Liquid Dose Pulmonary Instillation of Gentamicin PulmoSpheres® Formulations: Tissue Distribution and Pharmacokinetics in Rabbits

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Purpose. To assess the pharmacokinetics and biodistribution of gentamicin, delivered as PulmoSpheres® formulations in rabbit serum and lung tissue following intratracheal instillation in a perflubron vehicle.

Methods. Rabbits were anesthetized, intubated, and mechanically ventilated with O_2 (FiO_2 = 0.50). Animals were then given 5 mg/kg gentamicin either intravenously, intramuscularly (IM), or intratracheally (IT) gentamicin PulmoSpheres® formulation, instilled in 1.8 ml/kg of liquid perflubron vehicle. Serum and lung lobe sections were collected at multiple time points and assayed for gentamicin content.

Results. Serum gentamicin levels peaked at 64.7 μg/ml, 11.2 μg/ml, and 5.0 μg/ml following intravenous, IM, and IT administration, respectively. Absolute bioavailability at 8 h for IM administration was 76.8% and 57.0% when delivered IT. Although peak lung levels of drug were reached within 1 h, total lung gentamicin concentration after IT administration was more than two orders of magnitude greater than that achieved following IM administration (680,540 vs. 4,985 μg min, respectively) with significant levels of the antibiotic remaining in the lung even after 1 week.

Conclusions. High levels of gentamicin in lung tissue can be achieved by instillation of a gentamicin PulmoSpheres® formulation in a perflubron vehicle, termed liquid dose installation, without reaching toxic systemic levels allowing for increased local delivery of agents such as gentamicin at the site of the infection.

KEY WORDS: gentamicin; PulmoSpheres®; perflubron; lung; drug delivery; LiquiVent®.

INTRODUCTION

In 1962, Kylstra *et al.* (1) undertook the first liquid breathing study, demonstrating that mice could survive for prolonged periods of time when submerged in a saline solution providing that it was equilibrated with oxygen under hyperbaric conditions. Subsequently, Clark and Gollan (2) demonstrated that by substituting a liquid perfluorocarbon (PFC), which has a higher solubility for oxygen, they could support gas exchange under normobaric conditions. Using PFCs as an inert medium to open up the atelectic injured lung and support gas exchange in conjunction with conventional gas ventilation, a technique known as perfluorocarbon-associated gas exchange (3) or partial liquid ventilation™ (4) has been tested as a potential lung protective strategy for patients with acute lung injury or acute respiratory distress syndrome (5–7). Whereas preclinical as well as clinical studies with perflubron (perfluorooctyl bromide; LiquiVent®) have indicated that LiquiVent® may improve oxygenation and lung compliance (5,6), some of the properties of perflubron, such as its density, low surface tension, and high spreading coefficient (Table I), suggest that it may provide a good drug delivery vehicle for direct administration of drugs to the lung.

Preliminary studies with vasoactive drugs (8), antibiotics (9,10), plasmids (11,12), and lung surfactant (13–15) indicated that PFCs are effective vehicles for distributing drugs throughout the lung. However, these earlier studies used simple admixtures of aqueous drug solutions and PFC; and given the poor miscibility between the water and PFC phases, the drug-containing aqueous phase would rapidly float to the surface of the PFC phase. The dispersion in the lung resulted from the ventilator-induced breathing turbulent movement of the PFC phase. Alternatively, the drug containing aqueous phase can be administered first and followed by PFC delivery to disperse the aqueous dose. However, it is clear that a need exists for preparing stable dispersions of drugs in PFCs. It has recently been demonstrated that stable suspensions of drug particles can be prepared in PFCs by engineering the particles to be both hollow and porous (PulmoSpheres technology) (16–18).

One promising application of the intratracheal (IT) instillation of drugs in perflubron would be to treat hospitalized patients with severe pneumonia, in particular patients with hospital-acquired (nosocomial) pneumonia. The majority of nosocomial pneumonias are caused by gram-negative bacilli and the prognosis associated with these aerobic bacterial pneumonias is poor, with mortality rates as high as 70% being reported for nosocomial *Pseudomonas aeruginosa* infections. These high mortality rates are related to the necrotizing and hemorrhagic lung pathology of these types of pathogens, which renders local lung defenses less effective and makes adequate antibiotic penetration from the systemic route difficult, emergent drug resistance of nosocomial pathogens are necessitating higher doses of potentially toxic antibiotics, and then hospitalized patients are hosts with poor physiological reserve and impaired immune function.

Aminoglycosides, such as gentamicin sulfate, are known to be among the most effective antibiotics against these gram-negative bacilli, but are therapeutically limited because they are poorly absorbed by lung tissue following parenteral administration (~1%), and are dose limited by systemic toxicity (e.g., nephrotoxicity) (19). Direct IT instillation of aminoglycosides in aqueous vehicles have met with limited clinical success (20,21). Animal models have shown that such delivery is localized to the central airways with little peripheral deposition (22–24).

In this report we present the tissue distribution and pharmacokinetics of gentamicin following delivery of a gentamicin-PulmoSpheres® formulation by IT instillation to healthy rabbit lungs in a perflubron vehicle. The implications for improved local vs. systemic effects with this approach are discussed.

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Table I. Comparison of the Physical Characteristics of Perflubron (LiquiVent®) and Saline

Physical property	Perflubron	Saline
Gas Solubility		
Oxygen	53 vol%	2 vol%
Carbon dioxide	210 vol%	70 vol%
Surface tension	18 mN/m	73 mN/m
Density	1.92 g/cm^3	1.00 g/cm^3
Spreading coefficient	+2.7 mN/m	n/a
Vapor pressure	11 torr	47 torr
Kinematic viscosity	1.1 centistokes	1.0 centistokes

MATERIALS AND METHODS

Preparation of Gentamicin PulmoSpheres® Formulations

The PulmoSpheres® microparticles were manufactured using a spray-dry process. An aqueous solution was prepared by mixing the following two solutions, A and B, immediately prior to spray drying. Solution A consisted of a fluorocarbon-in-water emulsion in which 27 g of perfluorooctylbromide (perflubron, Alliance Pharmaceutical Corp, San Diego, CA) was dispersed in 145 g of deionized (DI) water with the aid of 4.2 g of egg phosphatidylcholine (EPC-3, Lipoid, Germany) emulsifier and 0.135 g of sodium oleate (Sigma, St. Louis, MO). The emulsion was prepared by first dispersing the lipids in hot DI water with a T-25 ultraturrax at 9,000 rpm for ~5 min. The fluorocarbon was then added dropwise under mixing. The coarse emulsion was homogenized under high pressure (18,000 psi) for five discrete passes with an Avestin Emulsiflex C5 (Avestin, Otawa, Canada). Solution B contained 3.54 g of gentamicin sulfate (63% active gentamicin by weight) (Amresco, Solon, OH) dissolved in 5 g of hot DI water. The combined feed solution was spray-dried with a standard B-191 Mini spray-drier (Buchi, Flawil, Switzerland) under the following conditions: inlet temperature, 85°C; outlet temperature, 58°C; aspirator, 100%; pump, 1.1 ml/min; nitrogen flow, 2,400 l/h. The mean volume aerodynamic particle size of the dry powder was measured using a time of flight particle sizer, Aerosizer (TSI, St. Paul, MN) (Aerodisperser module) and was found to have an aerodynamic diameter of 2.2 μm. Scanning electron microscopy images were used to corroborate the particle size measured by the aerosizer.

The relative suspension stability was evaluated by measuring the optical density of a powder dispersion (approximately 1mg/ml in perflubron) using a Horiba Capa 700 photosedimentation particle sizing instrument (Horiba, Irvine, CA) at a speed of 3,000 rpm for a period of 5 min, 21 s.

Addition of perflubron to the hollow porous microspheres results in the formation of a suspension we have termed a homodispersion™ in which the perflubron phase penetrates through the pores in the particle wall into the hollow particle core to produce a stable suspension in the perfluorochemical liquid with slow creaming rates and little evidence of particle flocculation (16).

Animal Model

The experiments conducted in this study adhered to the "Principles of Laboratory Animal Care" and were approved by the Alliance Pharmaceutical Corp. Animal Care and Use Committee. New Zealand white rabbits, ~2 to 3 months of age and weighing 3.2 to 3.5 kg, were anesthetized with an intramuscular (IM) injection of an anesthetic cocktail containing a mixture of ketamine, acepromazine, and xylazine. Central ear arteries were cannulated to monitor arterial blood pressure and arterial blood gases. Ear veins were cannulated for infusion of maintenance anesthesia, supplemental fluids, and blood collection. Rabbits were intubated and mechanically ventilated with a volume-limited ventilator (Harvard Instruments, Woburn, MA) at an FiO_2 setting of ~0.50. Tidal volume was set at ~9 ml/kg and respiration rate was set from 15 to 35 breaths/min. Throughout the experiment, ventilation settings were corrected to maintain PaO_2 levels above 100 mm Hg and $PaCO_2$ levels between 30 to 45 mm Hg.

All of the treatment groups received a total gentamicin dose of 5 mg/kg, and included: (i) gentamicin PulmoSpheres® instilled IT in a perflubron volume of 1.8 ml/kg (i.e., 10% of the functional residual capacity of the rabbit lung); (ii) an aqueous gentamicin sulfate preparation (Fermenta Animal Health Co, Kansas City, MO) injected IM; or (iii) gentamicin sulfate in 5% dextrose solution (SoloPack Laboratories Inc, Elk Grove Village, IL) administered intravenously (IV). Blood samples were drawn at baseline, 15, 30, 45 min, 1, 2, 4, and 8 h post-administration in the IT and IM groups and 0.5, 5, 10, 20, 30 min, 1, 1.5, 2, 2.5, 3, 3.5, and 4 h post-injection in the IV group. Serum was processed and assayed for gentamicin by a method described below. Following anesthesia, animals were euthanized with an intracardiac injection of saturated potassium chloride, and their lungs were lavaged on the vascular side with phosphate-buffered saline (PBS) prior to being harvested. The lobes were homogenized in a small volume of PBS using a Tissue Tearor (Biospec Products, Bartelsville, OK) and freeze-dried. Dried samples of known weight were resuspended in a known volume of PBS and assayed for gentamicin.

Immunological Gentamicin Assay

Serum gentamicin concentrations were assayed at Biological Testing Services (San Diego, CA) using an Abbott AxSYM system (Abbott Laboratories, Abbott Park, IL) or at UCSD Medical Center by enzyme-linked immunosorbent assay (Emit 2000, Syva Co, San Jose CA). The sensitivity of the immunoassay is 0.3 μg/ml.

Functional Gentamicin Assay

Escherichia coli (DH5a, Clonetech, San Diego, CA) were grown in Luria Broth to an optical density (OD_{600nm}) of 1.0. Mueller Hinton Agar plates were streaked with the *E. coli* to yield a continuous "lawn" of growth on the plate surface after overnight incubation. Lung tissue homogenates were added to sterile sensitivity discs (20 μl per disc) and then placed onto the bacteria-seeded agar plates. Unknown serum and lung homogenates were first heated at 56°C in a water bath for 45 min to denature all complement in the samples that may interfere with the assay. After overnight incubation at 37°C, the circular zones of non-bacterial growth, or zone of inhibition, surrounding the discs on the agar plates were measured using a calibrated eyeglass. Gentamicin concentrations were determined by interpolation from an external standard

curve prepared at known gentamicin concentrations ranging from 1.99 to 63.8 μg/ml. The sensitivity of the assay was less than 2.0 μg/ml.

Data Analysis

Data are presented as mean ± SE. Areas under the serum concentration-time curve (AUC) values were calculated using the trapezoid rule. The absolute systemic bioavailability of gentamicin following IM or IT administration is given by Eq. 1:

$$B = \left(\frac{AUC}{AUC_{IV}}\right) \times \left(\frac{dose_{IV}}{dose}\right) \times 100 \quad (1)$$

All gentamicin data referred to in this report are from immunological analysis. Functional gentamicin analysis was performed randomly to confirm the immunological data and to assure that the antibiotic retained full bioactivity following formulation.

Control animal's lungs were used to estimate lung weights relative to total animal weight and lung lobe weights as a percent of the whole lung weight. The individual lung lobes were found to have the following relative weights: left upper, 12.4%; left lower, 32.6%; right upper, 9.4%; middle, 10.3%; right lower, 35.3%; and total weight of the lung, 1.1 g/kg body weight. From this, the whole lung gentamicin concentration was estimated by summing the lobe concentrations as follows: Total lung gentamicin (mg/kg) = (each lung lobe gentamicin (mg/g) × (% total lung weight of lobe) × (1.1 g/kg lung dry weight).

RESULTS

Systemic Gentamicin Pharmacokinetics

Mean serum gentamicin levels following IV, IM, and IT administration are plotted in Fig. 1. Pharmacokinetic parameters are derived in Table II. The total concentration of gentamicin administered was held constant at 5 mg/kg. Following IV administration the serum gentamicin levels peaked at a maximum concentration, C_{max}, of 64.7 μg/ml. This is significantly higher than the clinical threshold for potential nephrotoxicity of 12 μg/ml. The levels persisted above 12 μg/ml for more than 30 min. The minimum inhibitory concentration (MIC) for gentamicin in treating most strains of *P. aeruginosa* infections is ~8 μg/ml (19). Levels of serum gentamicin fall below this level after only 1 h, illustrating the small therapeutic index for these types of antibiotics. The C_{max} value may be attenuated by IM injection. In this case, peak IM levels were observed ~15 min post-injection (t_{max}), with a C_{max} of only 11.2 μg/ml. Over the 4-h period tested, the absolute bioavailability for IM administration was found to be 76.8 %.

Direct instillation of gentamicin PulmoSpheres® formulations into the lung resulted in C_{max} serum values of only 5 μg/ml, which is significantly less than the threshold for nephrotoxicity. The pharmacokinetic profile was also altered with t_{max} occurring at a later time point (60 min) and a relatively flat pharmacokinetic profile over the test period. The absolute bioavailability over 4 h was 57.0%, which is slightly lower than that achieved following IM injection. However, the magnitude of the serum gentamicin concentrations obtained following IT delivery are important only from the standpoint of drug safety, because it is the drug concentration at the site of the infection that is the important factor for efficacy, and high local concentrations are achieved by IT administration (see Results) (6).

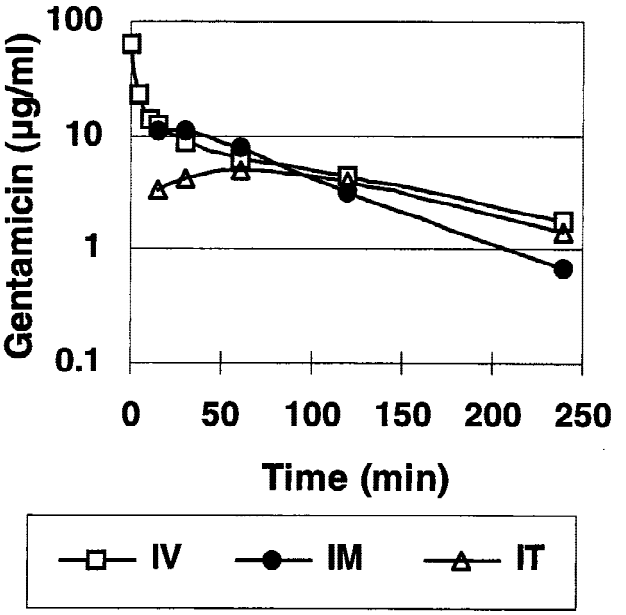

Fig. 1. Rabbit serum gentamicin concentrations following IV, IM, or IT administration. Total gentamicin dose delivered over 4-h time frame via IV (n = 3–5), IM (n = 3–10), or IT (n = 2–17) was 5 mg/kg.

Gentamicin Pharmacokinetics in Lung Tissue

The concentration of gentamicin in lung tissue was also determined following administration by IM injection or liquid dose instillation IT. The total gentamicin concentrations in the lung are collected in Table III and plotted in Fig. 2. The poor bioavailability for gentamicin in the lung following systemic administration (IM injection) is readily apparent. The total lung concentrations are approximately two orders of magnitude less than those achieved following direct IT instillation. The bioavailability in the lung achieved by IM injection relative to direct IT instillation, B_{IT}^{lung} can be calculated according to Eq. 2:

$$B_{IT}^{lung} = \left(\frac{AUC_{IM}}{AUC_{IT}}\right) \times \left(\frac{dose_{IT}}{dose_{IM}}\right) \times 100 \quad (2)$$

Over the first 4 h following IM gentamicin administration, B_{IT}^{lung}, was found to be only 0.73%, illustrating the difficulties that gentamicin has in crossing the endothelium into lung tissue (Table IV). After 4 h, the levels of gentamicin in lung

Table II. Systemic Pharmacokinetic Parameters of Gentamicin Delivery via Designated Routes of Administration[a]

Mode of administration	C_{max} (μg/ml)	t_{max} (min)	AUC (μg min ml^{-1})	B (%)
IV	64.7	0.5	1,426.1	100.0
IM	11.2	15.0	1,095.3	76.8
IT	5.0	60.0	813.4	57.0

[a] Calculated parameters: maximum concentration (C_{max}), peak time point (t_{max}), area under the curve (AUC), bioavailability (B).

Table III. Total Rabbit Lung Gentamicin Area under the Curve (AUC) Data following Intratracheal (IT) or Intramuscular (IM) Administration

Time (min)	AVE (μg/total lung)	AUC (μg/min)
IT		
0	0.0	57,838.9
60	1,927.9	341,061.6
240	1,861.6	281,639.7
480	485.3	400,989.4
1,440	350.0	362,127.1
2,880	152.9	282,068.3
4,320	238.8	1,273,021.1
10,080	203.2	
	8 h AUC	680,540.2
	168 h AUC	2,998,746.3
IM		
0.0	0.0	730.7
60.0	24.3	3,075.8
240.0	9.8	1,178.1
480.0	0	
	8 h AUC	4,984.8

tissue were below the limit of quantitation. In contrast when the gentamicin was delivered by liquid instillation directly to the lung, the levels of gentamicin remain high for at least 1 week (168 h) at levels more than an order of magnitude higher than the peak value obtained following IM administration. The B_{IT}^{lung} value calculated over this time period was 0.16%. Thus high drug levels are achieved following IT delivery without reaching correspondingly high systemic levels of gentamicin (i.e., $C_{max} < 5$ μg/ml).

It is clear that high concentrations of gentamicin can be achieved in lung tissue following direct IT instillation. However, the question remains whether the drug is effectively distributed throughout the lung by this method. The biodistribution of gentamicin across the various lung lobes is illustrated in Fig. 3. Little interlobe differences in gentamicin concentration are noted following IM administration.

Levels of gentamicin in all of the lobes were found to be

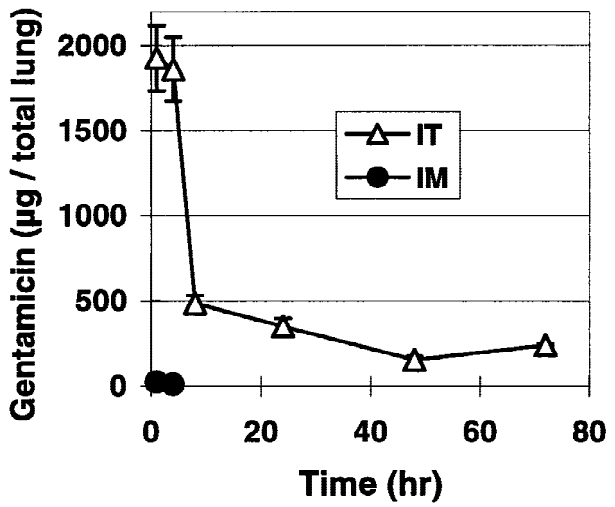

Fig. 2. Total rabbit lung gentamicin concentrations post-IT (n = 2–3 per time point) or IM (n = 2 per time point) delivery.

Table IV. Whole Lung Pharmacokinetic Parameters following Gentamicin Delivery via IM and IT Routes of Administration[a]

Mode of administration	C_{max} (μg)	t_{max} (min)	Whole lung AUC at 8 h (μg min)	B_{IT}^{lung} at 4 h (%)
IM	24.4	60.0	4,984.8	0.73
IT	1,928.0	60.0	680,540.2	100

[a] Calculated parameters: maximum concentration (C_{max}), peak time point (t_{max}), area under the curve (AUC), bioavailability in the lung achieved by IM injection relative to direct IT instillation: $B_{IT}^{lung} = (AUC_{IM}/AUC_{IT}) \times (dose_{IT}/dose_{IM}) \times 100$.

one to two orders of magnitude higher following liquid dose installation than those achieved following IM administration and persisted at levels above the MIC for periods of at least 1 week. The functionality of the tissue resident gentamicin following IT administration was confirmed using a bioassay. Some differences were noted in the total concentration of gentamicin in the various lobes with the lower lobes exhibiting somewhat higher levels, suggesting a gravitational effect. Nonetheless, the upper lobes still received large concentrations of antibiotic.

DISCUSSION

It is estimated that 300,000 cases of hospital acquired lower respiratory infections occur annually in the United States. Mortality rates associated with nosocomial pneumonia range from 20 to 50%, due in part to difficulties in treatment and increased bacterial resistance to available antibiotics (25). Drug resistance is often an issue of increasing the threshold concentration of antibiotic required to reach the MIC. Although in theory this can be countered by increasing the dose to the maximum tolerated dose. Unfortunately, dose-limiting toxicities associated with increasing systemic levels limit the

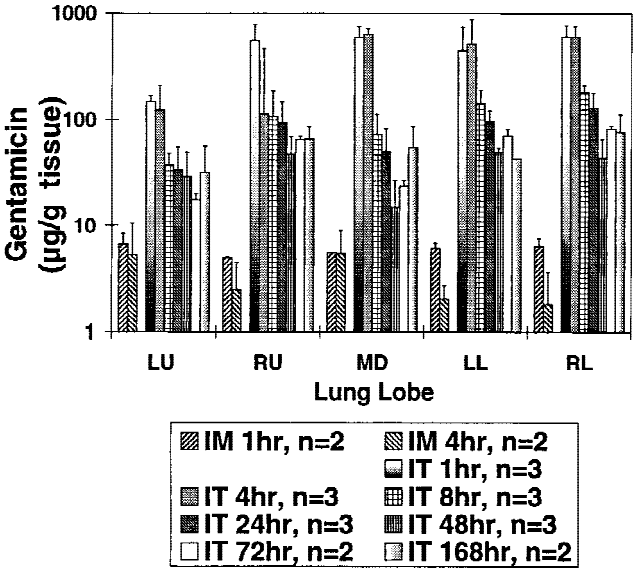

Fig. 3. Gentamicin concentrations in rabbit lung lobes following IT administration of a gentamicin PulmoSpheres® formulation vs. IM gentamicin administration. Lobe designation as follows: LU, left upper; RU, right upper; MD, middle; LL, left lower; RL, right lower.

extent to which the dose can be increased (25). For example, the MIC for gentamicin is ~8 μg/ml for *P. aeruginosa* infections, but maintaining gentamicin serum concentrations greater than 12 μg/ml induces ototoxicity and nephrotoxicity. Furthermore, systemic administration is an ineffective way to attain high pulmonary concentrations due to the poor transport of the aminoglycoside across the pulmonary endothelium into the airways (19,25). Whereas several attempts have been made to deliver such antibiotics locally to the lung, traditional aqueous-based aerosols tend to deposit in the central airways and fail to reach the peripheral regions of the lung where the sites of infection are most likely to occur.

In the present study we have examined the potential for delivering gentamicin locally to the lungs by liquid dose instillation of gentamicin microspheres in a perflubron vehicle. These gentamicin microspheres form stable suspensions in perflubron without any need for alcohol and additional fluorinated surfactants. Gentamicin levels in lung tissue following direct IT administration were approximately two orders of magnitude higher than were achieved following IM administration of an equivalent dose. Despite the high local concentrations, the serum gentamicin concentrations remained low following IT administration, significantly less than the threshold concentrations required for nephrotoxicity. Minimal interlobe variability was noted in tissue gentamicin concentrations, and these concentrations were all significantly higher than were achieved following IM administration. Surprisingly, the gentamicin tissue concentrations remained high (above the MIC) for periods of at least 1 week following IT instillation. This profile of increased lung antibiotic concentration over a sustained period of time could be advantageous in reduction or prevention of selective bacterial resistance when using aminoglycosides, as this type of antibiotic exhibits concentration-dependent killing with time (26,27). In fact, dosing regimens of targeting high peak concentration relative to MIC appear to yield the best clinical outcome (28).

Overall, local delivery can offer a number of important advantages for pulmonary infections relative to current systemic approaches. First, it is possible to give a much higher local concentration directly to the site of the bacterial infection and therefore match the resistance conferred by the increased MIC of the resistant bacterial strain. For example much of the resistance of *P. aeruginosa* to gentamicin results from alterations in the transmembrane potential of the bacteria. This effectively raises the MIC two- to fourfold. Simply increasing the systemic concentration of gentamicin to overcome the MIC is not feasible because of the associated nephrotoxicity. It can be overcome, however, by providing local treatment in the lung.

Second, even without the development of increased resistance, many classes of antibiotics exhibit increased effectiveness with increased concentration: these include the macrolide antibiotics, the aminoglycosides, and the fluoroquinolines. Again significantly higher doses can be augmented by local delivery without the associated increase in systemic toxicity resulting in a more effective cure and first line therapy.

Third, gram-negative bacterial lung infections can result in lung injury that ultimately shunts blood flow away from the site of the injury. Therefore, systemic treatment will result in the least efficient delivery to the infected area because of poor perfusion. The introduction of perflubron into the injured lung may aid by both facilitating drug delivery to the infection site as well as improving blood flow to the diseased portion of the lung, thereby allowing drug access to the site of the infection. In addition, instillation of the highly surface-active liquid perflubron vehicle allows for effective wetting of the entire lung surface.

Finally, certain antibiotics that are potent against gram-negative bacteria may have limited application for pneumonia because of poor bioavailability to the alveolar surface due to the diffusion barrier posed by the vascular endothelium. The local delivery of such agents (e.g., gentamicin) allows for increased drug at the site of the infection.

The fact that lung gentamicin concentrations remain high for a long period of time (more than 1 week) following IT administration suggests that this approach may require infrequent dosing to achieve the desired clinical effect. This is especially important for liquid dose installation applications considering the potential invasive nature of the proposed technique, namely direct instillation via a bronchoscope or endotracheal tube. In addition, this retained pulmonary antibiotic concentration may also reduce the potential buildup of resistance due to the reduced need for patient compliance in maintaining high levels of drug over time. In the present study, the gentamicin PulmoSpheres® formulation was administered in a total perflubron volume of only 1.8 ml/kg (i.e. one-tenth of a functional residual capacity). A single dose administered through the side-port of the endotracheal tube to intubated patients or via bronchoscope may be all that is required.

Concurrent IV antibiotic therapy with another class of antibiotics, which effectively penetrates the lung from the systemic side may also be recommended to further lower the risk of developing resistant bacterial strains.

Although this study focused on the pharmacokinetics and biodistribution of gentamicin following IT instillation in a perflubron vehicle in healthy rabbits, a recent parallel study has shown significant improvements in survival for rats in an acute *Streptococcal pneumoniae* model (29). These studies showed a low mortality rate (13%) following IT administration of an ampicillin PulmoSpheres® formulation compared with a high mortality rate (73%) in animals treated by direct IM injection of ampicillin.

Significantly prolonged lung pharmacokinetics were also observed following IT administration, consistent with the results presented here. Taken as a whole, these studies support the potential of PulmoSpheres® formulations for treating severe pneumonia in hospitalized patients.

CONCLUSIONS

A spray-drying method has been used to create hollow porous microspheres of gentamicin. Suspension of the gentamicin microspheres in a perflubron vehicle results in stable suspensions suitable for reproducible administration to the lung. Liquid dose instillation of the suspension results in local lung concentrations ~100 times higher than can be achieved following IM or IV administration of an equivalent dose. The high local lung concentrations achieved following IT administration do not result in correspondingly high systemic concentrations of gentamicin. In fact, the serum gentamicin concentrations remain significantly less than the threshold for nephrotoxicity.

Lung concentrations remain high for at least 1 week fol-

lowing IT administration. This profile of increased lung antibiotic concentration over a long period of time could be advantageous in reduction or prevention of selective bacterial resistance when using aminoglycosides, as this type of antibiotic exhibits concentration-dependent killing with time.

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