

Nasal peak inspiratory flow through Turbuhaler[®] in children with symptomatic rhinitis and in healthy children

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Topical treatment of allergic or vasomotor rhinitis is possible by means of pressurized metered dose inhalers, aqueous spray, or dry powder inhalers. In children, little is known about nasal drug delivery by dry powder inhalation. The airflow through the device is critical for the drug release and a sufficient nasal inspiratory flow is needed for intranasal drug delivery from a dry powder inhaler. In order to investigate from what age children with allergic or vasomotor rhinitis can reliably use such a device, device-dependent nasal peak inspiratory flow (DnPIF) was measured. The maximal DnPIF was measured in children aged 4–13 years making use of a dry powder inhaler (Turbuhaler[®]) connected to a spirometer (Vitalograph[®]). In the clinically relevant context, instructions from the doctor and one week's use of a Turbuhaler at home were found to be sufficient to obtain a good inhalation technique and were shown to improve DnPIF at least as effectively as visual feedback training at the clinic. Children with rhinitis, as well as healthy children from the age of 6 years, were able to generate a DnPIF sufficient to obtain a reliable nasal delivery of a dry powder drug dose. DnPIF values correlated with age. Consequently, a recommendation to use a nasal Turbuhaler from the age of 6 for topical drug delivery in the treatment of allergic or vasomotor rhinitis seems reasonable.

J. G. C. M. van Zoest¹, A. M. van der Weij¹, E. J. Duiverman¹, A. Akerlund² and J. M. Kouwenberg¹

¹Juliana Children's Hospital, Department of Paediatric Pulmonology, The Hague, The Netherlands, ²AstraZeneca Clinical R & D, Lund, Sweden

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J.M. Kouwenberg
Department of Paediatric Pulmonology
Juliana Children's Hospital
Sportlaan 600
2566 MJ The Hague
The Netherlands
Tel.: +31 70 312 7200
Fax: +31 70 312 7351

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Dry powder inhalers (DPIs) require a certain amount of inspiratory effort by the patient to bring the medication into the respiratory tract. For pulmonary diseases, a peak inspiratory flow (PIF) sufficient for drug release can be generated by almost all patients. This includes patients with acute asthma, patients with chronic obstructive pulmonary disease (COPD), and children from the age of about five years. DPIs for delivery of topical drugs intended for treatment of nasal mucosal disease, i.e. glucocorticosteroids, have been shown to be effective anti-inflammatory treatment in such a formulation. It is important that the patient is given the correct instructions for use, i.e. to produce a deep and forceful inhalation (1,2). There is an element of training, and patients increase their PIF after repeated use

of a dry powder device for oral inhalation. In asthmatics this is most relevant for patients with a PIF in the lower range.

Nasal Turbuhaler[®] delivering budesonide (Rhinocort[®]) is used for the treatment of children suffering from allergic or vasomotor rhinitis. It is not known whether children can generate a nasal flow through the device that is sufficient to release the drug and to deliver it intranasally. Potential limiting factors for breath-activated devices in pediatric use are limitations in the understanding of instructions, in coordination and in nasal inspiratory airflow capacity. The latter is more likely in children, who are often troubled by nasal blockage caused by rhinitis.

The aim of this study was to evaluate whether children suffering from rhinitis, as compared with

Table 1. Demographic data

	Rhinitis (n=63)	Healthy (n=117)
Age (years)	8.2 (2.6)	7.6 (2.6)
Sex (male/female)	41/22	54/63
Weight (kg)	31.8 (11.5)	29.7 (10.5)
Height (cm)	133.7 (17.0)	130.4 (17.1)
Severity of rhinitis symptoms (none/mild/moderate/severe)	13/23/23/4	not applicable

healthy children, after instructions and one week's use at home can achieve a device-dependent nasal peak inspiratory flow (DnPIF) sufficient to actuate a reliable dose of a powder drug loaded in a Turbuhaler, and to investigate any age-dependency.

Subjects and methods

Patients

In an open single-center study in the Netherlands, one group of children diagnosed as having allergic rhinitis and one group of healthy children were enrolled. Children (n=63; age 4–13 years) with rhinitis, recruited from the outpatient clinic of the Juliana Children's Hospital, were enrolled between March and May 1996. Sixty-two children completed the study. A control group of healthy children (n=124; age 4–13 years) from a primary school in The Hague was also enrolled. Seven children had a diagnosis of rhinitis and were regarded as non-viable in the healthy group. They were not eligible in the rhinitis group because they followed a slightly different protocol. One child dropped out owing to other illness. Hence, 116 healthy children completed the study. Demographic data of all children are shown in Table 1.

In the patient group, nasal blockage was a symptom in 38% (24/63) of the children, being bilateral in 13% (8/63). All but one (62/63) had a concomitant diagnosis of asthma. In the healthy group, nasal blockage was reported by 12% of the children (14/117) and in 3% (4/117) blockage was bilateral.

Written informed consent was obtained from all children/guardians and the study was approved by the local medical ethics committee.

Study procedures

At the first visit the medical history was taken and nasal examination was performed prior to each measurement; nasal blockage was assessed by the investigators by direct observation of the child sniffing through each nostril successively, while blocking the contralateral side with a finger. At

inclusion, nasal inspiratory peak flow measurements (DnPIF1) were performed in both groups through an empty Turbuhaler connected to a Vitalograph Compact Spirometer (no. 42400, Maids Moreton House, Buckingham, UK). The highest DnPIF of three attempts was registered per nostril. To ascertain that the healthy children used the Turbuhaler correctly, they also practised this with a Turbuhaler usage trainer (TUT) (AstraZeneca R&D, Research Electronics, Lund, Sweden). This electronic flow meter gives the child a visual feedback on inspiratory performance through three indicator lamps set to light up at flows of 28, 34 and 40 l/min.

All children were provided with an empty Turbuhaler inhaler and a diary. They were instructed to use the Turbuhaler twice daily for one week and to record this in their diaries. After one week's use at home, the children returned for the second visit. Again the nose was examined and instructions on how to use the Turbuhaler were given. Once more, nasal inspiratory measurements were performed (DnPIF2). Instructions on how to use the Turbuhaler were repeated, followed by practice inhalations with visual feedback by TUT, for the first time in the rhinitis group and for the second time in the healthy group. Subsequently, the third nasal inspiratory measurements were performed (DnPIF3). Two investigators (JvZ, AvdW) carried out all measurements.

In vitro measurements of delivered doses at different flows

The mean amount of budesonide delivered from the inhaler was determined at a range of applied flows (20–60 l/min). Each of the 200 doses contained in an inhaler was sucked onto filters at the indicated flow using a sucking time of 2 s. The initial, middle and end doses were analytically determined by spectrophotometric measure-

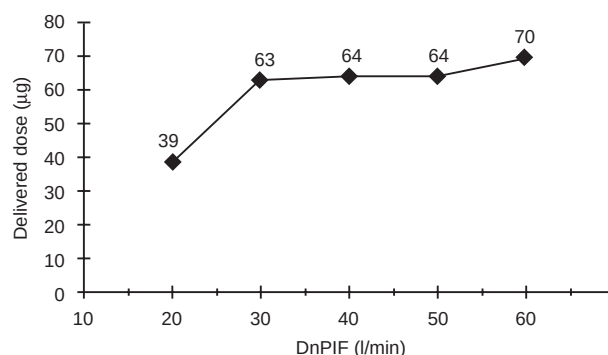


Fig. 1. Delivered doses *in vitro* from a metered dose of 100 µg at different inspiratory flows measured through the device.

ments at 243 nm on methanol solutions prepared from the filters.

Analysis

For each set of measurements, the mean of the highest values of DnPIF1, DnPIF2 and DnPIF3 for both nostrils was calculated and retained for analysis. Statistical analysis was performed by a two-sample *t*-test to compare both groups of measurements before the training with TUT at visit 2 (DnPIF2). A paired *t*-test was used to analyze the change from baseline after training for each group. A linear regression model was applied to analyze the relationship between DnPIF and age.

Results

The mean doses delivered in the *in vitro* experiment from a metered dose of 100 µg at flows from 20 to 60 l/min are indicated in Fig. 1. The mean delivered doses increased with flow but levelled out at a plateau dose of 63–64 µg from a flow of 30 l/min, eventually reaching a maximum of 70 µg at 60 l/min.

Patient compliance was assessed by counting the number of remaining dose actuations in returned Turbuhaler inhalers. Good compliance was defined as at least 24 performed actuations, i.e. ≤ 176 remaining dose-actuation clicks in the returned inhaler from a total of 200 loaded. Compliance was good in 79% of the children with rhinitis, and in 80% of the healthy children.

After instructions at the first visit the rhinitic children accomplished a mean DnPIF (SD) of

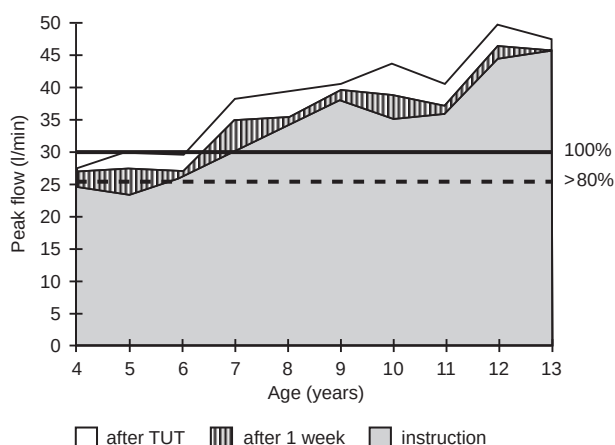


Fig. 2. Mean peak inspiratory airflow in rhinitic children after instruction only, additional effect reached after 1 week's use, and further additional effect after visual biofeedback by Turbulhaer[®] usage trainer (TUT) in children of different ages. The delivered plateau dose is indicated by the continuous line, and the dotted line indicates at least 80% of it.

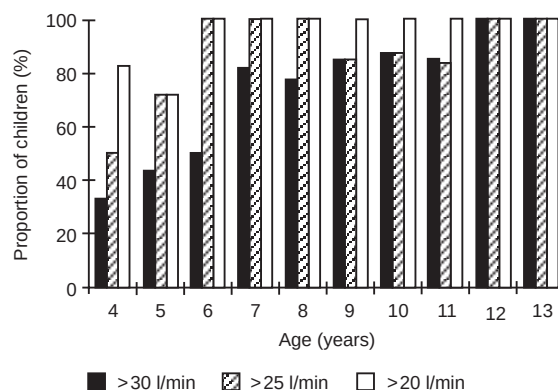


Fig. 3. Proportion of rhinitic children at different ages reaching critical inspiratory airflows through Turbuhaler[®] after 1 week's use.

32.9 l/min (11.0), vs. 33.8 l/min (10.7) for healthy children; the difference was not significant. After one week's use at home, corresponding means were 34.9 and 37.6; the differences were likewise not significant ($p=0.15$). The improvement after one week's use within the groups was, however, significant: 2.0 l/min (7%) ($p=0.006$) in the rhinitic children and 3.8 l/min (11%) ($p<0.001$) in the healthy children. Visual feedback training with TUT during visit 2 gave a further improvement of DnPIF3 in both groups of 3.0 l/min ($p<0.001$ for both). The effect of one week's use and TUT on mean DnPIF by age in the rhinitic children is shown in Fig. 2. DnPIF-values increased with age and there was a weak but statistically significant correlation between age and DnPIF2 in rhinitic children ($r=0.55$; $p<0.001$) and in healthy children ($r=0.54$; $p<0.001$).

In an analysis of the proportion of rhinitic children capable of achieving critical inspiratory flows, all 6-yr-olds in the rhinitis group were found to accomplish at least 25 l/min (Fig. 3). At this flow rate, more than 80% of the delivered plateau dose would be delivered intranasally. Fifty per cent of the 6-yr-old children and 80% of the 7-yr-old children achieved at least 30 l/min, which means that those individuals should have reached plateau dose delivery intranasally.

Discussion

The finding in this study, comparing nasal inspiratory flow in rhinitic children with healthy children, that children in both groups were able to generate similar mean flows is somewhat surprising. Nasal blockage was more than three times as common in the rhinitic children but this does not seem to have influenced the ability to inhale through a Turbuhaler.

The values were measured with an empty Turbuhaler connected to a Vitalograph spirometer, a set-up that could be useful for evaluation of any device where delivery is determined by airflow. A certain resistance is caused by Turbuhaler, therefore the DnPIF values can be expected to be lower than rates measured with the nose being the only resistor. Adult patients with rhinitis reach mean DnPIF values of 54 l/min (3). Even if DnPIF values in children are considerably lower than in adults, still, at a DnPIF of 30 l/min the same dose as in adults, i.e. the plateau dose, will be delivered from the device according to the *in vitro* data.

One week's use of Turbuhaler at home improved the DnPIF values marginally, by around 10% in both groups.

The effect of practise is known also to occur with the repetition of other peak flow measurements (1). Consequently, the optimal benefit of a Turbuhaler might not be reached until after some time of use. The small additional improvement after visual feedback is of a magnitude comparable to that achieved after one week's use at home. In the lowest ages, children incapable of achieving a sufficient DnPIF may benefit from the mean 10% increase induced after visual feedback.

The first indicator lamp of TUT corresponds to an airflow of 28 l/min. At this flow more than 90% of the plateau dose will be delivered (interpolated data). The lamp will give visual feedback to the child and confirm the use of an efficient technique. In the healthy children, visual feedback by TUT was given after the instructions at the first visit for the DnPIF1 recordings, because the healthy children were less likely to be familiar with the use of any nasal treatment. Any benefit from the use of TUT as a complement to instructions at the first visit would have been detected in the DnPIF2 recordings. No differences were found between the groups at the second visit, consequently, the use of a TUT seems to be of minor, if any, benefit. This is in agreement with data from asthmatics, where a 22% increase was found in oral PIF through a Turbuhaler after two week's training at home (1). In the asthmatics, training at home was superior to training with a TUT at the clinic.

Rhinitic children from the age of 6 yr were able to generate an airflow through a nasal Turbuhaler sufficient to deliver a reliable dose.

Indeed, all children as young as 6 yr with rhinitis could achieve a flow of 25 l/min, which is sufficient to deliver more than 80% of the plateau dose delivery (interpolated data). Hence, for practical purposes, rhinitic children aged 6 and up can be assumed to be able to benefit from a dose delivered from a Turbuhaler. A flow of 20 l/min or more could be accomplished by more than 80% of the 4-yr-old children. At this flow, around 65% of the plateau dose will be delivered to the patient and, even if a substantial dose reaches the target organ, in this youngest age group the dose would tend to be less reliable.

At the flows achieved by the children, nasal inhalation would lead to mainly nasal deposition. With nasal inhalation through a Turbuhaler at a flow of 30 l/min, the mean bronchial deposition in adults has been assessed to be 4% (4). Because inhaled volume, rather than flow rate, is a contributing factor to the bronchially deposited fraction, the smaller tidal volumes in children are likely to cause an even lower fraction of bronchial deposition.

Taken together, the data presented in this study indicate that it is reasonable to recommend the use of a nasal Turbuhaler for topical drug delivery in the treatment of rhinitis in children aged 6 yr and over.

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