Dry powder inhalers for rescue applications

A variety of indications would benefit from more patient-centric inhalation devices, which also offer advantages over orals and injectables

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Acute or emergency situations that require medication instantly, to relieve symptoms or even save lives, are numerous. Usually, such rescue medication is slowing down a life-threatening physical process to provide the patient with more time to be admitted to medical care. In contrast to their urgent need, most of these medications are complex to prepare for use or too invasive for patients to use them without hesitation. Therefore there is a demand for easier rescue therapies that enable fast (self-) administration with minimal thresholds. Ready-to-use pre-filled dry powder inhalers (DPIs), which patients can have with them at all times, offer this potential.

Dry powder inhalers in emergency situations

Inhaled drug delivery is an emerging route for treatment of lung diseases, with clear advantages over oral and intravenous routes. However, inhalation has some inherent advantages over other routes for systemic indications too.[1,2,3] Compared with oral administration, first-pass metabolism can be avoided, allowing the medication to be delivered directly to the lungs. This also permits more rapid absorption of active pharmaceutical ingredients thanks to the large area of air sacs (~100m^2) with only a thin (0.1-0.2µm) and highly vascular epithelial layer. Uptake can be further improved by making particles with optimal size, shape and excipient composition, finally resulting in faster onset of action. Furthermore, pulmonary delivery provides needle-free dosing for patients suffering from trypanophobia.

Delivery directly to the lung is typically achieved by an aerosol in the form of a spray. Nebulisers, pressurised metered-dose inhalers (pMDIs) and DPIs are the three primary technologies used to form sprays for pulmonary drug delivery. Nebulisation is not optimal for rescue applications as the device is relatively large, has long aerosolisation times and requires dismantling and preparation before, as well as cleaning after each use. Most patients cannot use pMDI effectively, since they require high coordination between actuation and inhalation. This makes them less suitable for rescue therapies too. Generally, DPIs offer many advantages over other inhalers, such as storage stability and applicability for water-soluble and insoluble drugs. From a user perspective, DPIs usually have a short administration time, are easy to use and have high-dose delivery capability. Further, DPIs are breath-actuated, disposable and make use of propellants obsolete.

There are various DPI options, most being capsule-based inhalers whereby capsules are removed from blister packs and put into the inhaler device. They need to be manipulated or sometimes even assembled prior to inhalation. Many DPIs also need cleaning after use to ensure safe and efficacious subsequent inhalations. In an acute situation, the inhalation procedure should be made as simple and straightforward as possible by minimising the number and complexity of potentially erroneous handlings prior to use. This makes capsule-based inhalers less suitable. Therefore pre-filled, ready-to-use, disposable inhalers are the best choice.

Applications for rescuehalers

Although the term 'rescue medication' (also called 'emergency medication' and 'escape medication') is often used in the context of chronic obstructive pulmonary disease (COPD) and asthma, it may be applied to a much wider range of indications. Actually, it refers to medicines administered to relieve acute conditions that are normally controlled with prophylactic medicine and/or lifestyle. Indications treated can be local and systemic.

Since inhalation provides fast and non-invasive delivery with quick, local pulmonary distribution and/or fast uptake into circulation, it is ideal to deliver rescue medications that patients administer themselves. Combining this with a pre-filled inhalation device that requires little manipulation before inhalation provides fast, safe and effective treatment. Pre-filled DPIs are probably best suited for this application when they are compact, easily portable and quickly usable an emergency situation.

There are many situations and indications where this is applicable, such as:

- Severe allergic reactions and anaphylaxis
- Cardiovascular issues, eg, arrhythmic situations (the pulmonary vein directly transports medication into the heart)
- Neurological conditions, eg, epilepsy, Parkinson's disease (PD) and potentially mental disorders
- Sudden attacks or failures, eg, angioedema, asthma
- Pain or breakthrough pain, eg, migraine, cancer pain
- Vaccination. Although perhaps not acute, an easy-to-use, one-off inhaler can certainly help with vaccinating large groups globally.

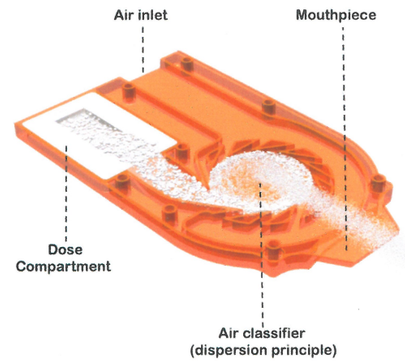

Figure 1. Bottom plate of the new DPI during the inhalation process

While many more applications could be listed here, what they have in common is that pulmonary delivery provides an easy way to quickly administer a therapy with less stability concerns and, as a non-invasive solution, more widely acceptable. A few cases are explained in more detail below.

Levodopa DPI – OFF episodes in PD

Levodopa, the precursor of dopamine, is very effective in treating the motor symptoms of PD patients. Oral levodopa in the form of tablets is effective in suppressing the symptoms in early stages of PD, although absorption via this route is highly dependent on, for example, gastric emptying and simultaneous absorption of protein-rich food.[4] Also, levodopa has a short half-life of approximately 1-2 hours, therefore its absorption after oral ingestion is unpredictable, resulting in highly variable levodopa plasma levels.
With disease progression the therapeutic window of levodopa narrows and fluctuating plasma levels after oral ingestion more often lead to 'motor fluctuations' of under-treatment (OFF phases) and over-treatment (dyskinesias). Routes of administration for levodopa other than the oral route avoid gastric and food-intake issues and may therefore be more suitable for rescue treatment. An example is the pulmonary administration of levodopa, for which several inhalers have been developed in recent years.

Luinstra et al investigated whether PD patients were able to use a correct inhalation technique during an OFF phase.[5] They recorded inhalation profiles in 13 patients with a 'unified PD rating scale' (UPDRS) part III score ≥25 during inhalation through a specially developed test inhaler with an adjustable air resistance. This showed that even in an OFF phase, PD patients mastered a correct inhalation technique for the use of most DPIs, based on measured inhaled volume, inhalation force and duration of the breathing pause after inhalation. In another study, they showed that PD patients were able to remove a powder inhaler from its packaging and prepare it for use in the OFF phase.[6] They concluded that an OFF phase did not constitute an obstacle to the use of an inhaler and therefore inhalable levodopa. This inhaler was developed at

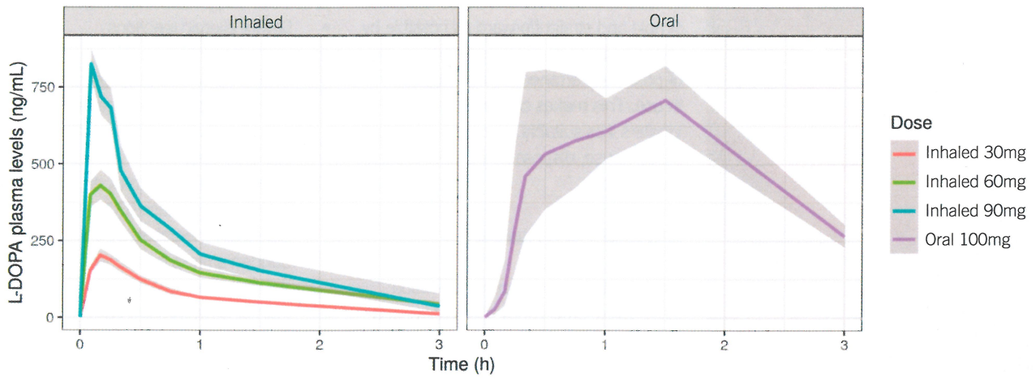

Figure 2. Comparison of plasma levels for inhaled and oral dosing of levodopa

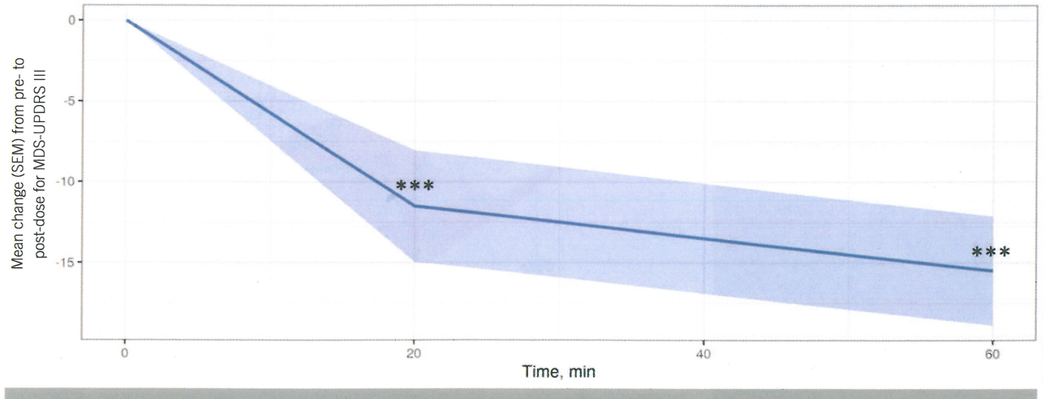

Figure 3. Change from before to after dosing for UPDRS Part III score upon inhalation with test device (N=8). Figure shows arithmetic means (solid lines) and standard error of the mean (SEM, shaded regions). ***, P ≤ 0.001

Groningen University in the Netherlands (**Figure 1**). The pre-loaded, single-use inhaler was more user-friendly for PD patients than other DPIs that needed loading and changing of capsules, including another levodopa DPI.[7] Early pharmacokinetics (PK) and tolerability studies in patients showed that the new device's t_{max} was reached within 10-15 minutes after inhalation (mean ± SD:10 ± 4 minutes), much faster and with less variation in plasma concentrations than after oral intake of levodopa (60 ± 35 minutes) (**Figures 2** and **3**).[8] Usability and pharmacological data from this new, rescue-type DPI, which comes to the patient pre-filled and easy to use, presents a promising solution for this group.

Epinephrine for anaphylactic shock

Another application of DPI for rescue therapy is in the treatment of anaphylactic shock, resulting from incidents such as insect stings or food allergies, with epinephrine (EPI). In this instance, the patient urgently needs a treatment in an acute, life-threatening situation.

EPI is the most effective drug available to treat allergic reactions and anaphylaxis. Over the years, Epipen or EPI autoinjectors, containing EPI for self-administration, have led to many untimely and incorrect treatments, leading to anaphylaxis and even death, as a result of patients' (1) reluctance to inject themselves and (2) incorrect use by over 50% of them. Immunologists and emergency physicians have noted that many patients, and even GPs, are reluctant to use this treatment owing to a fear of needles.

Easier-to-use devices are therefore required, and the airways have received significant attention recently as a means for EPI administration. A good option would be an inhalation device that the patient could carry at all times, without major limitations, and which could be operational in seconds.

The large absorption area of the lungs (>100 m^2) ensures a rapid uptake that is much more reproducible than with nasal delivery, for example. Also, many allergy patients are used to using inhalers, so there is no major barrier in that respect.

Clinicians from Groningen University and Groningen UMC recently tested a non-invasive EPI DPI, which prevents the major issues associated with injections and nasal delivery, drastically lowers the barriers to deployment and is more effective. In the PK study, inhalation was compared with injection of EPI, which showed excellent in vitro and phase I performance, plus very rapid t_{max} (1.8-2.4min) combined with short exposure (comparable to IV bolus), that allowed for repeated treatment without dose stacking.[9] Inhaled EPI was well tolerated, did not raise safety concerns and was found to be a promising alternative to injections for rescue treatment of anaphylaxis.

Vaccination

Most of the pandemics of recent centuries originated from viruses that evolved to infect the respiratory tract, primarily because, via this route, they can easily transmit between hosts.[10] Intuitively, vaccination campaigns should target the viral portal of entry, thereby exploiting the local immune system developed during millennia of evolution. Paradoxically, though, the pulmonary route is often neglected, with the vaccination dogma still being centred on injection-based administration.[11] Recently Heida et al argued that pulmonary administration, preferred over the nasal, deserves more attention in the search for novel strategies against respiratory virus infections.[12] Their main advice is to no longer neglect the pulmonary administration and develop new vaccines for this route. Recent examples show a lot of progress in this area.[13,14]

Pre-filled and ready-to-use DPIs offer major advantages over current vaccination routes (mainly injectables) and the advantages are similar to the general advantages of powder over liquids and of inhalers over needles: manufacturing, handling, distribution and use are easier than for injectables; no thresholds for people with fear of needles, plus greater ease of use for broad groups of people without intervention from physicians or nurses.

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