Expert Opinion

The 15th International Society of Aerosols in Medicine Congress

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This international meeting brought together ~ 250 delegates from the pharmaceutical industry, academia, hospitals and government agencies, to discuss the latest research and development on areas related to inhalation aerosols. Fundamental science and applied research encompassing both the biological and physicochemical aspects were presented. There was a wide range of topics covered, from immune modulation to pharmaceutical regulatory issues, including aerosol clearance; industry innovations; aerosols and *in utero* effects; technical advances in imaging; inhalation catastrophes; as well as recent advances and future directions in aerosol delivery systems. This biennial congress has provided an excellent forum for stimulating fruitful discussion of aerosols in medicine.

Keywords: aerosol inhalers, inhalation drug delivery, pharmaceutical aerosol

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1. Overview

The 15th International Society of Aerosols in Medicine (ISAM) Congress was held in Perth, Australia from the 14 – 18 March, 2005. The Congress continued to provide the premier opportunity for presenting clinical research, along with basic and applied science, related to the aerosol field.

2. Meeting highlights

The first day was an optional workshop that began with a morning session (presented by Andy Clark, Nektar Therapeutics) on *in vitro* aerosol particle size and output analysis. Fundamental mechanisms governing aerosol deposition and parameters that determine how the particle properties affect the size measurement were covered in detail. Different cascade impactors/impingers and laser diffraction methods were also discussed along with the problems in general. The use of pressure drop across an inhaler, instead of air-flow rate, as a more meaningful descriptor when measuring therapeutic aerosol particle size was emphasised. The workshop was highly informative for new researchers to the field dealing with analysis of therapeutic aerosols. The afternoon session (Stefan Eberl, Royal Prince Alfred Hopsital) was about medical imaging with a key focus on single photon emission computed tomography (SPECT). Planar γ-camera scintigraphy is well established for measuring the deposition and clearance of radiolabelled aerosols. However, SPECT provides three-dimensional information of the radioactivity distribution, thus potentially offering superior assessment of aerosol deposition patterns. Although planar imaging will likely continue to be used, tomographic studies will become more popular as it can offer additional information and insight into aspects of aerosol deposition and clearance.

The Congress opening plenary lecture (John Upham, Telethon Institute for Child Health Research) on the second day was on the basic aspects of innate and adaptive immune systems related to the respiratory tract, and how immune regulation due to inhaled particles can modify the immune response. Inhalation tolerance

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occurs from repetitive inhalation of innocuous proteins, which leads to IgE-selective tolerance and subsequent protection against respiratory allergy. In contrast, intolerance occurs when inflammatory stimuli are involved. The second talk (Fernando Martinez, University of Arizona) on inhaled farm animal products and their effect on asthma showed that children exposed to allergens in farms have less risks of asthma, which may be due to early exposure to allergens, including microbials and fungi. Air pollution affects the severity, not the development, of asthma. Paradoxically, allergen levels in farms have not been found to be higher than nonfarm environments. However, the levels of muramic acid and endotoxin, which are cell components of Gram-positive and -negative bacteria, respectively, are higher in farm mattresses. It was also reported that more exposure to endotoxin decreases hayfever risks. The following two talks (Jose Valdespino, National Institute of Public Health of Mexico; and Teresa Aguado, World Health Organization) were on aerosol delivery of vaccines with a focus on the Measles Aerosol Project. Aerosol immunisation was found to be at least as immunogenic as via the percutaneous route and with lower adverse effects. Besides measles, aerosol immunisation could be used for other diseases such as rubella and mumps. The potential elimination of syringes and needles along with their disposal could mean a substantial saving in costs and improvement in safety. The risks of aerosol immunisation may involve potential exposure of the vaccine to the brain through the nasal pathway, and possible contamination of the delivery system. The latter can be minimised by using disposable facemasks, mouthpieces or unit dose devices. Another risk is the environmental spread of the aerosolised vaccine, leading to low-dose exposure of the vaccine to the healthcare workers over a long period of time. The goal of the Measles Aerosol Project is to license at least one method for inhalation delivery of currently licensed measles vaccines that is safe, immunogenic and easier to administer than injections [1]. Administration would be via nebulisation using at least three devices and, if possible, a dry powder inhaler (DPI). As biological products may degrade during nebulisation, a rapid stability indicating assay has been developed for the measles vaccines. The late-morning session dealt with regulatory issues, particularly on the bioequivalence of inhalation products, with views representing the FDA, the UK Medicines and Healthcare product Regulatory Agency, the clinicians and the industry. It was emphasised that both the safety and therapeutic equivalence must be demonstrated, and that advice from the regulatory authorities should be sought at the start. From the industry perspective, the number of patients required for the bioequivalent study can become unrealistically high [2].

The afternoon session centred on the clearance of inhaled particles from the airways, and factors affecting the retention time of therapeutic aerosols within the lungs. A thorough review (Lisbeth Illum, IDentity) on the nasal clearance alluded to the low nasal bioavailability of polar drugs (including proteins and peptides) being due to their poor membrane permeability, coupled with rapid mucociliary clearance in the nasal cavity (with a half-time of ~ 15 – 20 min). Nasal bioadhesive systems delay clearance and, hence, prolong absorption and increase nasal bioavailability. Modification of the membrane transport pathways may also be involved in the enhancement of absorption. This was followed by a detailed talk (Christopher O'Callaghan, University of Leicester) on the cilial function and the role of cilia in clearance, and concluded with a review (Lily Daviskas, Royal Prince Alfred Hospital) on the use of hyperosmolar agents for clearance in diseased airways. Convincing evidence has shown that osmotic agents, such as hypertonic saline and mannitol powder, increase mucociliary clearance from the airways of patients with asthma, cystic fibrosis (CF) or bronchiectasis. The mechanism is not fully understood as yet, but it is likely to be related to increased water volume and changed properties of the mucus. This is particularly interesting as sodium chloride and mannitol are small molecules, widely used as pharmaceutical excipients, in contrast to recombinant human deoxyribonuclease being the state-of-the-art high-tech protein drug being used for CF treatment.

The late-afternoon session was dedicated to industry innovation and, thus, especially relevant to drug delivery. The Staccato™ technology (Peter Lloyd, Alexza Pharmaceuticals) involves vaporisation of drug film coated on a metal substrate by rapid heating, followed by condensation of the vapour to form a fine aerosol in the cool air entrained during inhalation. As the heating time is short (< 100 ms) chemical degradation will be minimal. The dose output (~ 0.1 mg) is low but ideal for potent drugs that will vaporise under heat without decomposition [3]. Being unique in the aerosol generation mechanism, and distinctly different from the existing technologies of other pharmaceutical inhalers, the Staccato inhaler was presented to the public for the first time. Wet aerosol devices include updates on the Aerodose® (Jim Fink, Aerogen), AERx® device (Jeff Schuster, Aradigm Corp), Respimat® (Michael Spallek, Boehringer Ingelheim Pharma) and the Adaptive Aerosol Delivery™ (AAD) system (John Denyer, Profile Respiratory Systems). The Aerodose device has the advantages of minimal heat generation (compared with ultrasonic nebulisers) and low shear during aerosol production (compared with air jet nebulisers). In addition, the device comes with many accessories, making it highly adaptable for different applications, including the intensive care unit setting. The AERx inhaler was originally developed for highly efficient lung deposition via the use of small particles and controlled aerosol inhalation [4]. However, being battery-powered, it is relatively large and heavy, as well as being limited by the battery life. The AERx-Essence® inhaler has been developed as a smaller, low-cost, non-electronic and fully mechanical device, while maintaining the basic mechanism of aerosolisation by extruding a drug solution through tiny laser-drilled holes. A key element to the successful development is due to the nanotechnology enabling the drilling of

submicron-size holes for the blister containing the liquid. Respimat® Soft Mist™ Inhaler was launched in Germany in early 2004 as the product Berodual® (Boehringer Ingelheim Corp., containing fenoterol 50 µg and ipratropium bromide 20 µg in the same liquid). Compared with the propellant-driven metered dose inhalers (MDIs), the aqueous aerosol moves much more slowly (0.8 m/s) and has a longer spray duration (1.5 s), which are expected to reduce the oropharyngeal deposition and simplify coordination between aerosol actuation and inhalation. Unlike conventional nebulisers, the AAD system monitors the patient's breathing pattern and matches the aerosol output time to the inspiratory phase of the breathing. Talks presented on the innovations of DPIs included technologies by Innovata Biomed (Julie-Ann Penton), Nektar Therapeutics (Andy Clark), Vectura (John Staniforth), and Oriel Therapeutics (Anthony Hickey). Combination aerosol products that contain two medications, such as a bronchodilator and an inhaled steroid in a single inhaler, have become increasingly popular as they help simplify the treatment regimen and provide convenience for patients requiring two different inhalers. Distinct from other combination DPI products having two different drugs in a single formulation, Innovata Biomed has created a new combination DPI platform by having separate reservoirs, metering units and pathways for two drugs in a single inhaler. The Nektar pulmonary delivery technologies featured the use of active device (the Exubera®) to decouple aerosol performance from patient's inhalation effort and the glass- and lipid-based systems for powder formulations. Both the lipid-based formulations, such as the Pulmosphere™ and the sugar glasses containing peptides or proteins were prepared by spray drying. The stability of glassy systems will be maintained, provided that the storage temperature is below the glass transition temperature [5]. The talk from Vectura focused on rapid response for erectile dysfunction and other systemic aerosol therapies. The Oriel device is another active DPI. In the presentation, fundamental factors affecting powder dispersion, including interparticulate forces, dynamic repose angle and power input to the DPI, were also included.

The third day began with a session on aerosols and *in utero* effects, which highlighted how particles inhaled by the pregnant mother can affect the fetal immune system, as well as how genetics can influence fetal immune responses to such particles. The talks (Susan Prescott, University of Western Australia; Wayne Thomas, Telethon Institute for Child Health Research; Fernando Martinez; Steve Stick, Princess Margaret Hospital for Children) included prenatal development of the immune system and how it can be modified; effects of environmental and therapeutic inhaled particles on the fetus; genetics and inhaled environmental interactions *in utero;* and tobacco smoke and its effect on the fetus. The late-morning session (Dale Bailey, Royal North Shore Hospital; Stefan Eberl; Myrna Dolovich, McMaster University; Harm Tiddens, Erasmus University Medical Center/Sophia Children's Hospital) on technical advances in imaging was pertinent to aerosol drug delivery. The latest progress in using imaging techniques to assess aerosol delivery and clearance were covered. SPECT, positron emission tomography (PET), high resolution computed tomography (CT) and magnetic resonance imaging (MRI) were each reviewed thoroughly with relevant examples given. Whereas SPECT and PET provide the aerosol deposition and clearance information, CT and MRI generate the anatomical data. The application of multi-modality combining SPECT or PET with CT to provide simultaneous functional and anatomical data were highlighted. PET has a better resolution (4 – 6 mm) than SPECT, and is able to provide absorption, disposition, metabolism and elimination information of an inhaled drug, but the requirements of a nearby cyclotron facility, specialised radiosynthesis procedure and high initial set-up cost have limited its widespread use for aerosol studies. Due to these limitations, SPECT has become more popular compared with PET. However, in the past, SPECT has been associated with long image acquisition time, which made it unsuitable for materials with fast clearance. Recent advance in SPECT has enabled data acquisition to be completed in < 1 min using multi-detector camera systems. This opens the exciting opportunity of performing dynamic studies for aerosol clearance in the lungs using SPECT [6,7].

The afternoon session covered topics on the importance of particle size for inhaled therapy in humans; particle size as a determinant of dose in experimental animal models; the importance of the ultrafine particulate fraction (< 0.1 µm) for health outcomes in humans; and the relationship between indoor and outdoor particulate levels (fine and coarse fractions) and the implications of this for personal exposure. The talks (Peter LeSouef, University of Western Australia; Ian Gilmour, US Environmental Protection Agency; Wolfgang Kreyling, GSF - National Research Centre for Environment and Health; Peter Franklin, University of Western Australia) were on dose considerations of inhaled corticosteroids and other drugs in humans, dose considerations in animals, health effects of ultrafine aerosols, and particulate air pollution and personal exposure.

On the fourth day, an initial session on inhalation catastrophes, including those of asbestos and other industrial dusts, aerosols generated by bushfires and collapsing buildings, as well as severe acute respiratory syndrome, was followed by the students' best oral presentations. Of particular interest to drug delivery were three talks on aerosol inhalers. Particle interactions in suspension-type MDIs are important as they affect the physical stability of the formulation. The talk by Daniela Traini (University of Sydney) was on investigating particle interactions in nonaqueous model suspensions. The interparticulate force and surface energy of the particles were obtained by atomic force microscopy (AFM) and contact angle measurement using goniometry, respectively. A correlation was found between the AFM results and prediction based on the van Oss theory of surface free energy. The results also showed that the surface energy of drug particles is

strongly affected by the polar component of the force of interaction. The talk by Matthew Coates (University of Sydney) on quantifying the critical turbulence levels for optimal DPI performance demonstrated how computational fluid dynamics (CFD) simulation coupled with experimental measurement of powder dispersion can provide in-depth understanding of the effect of inhaler design on the aerosol performance. The presence of a grid in the mouthpiece not only converts the tangential flow into axial flow for the aerosol, but also increases the turbulence intensity immediately after the grid. For the Aerolizer® (Novartis Pharmaceuticals) DPI, a critical turbulence level to maximise the dispersion performance of mannitol was identified at a flow of 65 l/min [8,9]. It is well known that aerosols produced by MDI contain electrostatic charge, but the details of charge dependence on the particle size and mode of actuation are unknown. The talk by Philip Kwok (University of Sydney) provided clear evidence to show that Ventolin® (Allen & Hanburys) aerosols generated from continuous actuations were negatively charged, whereas those from noncontinuous actuations (i.e., with rest periods of ≥ 1 h) were bipolarly charged. The difference in the electrostatic characteristics may have an impact on lung deposition.

The afternoon session (Ana Maria Henao-Restrepo, World Health Organization; Anthony Hickey; David Parsons, Women's & Children's Hospital; Günter Oberdörster, University of Rochester) was focused on the technical aspects of aerosol delivery of vaccines and antibiotics, as well as gene therapy by inhalation to adults and children, including characterising delivery devices and selecting devices for optimal delivery. Nebulisation for delivery of antimicrobials was discussed. Depending on the diseases that require antimicrobial agent treatment, the efficacy and safety can be enhanced by local delivery using inhalation aerosols. As toxicity is related to the systemic exposure to the drug, higher efficiency of the delivery would reduce dose requirements. For CF, the mutation with the cystic fibrosis transmembrane conductance regulator gene can be reversed by gene therapy and partial gene correction may be enough for the treatment. A major challenge is to get the gene particles past ciliated cells to reach the tight junctions. Gene therapy for CF is not available yet as there is currently only a temporary correction effect, and inflammation can occur with dosing due to immune response.

The last day had a special focus on recent advances in inhalation aerosols used for local and systemic therapeutic effects in the lungs. In addition, the latest research into factors affecting patient adherence to prescribed inhaler therapy was presented. The first talk (Igor Gonda, Acrux) on systemic delivery via aerosols highlighted the rapid onset of action for small molecules (e.g., analgesics morphine and fentanyl), when delivered to the alveoli. Peptides and proteins currently delivered by needle injection can potentially be absorbed from the lungs. The absorption mechanism is still not clearly understood, and a pathway involving pores through which the macromolecules can be absorbed was proposed. Although concerns exist about the potential adverse immuno-response to inhaled proteins, there is not much data on the safety issues. The second talk (Sunalene Devadason, University of Western Australia) on the advances in delivery to infants and young children covered the influence of patient factors, such as usage techniques and adherence. A new device, Funhaler® (InfaMed Ltd), was designed to increase adherence of children to MDI medications. It is a spacer incorporating toy components that encourage and reinforce correct inhalation techniques through aural and visual feedback. Studies had shown that the aerosol output from the Funhaler is not significantly different to those from conventional spacers. The talk (Gerry Smaldone, State University of New York) on advances in aerosols for adult respiratory diseases recognised the importance of breathing pattern in aerosol delivery and deposition. Forceful exhalation after aerosol inhalation can result in collapse of the airways, with the aerosol particles trapped inside the airways. Targeted delivery reduced systemic toxicity, as exemplified by aerosolised cyclosporin used to reduce rejection in lung transplantation. Other new fronts included the minimisation of ventilator-associated pneumonia in intubated patients in intensive care units, and the importance of the patient/device interface to prevent face and eye deposition. A key issue from the talk (Mark Everard, Sheffield Children's Hospital) on the advances in promoting adherence to inhaled therapy was the compliance problems; patients need devices that they can and will use.

The final session of the ISAM Congress was on the future directions in delivery systems. The talk (Johannes Wildhaber, University Children's Hospital of Zurich) on potential new approaches to solving problems of delivery to children highlighted the lack of knowledge of aerosol delivery to preschool children, and the requirements of special aerosol delivery devices and techniques for this age group. The next talk (Hak-Kim Chan, University of Sydney) reviewed the current and future directions for dry powder aerosol delivery systems, including powder production, formulation, dispersion, delivery and deposition of the powder aerosol in the airways. Insufficiency of conventional powder production by crystallisation and milling has led to spray drying as an alternative. Novel precipitation methods (e.g., controlled by high gravity or using supercritical fluids) have also been developed. Recent performance of powder formulations has been improved significantly through the use of engineered drug particles and excipient systems. Relative humidity is critical to the performance of DPI products via capillary force and electrostatic interaction. Electrostatic charge of different particle size fractions of an aerosol can now be measured using a modified electrical low-pressure impactor [10]. The use of CFD simulation to improve DPI design, along with the importance of a systematic approach of studying variables of both particle and patient on lung deposition of DPI using γ-scintigraphy, were also highlighted. The talk (Warren Finlay, University of Alberta) on liquid atomising–nebulising and other methods of producing aerosols, covered the paradigm shift from the

inferior traditional nebulisers to the smart atomisers, which have features such as synchronising delivery with patient's breathing (AERx), providing feedback and data storage as well as measuring and estimating the delivered dose (AAD) and even controlling breathing manoevres (AKITA, Inamed) [11]. Other devices included the AeroEclipse® (Trudell Medical International) breath-actuated nebuliser and the eFlow® (Pari Aerosol Research Institute), which uses a vibrating mesh to generate the aerosol droplets. It was argued that nebulisers are the device of choice for delivery of the increasingly popular smart nanoparticles in the future. Nanofabricated aerosols were shown through the glancing angle deposition technique that can be used to produce smart particle with controlled three-dimensional nanoscaled structures. The final talk (Andy Clark) on the update of innovations in aerosol delivery covered systems using a vibrating mesh (Omron, Aerogen and eFlow, Pari); ultrasonic vibration (the Oriel device and Micro-Dose); extrusion (AERx); opposing liquid jets (Respimat); electrospray (Mystic™, Battelle); and heat volatilisation (Alexza, Chrysalis). Although the lung deposition efficiency of some of these new inhalers is > 70%, it was queried whether further promotion in this direction would be worthwhile.

3. Expert opinion and conclusion

Inhalation drug delivery has advanced from the products of a single bronchodilator drug to combination drugs for asthma, along with inhaled insulin, analgesics and other molecules when a rapid onset of action is required, as well as aerosolised vaccines. To achieve this, a variety of high performance delivery systems with enhanced patient compliance has been gradually appearing on the market. The multi-disciplinary research involving medical, pharmaceutical and engineering collaboration has provided a cutting-edge approach to understand and solve the issues related to delivery. The 15th ISAM Congress did not simply represent the old technologies with updates, but more importantly, many novel ideas were discussed: the medical applications; inhaler technology; nanotechnology; computer simulation; and characterisation techniques, to push the frontier of aerosols in medicine into exciting new directions.

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