collaboration with deCODE to develop DNA-based diagnostics from the results of deCODE's genetic studies. This alliance will complement the existing drug discovery partnership between the two companies, and involves Roche providing research funding, milestone payments and product royalties to deCODE.

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Intelligent inhalers for systemic administration?

Rebecca N. Lawrence, News & Features Editor

Promising results from a study with a new intelligent inhalation technology in asthmatic children has prompted the development of the technology for use in a variety of other conditions, including the administration of systemic drugs. The six-month study using the Adaptive Aerosol Delivery (AAD™) system from Profile Therapeutics (Bognor Regis, West Sussex, UK) was shown to improve accuracy of dose delivery, decrease the quantity of drug required and improve compliance compared with conventional nebulizers.

One of the problems found with many nebulizer systems is that they are dependent on the breathing pattern of the patient, the way the nebulizer system is used (which can cause variability of sometimes >60%)[1] and the drug output characteristics of the nebulizer[2]. Every patient breathes differently, especially in relation to flow, volume and frequency[3]. If the patients' inhalation flow rate does not exceed the nebulizer flow rate, then more of the nebulizer output is wasted and this is particularly important in dosing for the paediatric population[4]. Using nebulizers has been found to waste up to 60–70% of the drug as only 30–40% of the respiratory cycle is accounted for by inspiration[5,6]. The quantity of drug actually inhaled by the patient is especially important for the administration of drugs with a narrow therapeutic window.

The system

The AAD technology was designed to try to avoid these problems by delivering the drug only during the optimal phase of inspiration (i.e. the first 50% of each breath). Sensors in the system monitor the flow rate and the length of the first three breaths of the patient before starting the dose. The results are then averaged and used to calculate the correct quantity of drug to be delivered into each breath. The patient's breathing is then monitored every 30 msec during dosing to enable the device to adapt the release of aerosol to changes in the

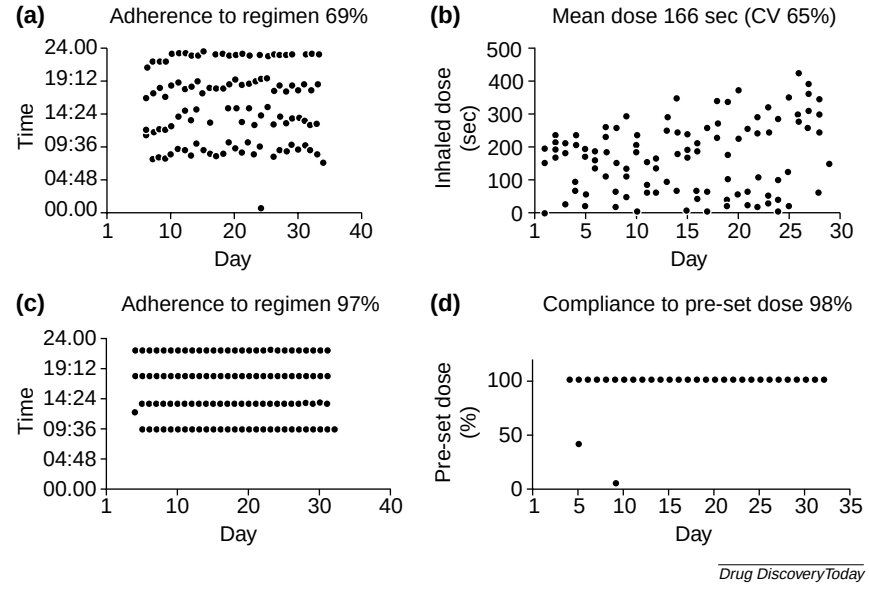

Figure 1. Patient adherence with four-week domiciliary use of conventional nebulizers (a) and (b) compared with using the AAD system (c) and (d) for the treatment of COPD. All patents were aged over 65 years. In (a) and (b), the regimen consisted of 2.5 mg salbutamol four times daily. In (c) and (d), the regimen consisted of 2.5 mg salbutamol plus 500 μg ipatropium bromide four times daily.

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patient's breathing pattern. John Denyer, Chief Technical Officer at Profile Therapeutics says: 'this mechanism enables very efficient drug delivery with little drug wastage'.

The first of these AAD technologies (HaloLite™) was developed in conjunction with AstraZeneca and was designed purely for use with the steroid, budesonide or the bronchodilator, salbutamol. *In vitro* results looking at particle size characteristics in the output of sodium fluoride from the device showed consistent particle sizes across the pulse range and a linear output across the pulse time[7]. Tests *in vivo* in human subjects examining the delivery of 315 mg saline to asthmatic and healthy subjects showed that 100% of the dose was administered with less than 3% of the delivered dose being exhaled by the patients. Furthermore, patient adherence to the regimen and the level of dose actually administered were significantly better over a four-week period in patients using the AAD system compared with those using conventional nebulizers (Fig. 1)

The latest study has examined the effect of differing regimens of budesonide delivered to 125 asthmatic children (aged from seven months to seven years) through the HaloLite system. Subjects were divided into three groups and given 100 μg twice daily for 2, 6 or 12 weeks followed by 25 μg twice daily for the remainder of the total six-month period. Response to therapy was measured in terms of day- and night-time asthma symptom scores, exacerbation rates and key inflammatory markers. The study showed that 75% of the children received the entire prescribed dose and the mean compliance was 83.5%.

This data was then compared with past data from AstraZeneca's application for drug approval of budesonide using conventional nebulizers. Denyer confirmed that the same baseline scores were used in both studies and the scoring systems were the same. Denyer says: 'The results showed nearly a twofold improvement in asthma scores in our study using only 25 μg twice daily compared with the data from AstraZeneca, even at their highest dose (1000 μg daily).'

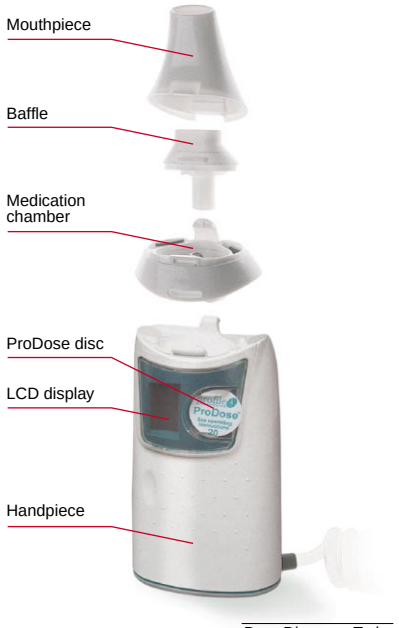

Figure 2. Breakdown of the ProDose AAD system.

Ongoing clinical trials

The HaloLite system is already on the market but is currently in a number of clinical trials for conditions such as cystic fibrosis, for example with Forum Bioscience (UK) for the delivery of antibiotics. However, Mike Weetman, Business Development Director of Profile Therapeutics points out that the HaloLite system was designed only to be used for steroids and bronchodilators. The company has therefore developed a system called ProDose (Fig. 2), which includes a disc containing a radiofrequency transmitter. Weetman explains that: 'This enables the drug dose, the expiry date and the number of treatments to be programmed into the device, either by the company or by the doctor if the treatment regimen changes.' He added that: 'The device also enables programming such that several doses can be taken out of one vial reducing drug wastage, and it can provide the Healthcare provider with valuable feedback regarding patient compliance, enabling its potential usage in new e-healthcare programmes.'

Recruitment has now been completed for a Phase III clinical study in conjunction with Schering AG for the use of an AAD system in the delivery of Iloprost for the treatment of pulmonary hypertension. Denyer suggests that this technology can be used to deliver any inhaled product to patients, e.g. for the treatment of asthma, COPD, cystic fibrosis, lung complications associated with HIV/AIDS and other lung disorders. It also suggests that it could be used for the delivery of drugs into the systemic circulation through the lungs because of the accuracy of the system.

A third system has also been designed called the Intelligent MDI/DPI system, which is essentially the same technology applied to a spacer system, and will be most useful for paediatric patients. This system is currently in clinical development and is supported by a partnership with Leicester University (Leicester, UK). With the increase in the number of proteins and peptides on the market, the company aims to start developing this system along with the other AAD systems for use with these compounds in the near future.

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