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ORIGINAL ARTICLE

Automated actuation of nasal spray products: determination and comparison of adult and pediatric settings

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Abstract

Objective: To determine and compare patient-relevant settings for automated nasal spray actuation stations from adult and pediatric hand data. *Methods*: Twenty adults and 20 pediatric participants were asked to spray Flonase® Nasal Spray six times in a Hand Actuation Monitor, which records force and displacement data in 5-ms increments. Settings for force- and velocity-controlled actuation stations were determined from the data using a predefined set of calculations. *Results*: For force-controlled settings, hand spraying by children resulted in lower actuation forces, and longer force rise, hold and fall times. Pediatric velocity-controlled actuator settings were lower for travel, compression velocity, and release velocity compared with adults. The pediatric spray weight recorded during hand spraying was significantly lower than the spray weight generated by adult participants. Adult participants were able to generate full sprays with each attempt, whereas 11 out of 120 actuations performed by pediatric participants resulted in partial and 'no spray' events. No differences in spray weight were detected in participants who chose to actuate the nasal spray using both hands. *Conclusions*: A predefined set of calculations was used to determine patient-relevant settings from force and displacement hand data for force- and velocity-controlled automated actuation stations. This study determined and quantified, for the first time, the differences in hand spraying between adults and children.

Key words: Automated actuator, force, hand actuation monitor, nasal spray, pediatric, velocity

Introduction

Intranasal administration is used to deliver locally and systemically acting drugs. Ease of administration, an accessible epithelial surface, and an extensive capillary system facilitate rapid onset of action and make nasal delivery a viable, noninvasive alternative to injections[1–3]. It may also serve as a route to bypass the blood–brain barrier by way of the olfactory region[4–6]. Manual spray pumps are the most common device used for intranasal administration and are usually selected to provide dosing precision and reproducibility[7,8].

Nasally administered corticosteroids are an effective and commonly used method to treat rhinitis, generating $1.6 billion in direct sales in 2000[9,10]. The prevalence of seasonal and perennial allergic rhinitis is estimated at 10–30% for adults and 40% for children, resulting in over $11 billion in total direct and indirect costs in the United States[10]. Pediatric studies are recommended by the FDA to curb off-label use if a drug is likely to be prescribed for children. Subsequently, all package inserts for intranasal corticosteroids sold in the United States list an indication for pediatric participants, with the minimum age for most being 6 years old. The exceptions are age 2 years for Nasonex® Nasal Spray (mometasone furoate monohydrate, Schering Corporation, Kenilworth, NJ, USA) and Veramyst® Nasal Spray (fluticasone furoate, GlaxoSmithKline, Research Triangle Park, NC, USA), and age 4 years for Flonase® Nasal Spray (fluticasone propionate, GlaxoSmithKline). The focus of pediatric studies is generally on drug safety, but virtually no studies seek to determine whether adult versus pediatric hand spraying potentially results in differences in dosing and deposition.

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The device, formulation, and manner by which the patient actuates the nasal spray pump are the three factors that generally determine the properties of the emitted spray. Several studies have elucidated how device design and formulation of a nasal drug product influences the characteristics of the emitted spray. Viscosity, rheological properties and, in some cases, surface tension have been shown to affect the droplet size, spray pattern and plume angle of the emitted spray[8,11–13]. With increasing viscosity, droplet size increases, spray pattern area decreases, and plume angle decreases. The size and shape of the nozzle, which is the opening by which the formulation exits the actuator assembly, impacts the droplet size and spray pattern[11,14]. Other device features also impact the characteristics of the spray, such as the force constant of the spring in the pump, and the volume of the pump metering chamber.

As hand spraying can introduce variability not related to the drug product, the FDA recommends that pharmaceutical companies use automated actuators to perform spray testing in lieu of hand spraying by analysts[15]. The resultant variation in shot weight delivery is less when using automated actuators than when hand spraying is employed[16]. The two types of automated actuator systems, force-controlled and velocity-controlled actuators, mimic the force versus time and displacement versus time profiles, respectively, generated by hand spraying. The force-controlled systems are pneumatically driven, whereas the velocity-controlled systems are servo (electrically) controlled. The FDA states that 'settings would be relevant to proper usage of the product by the trained patient', which 'may be available from pump suppliers'[15]. However, there are no publications that demonstrate how pump suppliers generate such data and which, if any, trained patient populations they use. In lieu of supplier recommendations, FDA recommends conducting 'exploratory studies in which the relevant parameters are varied to simulate in vitro performance upon hand actuation'[15]. Unfortunately, relevant parameters (automated actuator settings) and the methods by which they are obtained are rarely disclosed in sufficient detail to understand how they relate to the use of the product by a patient. Although FDA recommends conducting exploratory studies, it does not seek a justification of the settings, only that 'selected settings used for the in vitro study would be specified'. These recommendations seem contradictory in that FDA recommends disclosing the actuator settings but not the methods by which they were obtained. This may lead to the use of settings that optimize the in vitro performance instead of representing how a patient is likely to use the product.

Several studies have tested a range of different automated actuator settings on the emitted spray characteristics. Increasing actuation force resulted in a reduction in droplet size distribution[11,17]. An increase in force rise times showed a corresponding increase in droplet size and distribution width[17]. Guo and Doub investigated the effect of velocity-controlled settings on spray characteristics and found that increasing stroke length (travel of the nasal spray pump) showed a linear relationship with spray weight, until reaching a plateau at long stroke length[14]. Compression velocity was the main determinant of plume geometry, spray pattern, and droplet size[14]. Other velocity-controlled settings that were tested showed little or no effect. Other studies have attempted to elucidate patient-relevant settings, either by selecting actuator settings that result in similar spray characteristics generated by hand spraying[11], or by enrolling a small number of volunteers to actuate nasal sprays filled with water[14,16,18,19]. In the case of the volunteer studies, only velocity-controlled settings were determined, which were usually adjusted to deliver an optimum spray weight, and detailed methods used to calculate actuator settings from hand spraying were not disclosed. Volunteer recruitment or institutional review board approvals are never mentioned, which suggest that volunteers may be analysts and technicians who are typically trained to minimize variability.

The aim of this study was to collect and compare adult and pediatric hand data, and apply a predefined set of calculations to determine settings for automated actuators. We also investigated whether the handedness of the participants caused differences in the settings or spray weight recorded during the hand spraying.

Methods

Materials and equipment

Participants were asked to spray Flonase® Nasal Spray, 50 μg (fluticasone propionate, GlaxoSmithKline), a commercially available prescription nasal spray used primarily for the treatment of allergic and nonallergic rhinitis, in a nasal spray pump Hand Actuation Monitor (HAM, InnovaSystems, Inc., Moorestown, NJ, USA). The monitor is equipped with a load cell and linear variable displacement transducer that measures force and displacement in 5-ms intervals during an actuation. Settings were derived for two automated actuation systems: the force-controlled MightyRunt (MR) and the velocity-controlled velocity actuator (VA, both from InnovaSystems, Inc.). All equipment was calibrated daily before use.

Study protocol

This study was approved by the University of Maryland, Baltimore Institutional Review Board. Informed, written consent was obtained in the adult and pediatric studies from each participant or parent/guardian, respectively, and the study was conducted under the terms of the Declaration of Helsinki. Twenty adult participants between the ages of 18–64 years were recruited through flyers posted around the University of Maryland, Baltimore campus. Twenty pediatric participants between the ages of 8–12 years were recruited by

researchers through the University of Maryland School of Medicine. The pediatric age range was restricted so only children more likely to autonomously spray the Flonase bottle would be prospects for recruitment. Prospective participants were excluded if they could not hold the nasal spray autonomously in the HAM and/or reported previous research experience using inhalers or nasal sprays. Prior prescribed use of a nasal spray or inhaler was not an inclusion/exclusion criterion in this study. One prospective pediatric participant was excluded for being unable to autonomously spray Flonase in the HAM. Participant gender and dominant hand was recorded.

Collection of hand data

In-date, primed Flonase bottles were weighed and shaken before each spray by participants. According to the labeled instructions, participants actuated Flonase vertically holding their thumb on the base of the bottle and their index and middle fingers on the pump flanges. Participants were allowed to use different fingers on the flanges when they indicated using alternate fingers during typical at-home use. So that no drug was administered during this study, participants mimicked delivery to the target nostril by holding the nasal spray to the side of their head and spraying into a waste collection container held at approximately the height of their nose. Data collection was performed on six sprays, with three sprays mimicking delivery to each nostril. Spray weights were determined for each individual actuation. Six sprays exceed the product labeling, hence a waste collection container was used rather than spraying into the nose, but in other respects 'trained patient' conditions were simulated as closely as possible. The HAM transmitted data to an integrated computer for subsequent analysis, and participants were not shown results to avoid learning associated with repeated use. Targeted nostril order and hand selection were not dictated, but were recorded for handedness analysis. For one adult participant, force and displacement data for one actuation were not saved properly and were therefore excluded from analysis, although the handedness and spray weight was recorded.

Determination and analysis of actuator settings

Actuation force, force rise time, force hold time, and force fall time settings, which are needed for operation of the MR force-controlled system, were determined using a predefined set of calculations. The definitions and calculations associated with the force-controlled settings are shown in Table 1. A travel setting is not used to operate the force-controlled actuator because the actuator automatically decreases the applied force after reaching the maximum force value (as specified by the actuation force setting). However, if the actuation force applied to the pump is too large, damage to the pump is possible.

Table 1. Definitions and calculations of force-controlled settings derived from the force versus time profiles for use on the MR actuation system.

Force-controlled setting	Definition	Calculation
Actuation force (kg)	Maximum force during the actuation	The maximum instantaneous value in profile
Force rise time (seconds)	Time to reach maximum force while firing the pump	Time from initial force to 95% of the maximum achieved force
Force hold time (seconds)	Length of time maximum force is held	Duration instantaneous force exceeds 95% maximum achieved force
Force fall time (seconds)	Time to minimum force after release of the pump	Time from 95% maximum force to baseline force

Table 2. Definitions and calculations of velocity-controlled settings derived from the displacement versus time profiles for the VA actuation system.

Velocity-controlled setting	Definition	Calculation
Travel (mm)	Displacement of the pump	The maximum displacement in the profile
Compression velocity (mm/s)	Linear velocity while compressing the pump	Upward slope found by best fit linear regression between 10% and 90% of the maximum displacement
Velocity hold time (seconds)	Length of time the pump is held in the compressed position	Time period between 90% maximum displacement values
Release velocity (mm/s)	Linear velocity related to releasing the pump	Downward slope found by best fit linear regression between 10% and 90% of the maximum displacement

Velocity-controlled settings, including compression velocity, velocity hold time, and release velocity, were calculated for the VA system (Table 2). Although the travel of the pump was not necessary for VA operation, it was determined because these values were required for velocity calculations and aided in the analysis of partial sprays. The hand data recorded in this study could be used to calculate all the settings necessary to operate automated actuators from other manufacturers.

The settings and spray weights resulting from adult and pediatric participant hand spraying were compared as were parameters derived from participants who

sprayed the bottle using both their dominant and nondominant hands. A two-tailed nonparametric Mann–Whitney test ($P < 0.05$) was performed to determine whether any statistical differences existed between the actuator settings and the spray weight from the adult and pediatric hand data. A two-tailed unpaired *t*-test ($P < 0.05$) assuming unequal variances was used to determine whether statistically different spray weights were generated when participants used both their dominant and nondominant hands to spray the nasal spray.

Results

Force-controlled settings

Force and displacement data were recorded from 20 adults and 20 children hand spraying Flonase in a HAM. Figure 1 shows the force and displacement versus time profiles recorded from three adult and three pediatric participants (raw data and profiles for all participants can be requested from the corresponding author). By visual inspection, the variability between profiles from a single participant ranged from apparently minor to quite extreme, but certainly each profile was unique. The pediatric force profiles, in general, showed lower attained forces and sometimes prolonged profiles. Variability between participants is demonstrated in Figure 2, which shows the force and displacement profiles corresponding to the first spray of each adult and pediatric participant. The pediatric displacement versus time profiles showed less overlap compared with the adults.

Adult and pediatric hand data were analyzed using a predefined set of calculations (Tables 1 and 2) to determine force-controlled (Table 3) and velocity-controlled (Table 4) actuator settings. The mean actuation forces achieved by pediatric and adult participants were 3.37 and 5.82 kg ($P < 0.0001$). The maximum forces achieved ranged from 1.74 to 6.49 kg for children and 2.44 to 8.64 kg for adults. Individual pediatric participant relative standard deviation (RSD) values ranged from 5.3% to 37.7%, with an overall variability of 31.0% RSD. Adult RSD values ranged from 3.7% to 28.4%. The global adult RSD value for actuation force was 24.0%. Four pediatric and six adult participants generated force versus time profiles that resulted in variability less than 10% RSD. Statistical differences in force fall time ($P < 0.0001$), hold time ($P < 0.0001$), and fall time ($P = 0.01$) were found

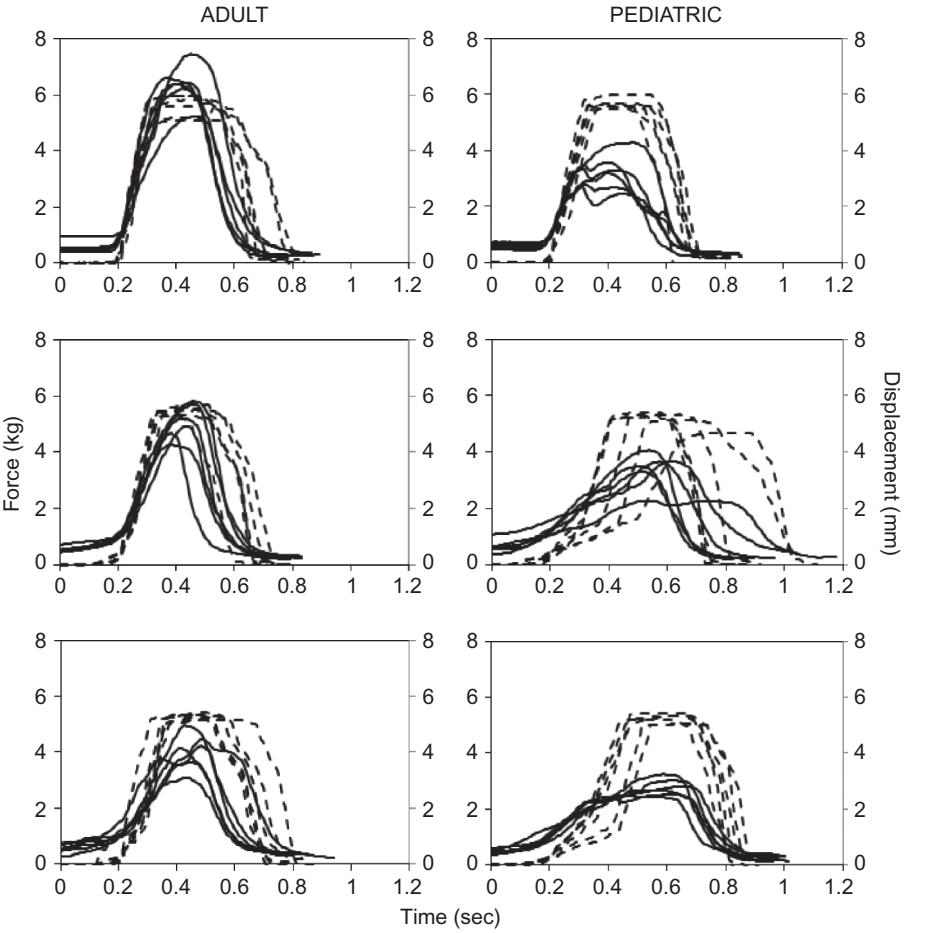

Figure 1. Force (solid) and displacement (dotted) versus time profiles from six actuations recorded using a HAM. Figures represent profiles from three adult and three pediatric participants (raw data and profiles can be requested from the corresponding author). In general, participant variability was greater for the pediatric participants.

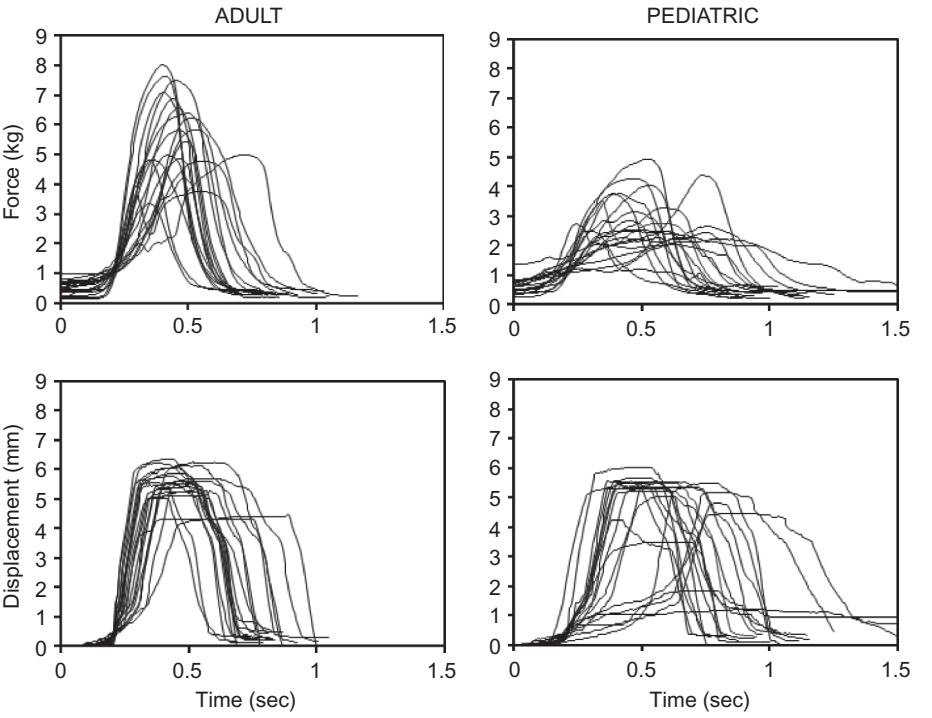

Figure 2. Adult (left) and pediatric (right) displacement and force versus time profiles recorded using a HAM. Each profile corresponds to the first spray recorded for each adult or pediatric participant. Adult participants showed less variability than pediatric participants.

Table 3. Force-controlled settings calculated from adult and pediatric participant hand data.

Force-controlled settings	Mean (SD) adult settings	Mean (SD) pediatric settings	*P*-values
Actuation force (kg)	5.82 (1.40)	3.37 (1.04)	<0.0001
Force rise time (seconds)	0.27 (0.08)	0.35 (0.17)	<0.0001
Force hold time (seconds)	0.09 (0.04)	0.13 (0.08)	<0.0001
Force fall time (seconds)	0.25 (0.06)	0.33 (0.19)	0.01

Table 4. Velocity-controlled settings calculated from adult and pediatric participants' hand data.

Velocity-controlled settings	Mean (SD) adult settings	Mean (SD) pediatric settings	*P*-values
Travel (mm)	5.62 (0.43)	4.99 (0.96)	<0.0001
Compression velocity (mm/s)	41.87 (13.53)	23.54 (14.34)	<0.0001
Velocity hold time (seconds)	0.25 (0.07)	0.27 (0.09)	0.15
Release velocity (mm/s)	34.87 (8.95)	24.41 (14.70)	<0.0001

between the pediatric and adult mean settings. Adult time settings from the force profiles showed lower variability compared with children with RSD values of 29.4–48.6% for FRT, 45.4–62.2% for FHT, and 22.7–57.1% for FFT.

Velocity-controlled settings

The travel of the pump achieved by adults (range: 4.15–6.54 mm) and children (range: 1.19–6.08 mm) in this study was significantly different ($P < 0.0001$). Travel by adults showed less variability with global RSD value of 7.7% compared with 19.3% RSD for children. The velocity hold time for both participant groups was relatively high at 35.0% RSD for children and 29.3% for adults ($P = 0.15$). Mean adult compression velocity of 41.87 mm/sec (RSD 32.3%) was significantly higher ($P < 0.0001$) compared with the mean adult release velocity of 34.87 mm/sec (RSD 25.7%). Pediatric velocities were lower, and the mean pediatric compression velocity of 23.54 mm/sec (RSD 60.9%) was not significantly different ($P = 0.71$) compared with the mean pediatric release velocity of 24.41 mm/sec (RSD 60.2%). When comparing adults to children, both the compression and release velocities showed significant differences (both $P < 0.0001$).

Spray weight

Figure 3 shows the mean spray weight ($n = 6$) for each participant. Adult participants generated sprays of consistent spray weight ranging from 0.5% to 2.3% RSD. The spray weights for pediatric participants were more variable, with RSD values ranging from 1.7% to 47.5%. Figure 4 depicts the global mean spray weight for both participant groups. The global mean spray weight of 88.2 mg (RSD 18.9%) generated by children was significantly less ($P < 0.0001$) than the adult mean spray weight of 95.0 mg (RSD 1.5%). Pediatric participants generated

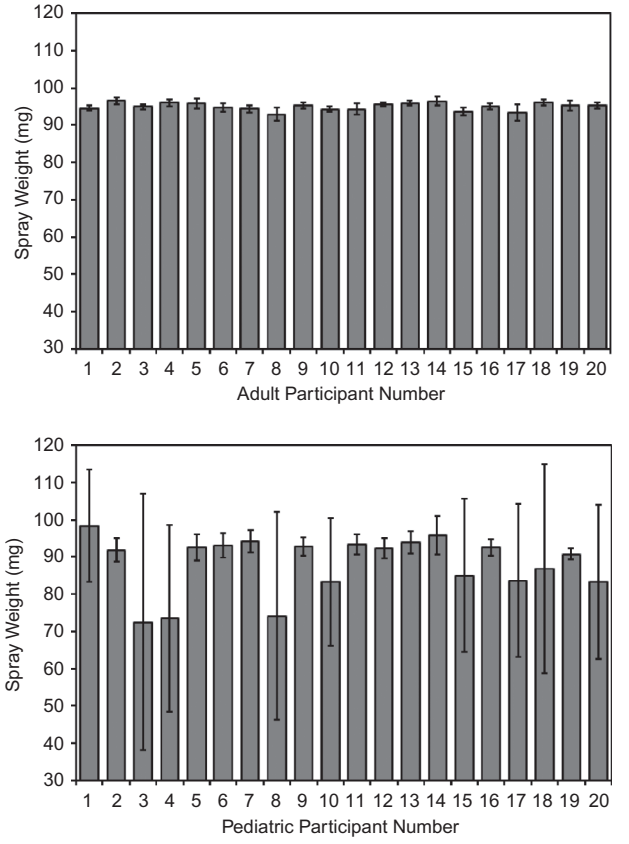

Figure 3. Mean spray weight resulting from hand spraying Flonase by each adult and pediatric participant. Error bars represent the standard deviation ($n = 6$ for each participant).

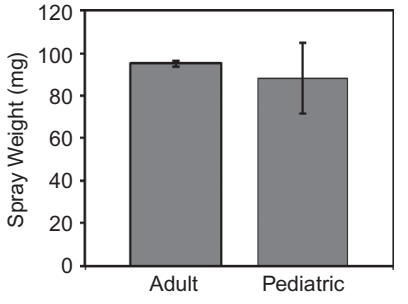

Figure 4. Global mean spray weight for the adult and pediatric participant groups (n = 120). Error bars represent the standard deviation. The global spray weight for the pediatric group showed a 7.7% difference compared with the adult group.

partial sprays (spray weight below 85% mean spray weight) for 11 sprays throughout the study, whereas adults were able to generate complete sprays each time.

Handedness

Out of 20 participants in each group, 18 adults and 18 children stated that their right hand was their dominant hand. Ten adults and eight children used only their dominant hand to first mimic spraying three consecutive times to the dominant-side nostril before spraying the three remaining to the other nostril (Table 5). Seven adult and eight pediatric participants used both their dominant and nondominant hands to coincide with the target nostril, beginning with their dominant hand. One adult and two pediatric participants also used both hands to spray into the coinciding nostril, but sprayed three times first with their nondominant hand. Of the 8 adults and 10 children who used both hands to spray, no statistically significant differences ($P < 0.05$) were found between the spray weights generated by each hand. One pediatric participant used the dominant hand to spray into alternating nostrils, beginning with the nostril corresponding to their dominant hand. Two adults and one child used other handedness techniques.

Table 5. Percentage of adult and pediatric participants using their dominant and nondominant hands

	Adult participants (%)	Pediatric participants (%)
Spray using only dominant hand	50	40
Spray using both hands to coincide with target nostril, beginning with dominant hand	35	40
Spray using both hands to coincide with target nostril, beginning with nondominant hand	5	10
Alternate hands to coincide with target nostril	0	5
Other technique	10	5

Discussion

As the load cell and displacement transducers were time-indexed, we now have a better idea of how people interact with a nasal spray pump during an actuation. The patient applies a baseline force to hold the nasal spray in their hands without initiating movement of the pump (Figure 5). This is usually evidenced in the beginning of the force versus time profile as a horizontal or nearly horizontal portion of the curve. The linear variable displacement transducer monitors the movement of the pump when the participant overcomes the opposing forces of the bottle, which can be attributed mostly to the spring in the pump. The participant applies an increasing force until they recognize complete compression of the pump, or if incomplete compression occurs, until they cannot exert a higher applied force. Typically, the force profile lags behind the displacement profile, wherein the patient continues to apply force to the pump even though complete compression has been achieved and the spray has been generated. Because of this lag, it would be beneficial to have an automated actuator setting that

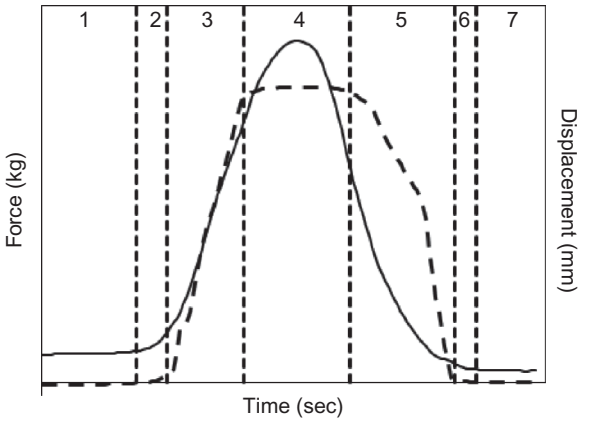

Figure 5. Relation of force (solid) and displacement (hatched) versus time profiles recorded by a HAM to hand movements and bottle displacement. Vertical lines are approximations of the different events that occur during the actuation. (1) Baseline force applied to hold the pump at rest. (2) Increasing force applied, but no movement of the pump. (3) Compression phase, force exceeds the opposing force of the spring, which initiates movement of the pump. (4) Maximum compression phase, patient continues to apply force before encountering resistance at full displacement of the pump, at which point they respond by decreasing force. (5) Release phase, patient reduces force and pump returns to its resting position as the spring in the pump expands. (6) Pump is at resting position while force continues to decrease to baseline force. (7) Resting position of the pump at baseline force.

controls the force applied to the pump when it reaches maximum travel. The force hold time is usually transient, because most participants begin to release the pump after exerting a maximum force. During the force fall time, the applied force on the pump decreases until it reaches the baseline force of the participant holding the pump. During this decrease, the spring relaxes and the pump returns to its original, resting position. In general, the force versus time profile is curved, whereas the pump displacement profile can be split into roughly three linear sections according to the compression, maximum compression, and release phases.

The relation of force and displacement recorded during hand spraying are in contrast to actuation by a velocity-controlled system, where a higher actuation force and an increased force rise time are needed when pump travel is increased[14]. In an electrically driven velocity-controlled system, a constant velocity is achieved regardless of the forces used during the compression and release of the pump. Velocity-controlled actuators vary the force applied to the nasal spray pump during the actuation to maintain a constant compression or release velocity, whereas a force-controlled actuator applies an increasing force that results in travel of the pump. Force-controlled actuators more closely mimic the situation of a patient actuating a pump, whereby the application of force by the patient causes the pump to travel.

This study focuses on the hand technique used by participants, but other factors can potentially influence the force and displacement profiles. The shape of the profiles is specific to the device being used. The force constant of the spring in the pump dictates how difficult it will be to compress the pump and how much force needs to be applied by the patient before the pump initiates movement. In pumps that are very difficult to actuate, incomplete or no spray events may occur more frequently by patients who cannot attain high actuation forces. Although we tried to design a study to reflect actual modes of patient use, we cannot eliminate the possibility that the size and weight of the HAM instrumentation could have exerted an influence on our findings. Participants simulated real-use, but did not dose directly into the nose, which could also influence the profiles.

Learning was described by comparing the settings between the first three and last three sprays generated by each participant. However, this method of determining learning is complicated if the participant used both hands to actuate the nasal spray. Although some differences (data not shown) were found between the first three and last three sprays for some participants, the occurrences are in the minority and none of the participants showed learning in more than two different settings. Two pediatric participants (one switched hands) and three adult participants (two switched hands) showed differences in two settings. Although learning cannot be completely negated, it did not seem to influence the results of this study of how participants actuated the nasal spray.

This study used a predefined set of calculations to determine patient-related actuator settings from adult and pediatric participant data. It is important to note that the definitions are subjective and modifications can be justified. For example, velocities were calculated by determining the slope of the best fit line using data between 10% and 90% of the maximum travel. This accounted for most of the data along the compression and release phases without including the acceleration and deceleration sections of the profile.

We found that the variation within and between adult and pediatric participants could be very high, but in general the variation was greater in children. When comparing adults with children, we found significant differences in the actuation force, force rise time, force hold time, force fall time, travel, compression velocity, and release velocity settings. Only velocity hold time was not significantly different. The differences associated with hand spraying by children led to a significant reduction in spray weight compared with adults. Although differences were measured in vitro, it is not known whether these will translate into in vivo differences between adults and children. Although adults were able to generate full sprays for each mimicked dose, children failed to generate full sprays 11 times out of 120 attempts. Optimally, the product should be able to operate consistently under different applied forces, velocities, and so on, to generate a spray with the same characteristics to ensure consistent delivery to the patient.

Hand selection is not often dictated to patients in product instructions, although it has been shown to have a relationship on the occurrence of epistaxis (nosebleeds), a common side effect of intranasal steroid use, based on the direction of the spray toward the septum[20,21]. Fifty-five percent of the adult participants and 45% of the pediatric participants used their dominant hand regardless of nostril selection, whereas 40% of the adult and 50% of the pediatric participants used both their dominant and nondominant hands to coincide with the target nostril. None of the participants mimicked spraying using the hand opposite to the target nostril, which is most likely to direct the spray away from the septum and decrease the likelihood of epistaxis.

Conclusions

This study quantified, for the first time, the differences in hand spraying between adult and pediatric participants. A predefined set of calculations described how force and displacement data obtained by hand spraying were used to operate force and velocity-controlled automatic actuators. Based on our findings, we think it is appropriate to investigate the hand techniques representative of the intended age group(s) and assure the product would function properly in the hands of a trained patient. We encourage the submission of results using a range of automated actuation settings (both high and low), to facilitate an understanding of how the product would likely perform in the hands of different patients. Future device selection can be geared toward minimizing changes in dosing and spray characteristics when different hand techniques are used. Subsequent studies will measure the effect of variability related to adult and pediatric hand spraying on the spray weight, droplet size, and spray pattern of the nasal spray.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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