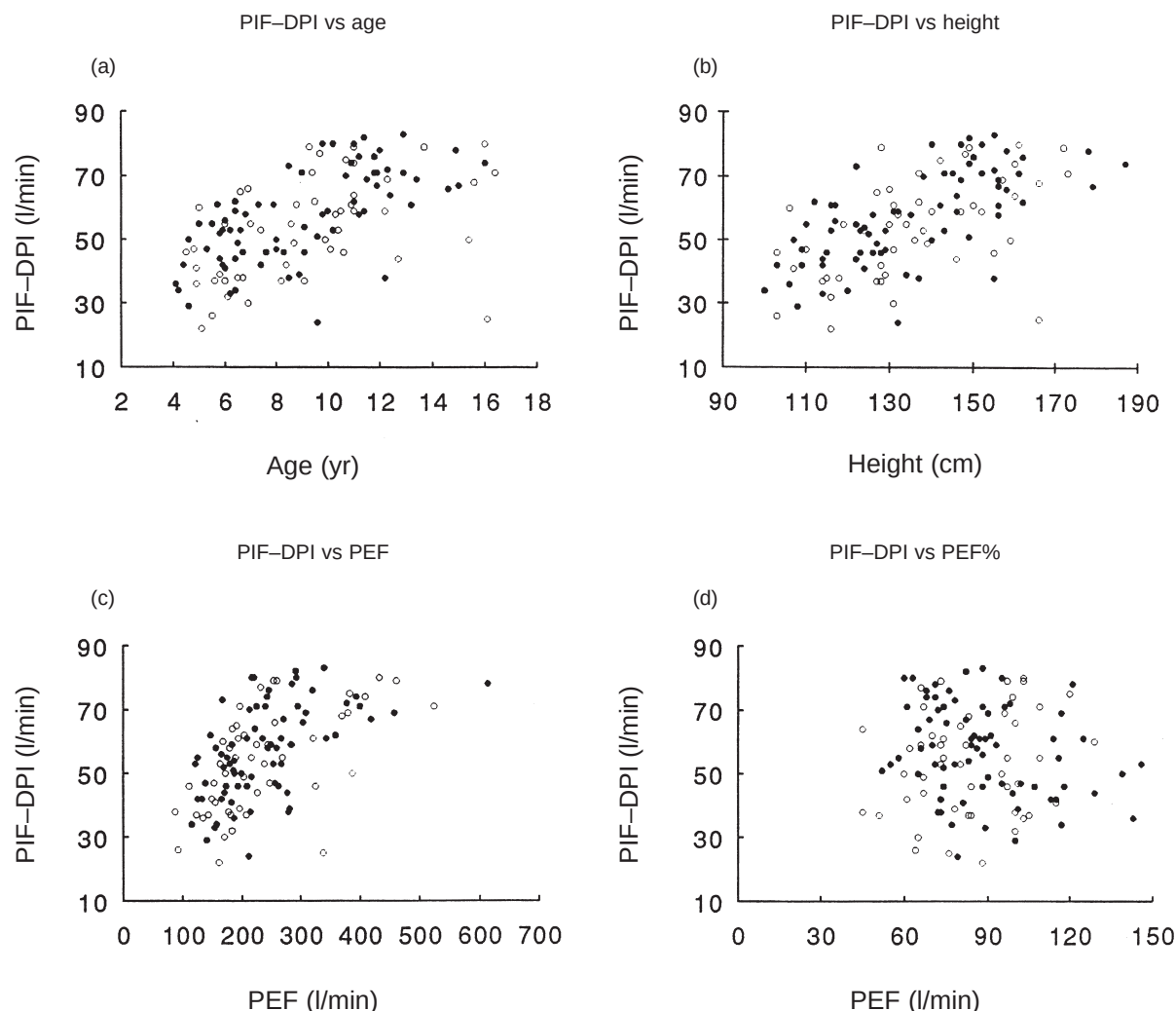


Fig. 2. The peak inspiratory flow through an Easyhaler[®], (PIF_{EH}) (= PIF-dry powder inhaler, DPI) was significantly correlated with age (a), height (b), and peak expiratory flow (PEF) (c). The level of obstruction (PEF percentage) was not correlated with PIF_{EH} (d). $n = 120$; $\circ$ = girls; $\bullet$ = boys.

(218 ± 47 l vs. 216 ± 49 l; $p=ns$), and MEF_{50} (2.1 ± 0.6 l vs. 2.1 ± 0.5 l; $p=ns$) (Fig. 3). Two girls, aged 5 and 7 yr, inhaled salbutamol with a PIF_{EH} of 16 l/min. Even with such a low inspiratory flow it was possible to produce bronchodilatation almost equal to that obtained with an MDI-cum-spacer.

Discussion

This study shows that in asthmatic children, 4–16 yr of age, the PIF through the novel DPI, Easyhaler, is correlated with age, height, and PEF. Similarly, Pedersen et al. found that the PIF through the Turbuhaler[®] (Astra Draco AB, Lund, Sweden) was correlated with age and PEF in 265 non-asthmatic children aged 3.5–15 yr (1). Meanwhile, Brown et al. reported that the PIF through the Turbuhaler was correlated with PEF

only weakly in 99 asthmatic adults with obstruction (9). Both the Easyhaler and the Turbuhaler are powder inhalers that allow higher inhalatory flows compared with the older, fenoterol capsule-loaded, powder inhaler (Boehringer Ingelheim, Ingelheim am Rheine, Germany). Among normal children aged 3.5–15 yr, PIF through the fenoterol powder inhaler correlated only weakly with age and PEF (4).

In vitro studies have shown that an inspiratory flow of 28 l/min through the Easyhaler is almost as effective as higher flows for the optimal use of this inhaler (10). In our study, only four children (3%), aged 5, 6, 10, and 16 yr, had PIF_{EH} values below this level. Also, equal degrees of bronchodilatation were produced after equal doses of salbutamol through the Easyhaler and through an MDI with a spacer, among the children with asthma, as observed in several previous studies

Table 1 The individual lung function values before and after bronchodilation

N	Age	Day	FEV ₁ %	FEV ₁ (l)	PEF%	MEF ₅₀ %	PIF _{EH} (l/min)
1	6.9	1*	94–105	(1.68–1.87)	82–95	56–78	
		2†	71–77	(1.27–1.37)	65–73	62–76	16
2	9.6	1	64–77	(1.65–1.96)	49–64	51–63	
		2	76–84	(1.95–2.15)	62–68	57–71	70
3	8.4	1	82–95	(1.37–1.58)	61–73	72–82	
		2	73–79	(1.21–1.32)	57–68	75–69	47
4	7.9	1	90–103	(2.00–2.29)	78–92	73–106	
		2	86–99	(1.92–2.20)	82–92	69–109	50
5	6.0	1	95–102	(1.45–1.56)	78–90	70–94	
		2	73–97	(1.11–1.48)	72–91	51–84	44
6	10.7	1	85–92	(1.72–1.90)	72–86	64–51	
		2	85–92	(1.72–1.85)	73–82	66–92	80
7	6.2	1	92–104	(1.57–1.77)	71–81	70–93	
		2	108–117	(1.85–2.00)	66–80	100–108	50
8	6.0	1	101–107	(1.75–1.86)	70–84	120–136	
		2	100–110	(1.74–1.91)	63–76	115–136	55
9	9.1	1	87–101	(1.32–1.54)	83–79	60–79	
		2	92–102	(1.41–1.55)	68–87	61–76	48
10	11.8	1	85–97	(1.94–2.21)	74–87	71–103	
		2	82–97	(1.87–2.20)	74–89	62–108	73
11	11.8	1	72–85	(1.86–2.21)	68–79	50–69	
		2	71–88	(1.86–2.28)	69–83	55–70	61
12	5.0	1	69–78	(1.01–1.14)	46–63	(0.99–1.81)‡	
		2	68–62	(0.99–0.91)	53–71	(1.51–1.76)‡	16
13	8.8	1	64–72	(1.13–1.28)	74–92	43–50	
		2	69–74	(1.22–1.31)	87–94	44–37	59
14	6.6	1	77–89	(1.15–1.33)	55–66	54–56	
		2	86–95	(1.29–1.41)	53–80	57–83	49
15	9.9	1	74–81	(1.46–1.61)	57–68	56–76	
		2	66–78	(1.31–1.55)	56–64	50–66	65

* On d 1, salbutamol was given with a metered dose inhaler (MDI) + spacer. The data represents results before and after salbutamol administration, respectively, for every patient.

† On d 2, salbutamol was given through the Easyhaler®. The data represents results before and after salbutamol administration, respectively, for every patient.

‡ Mean expiratory flow at 50% of vital capacity (MEF₅₀) values are given in absolute values (l/min) as predicted values were not available for children under 6 yr of age. Forced expiratory volume in 1 s (FEV₁), peak expiratory flow (PEF), and MEF₅₀ values are expressed as a percentage of the predicted value (except where indicated otherwise). FEV₁ values are given also in absolute values (l/min).

comparing different MDIs and DPIs in adults (1, 5–8, 11–15). A good bronchodilatory effect was also achieved with an inspiratory flow of only 16 l/min through the Easyhaler. The good clinical response, probably with deposition of a smaller amount, may result from the positioning of the salbutamol dose of 0.2 mg at the higher end of the dose–response curve. It will be important to confirm the results of this study by a double-blind, controlled study.

The individual doses of the drug delivered from the Easyhaler showed only slight variation (10). Even more important than the uniformly delivered amount of active substance is the respirable fraction of the drug deposited in the lungs. In asthmatic adults, pulmonary deposition of salbutamol via the Easyhaler was from 15 to 33% of the total dose (8). In another study in healthy adults, the pulmonary deposition of salbutamol

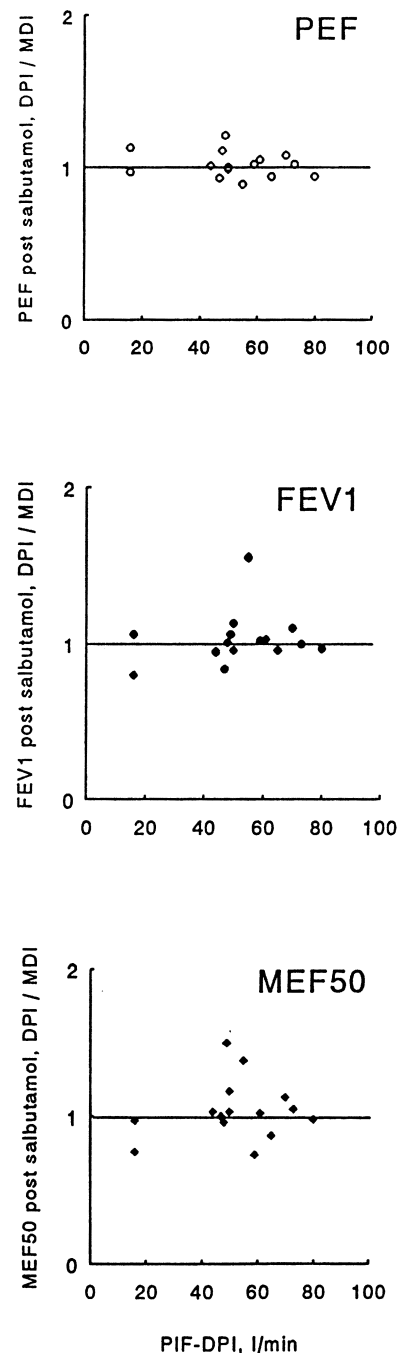


Fig. 3. Similar bronchodilation was produced by 0.2 mg salbutamol given either with the Easyhaler® or with a metered dose inhaler (MDI)-cum-spacer, related to the peak inspiratory flow through an Easyhaler (PIF_{EH}). n = 15.

from the Easyhaler was similar to that from an MDI (29% and 26%, respectively) (16). With the Easyhaler, a trend was observed towards higher pulmonary deposition of salbutamol with higher PIF values (10). In children, careful and repeated tuition in the use of the device is required before using these devices, and results in a higher inspiratory flow (17, 18).

In conclusion, PIF through a new multi-dose powder inhaler, the Easyhaler, was correlated with age, height, and PEF, while the level of obstruction was not correlated with PIF_{EH}. In this open, non-randomized study, equal degrees of bronchodilatation were produced after equal doses of 0.2 mg salbutamol through the Easyhaler and through an MDI with a spacer. Informed use of the Easyhaler can be recommended for children of 6 yr and upwards.

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