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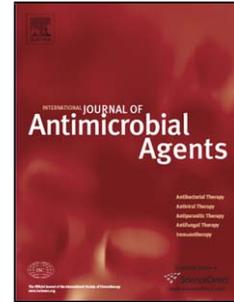
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Pulmonary drug delivery systems for antimicrobial agents: facts and myths

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ABSTRACT

Inhaled antimicrobial agents are used for the treatment of respiratory tract infections due to Gram-negative bacteria, mainly *Pseudomonas aeruginosa*. The effectiveness of the inhaled antimicrobial therapy is believed to correlate with the delivery system used. The objective of this review was to search for data supporting differentiation in clinical effectiveness between systems used for pulmonary delivery of antibiotics, including delivery using disposable nebulisers and oxygen flow. Published studies in peer-reviewed journals comparing the effectiveness of pulmonary drug delivery systems for antimicrobial agents were retrieved. The studies found were either in vitro or Phase I and Phase II clinical studies. Differences in in vitro parameters may affect the in vivo efficacy of the devices, and in vivo differences may imply differences in clinical effectiveness. The main difference between newer and older devices is the time needed for antibiotic delivery. Interpretation and association with clinical effectiveness is difficult. In conclusion, Phase III clinical trials comparing the clinical effectiveness of delivery systems, including delivery using a hospital's oxygen flow and disposable nebulisers, do not exist. Cost is an important parameter, which may be counterbalanced in cystic fibrosis patients by a better quality of life and a greater adherence to treatment.

1. Introduction

Inhaled antimicrobial agents have been in clinical practice long before their use was officially approved in 1998. The rationale for the development and usage of inhaled antibiotics was the greater concentrations of antibiotics achieved in the lungs compared with parenteral antibiotics as well as lesser systematic adverse events [1,2]. In addition, non-availability of systemic treatment is a reason for administering drugs via the respiratory route [3].

Several antimicrobial agents are delivered directly to the lungs [4]. The only formal indication for these agents is in the treatment of cystic fibrosis (CF) patients suffering from Gram-negative, including *Pseudomonas aeruginosa*, lung infection or colonisation (Table 1). Off-label, inhaled/aerosolised antibiotics have been used for the treatment of patients with nosocomial pneumonia [5], including multidrug-resistant Gram-negative nosocomial pneumonia [6]. They have also been used for the prevention of ventilator-associated [7] and intensive care unit-acquired pneumonia [8].

The effectiveness of the inhaled antibiotic therapy is believed to correlate with the delivery device used. Differences were found in vitro in older studies between device/drug combinations [9–11], underlining the importance of the correct choice of device/drug combination in clinical practice.

2. Devices commonly used for pulmonary delivery of antibiotics

Currently there is a considerable number of pulmonary drug delivery devices, used officially and unofficially. The large number and variation in characteristics of these devices has led the US Food and Drug Administration (FDA) to the decision to approve only the devices used with the drug during clinical trials [12].

Nebulisers [jet (pneumatic) and ultrasonic] are the most commonly used delivery devices. Ultrasonic nebulisers are considered efficient in delivering medicines but have some considerable limitations, such as cost and maintenance problems [13]. Compressed gas delivered over the drug solution is the way in which jet nebulisers produce aerosol. The simpler and more economic means of administration is by disposable nebulisers and oxygen supply. There are different types of jet nebulisers; unvented, vented (breath-enhanced) and breath-actuated [14]. Breath-enhanced nebulisers are considered more efficient compared with unvented nebulisers since less quantity of drug is wasted [15,16]. The limitations of jet nebulisers are mainly related to the requirement for a compressor [12] and to the amount of drug wasted during exhalation [14].

Dry-powder inhalers (DPIs) are small portable devices. Co-ordination of actuation and inhalation is not needed and the device is able to deliver high loads of drug to the lungs [12]. The main disadvantage of the device is the need for repeated doses if the amount of medicine contained in the capsules or blisters used is not sufficient.

Newer devices have become available during recent years including, among others, vibrating mesh and adaptive aerosol delivery (AAD) devices. A major advantage of the vibrating mesh devices over jet nebulisers is that they do not require a compressor. Less quantity of drug is wasted using these devices and the nebulisation time is shortened [17]. AAD devices are breath-actuated devices, able to inspect the patient's breathing pattern and to adjust aerosol delivery [18]. They release the medicine during the first 50–80% of inspiration, reducing the amount of drug wasted during exhalation. A major disadvantage is the need for a compressor, but a newer AAD device also uses the vibrating mesh technology and thus does not need a compressor.

3. Characteristics of a pulmonary drug delivery system

The characteristics of pulmonary drug delivery systems are related to their effectiveness, cost and treatment compliance.

Efficacy is related to the amount, concentration and distribution of the drug delivered into the lungs. The size, distribution of the size, and speed of aerosol particles are of great importance. Large ($>5 \mu\text{m}$) particles travelling with high velocity are more likely to be entrapped in the upper airways and not to enter the lower respiratory system [19]. Also, smaller aerosol particles are more homogeneously distributed in the lungs compared with larger ones [20].

Cost is assessed not only by the buying cost but also according to the maintenance cost. The amount of medicine wasted during the delivery procedure is also an important cost parameter. Last, but not least, is the compliance of the patient to the treatment. Nebulisation duration and ease of use of these devices are important parameters to help patient adherence [21].

4. Studies comparing devices used for pulmonary delivery of antibiotics

4.1. Tobramycin

The first antibiotic agent approved for lung delivery was tobramycin nebuliser solution (TNS). The drug has received approval by the FDA and the European Medicines Agency (EMA) (Table 1). There are considerably more studies published related to the delivery device of tobramycin compared with other agents (Tables 2 and 3). Other formulations of tobramycin (liposomal, dry powder) [34,35] are currently under study and have received an orphan drug designation by the EMA. For delivery of the drug to the lungs, the manufacturer of TNS suggests that the medicine should be delivered using a certain type of breath-enhanced nebuliser (PARI LC[®] PLUS Reusable Nebulizer) and a certain type of compressor (DeVilbiss[®] Pulmo-Aide[®] Air Compressor) [36]. The same is suggested in the latest US package insert in the 'Dosage and administration' section [37]. On the other hand, in the UK the

recommended devices are a PARI LC PLUS nebuliser with any suitable compressor [38].

In the first large study demonstrating the efficacy of inhaled tobramycin in 72 CF patients [39], tobramycin was delivered to the lungs using an ultrasonic nebuliser (UltraNeb 99/100). In two other clinical trials performed later with 520 CF patients [40], TNS was delivered using the PARI LC PLUS nebuliser and the Pulmo-Aide compressor. Finally, in a smaller, placebo-controlled study, the PARI BOY[®] jet nebuliser/compressor system was used [41]. It is of interest that the type of nebuliser used in the Phase III clinical trials [39,40] affected the choice of nebuliser in other studies with scope other than device testing [42–44].

Motivated by the disadvantages of the ultrasonic nebuliser used in the first study (increased cost and maintenance problems) [39], a multicentre, randomised study performed in 1997 in 68 CF patients [13] compared the effectiveness and safety of the abovementioned ultrasonic nebuliser with two jet nebuliser systems. The study found 93% and 87% of patients using the Sidestream[®] and the PARI LC nebulisers, respectively, had adequate peak sputum tobramycin concentrations. The median peak sputum concentrations were statistically significantly higher ($P = 0.02$) in favour of the PARI LC compared with the Sidestream nebuliser (452 $\mu\text{g/g}$ vs. 393 $\mu\text{g/g}$, respectively). Treatment time was significantly shorter with the PARI LC nebuliser

compared with the Sidestream nebuliser (median duration 10 min and 15 min, respectively; $P < 0.01$).

A study published in 1998 compared in vitro the currently recommended vented nebuliser (PARI LC PLUS) with a traditional unvented nebuliser (Hudson 1730 'T' Up-Draft 11) [22]. They were both attached to a Pulmo-Aide compressor. In the absence of respiratory flow there were no differences. When inspiratory flow was attached to the vented nebuliser, the rate of total drug output was increased compared with the unvented nebuliser, minimising the amount of medicine lost. Moreover, in the presence of inspiratory flow the duration of nebulisation was shorter for the vented nebuliser. Another in vitro study compared commercially available jet and ultrasonic nebulisers [23]. Particle size distribution, output of tobramycin and output rate of tobramycin solution were recorded. Of the 14 nebulisers tested, only 3 were found to be acceptable.

In vitro studies have been performed to evaluate the suitability of various compressors with the PARI LC PLUS nebuliser. Two studies [24,25] compared several compressors with the Pulmo-Aide compressor when attached to the PARI LC PLUS nebuliser. Delivered dose and particle size distribution were common criteria used for comparison. Most of the compressors tested were found to be acceptable for the delivery of TNS. Another in vitro study published in 2003 [26] compared five different compressors. The authors ranked the compressors in preferred order, using as the main criteria the droplet size distribution and the nebulisation time.

A recent study [27] tested the best two compressors according to the abovementioned study (CR60 and Porta-Neb) [26] in a small number ($n = 10$) of CF patients. Maximum tobramycin concentration (C_{\max}) and area under the concentration–time curve (AUC_{0-6}) in serum were higher using the CR60 compressor than with the Porta-Neb compressor. C_{\max} values were 0.70 mg/L vs. 0.54 mg/L ($P = 0.005$) and AUC_{0-6} values were 2.54 h mg/L vs. 2.01 h mg/L ($P = 0.017$) for the CR60 and Porta-Neb compressors, respectively. Nebulisation time was shorter using the CR60 compressor (13.2 min vs. 16.1 min; $P = 0.022$). This was the main reason why the CR60 compressor was preferred by most patients.

A quite recent study recruited 53 CF patients and tested a breath-actuated, vibrating mesh device (AeroDose 5.5 RP) [17]. The pharmacokinetic/pharmacodynamic (PK/PD) parameters were comparable with the PARI LC PLUS/Pulmo-Aide nebuliser system if 90 mg of tobramycin was administered via AeroDose. Mean C_{\max} and AUC_{0-8} using the jet nebuliser and AeroDose systems were 985.65 $\mu\text{g/g}$ vs. 958.00 $\mu\text{g/g}$ and 1471.16 $\mu\text{g/h/g}$ vs. 1275.23 $\mu\text{g/h/g}$, respectively. Mean nebulisation time was longer using the jet nebuliser (17.7 min) compared with AeroDose (8.0 min).

Lately, the efficacy of PARI eFlow[®], a vibrating mesh device, compared with the PARI LC PLUS/Pulmo-Aide system for lung delivery of tobramycin has been of interested.

Interest is growing since delivery of tobramycin with this device has also received an orphan drug designation by the EMEA [45].

Radiolabelled tobramycin was administered in six healthy subjects using both the PARI LC PLUS/Pulmo-Aide system and eFlow [28] and lung deposition was measured. Mean lung deposition of the charge dose and mean absolute pulmonary delivery of tobramycin were 16.6% vs. 32.0% and 49.9 mg vs. 43.9 mg for the breath-enhanced nebuliser and eFlow, respectively. eFlow was faster since the mean administration time was 2.52 min compared with 10.9 min with the traditional system.

An in vitro study [29] compared some of the characteristics of the two delivery systems/devices, including performance after a 6-month period. The eFlow was found to produce larger particles with less variability compared with LC PLUS nebulisers. Because of that, a larger portion of the medicine could be deposited in the upper airways when using eFlow. The performance of both devices was decreased after a period of 6 months of use, and replacement of the vibrating mesh of the eFlow appeared to be necessary after a period of time.

The latest study published is a randomised, open-label, multicentre study in 25 patients with CF and chronic *P. aeruginosa* lung infection [30]. eFlow was again found to be significantly faster compared with the jet nebuliser (10.5 min faster on Day 1 of treatment and 7.7 min on Day 15; $P < 0.0001$). The PK/PD parameters measured and the incidence of adverse events were comparable between the two devices.

4.2. Colistimethate (colistin)

Colistin is used either as a solution for nebulisation or as powder for inhalation [46]. There are main two formulations for the delivery of colistin directly to the lungs, colistin sulfate and colistimethate sodium. The latter is associated with fewer adverse events and is thus preferred. According to some authors, the terms colistin and colistimethate sodium should not be used interchangeably because the chemistry and PK/PD properties between them are substantially different [47]. Inhaled powder of colistimethate sodium has been characterised by the EMEA as an orphan medicinal product [48]. At present it is not approved by the FDA [49]. Colistimethate sodium can be found with alternative names, such as colistin sulfamethate, colistin methanesulfate, colistin sulfonyl methate and pentasodium colistimethanesulfate [50].

Each pack of colistimethate sodium also contains a disk to enable use with the I-neb[®] AAD[®] System, a third-generation AAD system that does not require a compressor. Noteworthy, in the summary of product characteristics it states that it can be used with 'any conventional nebulizer suitable for delivery of antibiotic solutions' [51].

Comparison of lung deposition of colistin using an ultrasonic and a pneumatic nebuliser in four patients suffering from CF and lung colonisation with *P. aeruginosa* was the aim of a study published in 1996 [31]. Deposition of the medicine was expressed as a percentage of the nebuliser dose. Using the pneumatic nebuliser,

pulmonary drug deposition varied from 5.6% to 27% and with the ultrasonic nebuliser from 9.5% to 14%. In three of four patients the results with the pneumatic nebuliser were superior or at least equal compared with the ultrasonic nebuliser. The authors concluded that pneumatic nebulisers offer a reliable alternative.

A study in 2001 compared the effectiveness of two nebulisers for the delivery of colistin in three CF patients [32]. The first nebuliser was a disposable unvented Hudson 1730 Updraft II and was attached to a dry gas source at 6 L/min, simulating hospital administration. The other was a breath-enhanced nebuliser (PARI LC[®] STAR) attached to a PARI PRONEB[®] TURBO compressor. The two nebulisers were found to be effective for the delivery of colistin. However, the portable PARI LC[®] STAR system was found to be more effective in the deposition of drug to the lungs since it delivered 56% of the charge dose compared with 22% delivered by the unvented Hudson 1730 Updraft II system.

In a more recent study, two nebuliser systems were compared for their ability to deliver colistin to the lungs [18]. A jet nebuliser system (PARI LC PLUS and PARI BOY compressor) and a first-generation AAD system (HaloLite[®]) were tested. The study population was 15 CF patients with lung colonisation from *P. aeruginosa* requiring daily inhalation of colistin. Lung deposition, the colistin concentration in sputum and the load of *P. aeruginosa* were recorded. Lung deposition was higher with the PARI LC PLUS ($P < 0.0001$), but when calculated as a percentage of the charge dose HaloLite was more efficient (mean percentage of charge dose deposition

30.79% vs. 19.75% with PARI LC PLUS; $P < 0.04$). Time to nebulise was significantly shorter with the HaloLite nebuliser compared with the jet nebuliser (mean time 298 s vs. 382.5 s, respectively; $P < 0.001$). Differences in sputum concentrations of colistin and *Pseudomonas* load were not statistically significant.

Finally, a study published in 2007 compared delivery of colistimethate as a dry powder inhalation using a Twincer[®] DPI with nebulisation [33]. AUC_{0-4} and C_{max} were significantly different in favour of the nebuliser system ($P = 0.02$). The inhaler was well tolerated by patients.

4.3. Aztreonam

After receiving an orphan drug designation in 2007 [52], inhaled aztreonam recently received a conditional marketing authorisation by the EMEA [53]. On the other hand, the FDA requested the performance of another clinical trial [54]. In the ongoing clinical trials, eFlow is used as the delivery device [55]. Consequently, if the medicine is finally approved by the FDA, eFlow will be the recommended device.

5. Discussion

To our knowledge, there is no clinical trial comparing the clinical effectiveness of pulmonary drug delivery systems for antimicrobial agents. A systematic review published in 2001 regarding the cost effectiveness of inhaler devices used in

bronchial asthma and chronic obstructive pulmonary disease is of great interest [56]. The authors concluded that the cheapest inhaler device should be used as first-line treatment unless other reasons are identified.

Some of the studies described above are in vitro studies comparing parameters that may affect the in vivo efficacy of these devices. The clinical studies described, either Phase I or Phase II, mainly in CF patients, focus on safety and PK/PD parameters. These parameters may imply the clinical effectiveness of the devices used, but patient specific characteristics, such as inhalation patterns and obstruction of the airways, may be responsible for variability in the results. The interpretation and association with clinical effectiveness of these PK/PD parameters is difficult. For example, according to some authors, a high sputum concentration may reflect a high concentration in the upper and less concentration in the lower airways, resulting in lower clinical effectiveness [30]. These studies also focused on the time needed for the delivery of the antibiotic. Improved (minimised) delivery time is associated with a better quality of life and greater adherence to treatment.

Inhaled antibiotics are primarily used by CF patients, mainly at home, for long periods of time. In these patients, practical issues, such as the time needed for drug delivery and the size of the device, are of interest. Cost is also an important parameter since newer devices appear to cost more than the previous ones. For example, the HaloLite nebuliser, which is now superseded, cost five times more than the jet nebuliser/compressor system [18]. Also, the eFlow costs ca. €560, plus the annually

replaced parts [57], whereas the PARI LC PLUS/Pulmo-Aide system costs ca. €125 in various certified online stores. Thus, differences between healthcare providers may reflect the amount of money spent by each patient and his/her family in order to receive proper treatment. However, equally important parameters as cost are compliance with treatment and quality of life. The less time these, mainly young, patients spend using a nebuliser along with the ability to carry their drug delivery system easily makes their life as close to normal as possible. This may counterbalance the increased cost paid for their treatment.

However, not only CF patients receive aerosolised antibiotics. Off-label, hospitalised patients also receive aerosolised antibiotics. These two groups of patients differ in terms of pulmonary delivery of antibiotics. For example, parameters such as the size of the device, nebulisation (delivery) time and noise are not a concern when treating hospitalised patients. However, cost is of great concern, especially when added to the already increased cost needed for the treatment of a critically ill patient. In some studies, with encouraging results for further investigation [58,59], aerosolised antibiotic was given using common and economic ways, via the ventilator circuit or using disposable nebulisers and oxygen flow, thus reducing the cost of treatment.

We recognise the importance of quality of life, but the cost of the delivery system must not be an obstacle for the treatment of patients especially if clinical effectiveness does not differ. It will be of great interest whether future Phase III clinical trials

include a treatment arm comparing the clinical effectiveness between delivery methods, such as a newer device and a disposable nebuliser using oxygen flow.

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Table 1

Antibiotics used for pulmonary delivery

Drug	Approval	Indication
Tobramycin (nebuliser solution)	FDA/EMA	Cystic fibrosis, <i>Pseudomonas aeruginosa</i> lung infection
Tobramycin (liposomal)	EMA ^a	Cystic fibrosis, <i>P. aeruginosa</i> lung infection
Tobramycin (inhalation powder)	EMA ^a	Cystic fibrosis, <i>P. aeruginosa</i> lung infection
Colistimethate sodium	EMA ^a	Cystic fibrosis, <i>P. aeruginosa</i> lung infection
Aztreonam	EMA ^b	Cystic fibrosis, Gram-negative bacteria lung infection, including <i>P. aeruginosa</i>

FDA, US Food and Drug Administration; EMA, European Medicines Agency.

^a Orphan drug designation.

^b Conditional marketing authorisation.

Table 2

Studies published in peer-reviewed journals comparing devices used for pulmonary delivery of tobramycin

Reference	Study test (comparison)	In vitro/clinical study (no. of patients)	Comparison method
Eisenberg et al., 1997 [13]	Jet and ultrasonic nebulisers	Clinical study (68)	Peak sputum concentration, nebulisation time, safety
Coates et al., 1998 [22]	Vented versus unvented nebuliser	In vitro	Total drug output, rate of total drug output, nebulisation time
Le Brun et al., 1999 [23]	Jet and ultrasonic nebulisers	In vitro	Particle size distribution, drug output, rate of drug output
Standaert et al., 2000 [24]	Compressors	In vitro	Particle size distribution, nebulisation time
Dennis and Pieron, 2002 [25]	Compressors	In vitro	Aerosol size, total aerosol output, nebulisation time
Geller et al., 2003 [17]	Vibrating mesh device versus jet nebuliser	Clinical study (53)	Sputum and serum T_{max} , C_{max} and AUC, nebulisation time, safety
De Boer et al., 2003 [26]	Compressors	In vitro	Droplet size distribution, flow rate, drug output, nebulisation time
Westerman et al., 2008 [27]	Compressors	Clinical study (10)	Patients' experiences, serum C_{max} , AUC and T_{max} , nebulisation time, safety

Coates et al., 2008 [28]	Vibrating mesh device versus jet nebuliser	Clinical study (6)	Lung deposition of the charge dose, absolute pulmonary delivery, nebulisation time
Rottier et al., 2009 [29]	Vibrating mesh device versus jet nebuliser	In vitro	Particle size distribution, nebulisation time
Hubert et al., 2009 [30]	Vibrating mesh device versus jet nebuliser	Clinical study (25)	Sputum and serum T_{max} , C_{max} and AUC, nebulisation time, safety

T_{max} , time to maximum concentration; C_{max} , maximum concentration; AUC, area under the concentration–time curve.

Table 3

Studies published in peer-reviewed journals comparing devices used for pulmonary delivery of colistin

Reference	Study test (comparison)	In vitro/clinical study (no. of patients)	Comparison method
Gagnadoux et al., 1996 [31]	Jet and ultrasonic nebulisers	Clinical study (4)	Lung deposition of the charge dose
Katz et al., 2001 [32]	Jet nebulisers	In vitro and clinical study (3)	Rate of drug output, total drug output, particle size distribution
Byrne et al., 2003 [18]	Adaptive aerosol delivery device versus jet nebuliser	Clinical study (15)	Sputum colistin levels, sputum load of <i>Pseudomonas aeruginosa</i> , nebulisation time
Westerman et al., 2007 [33]	Dry-powder inhaler device versus jet nebuliser	Clinical study (10)	Serum T_{max} , C_{max} and AUC, questionnaire, nebulisation time, safety

T_{max} , time to maximum concentration; C_{max} , maximum concentration; AUC, area under the concentration–time curve.