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Clinical effect of Diskus™ dry-powder inhaler at low and high inspiratory flow-rates in asthmatic children

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Clinical effect of Diskus™ dry-powder inhaler at low and high inspiratory flow-rates in asthmatic children. K.G. Nielsen, I.L. Auk, K. Bojsen, M. Ifversen, B. Klug, H. Bisgaard. ©ERS Journals Ltd 1998.

ABSTRACT: *In vitro* studies with the Diskus™ inhaler at low and high flow rates show consistent doses of drug as fine particles <4.7 μm. The present study was designed to ascertain whether this *in vitro* flow independency translates into flow-independent clinical effect when the device is used by patients at low (30 L·min^{-1}) and high (90 L·min^{-1}) flow rates.

A pilot study in 129 children aged 3–10 yrs demonstrated that 99% of children of 3 yrs and above can generate a flow Š30 L·min^{-1} through the device, while 26% performed Š90 L·min^{-1}.

Eighteen children aged 8–15 yrs with exercise induced asthma inhaled placebo or salmeterol 50 μg at either 30 L·min^{-1} or 90 L·min^{-1}. Exercise challenges were carried out 1 h and 12 h after dosing. The maximum percentage fall in forced expiratory volume in one second (FEV_1) after exercise 12 h after treatment was significantly less after salmeterol at either flow rates as compared to placebo. There was no significant difference in the protection from salmeterol on the day of low-flow inhalation *versus* the day of high-flow inhalation.

Consistent *in vitro* fine particle dosing from the Diskus™ inhaler translates into a consistent clinical effect at low and high flow rates in children.
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Dry-powder inhalers are becoming increasingly used for the administration of antiasthmatic medication in paediatrics, since no co-ordination of actuation and inspiration is required for their effective use and no propellants are used. However, patients need to generate sufficient inspiratory flow through these effort-dependent inhalers to aerosolize the drug efficiently. Flow dependency of the aerosolizing property differs between devices [1].

Diskus™ (Accuhaler™; Glaxo Wellcome, UK) inhaler is a new low resistance multidose drypowder inhaler, which has been designed to be comparable to the Diskhaler (Glaxo Wellcome, UK). *In vitro* studies indicate that Diskus™ inhaler delivers a consistent fine particle dose at flow rates of 28 and 60 L·min^{-1} [2].

It was the aim of the present study, to investigate if this *in vitro* consistency translates into consistent *in vivo* efficacy when the device is used by children at low and high flow rates. The flow rates were chosen from the results of a preliminary study (part I) in which the relationship between peak inspiratory flow (PIF) rate and age was determined. In part II of the study, the protective effect of salmeterol on exercise-induced bronchoconstriction (EIB) 1 h and 12 h after medication was used as the clinical outcome to study the efficiency of the aerosolizing properties of the Diskus when the children applied a high flow of 90 L·min^{-1} (according to the results of part I of the study) *versus* a low flow of 30 L·min^{-1}.

Patients and methods

Part I: PIF and Diskus

PIF as well as PIF through Diskus was studied in a randomly selected cohort of asthmatic children aged 3–10 yrs from the out-patient clinic; the aim was 20 children in each 1 yr age group. The children were included if they had a clinical diagnosis of asthma and were able to co-operate to perform a peak expiratory flow (PEF) measurement. They were allowed to take any type of concurrent treatment for their airway obstruction. Most (69%) were taking inhaled steroids. They were excluded if they were unable to inhale through the device following demonstration of its use, or if they were currently experiencing an exacerbation of asthma or had a lower respiratory tract infection.

The patients were trained to inhale as hard and fast as they could through a pneumotachograph run from a Master Screen unit (E. Jaëger & Co., Würzburg, Germany). Once the investigator was satisfied that the patient was able to perform the test correctly, measurements were taken. The inspiratory manoeuvres were performed three times and the highest of three technically acceptable measurements recorded. This procedure was subsequently repeated through the Diskus™ inhaler which was contained in an airtight box linked in series to a pneumotachograph.

Part II: EIB and salmeterol inhaled from Diskus at low and high flow rates

Exercise challenge. Forced expiratory volume in one second (FEV_1) had to be Š65% of predicted normal [3] at the prestudy visit and >50% pred on subsequent study days for an exercise test to be performed. Nasal clips were used. Relative humidity ranged 20–30%. Pulse telemetry was attached to the patient and the baseline cardiac frequency was recorded. The patients exercised on a treadmill with a 10% inclination and the workload was gradually increased over the first minute by adjusting the speed of the treadmill until a steady-state cardiac frequency of 170–190 beats·min^{-1} by the end of the first minute was achieved. The patients were exercised for 6 min with cardiac frequency measured at 2 min intervals. FEV_1 (best of three values) was measured by a dry spirometer (Vitalograph Ltd, Buckingham, UK) before trial medication, pre-exercise, immediately after stopping exercise and again at 3, 5, 10, 15, 20 and 30 min after exercise.

Inhalation at fixed flow rates. Before inhaling the study drug, patients were trained to inhale at fixed flow rates (30 and 90 L·min^{-1}) by monitoring the actual flow rate *via* the pneumotachograph with an on-line display on screen. They were trained to reach the required inspiratory flow rate as quickly as possible, the mean flow within the first 500 mL being within ±20% of the required flow. The actual mean inspiratory flow values were calculated as mean value of five equidistant points (100–500 mL) on a hard copy printout of the flow-volume curve. In addition, the total inspired volume during the procedure had to be Š80% of the maximum vital capacity (VC).

Patients. Children with asthma were included, if they had a baseline FEV_1 Š65% pred and a decrease in FEV_1 of Š15% following exercise challenge at the prestudy screen visit. Furthermore, they had to be able to inhale consistently through the Diskus™ inhaler at 30 and 90 L·min^{-1}. Eighteen children, 13 males and five females, aged 8–15 yrs (mean 12 yrs) and median (range) asthma duration of 7.5 (2–13) yrs were recruited and completed the study. Median (range) percentage fall in FEV_1 was 24 (15–55) % at the day of inclusion. Seventeen patients were using a short-acting bronchodilator and 14 used inhaled corticosteroids for control of asthma. Three patients were using the long-acting β_2-agonist formoterol.

Design. The study was designed as a randomized, double-blind, placebo-controlled, crossover, single-centre study in children with EIB. Eligible patients received each of the following treatments in random order from a Diskus™ inhaler on three separate study days: 1) salmeterol 50 µg (30 L·min^{-1}) and placebo (90 L·min^{-1}); 2) salmeterol 50 µg (90 L·min^{-1}) and placebo (30 L·min^{-1}); and 3) placebo (30 L·min^{-1}) and placebo (90 L·min^{-1}). In other words two inhalations were performed on each study day, no more than 5 min apart.

On each study day, exercise challenge tests were performed 1 h and 12 h after dosing. The study days were separated by 2–14 days and patients attended the clinic for a prestudy screen 1–14 days before the first study day. Short-acting β_2-agonists were discontinued 8 h before, and long acting β_2-agonist 24 h before each clinic visit.

Ethics. Approval for the study was obtained from the Copenhagen and Frederiksberg Ethics Committee (KF 02-243/94) and all patients and their parents or guardians gave written informed consent to participate in the study. The study was conducted according to the guidelines for Good Clinical Practice.

Statistics. The sample size of 18 patients provided a power of >80% in detecting a relative difference of 14%.

The primary efficacy parameter was the maximum percentage fall in FEV_1, calculated as:

$$\frac{\text{Pre-exercise } FEV_1 - \text{lowest postexercise } FEV_1}{\text{Pre-exercise } FEV_1}$$

The secondary efficacy parameter was the pre-exercise FEV_1.

Comparison between treatments was performed by non-parametric crossover analysis of maximum percentage fall in FEV_1 based on Wilcoxon rank sum test, using the van Elteren extension of Koch's method [4]. Since the intent was to show similarity between the two flow rates, criteria for equivalence were used for treatment differences of salmeterol at different flow rates. In previous studies, equivalence has been determined by the 90% confidence limits of the treatment difference being within a predefined range. No *a priori* ranges were determined for this study, so only 90% confidence limits are given. For all treatment differences involving placebo and salmeterol, 95% confidence limits are presented.

Pre-exercise FEV_1 was analysed parametrically for each time point, taking into account the crossover design. The model accounted for patient, period and treatment.

Analyses were performed with Statistical Analysis System (SAS) software. Differences were considered significant at a p-value less than 0.05.

Results

Part I: PIF and Diskus

One hundred and twenty nine patients completed PIF measurements. One hundred and twenty seven patients were able to generate a PIF Š30 L·min^{-1} through the device, while 26% generated a PIF of Š90 L·min^{-1}. A nonlinear relationship between age and PIF through the Diskus was found (fig. 1), in contrast to a linear relationship without the device (not shown).

Part II: EIB and salmeterol inhaled from Diskus at low and high flow rates

Only one patient failed to achieve a flow rate of ±20% of correct flow rate within the first 500 mL. This happened when he was randomized to salmeterol (30 L·min^{-1}) and placebo (90 L·min^{-1}). Two patients failed to achieve the criterion of inhaling Š80% of VC on one occasion each by only reaching 79% of maximum VC, but neither of these occurred during inhalation of active medication. All data were used for the all patients treated analysis.

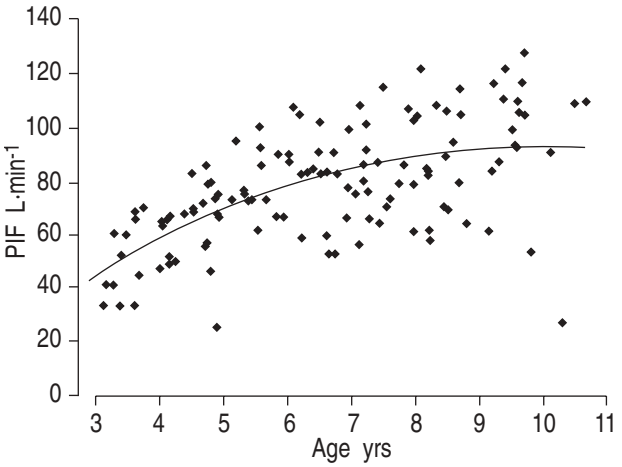

Fig. 1. – Relation between peak inspiratory flow rate (PIF) through the Diskus™ inhaler and age in 129 asymptomatic children.

The maximum change in cardiac frequency attained during exercise challenge did not differ significantly between treatments.

Pretreatment FEV1 did not differ between placebo, salmeterol inhaled at 30 L·min-1 and salmeterol inhaled at 90 L·min-1 (fig. 2).

One hour after dosing, pre-exercise FEV1 (fig. 2) as well as the maximum percentage fall in FEV1 following exercise challenge (fig. 3), were without significant difference between salmeterol 50 µg inhaled at the flow rates 30 and 90 L·min-1, whereas both salmeterol treatments were significantly superior to placebo both in bronchoprotective effect (p=0.017 for 30 L·min-1 and p=0.002 for 90 L·min-1) (fig. 3) and in bronchodilation (p=0.002 for salmeterol inhaled at 30 L·min-1 and p<0.001 for salmeterol inhaled at 90 L·min-1) (fig. 2).

Twelve hours after treatment there was no significant difference in pre-exercise FEV1 between the two salmeterol treatments, nor between placebo and any of the active treatments (p=0.36 for placebo *versus* salmeterol inhaled at 30 L·min-1 and p=0.07 for placebo *versus* salmeterol inhaled at 90 L·min-1) (fig. 2). There was a 3% median difference in maximum percentage fall in FEV1 between salmeterol 50 µg *via* Diskus™ at the flow rates of 30 and 90 L·min-1, 90% confidence limits -1 to +7%, which was not statistically significant (p=0.09). Active treatment was superior to placebo at both flow rates (fig. 4). The difference between placebo and salmeterol 50 µg at 30 L·min-1 was 8%, 95% confidence limits 2–16%, p=0.029. The corresponding figures for salmeterol 50 µg at 90 L·min-1 were 6%, 95% confidence limits 1–13%, p=0.032.

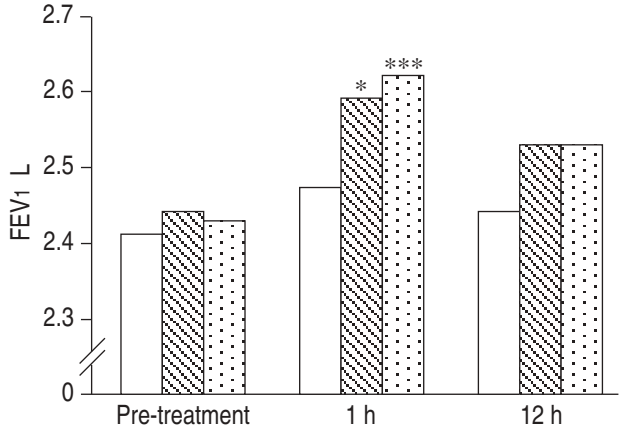

Fig. 2. – Mean pretreatment and pre-exercise forced expiratory volume in one second (FEV1) values at 1 and 12 h in 18 children before and after inhalation of placebo ( ), salmeterol inhaled at 30 L·min-1 ( ) and salmeterol inhaled at 90 L·min-1 ( ). *, ***: p<0.05, p<0.001 *versus* placebo.

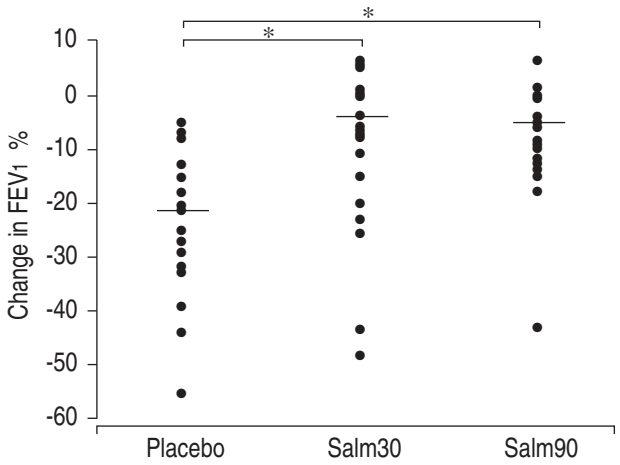

Fig. 3. – Maximum percentage decrease in forced expiratory volume in one second (FEV1) after exercise in 18 children, 1 h after inhalation of placebo, salmeterol inhaled at 30 L·min-1 (Salm30) and salmeterol inhaled at 90 L·min-1 (Salm90). Medians are indicated by horizontal bars. *: p<0.05.

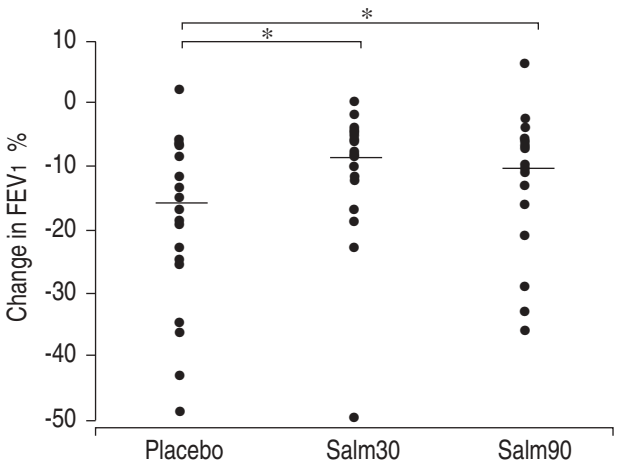

Fig. 4. – Maximum percentage decrease in forced expiratory volume in one second (FEV1) after exercise in 18 children, 12 h after inhalation of placebo, salmeterol inhaled at 30 L·min-1 (Salm30) and salmeterol inhaled at 90 L·min-1 (Salm90). Medians are indicated by horizontal bars. *: p<0.05.

No adverse events considered likely to be related to the study treatment were reported during the study.

Discussion

Dry powder inhalers such as Aerolizer (Italselber Farmaceuti, Italy) [5], Rotahaler (Glaxo Wellcome, UK) [6], Spinhaler (Fisons, UK) [7] and Turbuhaler (Astra Draco, Sweden) [8–10] are prone to reduced clinical efficiency at low inspiratory flow due to reduced efficiency of drug dispersion and emptying of the device. However, *in vitro*

studies with the Diskus™ inhaler demonstrate good dosing consistency with flows as low as 30 L·min^{-1} [2, 11]. In the present study we compared the clinical efficacy of salmeterol inhaled at high and low flow rates from the Diskus™ inhaler to study the clinical flow dependency of this new device.

In the pilot study, a nonlinear relationship between age and PIF through Diskus for children of 3–10 yrs was revealed. The relationship tends to be almost linear up to 8 yrs after which the curve reaches a plateau. The reason for this nonlinearity is not clear, and differs from the linearity found between age and PIF without device and through other dry powder inhalers such as Aerolizer [5]. Most children 3–10 yrs of age (99%) attained a flow above 30 L·min^{-1} through the Diskus, which was therefore considered the relevant lower flow limit. Twenty six per cent attained 90 L·min^{-1}, which was therefore considered a moderately high flow for asthmatic children using the Diskus. In the subsequent study the effect of salmeterol 50 μg from a Diskus™ inhaler was therefore studied at the low inhalation flow rate of 30 L·min^{-1} and compared with the same dose inhaled at the high flow rate of 90 L·min^{-1}.

The protection against EIB was used as the clinical outcome variable. The effect 12 h post-treatment was considered the effect variable of most interest, as the effect at that time is tapering off. Such marginal effect is likely to reveal the steep part of the dose-response curve, and is accordingly expected to reveal any clinical difference in the aerosolizing efficacy of the low and the high flow rates. By adding a bronchoconstrictor challenge at the end of the expected time-course of action from salmeterol, any *in vivo* flow dependency of the Diskus™ inhaler would most likely be revealed. A similar design was previously applied to reveal a flow dependent clinical effect of formoterol inhaled from an Aerolizer [5].

Maximum percentage fall in FEV_1 after exercise was not significantly different following salmeterol 50 μg inhaled at 30 L·min^{-1} and at 90 L·min^{-1}. This was true for exercise challenges carried out both 1 h and 12 h after dosing. Both salmeterol treatments, however, were significantly more effective than placebo in preventing EIB at 1 h and 12 h after dosing (figs. 3 and 4).

A dose of 50 μg salmeterol may be at the maximum of the dose-response curve and thereby explain why we did not find any difference in effect between the two-flow rates. However, the available two studies found that the effect from salmeterol is tapering off at doses below 50 μg delivered from metered-dose inhaler. A significant protective effect against EIB 12 h from administration of 50 μg salmeterol by metered-dose inhaler but not from 25 μg salmeterol, was demonstrated by DEBENEDICTS *et al.* [12]. Significantly greater protection against methacholine challenge from 50 μg than from 25 μg salmeterol by metered-dose inhaler, from 30 min to 12 h postdosing, was reported by SIMONS *et al.* [13]. Therefore, we chose to study the flow dependency of salmeterol from Diskus at a dose of 50 μg, assuming comparable lung dose from salmeterol Diskus and salmeterol metered-dose inhaler.

No differences between salmeterol inhaled from Diskus™ inhaler at 30 L·min^{-1} and salmeterol inhaled from a Diskus™ inhaler at 90 L·min^{-1} were seen for pre-exercise FEV_1 at either 1 h or 12 h after dosing (fig. 2). There were significant differences between both salmeterol treatments and placebo at 1 h, but not at 12 h after dosing (fig. 2), indicating a more long-lasting effect of salmeterol on protection against EIB than on bronchodilation. It is commonly reported that the bronchodilating effect of short-acting β_2-agonists is of longer duration than their protection against EIB [14, 15]. However, studies on long-acting β_2-agonists have previously reported that protection against bronchoconstriction is more long-lasting than the bronchodilating effect [12, 16, 17]. This points to a mechanism of action from the long-acting β_2-agonists which is different from that of the short-acting β_2-agonists [18, 19].

The study has attested to aerosolizing property of the Diskus™ being independent of flow performance within the flow range of 30–90 L·min^{-1}, which is the range relevant to 3–10 yr old children. This ability of Diskus™ to aerosolize efficiently even at the very low flow rate of 30 L·min^{-1} should however not be used to advocate the use of the inhaler in young children. Certainly, most children can perform the required forced inhalation. However, the distinction should be made as to whether the child is actually willing to do so under all circumstances. The distinction between physical ability and compliance in performing as required separates widely in age in young children. In young children it is recommended that, rather than using devices requiring forced inhalation, devices should be used that can provide treatment through passive breathing from a cloud of aerosol in a spacer or from a nebulizer [20].

However, the results indicate that the consistency of dosing over a wide range of flow rates seen with the Diskus™ inhaler on *in vitro* testing with respect to fine particle dose, translates into equal clinical efficacy at low and high flow rates. Patients can therefore be relied upon to receive adequate doses of drug when using the Diskus™ inhaler with minimal influence of inspiratory flow performance. This is of importance in children as well as in adults because compliance may often fail and less than optimal performance can be foreseen. Less than optimal inspiratory flow can therefore be expected intermittently in everyday use of effort-dependent inhalers. The present study confirms that the aerosolizing property of the Diskus™ is robust against such variability of peak inspiratory flow performance.

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