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Review

Delivery devices for the administration of paediatric formulations: Overview of current practice, challenges and recent developments

Jennifer Walsh[a,*], Deborah Bickmann[b], Joerg Breitkreutz[c], Maryvonne Chariot-Goulet[d], on behalf of the European Paediatric Formulation Initiative (EuPFI)

[a] Pharmaceutical Development, AstraZeneca, Bakewell Road, Loughborough, Leicestershire, LE11 5RH, United Kingdom
[b] Boehringer-Ingelheim Pharma GmbH & Co. KG, Respiratory Drug Delivery Germany, Binger Str. 173, 55218 Ingelheim am Rhein, Germany
[c] Institute of Pharmaceutics and Biopharmaceutics, Heinrich-Heine-University, Universitätsstrasse 1, 40225 Düsseldorf, Germany
[d] Pharmaceutical Sciences Department, Sanofi-Aventis, 1, avenue Pierre Brossolette, 91385 Chilly Mazarin, France

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ABSTRACT

The European Paediatric Formulation Initiative (EuPFI), a group consisting of paediatric formulation experts from industry, academia and clinical pharmacy was founded with the aim of raising awareness of paediatric formulation issues. It is imperative that paediatric medicines can be administered accurately to ensure the correct dose is provided and that the administration device is easy to use and acceptable from the patient's and carer's perspectives. This reflection paper provides an overview of currently available paediatric administration devices and highlights some of the challenges associated with, recommendations and recent developments in delivery devices for the oral, inhaled, parenteral, nasal and ocular administration of paediatric formulations, on behalf of the EuPFI.

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1. Introduction

The European Paediatric Formulation Initiative (EuPFI), a group consisting of paediatric formulation experts predominantly from industry, as well as academia and clinical pharmacy, was founded in 2007 with the aim of raising awareness of paediatric formulation issues. The current focus areas of the group include excipients, taste assessment, delivery devices for the administration of medicines,

* Corresponding author. Tel.: +44 1509 644567.
E-mail addresses: jenny.walsh@astrazeneca.com (J. Walsh), deborah.bickmann@boehringer-ingelheim.com (D. Bickmann), joerg.breitkreutz@uni-duesseldorf.de (J. Breitkreutz), maryvonne.chariot-goulet@sanofi-aventis.com (M. Chariot-Goulet).

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age appropriate dose forms and extemporaneous preparations. This reflection paper is written on behalf of the delivery devices group of the EuPFI and provides an overview of currently available paediatric administration devices and highlights some of the challenges associated with, recommendations and recent developments in delivery devices for the oral, inhaled, parenteral, nasal and ocular administration of paediatric formulations.

Since the new Paediatric Regulation came into force in the European Union in January 2007 (EC, 2006), a Paediatric Investigation Plan (PIP) outlining the paediatric drug product strategy needs to be agreed with the EMA's Paediatric Committee (PDCO) at an early stage of development. The paediatric population is divided by age into different sub-groups (ICH E11, 2000) and consideration needs to be given to the targeted paediatric population when developing age appropriate formulations and medical devices, since different age groups will have different requirements for optimal drug delivery.

It is imperative that formulations can be administered accurately to ensure the correct dose is provided. Furthermore, acceptability and ease of use of a device with which the product will be administered both from the patient and carer's perspectives is required to facilitate dosing and patient compliance. When developing paediatric formulations, it is therefore important to consider the requirement for a delivery device at an early stage in the development process. The device must be technically capable of delivering the required dose in a "user friendly" way. The need for and type of delivery device will depend upon the formulation, age of patient and route of administration. The interaction of pharmaceutical formulations and their administration device regarding incompatibilities or dosing accuracy are common issues that have to be considered not only in paediatric product development. The viscosity of a drug solution and the design of the corresponding dropper or the dispersing properties of an inhalation powder formulation and the inhalation device used are examples of critical interactions that influence the performance and quality of a pharmaceutical product. These issues are also addressed in regulatory guidances as for instance the reflection paper "Formulations of Choice for the Paediatric Population" by the European Medicine Agency. Frequency and duration of dosing may also have an impact on device requirements (CHMP, 2006).

Table 1 provides an overview of currently available administration devices and these are discussed below.

2. Oral delivery

The oral route is the most common route of administration for medicinal products. Solid oral dosage forms such as capsules or tablets that are intended to be ingested whole may be acceptable for children above the age of 6 years, depending on the ability of the child to swallow, and indeed are preferred by adolescents (CHMP, 2006). Recent studies have demonstrated the ability of some children as young as 2 years old to be able to swallow small tablets ("minitablets", e.g. 3 mm diameter) (Thomson et al., 2009). Delivery devices for solid oral dosage forms such as tablets and capsules are generally not required, since dosing accuracy is provided by the requirements for assay and uniformity of content and/or mass of the product. It should be noted that tablets that are designed to be split should have a break line that allows the tablet to be easily split by hand and all the subdivided tablet parts should comply with compendial requirements for content/mass uniformity.

For newborn infants (aged up to 28 days), infants and toddlers (1 month to 23 months) and young children (for example below 6 years) oral liquid dosage forms are the preferred option, and also allow flexible dosing. Typical target dose volumes are $\leq$5 mL for children under 5 years and $\leq$10 mL for those of 5 years and over (CHMP, 2006). For liquid dose forms that require administration with a measuring device, it is important that graduations on the dosing device are clear (e.g. embossed or printed) to enable accurate and precise dosing. In addition, the physical characteristics of the liquid in relation to the proposed dosing device must be considered (EMA, 2004; GIE, 2009).

Measuring spoons may be provided or purchased with oral liquid medicines. It is of note that the shape of such spoons can affect dosing accuracy. Indeed, spoons with a small base area appear to have better accuracy than those with a broad base area. Furthermore, graduations on dosing spoons that are often used to measure doses less than 5 mL can lead to inaccurate and variable dosing (Griessmann et al., 2007). Providing an appropriate medicine spoon with an oral liquid medicine is recommended and this helps avoid the use of inappropriate devices such as household spoons (teaspoons and tablespoons) being used to dose oral liquids, which can lead to inaccurate dosing (Aziz and Jameela, 1990; Madlon-Kay and Mosch, 2000).

Graduated measuring cups may be an alternative to measuring spoons, especially if volumes larger than 5 mL are required to be administrated, as they avoid multiple dosing operations. However, measuring or dosing cups have disadvantages, for example there is potential for residual liquid to remain in the device after administration of the dose, in particular with viscous liquids and suspensions. Furthermore, investigations comparing the accuracy of dosing of oral liquid suspensions using dosing cups, oral syringes and droppers have found that carers are more likely to measure unacceptable doses with dosing cups compared to the other devices, with the majority of errors resulting in overdose (Sobhani et al., 2008; Yin et al., 2010).

Oral droppers may be used to administer very small volumes of oral liquids, in particular for infants or where the liquid has an unpleasant taste. However, it is important that the dropper is held vertically to ensure accuracy and consistency of dosing (Brown et al., 2004).

Oral syringes (dispensers) tend to be the delivery device of choice for oral liquids administered to children by healthcare professionals in hospital. However, parents and carers may use oral syringes more frequently in young children up to the age of 3 years compared to older children (Kairuz et al., 2007). Indeed, there may be perceptions in older paediatric patients and their carers that oral syringes are only suitable for babies and infants.

Oral syringes have been found to provide more accurate and less variable dosing results than spoons (Griessmann et al., 2007; Dockhorn et al., 2010). To aid delivery of the dose, clear instructions should be provided on the correct filling of the syringe to avoid air bubbles, together with dosing information for different patient weights. In addition, oral syringes should be graduated with consistent units of measure, for example mL. The use of milligrams should be avoided as this could cause confusion. It should be noted that the use of kg as units of measure relating to the weight of the patient is acceptable in some countries. Should this approach be used, the syringe should only be used with a specific product to avoid dosing errors. Oral syringes with caps should be avoided due to the risk of choking from the cap.

Taking into consideration the observations described above, the recommended delivery device for oral liquids is an oral syringe. This delivery device should not be restricted to infants and toddlers, but may be used for older children requiring a liquid formulation, as long as the size and design of the syringe permits the necessary volumes to be accurately delivered. Thus during the development of an oral syringe, both the properties of the liquid and volumes required by the target patient population must be evaluated. Oral syringes provide the most accurate means of delivery and are easy to use; unlike droppers the angle of administration is not critical. Accuracy of dose is of particular importance for actives with high potency and/or narrow therapeutic window. In addition oral syringes have

Table 1
Overview of currently available delivery devices used for the administration of medicines to children.

Route	Administration device	Advantages	Disadvantages	Comments
Oral				
	Measuring spoon	Widely available Generally easy to use	Fixed volume – usually 5 mL May get variability in volumes measured from same spoon Shape of spoon can affect dosing accuracy Graduations can lead to inaccurate dosing Product may be spilled during dosing	Most commonly used delivery device – more accurate than household spoons
	Measuring/dosing cup	Widely available Multiple dosing operations may be avoided where larger volumes than 5 mL are required	Unacceptable doses more likely to be measured Multiple graduations may be confusing to carer May get residual volume remaining after dosing Product may be spilled during dosing	
	Droppers	Widely available Useful for administering very small volumes (drops)	Dropper must be held vertically to ensure accuracy and consistency of dose Drop size may be affected by physical properties of liquid	Tend to be used for babies and small children
	Oral syringe/dispenser	Provide more accurate and less variable dosing than spoons and cups Allow dose flexibility in terms of volumes that can be measured Various sizes available Angle of delivery does not affect dose Spillage of dose unlikely	Measurement of dose may be confusing to some carers May cost more than spoons or dosing cups	Syringes with caps should not be used to avoid risk of choking
Parenteral				
	Syringe pump	Provide precise and regulated infusion rates Remove the need for multiple injections	Adsorption of drug onto syringes and tubing needs to be considered Can be bothersome to patient (may hinder movement)	Use of paediatric syringe pumps recommended. Microbore tubing is recommended. Needle length can affect injection pain; short needles are less painful
	Pen device	Easier to use and transport than syringes Older patients can self administer May be more accurate than syringes (e.g. for low dose insulin)	Can be expensive	Customised pen devices available to facilitate compliance (e.g. pink, car-shaped)
Pulmonary				
	Pressurized metered dose inhaler (pMDI)	Widely available Low manufacturing costs Breath-actuated pMDIs available	Require a high degree of co-ordination abilities High oropharyngeal aerosol deposition (risk of possible side-effects)	Children $\leq$ 6 years should use a pMDI in combination with a valved holding chamber or a spacer
	Nebuliser (optionally with electronic control unit)	Widely available Require no co-ordination abilities Individually mixed drug solutions can be administered. Suitable for the treatment of severe asthma attacks	Expensive Require power and a greater maintenance Unwieldy to be transported Long application time	Children $\leq$ 4 years should use a facemask. The fit of the mask affects on the aerosol delivery efficiency Recently developed nebulisers using e.g. vibrating mesh technology provide smaller particles in shortened application times and offer an additional adapted aerosol delivery (AAD)
	Soft mist inhaler (SMI)	Require less co-ordination abilities due to a longer spray duration and slower aerosol velocity Reduction of oropharyngeal aerosol deposition (less unwanted side-effects)		Can be optionally combined with a valved holding chamber or spacer for children $\leq$ 4 years
	(Passive) Dry powder inhaler (DPI)	Require less co-ordination abilities as aerosol delivery is driven by the patient's inhalation Breath-actuated DPIs are available	Children $\leq$ 4 years cannot generate an appropriate inspiratory flow to obtain sufficient fine particles Should not be used during severe asthma attacks	Thorough training and monitoring is indispensable as each DPI requires its own special handling technique

Table 1 (*Continued*)

Route	Administration device	Advantages	Disadvantages	Comments
	Accessory devices (valved holding chamber/VHC, spacer)	Reduce in combination with pMDIs the required co-ordination abilities Reduction of aerosol deposition in the upper airways (less unwanted side-effects) With VHCs the aerosol can be inhaled by several breaths (enhanced lung deposition)	Possible side-effects due to facial and nasal aerosol deposition when used with a facemask	Recommended during severe asthma attacks. Children ≤ 4 years should use a facemask. Close fit of the mask is essential for an efficient aerosol delivery. Significant variation of aerosol delivery depending on the type and washing procedure used
Nasal	Syringes (optionally with attached spray device)	No-needle technique for systemic applications Require lower doses	Poor compliance in small children Difficult mode of application for parents/caregivers	Administration of volumes> 250 μL can cause dripping of formulation out of nostril or down the back of the throat, especially in children due to small dimensions of nasal cavity
	Atomising pump devices (mechanically, propellant- or electronically driven)	Small droplet sizes No-needle technique for systemic applications Require lower doses	Poor compliance in small children Difficult mode of application for parents/caregivers	Breath-powered devices available Administration of liquid and powder formulations possible
Ocular	Squeezable dropper bottles	Widely available Low manufacturing costs	Poor compliance in small children Difficult to handle for parents and caregivers Often require frequent dosing due to low bioavailability	Little research into paediatric ocular delivery devices Eye drop dispensers, intended for the use by geriatric patients and those with arthritis, could also be applied to children

Fig. 1. Medibottle® medicine delivery system (Savi Baby, USA).

the advantage of allowing for dose flexibility, which is of particular value when adjustment of dose is required, for example with respect to the weight of the paediatric patient.

2.1. Recent developments in oral delivery

In response to the challenges associated with the accurate and consistent delivery of paediatric formulations, over 100 patents have been filed for paediatric dosing devices. The majority of these relate to the delivery of liquids by the oral route, for example, modified feeding bottles such as Medibottle® (www.medibottle.com/) (see Fig. 1). This comprises a traditional baby bottle with an oral dispenser that slides into the centre sleeve of the bottle. The bottle is filled with milk or other drink and the dispenser is filled with the required dose of medicine and then inserted into the bottle. Whilst the baby is drinking, the dispenser plunger is quickly depressed to produce a squirt of medicine every few sips of the milk or drink. The medicine is swallowed by the baby and washed down by the milk/drink. This device would be acceptable for babies and infants, but less so for older children.

A number of patents exist for modified pacifiers and teats whereby the required dose of medicine is placed in a reservoir that is attached to a hollow nipple. The infant receives the medicine either by sucking the nipple or by the carer compressing the reservoir to force the liquid into the infant's mouth. An example of such a pacifier is shown in Fig. 2. As with the Medibottle®, this device is more appropriate for infants than older children. In addition, these devices are generally not very accurate, as it is difficult to ensure the full dose has been delivered, and only allow for the delivery of very small volumes.

Parvulet technology from Egalet comprises a plastic spoon containing a dry dose of product which is glued into the bucket. The spoon is immersed in water which causes the dry product to swell into a paste-like medicine, which can then be dosed to the patient. Another paste-spoon product has been developed using

Fig. 2. Baby Medicine Dispenser (Mothercare, England).

this technology whereby the active ingredient is covered by a micro-perforated foil (see Fig. 3). This improves the stability of the product, especially those that are sensitive to moisture. After immersing the spoon in water for several seconds, the ready-to take paste is formed. The foil cover is peeled off and the dose may be administered. This type of product which is most suitable for young children offers the convenience of single unit dosing and also avoids the risk of spillage.

Technologies such as Dose Sipping Technology (Breitkreutz and Boos, 2007) have also been developed. For sipping a single dose of small-sized pellets, the straw is held into the child's beverage. Any beverage is suitable except liquids containing natural fibres as these may cause the filter at the bottom of the straw (controller) to become blocked. When sipping through the straw the pellets reach the mouth together with the liquid. Internal studies of the manufacturer, Grünenthal GmbH, show that the Dose Sipping Technology increases children's compliance significantly. Such devices require some compatibility studies to be conducted to ensure the beverage is compatible with the drug. A dose-sipping device has recently been developed using this technology, whereby the oral syringe has an additional clamp ring to fix the prescribed dose and ensure exact measurement. An integrated straw with valve allows two-way administration: the pre-measured dosage may either be sipped with any favourite liquid or passively administrated to the child by smoothly shooting it into the mouth.

A "pill swallowing cup" has been developed to help patients who have difficulty in swallowing tablets (www.oraflo.com) The cup has a snap-on lid and a specially designed ribbed spout. Users fill the cup half full with a beverage, place the lid on the cup and drop the tablet into the spout. The tablet sits on a mesh above the liquid. The user then drinks naturally from the cup. The angle and flow of the liquid push the tablet to the back of the throat so it is easily swallowed.

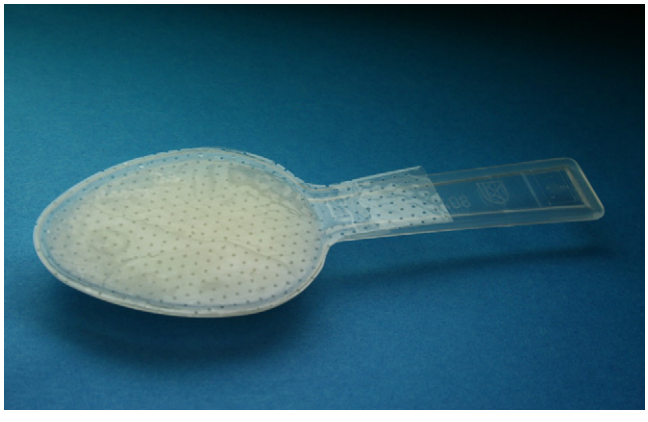

Fig. 3. Pulp spoon device with perforated film (Sandoz, Germany). This is immersed in water to form a ready-to take paste.

3. Delivery via inhalation

The administration of medication via the inhaled route is preferred for respiratory diseases such as asthma or cystic fibrosis since the therapeutic aerosol is delivered directly to its intended target with less systemic side effects compared to the oral route. Furthermore, the large surface and high permeability of the lung epithelium also provides the opportunity for a systemic application of aerosolized drug (Voshaar, 2005).

Inhalation devices for paediatric therapy should consider the special needs of children as they have a different airway anatomy, nature of pulmonary disease and inhalation pattern compared to adults. Also the cognitive development plays an important role. Children below the age of 3 years are often unable to adopt a required inhalation manoeuvre and even school children have difficulties to switch between different prescribed manoeuvres (Kamin and Kreplin, 2007). A close monitoring of their inhalation technique and an enhancement of compliance is essential for a successful therapy.

Particular recommendations with respect to the type of inhalation device for different age groups of children are provided below.

Pressurized metered dose inhalers (pMDIs) are a convenient therapeutic option in the treatment of paediatric airway diseases but due to a high required degree of co-ordination between actuation and inhalation the individual devices are usually not appropriate for children under the age of 6 years.

Add-on devices such as spacers or valved holding chambers (VHCs) which are compatible with the inhaler facilitate the use of a pMDI; little co-ordination is required and, a reduction of aerosol impaction in the upper airways leads to less unwanted side-effects and enhances lung deposition. Generally, children below the age of 4 years should use a VHC with a facemask since many of them have difficulties to inhale solely through the mouth (GINA, 2006). However, the precise age at which a facemask is not required will depend upon the mental capability of each individual child (Pedersen et al., 2010).

It is important that the facemask fits closely and comfortably on the child's face otherwise a large amount of drug will be lost (Sangwan et al., 2004; Smaldone et al., 2005). Lung dose, aerosol deposition in the upper airways and drug retention inside the add-on device can vary significantly among the different types of spacer/VHCs (Feddah et al., 2001; Barry and O'callaghan, 1999) and the applied washing procedures (Barry and O'callaghan, 1999). These are important considerations for the selection of drug dose. When a facemask is used, a certain part of aerosol which is inhaled through the nose will deposit on the nasal mucosa and can be absorbed leading to possible side-effects. Particle deposition can also take place on the face which may cause irritation if the face is not washed (Hess, 2008). During a severe asthma attack with lowered co-ordination abilities the use of a pMDI in combination with a spacer/VHC is recommended (GINA, 2006). If children of any age above 6 years are not able to co-ordinate actuation and inhalation through a pMDI, they should use an additional spacer or VHC device with a mouthpiece or one of the following alternative inhalers.

Breath-actuated pressurized metered dose inhalers are an alternative to conventional pMDIs as they have a special mechanism that automatically releases the aerosol when the patient inhales faster than a certain air flow rate. A manual actuation is also possible as it can be difficult to achieve these inhalation flow rates during a severe asthma attack. To assure that children reach the required minimal air flow rate the In-Check Dial device is a valuable

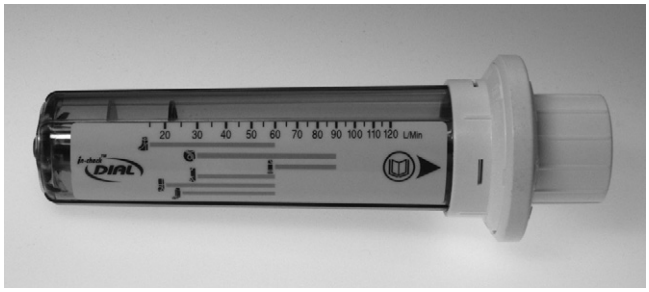

Fig. 4. The In-Check Dial device (Clement Clarke International Ltd., United Kingdom) with its imprinted scale for assessing the suitability of the chosen inhaler.

tool to control their peak inspiratory flows (Geldhof et al., 2001). Different air flow resistances of convenient inhalation devices can be adjusted and the suitability of each device for every individual patient can be assessed via an imprinted scale (see Fig. 4)

A new generation of liquid aerosol inhalation devices are soft mist inhalers (SMI) with a slowly moving aerosol cloud and a prolonged spray duration that give patients enough time to co-ordinate their inhalation manoeuvre with the device actuation. Furthermore, the amount of aerosol particles impacting in the oropharyngeal region is significantly reduced compared to pMDIs causing less unwanted side-effects (Newman et al., 1998). For children under the age of 4 years the SMI can be combined with a valved holding chamber plus facemask (see Fig. 5).

Ultrasonic and jet nebulisers are still widely used for the treatment of paediatric airway diseases despite being accompanied by several drawbacks. In most cases the devices are unwieldy to be used routinely and transported (especially for a home-based treatment), require power, need greater maintenance and tend to be expensive. Furthermore, the application time is much longer compared to pMDIs or SMIs and the heterogeneous particle size distribution of the generated aerosol is often not appropriate for children < 4 years (Wildhaber and Kamin, 2010). The success of therapy in children below the age of 4 years depends on the fit and how long the facemask must be worn (Smaldone et al., 2005). Indeed, many children become upset during the long inhalation time. The advantages offered by ultrasonic and jet nebulisers are the possibility to mix different active ingredients (individual composed for each patient) and to use it with medical solutions that are not available in other inhalation devices. They can also be used for the treatment of a severe asthma attack as they provide the opportunity to transport a higher medical dose over the long application time and no co-ordination abilities are required.

Dry powder inhalers (DPIs) are increasingly used as an alternative to pMDIs in the treatment of airway diseases as the required energy for particle dispersion is provided by the patient's peak

Fig. 5. On the right the Salbulair N Autohaler (IVAX Pharma GmbH, Germany) and the Spiriva Respimat Soft Mist Inhaler (Boehringer Ingelheim, Germany) with the AeroChamber Plus (Trudell Medical International, United Kingdom) valved holding chamber.

Fig. 6. Dry powder inhalers used in children. From left to right: The Budecort Novolizer (Meda AB, Sweden), the Asmanex Twisthaler (Essex, Germany), the Pulmicort Turbuhaler (AstraZeneca, United Kingdom) and in front the Serevent Diskus (GlaxoSmithKline, United Kingdom).

inspiratory flow and not by propellants. The implication of this is that the patient must achieve a certain inhalation flow rate to generate sufficient amount of fine particles that are required to reach the lung. Children below the age of 4 years cannot normally generate an adequate inspiratory pressure to obtain the necessary flow rate. Apart from physiological condition of a child, mental capacity as well as manual abilities will determine the choice of the system used as each DPI requires its own special handling and inhalation manoeuvre. A thorough training and monitoring of the child's technique is indispensable.

Generally, DPIs with a low air flow resistance are preferred in the group of children aged 4–6 years (see Fig. 6). Breath-actuated devices additionally assure that the aerosol is only delivered when the patient reaches a sufficient inhalation flow rate. Children above the age of 6 years are usually able to handle a DPI independently and to achieve peak inspiratory velocities that are satisfactory for a medium resistance inhaler (Adachi et al., 2006; Amirav et al., 2005). Since the quality of aerosolization and therefore the therapeutic success relies on the magnitude of the inhalation flow rate DPIs should not be used during severe asthma attacks where breathing is impaired.

3.1. Recent developments in pulmonary delivery

Since the key for successful inhalation therapy is the children's adherence, various spacer/VHCs have been developed during the last few years to improve children's compliance and to address their special needs. The Babyhaler is a valved holding chamber that is particularly designed for the use in infants providing a very comfortable mode of application. A non-electrostatic holding chamber with a universal adapter for all conventional pMDIs is the Vortex (http://www.pari.de/produkte/inhalierhilfe_vortexr.html) equipped with a funny facemask (see Fig. 7). The Watchhaler (http://www.watchhaler.com/) has a very appealing design limiting the inhalation flow rate (15 L/min) and providing a visual feedback of successful use. A very creative development is the Funhaler (http://www.avitamedical.com), a valved holding chamber with an internal spinning disc and a whistle. The disc spins and the device whistles when the child breathes normally, thus encouraging them to take their medication.

In response to the drawbacks regarding nebulisers mentioned above, newly developed nebulisers have implemented a vibrating

Fig. 7. Recently developed spacers/valved holding chambers. From left to right: The Vortex (Pari, Germany), the Funhaler (InfaMed Ltd., Malaysia) and the Watchaler (Actinaero GmbH, Germany).

mesh technology for aerosol generation resulting in smaller aerosol particles with shortened application times (e.g. eFlow® rapid). Also smaller and more portable devices (e.g. AeroNeb® Go, MicroAir™, I-Neb® AAD®) have been developed. This new technology also enables the administration of small medical volumes. The AKITA® JET system consisting of a nebuliser and an electronic unit is a newly developed device that controls and supplies air to the patient performing individually adapted breathing patterns via SmartCard technology. Due to higher costs its application is particularly useful to enhance the lung deposition of expensive medications (e.g. antibiotics like tobramycine).

As dry powder inhalers offer the opportunity to administer drugs that are poorly soluble it would be desirable to have active DPIs in combination with spacers/VHCs that would provide these active ingredients even to the youngest children (Bisgaard, 1998).

4. Parenteral delivery

There are several challenges in the delivery of parenteral products to paediatric patients, for example accuracy and consistency of dose, especially when small doses are required. Osmolarity of solutions, pH, fluid volumes and low infusion rates must also be considered (CHMP, 2006). It is necessary to balance the amount of fluid required to dilute a drug to an appropriate osmolarity with the amount required to dilute the drug so that an accurate dose can be measured, together with the daily fluid allowance for the child. Clear, easy to follow dose and administration instructions should be provided to help mitigate against potential medication errors. For example, incorrect rate of intravenous administration, incorrect dose and incorrect administration technique have all been reported with parenteral delivery to paediatric patients (Ghaleb et al., 2010).

The use of syringe pump delivery systems specifically designed for use with children has been found to offer the advantages of precise and regulated infusion rates and ease of administration (Ghaleb et al., 2010). Such systems may allow the preparation of medication in a range of syringe sizes (e.g. 1–60 mL), the setting of specific infusion rates and the delivery of small amounts of drugs in increments as small as 0.01 mL (McCurdy and Arnold, 1995).

The size of intravenous (IV) tubing lumen should also be considered when treating paediatric patients and it is recommended that micro bore tubing is used to decrease residual volume (McCurdy and Arnold, 1995). *In vitro* studies have shown that delivery of drug through large bore tubing (4 mm) took significantly longer than through small bore tubing (1.7 mm) (Arwood et al., 1984).

The potential for drug adsorption onto syringes and tubing should be investigated during development. For example, it has been reported that 10% of insulin dose may be adsorbed onto infusion sets with infusion rates of 1 mL/h. However, when higher infusion rates are used, no significant adsorption appears to occur, although insulin concentrations may be lower at the beginning of the infusion period compared to the end. In order to mitigate against the effects of drug adsorption, it is recommended to prime syringes and tubes before use (Jakobsson et al., 2009).

The use of "paediatric" vials containing 50 mg/mL of drug for IV infusion has been shown to improve dose precision in neonates compared to "adult" vials containing 250 mg/mL of drug (Allegaert et al., 2006). The development and use of such paediatric products should therefore be considered as "adult strength" IV products may be of concentrations requiring either low volumes or sequential dilutions, both of which may lead to error. However, it is recognised that the introduction of "paediatric" vials has the potential for confusion with the "adult" vial and will also lead to additional costs and complexity.

Accuracy and consistency of dose is important for children with Type I diabetes, who tend to require small doses of insulin. Investigations comparing pen devices with insulin syringes have shown that the pen devices were more accurate when measuring 1, 2 and 5 U of insulin. However the authors concluded that all the devices were inaccurate, especially the syringes, at delivering 1 U doses of insulin. In addition, both devices were comparable for doses greater than 5 U (Gnanalingham et al., 1998; Lteif and Schwenk, 1999). It is therefore recommended that pen devices should be used when administering up to 5 U of insulin to children. Pen devices also have the advantage of generally being easier to use and transport than syringes. Indeed, children from the age of 10 years are usually able to self administer insulin with a pen device. These devices also provide benefit to patients requiring larger doses of insulin.

Another treatment area where self administration by the patient is common is the delivery of growth hormone (hGH). The accuracy and patient evaluation of a pen delivery system for hGH, Kabipen, was assessed by Gluckman and Cutfield (1991). They found that the majority of patients preferred the Kabipen over conventional needle and syringe delivery. Furthermore, children over the age of 10 years were more likely to self administer hGH with the Kabipen. Both delivery systems were found to be of comparable accuracy. Therefore, it is recommended that pen injector type systems are used for the delivery of hGH. A number of pen devices for the delivery of growth hormone are available, including Easypod® (www.saizenus.com), NordiFlex®, NordiPen® (www.novonordisk.com/therapy_areas/growth_hormone/public/default.asp) (see Fig. 8) and Genotropin pen® and MiniQuick® devices (www.genotropin.com/content/about_devices.aspx, www.ypsomed.com/en/435.html).

The dimensions of needles used for paediatric delivery may affect the amount of pain experienced by the patient and the incidence of local reactions after immunisation. Therefore, consideration should be given to the size of needle selected and its intended use.

Dorchy et al. (2008) found that the use of different needle lengths for administration of insulin resulted in large differences in the injection pain experienced by diabetic children and adolescents. It was found that 8 mm length needles caused much less pain than 12.7 mm length needles.

The use of wide long needles (23 gauge/0.6 mm diameter/25 mm), narrow short needles (25 gauge/0.5 mm diameter/16 mm) and narrow long needles (25 gauge/0.5 mm diameter/25 mm) for infant vaccination (combined diphtheria, tetanus, whole cell pertussis and *Haemophilis influenzae* type b vaccine and a serogroup C meningococcal glycoconjugate vaccine) has been investigated by Diggle et al. (2006). Interestingly, they found that infants vaccinated with wide long rather than short

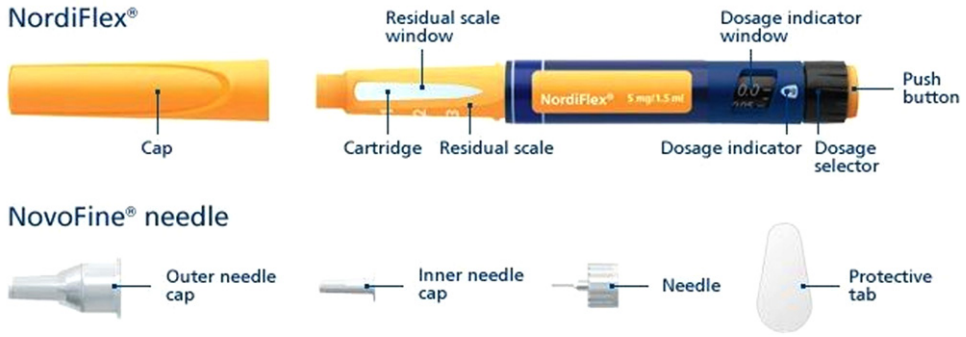

Fig. 8. Diagram of Nordiflex® device with NovoFine® needle, used for the delivery of growth hormone (©Novo Nordisk A/S).

narrow needles experienced significantly fewer local reactions. Little difference was found between needles of the same length, but in different gauges. It appeared that needle length rather than gauge was associated with reduced reactions and that long needles can significantly reduce vaccine reactogenicity. The authors suggest that this difference may be due to the longer needle ensuring delivery into an infant's thigh muscle.

4.1. Recent developments in parenteral delivery

Another challenge in paediatric parenteral drug delivery is the pain that can be associated with this route of administration, which can lead to patient anxiety, discomfort and in some cases poor compliance (for example with insulin administration). Although the use of topical local anaesthetics or distraction techniques can minimise pain, a number of needle-free drug delivery devices have been developed to mitigate against this issue. They have been used for the subcutaneous route of injection and in some cases the intramuscular route. These devices deliver the product (liquid or powder) under high pressure through a very small orifice, which is then able to penetrate the skin.

Examples include PharmaJet® (www.pharmajet.com/product.html) (see Fig. 9), J-Tip (www.jtip.com/) and Bioject® delivery systems (www.bioject.com/biojector2000.html). These devices have been used to administer large molecules such as insulin, vaccines and growth hormone and also local anaesthetic for example prior to IV cannulation. The SUMAVEL™ DosePro™ device has been developed for the delivery of sumatriptan and was approved by the FDA in 2009 (www.zogenix.com/).

The advantage of the needle-free devices is that they can aid compliance by reducing fear and also remove the requirement to handle and dispose of needles. However, they can cause occasional bruising and pain and variability in dose could result from differences in mechanical properties of the skin.

Some children and adolescents experience painful insulin injections and some also have fear of needles, both of which can hinder patient compliance. In order to facilitate insulin administration in these groups of patients, various indwelling catheters (cannulas) have been developed, for example Insuflon® (www.unomedical.net/au/section17/section02/index.asp). The catheter is placed subcutaneously and remains in place for an average of 3–5 days. The indwelling catheter consists of a plastic tube with a silicone membrane and a Teflon catheter. The insulin is deposited in the subcutaneous tissue and both pen injectors and syringes can be used for injections (Hanas, 2004).

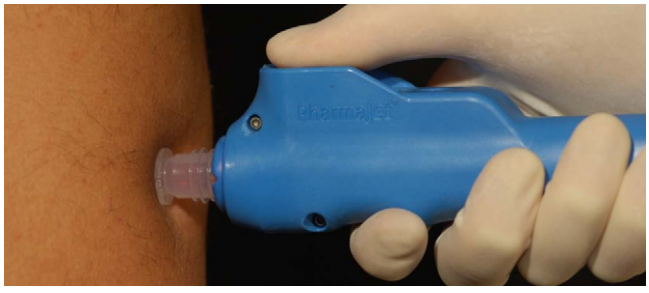

Fig. 9. PharmaJet® needle-free delivery device in use.

Another means by which insulin delivery may be made easier for the patient is the use of insulin pumps. These may be used by all ages of children, and provide a continuous infusion of insulin into the subcutaneous tissue, thereby eliminating the need for individual insulin injections. This may result in fewer large swings in blood glucose levels and allows flexibility about when and what the patient may eat. There are, however disadvantages to this type of delivery device in that they can be expensive, require the user to be fully trained and can be bothersome as the patient is attached to the pump all the time.

Further information together with examples of insulin pumps may be found from the following sources: http://www.children-withdiabetes.com/pumps/index.htm http://www.diabetes.org.uk/Guide-to-diabetes/Treatments/Insulin/Insulin_pumps/.

5. Nasal delivery

Drug delivery via the nose may be a useful route of administration for children. The nasal mucosa is richly vascularised which provides fast and direct access to the systemic circulation and may increase bioavailability of the drug compared to oral administration, without first-pass metabolism (Wilson et al., 1997; Goldman, 2006). For immunisation, the nasal route has the advantage of requiring lower doses of antigen compared to the oral route since the antigens are not exposed to low pH and proteases. Furthermore, nasal administration is a no-needle technique that can be conducted by the patient or carer.

There are however, some disadvantages of using the nasal route including the potential to cause temporary nasal irritation (Goldman, 2006) and limited maximum volume per dose, the usual volume being between 50 μL and 250 μL, depending on device and formulation. Greater volumes may lead to "dripping" whereby the formulation either runs out of the nostril or runs down the back of the throat of the patient. Indeed, the ability to deliver small volumes is especially important when dosing children, whose nasal cavities are smaller than those of adults.

The nasal route can be used for local and systemic conditions. For example steroids such as beclometasone diproprionate (Beconase®) and triamcinoline acetonide (Nasacort®) can be used for the relief of allergic rhinitis. (It should be noted that the regulatory status of these products with respect to paediatric use differs from country to country.)

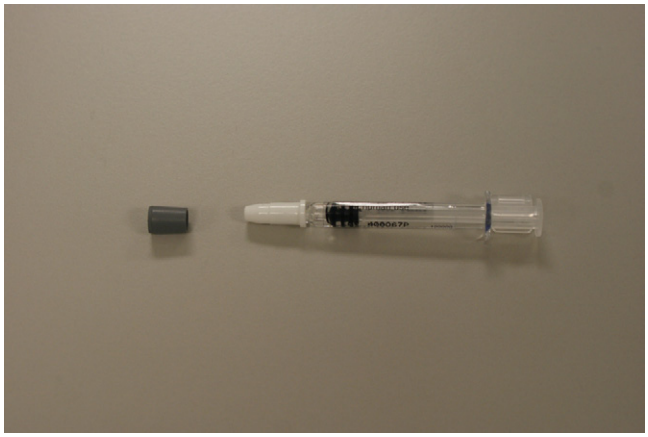

Fig. 10. Typical syringe nasal spray device.

Benzodiazepines such as midazolam have been used intranasally in children for seizure cessation and as a pre-operative sedative. In addition, ketamine has been used for sedation and fentanyl (Goldman, 2006) and diamorphine have been used for analgesia (Wilson et al., 1997). Intranasal administration of triptans may be used for the relief of migraine in adolescents (for example zomitriptan, Zomig® and, sumatriptan, Imigran®). The intranasal route may be preferred by migraine patients experiencing nausea and vomiting.

The nasal delivery of vaccines is a growing area of interest, as this avoids the use of needles, which some children (and adults) may find distressing. Influenza vaccine (FluMist®), is an example of an intranasal vaccine which has been widely used (www.flumist.com/).

Various devices are available for delivery to the nose. Syringes which may optionally have a spray device attached for inserting into a nostril have been used (Goldman, 2006) (see Fig. 10). It is important to take into account any dead space volume of such devices to ensure the correct dose is delivered to the patient (Bizos and Smith, 2009). Atomising pump devices may also be used. (www.valois.com/pharma/index.php, www.pfeiffer-group.com/) (see Fig. 11). The pack comprises a glass or polypropylene bottle which contains the formulation, an atomising spray pump device with nozzle and dust cap. To operate the device, the dust cap must be removed, the nozzle placed in one nostril whilst closing the other with a finger, the patient must breathe in through the nose and at the same time press firmly down on the collar of the spray device. This will deliver a metered dose of drug into the nostril. The nozzle should be removed from the nostril and the patient should breathe out through the mouth. Since a certain level of co-ordination is required for such devices, they may be less suitable for very young children.

Fig. 11. Typical atomising spray pump device.

The BD Accuspray™ (www.bd.com/) is a single-use nasal sprayer for mono-dose or bi-dose administration. The formulation is contained within a pre-filled syringe or type I glass stoppered vial, and this is assembled into the device, which consists of an actuator and holder. To operate the device, the cover must be removed from the nozzle of the holder, the nozzle placed in one nostril, and the patient must breathe in gently through the nose whilst pressing the plunger. This will cause the liquid in the syringe or vial to be released and delivered as a spray to the nose.

5.1. Recent developments in nasal delivery

As a result of growing interest in the nasal route as an alternative to oral and parenteral delivery, there have been some recent developments in nasal delivery devices. However, it appears that these are focussed on dosing to adults rather than children.

The ViaNase™ delivery system (www.kurvetech.com/devices.asp) is an electronic atomiser for liquid formulations. This device has been developed to optimise droplet size and trajectory with the aim of creating greater saturation of the nasal cavity.

OptiNose™ has developed breath-actuated nasal delivery devices for liquids and powders (www.optinose.com/). The device technology takes advantage of the posterior connection between the nasal passages persisting when the soft palate automatically closes when breathing out (exhaling). Blowing into the delivery device triggers release of liquid or powder particles into an airflow, which enters one nostril via a sealing nozzle and exits through the other nostril.

6. Ocular delivery

Current drug delivery to the eye may be in the form of topical application, systemic administration or direct intraocular/periocular injections (Sultana et al., 2006). The eye may be divided into the anterior segment, comprising the cornea, anterior chamber, iris, posterior chamber, ciliary body and lens, and the posterior chamber, comprising the vitreous, retina, retinal pigment epithelium and choroid (Yasukawa et al., 2005). The type of dosage form prescribed will depend upon the part of the eye that requires treatment. For example, disorders of the anterior segment are commonly treated with topical dose forms such as eye drops, suspensions and ointments. Treatment of the posterior segment may require systemic drug administration or periocular or intravitreal injections (Yasukawa et al., 2005; Gaudana et al., 2009; Ghate and Edelhauser, 2006).

In recent years, there have been huge advances in the development of ocular drug delivery systems such as polymeric inserts, discs, rods, pellets, corneal shields, liposomes and microspheres (Sultana et al., 2006; Yasukawa et al., 2005, 2006; Gaudana et al., 2009; Ghate and Edelhauser, 2006; Conway, 2008; Pijls et al., 2007; Nagarwal et al., 2009). The key aim of these drug delivery systems is to provide prolonged drug release within the eye and also to avoid the use of injections to the eye which can lead to complications.

The majority of paediatric ocular delivery uses topical treatments, for example treatment with antibiotics or steroids or for the dilation of the pupils to facilitate examination of the back of the eye. Indeed, the research into the drug delivery systems outlined above has focussed on adult populations, and so no further information or discussion on these systems is provided.

Over 90% of ophthalmic formulations are provided in the form of eye drops (Gaudana et al., 2009). These are commonly provided in

squeezable dropper bottles. Aqueous eye drop solutions are rapidly diluted and washed from the eye surface and only a small fraction (approximately 5%) of the applied drug dose is absorbed (Gaudana et al., 2009; Ghate and Edelhauser, 2006; Conway, 2008). Furthermore, some of the dose may be spilled onto the cheeks.

As a result of the low bioavailability of the drug being applied, it is often necessary for frequent dosing. This has the potential disadvantage of poor patient compliance as doses can easily be missed.

Many children find the application of eye drops or ointment uncomfortable or even frightening and this can further compound poor compliance in paediatric patients. The technique of dosing eye drops or ointment is therefore particularly important in this patient group. It is recommended that children lie down and look upwards overhead at something whilst being dosed. The lower eye lid should be gently pulled down using a clean hand to allow the application of the medication, by gently squeezing the eye drop bottle or in the case of ointments, gently squeezing the tube. For eye drops, a clean tissue may be used to help absorb any spills that may occur. The upper eye lid should not be touched nor should the dropper or end of the ointment tube be allowed to touch any parts of the eye. This is to reduce the risk of contamination.

6.1. Recent developments in ocular delivery

Despite the challenges in ocular delivery to paediatric patients outlined above, there appears to be little, if any research into delivery devices of eye drops or ointments for children.

Indeed, innovations in this area have focussed on devices that can facilitate ocular delivery in geriatric and arthritic patients who may have problems squeezing and/or positioning eye drop bottles correctly. An example of such a device is the Opticare eye drop dispenser® (www.cameron-graham.co.uk/) (see Fig. 12) which is designed to be used with most eye drop bottles. The bottle is placed inside a retainer which is then closed to keep the bottle in place. The eyepiece is opened and the bottle cap is removed. The eyepiece is then closed and the lid of the eyepiece rested on the upper eye socket. The lower eye lid is pulled down by the patients and the slide panels of the retainer squeezed to deliver the eye drops. The bottle cap is then replaced after use.

The Opticare Arthro® is specifically designed for patients with arthritis. This device works in a similar manner to the Opticare eye drop dispenser®, except that is has extended arms to help users squeeze the eye drop bottle with minimal effort and an eye piece that swivels so that the position of the device can be adjusted.

Another device to assist in the delivery of eye drops is the Auto-Drop eye drop dispenser (www.owenmumford.com/en/range/9/autodrop.html). This device clips on the majority of eye drop bottles and has a small "lip" that holds the lower eyelid open to prevent blinking. The Autodrop should be opened and the cap of the eye drop bottle loosened. The keyhole slot around the base of the bottle neck should be located below the thread. The eye drop bottle cap should then be removed and the lid of the Autodrop slid around the keyhole slot at the base of the bottle neck. The Autodrop should then be closed, the lower eyelid held down and the Autodrop placed over the eye with the lip against the cheek. The patient should tilt their head backwards, look through the pinhole and gently squeeze the bottle to release the eye drops.

There is therefore a need for the development of devices to assist in the delivery of ocular topical products such as eye drops and eye ointments to paediatric patients.

Fig. 12. Opticare® eye drop dispensers, containing eye dropper bottles (Cameron Graham, United Kingdom).

7. Conclusions

To ensure the accurate and consistent administration of paediatric formulations it is important to consider the requirement for and design of the delivery device early in the development programme.

It is important that the appropriate delivery devices are readily available to patients and that there are sufficient incentives and rewards in place for them to be routinely supplied.

Although many paediatric drug delivery devices have been developed, some of which may offer tangible patient benefits, there appear to be very few available on the market. This will require studies to be conducted into their cost effectiveness, of which compliance will be a major factor.

It is interesting to note that although many of device innovations will improve the accuracy and ease with which paediatric dosage forms may be administered, relatively few appear to be readily accessible. This is likely due to high market entry barriers such as cost. The refunding by health insurance bodies may be especially critical if the newly developed products are more expensive than the conventional products. For instance, the straw with clarithromycin is not refunded by the German health system. It is questionable whether all parents are willing to pay for the improved product or whether they will try to administer old-fashioned alternatives. In addition, many novel technologies are protected by patents, so interested companies would have to pay royalties for using the device, making the cost more prohibitive.

The matter of expense plays also an important role when considering the use of delivery devices in developing countries. For example commercially produced valved holding chambers or spacers to treat childhood asthma are mostly unavailable or too costly as it is the case for many medicines in low economy regions. Hence, the use of inexpensive home-made spacer devices (e.g. plastic bottles, disposable paper cups, feeding bottles) is recommended. A valved holding chamber with a facemask that is entirely made of paper is provided by Respira Design (www.respiradesign.org), showing an interesting approach how low-cost devices could be designed.

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