Pulmonary versus Systemic Delivery of Antibiotics: Comparison of Vancomycin Dispositions in the Isolated Rat Lung

María José de Jesús Valle, Francisco González López, Alfonso Domínguez-Gil Hurlé, and Amparo Sánchez Navarro

Pharmacy Department, University of Salamanca, Licenciado Méndez Nieto, s/n 37007, Salamanca, Spain, and University Hospital of Salamanca, Salamanca, Spain

Received 24 January 2007/Returned for modification 5 April 2007/Accepted 23 July 2007

Vancomycin dispositions in the respiratory system were compared after systemic and inhalatory administration under two respiratory conditions using the isolated-lung model. Inhalatory delivery led to much higher drug levels in pulmonary tissue and fluids. The respiratory pattern affects vancomycin disposition in the pulmonary system regardless of the administration route.

Pulmonary drug delivery is an efficient method for the passive targeting of drugs used in the treatment of pulmonary diseases such as asthma, bronchitis, emphysema, and respiratory infections. Nebulization of antibiotics has relevant advantages compared to other administration modes: drug access to all regions of the respiratory system, prolonged delivery periods, and the avoidance of extensive systemic exposure to drugs are some of the most interesting features of this practice (6, 9). Vancomycin is a glycopeptide drug indicated for the treatment of serious, life-threatening infections caused by gram-positive bacteria that are unresponsive to other, less toxic antibiotics (11, 17), and this is the drug of choice for the treatment of bronchopneumonia due to methicillin-resistant Staphylococcus aureus (MRSA), particularly in the case of patients undergoing mechanical ventilation (3). Renal impairment and ototoxicity are the most significant side effects, being the consequences of excessive drug accumulation (15). Owing to the interest in obtaining information about vancomycin disposition after pulmonary delivery, the aims of the present study were to compare the kinetics of this glycopeptide in the pulmonary system after systemic and inhalatory delivery and to evaluate the influence of the respiratory pattern on administration by both routes.

Experimental protocol. Twenty-four male Wistar rats with a mean body weight of 239.89 ± 19.96 g were used. Twelve hours prior to the experiments, the animals were isolated in cages and allowed access to tap water ad libitum. The housing and experimental treatment of animals were in accordance with the current Spanish legislation and complied with the principles of laboratory animal care. The animals were randomly distributed into four groups: (i) systemic administration, 60 respirations per minute (rpm), 8.4-ml/kg tidal volume; (ii) systemic administration, 30 rpm, 16.7-ml/kg tidal volume; (iii) inhalatory administration, 60 rpm, 8.4-ml/kg tidal volume; and (iv) inhalatory administration, 30 rpm, 16.7-ml/kg tidal volume. The inspiration/expiration ratio was 0.8. The method used to isolate lungs and to keep them artificially perfused and mechanically ventilated has been described in depth previously (13). A dose of 500 μg of vancomycin was administered by the systemic or inhalatory route. For pulmonary administration, 700 μg of drug was dissolved in 7 ml of distilled water. Nebulization was performed using a nebulizer device (ultrasonic aerosol generator 700/700-UV TSE system) connected to the artificial ventilation system in such a way that 5 ml reached the lungs through the cannula for 20 min (nebulization flow rate, 15 ml/h; droplet size range, 1 to 2 μm). Effluent fluid (EF) collection started at the same time as drug administration using a fraction collector (Gilson FC 203B) programmed at different sample times. Bronchoalveolar lavage (BAL) was carried at the end of experiments using 1.2 ml/kg of 0.9% saline solution. Then, the lung was excised, weighed, and used for vancomycin quantification. Drug concentrations in all samples were measured by high-pressure liquid chromatography showing a quantification limit of 0.1 μg/ml with a variation coefficient under 9%.

Pharmacokinetic analysis. Area under the curve and mean transit time (MTT) were estimated from EF drug levels by statistical moment theory (21). Additional assays under the same experimental conditions but without the tissue were carried out to correct for the influence of the device. The distribution volume of the drug in the lung ($V^*$) was calculated as the product of the MTT and the perfusion flow rate (5 ml/min) (20).

The distribution coefficient ($V/L_w$) was also determined, $L_w$ being the weight of the isolated lung. Partition coefficients were estimated from simultaneous concentrations in the three types of samples analyzed.

The nonparametric Kruskal-Wallis (10) test was used to compare results. Figure 1 shows mean concentration curves of vancomycin in EF after systemic administration; Table 1 shows the corresponding statistical moments and derived parameters. The respiratory mode significantly affected the kinetic profile and parameter values of vancomycin in the isolated lung for systemic and inhalatory administration. Figure 2 depicts curves of mean vancomycin concentrations in EF for the latter route.

Comparison of systemic and pulmonary administration of
vancomycin revealed limited access of the drug to the systemic space when administered by inhalation, regardless of the respiratory pattern. In contrast, as shown in Fig. 3, pulmonary delivery led to high levels in BAL fluid (BALF) as well as in lung tissue, while systemic administration elicited undetectable concentrations in BALF (<0.1 μg/ml) and very low drug levels in lung tissue (0.10 ± 0.04 and 0.11 ± 0.05 μg/g). Table 2 shows mean partition coefficients of vancomycin for the two administration modes and both respiratory patterns.

The results indicate that vancomycin has a limited ability to cross the alveolar-capillary membrane, regardless of the side the drug is located on. For both administration routes, vancomycin largely remained on the administration side, as it was undetectable on the other side of the barrier after systemic delivery and detectable at extremely low levels after inhalation. Since vancomycin is a hydrophilic molecule with a high molecular weight, its distribution is probably controlled by membrane permeability instead of by tissue flow. For this kinetic situation, maintenance of serum levels for as long a period as possible is the best strategy to improve drug transference. This would explain why some clinical studies have related the continuous infusion of vancomycin to better outcome rates in cases of pneumonia (1, 7, 8). Unfortunately, no data on BALF/serum ratios were provided in those studies, although Byl et al. (2) found more sustained levels in pleural exudates after continuous infusion compared to intermittent administration. Although maintenance of high serum levels would be recommended to improve alveolar-capillary membrane transference for this drug, such an approach could lead to an increased risk of renal impairment and ototoxicity; pulmonary delivery would be an alternative, with minor risk of drug-induced otic and nephrotoxicity, since this administration route leads to lower systemic exposure.

The present study also confirms the effect of the respiratory pattern on the pulmonary disposition of vancomycin, as EF drug profiles and parameters showed significant differences regardless of the administration route. The respiratory mode corresponding to 30 rpm and a 4-ml tidal volume led to higher alveolar-capillary membrane transference not only for pulmonary delivery but also for systemic administration, likely due to the increase of residence time of the drug and the extension of the transference area. Previous

### TABLE 1. Pharmacokinetic parameters of vancomycin in lungs after systemic administration

<table>
<thead>
<tr>
<th>Respiratory mode</th>
<th>AUC&lt;sub&gt;0-∞&lt;/sub&gt; (μg · min/ml)</th>
<th>MTT (min)</th>
<th>V/Lw (ml/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>60 rpm, 2-ml tv</td>
<td>109.75 ± 10.36</td>
<td>0.47 ± 0.11</td>
<td>1.89 ± 0.10</td>
</tr>
<tr>
<td>30 rpm, 4-ml tv</td>
<td>128.54 ± 25.71</td>
<td>0.78 ± 0.19*</td>
<td>2.82 ± 0.66*</td>
</tr>
</tbody>
</table>

* Data are means ± standard deviations. AUC<sub>0-∞</sub>, area under the concentration-time curve from zero to infinity; tv, tidal volume. *, P < 0.05.

### TABLE 2. Partition coefficients of vancomycin

<table>
<thead>
<tr>
<th>Route and respiratory mode</th>
<th>Partition coefficient (mean ± SD)</th>
<th>BALF/EF</th>
<th>Lung tissue/EF</th>
<th>BALF/lung tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60 rpm, 2-ml tv</td>
<td>0.49 ± 0.34</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 rpm, 4-ml tv</td>
<td>0.50 ± 0.43</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60 rpm, 2-ml tv</td>
<td>&gt;17.89</td>
<td>&gt;9.44</td>
<td>4.69 ± 5.42</td>
<td></td>
</tr>
<tr>
<td>30 rpm, 4-ml tv</td>
<td>17.89 ± 10.86</td>
<td>9.44 ± 6.00</td>
<td>7.10 ± 4.90</td>
<td></td>
</tr>
</tbody>
</table>

* tv, tidal volume.
data from Martonen and Katz (14) show that increased tidal volumes and breath-holding times improve deposition in the pulmonary region. Although that work was performed for dry powder instead of nebulized solution, their finding might also apply to our case.

The interest in the use of pulmonary delivery of vancomycin to reach high concentrations in pulmonary secretions is unquestionable. The results of our study show a BALF/EF partition coefficient value of 17.89 for pulmonary delivery (30 rpm and a 4-ml tidal volume), while this parameter cannot be estimated for the systemic route owing to the low concentration reached in the BALF. For the more unfavorable transport condition, the influence of the route seemed to be even greater. Not only is the BALF/EF partition coefficient favorable for this administration route, but the lung tissue/EF ratio is too, since this had a value of 9.44 after inhalation delivery versus 0.49 or 0.50 for systemic route. According to our results, the dose administered (500 μg, corresponding to 2 to 3 mg/kg) affords an excellent partition coefficient, but higher doses (10 to 20 mg/kg) would be needed in humans to achieve BALF and lung tissue levels as high as possible. Nebulization of a more concentrated solution would also be a recommended practice to improve lung tissue and fluid levels.

The experimental approach using the isolated rat lung may be a useful model for pulmonary drug delivery studies, although it has shortcomings related to the difficulty involved in obtaining accurate estimates of the dose delivered to the lung and bioavailability together with limitations due to the artificial perfusion medium used, which lacks some nutrients. This circumstance may be linked to our findings of low systemic levels reached after pulmonary delivery, since data from Franz et al. (4) have shown that systemic levels after the pulmonary delivery of gentamicin and vancomycin are lower for surfactant-depleted animals. Also, Veldhuizen et al. (18) found that pulmonary surfactant is altered during mechanical ventilation, so this point should be controlled when this experimental model is used.

The few available data in clinical practice (19, 5, 12, 16) indicate that pulmonary administration of vancomycin is safe.
and well tolerated, contributing to the elimination of MRSA from the sputum and improving the clinical conditions of cystic fibrosis patients suffering from chronic lung infection. Clinical assays aimed at determining the most appropriate delivery conditions as well as the suitability of systemic coadministration, the potential increase in patient sensitivity, and the influence of the respiratory pattern on drug disposition would be of great interest to determine the usefulness of the pulmonary inhalation of vancomycin. In conclusion, pulmonary administration of vancomycin appears to be an alternative for the treatment of MRSA lung infections, since it allows high drug concentration of vancomycin to be achieved. In conclusion, pulmonary administration, the potential increase in patient sensitivity, and the influence of the respiratory pattern on drug disposition would be of great interest to determine the usefulness of the pulmonary inhalation of vancomycin. In conclusion, pulmonary administration of vancomycin appears to be an alternative for the treatment of MRSA lung infections, since it allows high drug concentration of vancomycin to be achieved. In conclusion, pulmonary administration, the potential increase in patient sensitivity, and the influence of the respiratory pattern on drug disposition would be of great interest to determine the usefulness of the pulmonary inhalation of vancomycin. In conclusion, pulmonary administration of vancomycin appears to be an alternative for the treatment of MRSA lung infections, since it allows high drug concentration of vancomycin to be achieved.

We acknowledge the Consejería de Educación de la Junta de Castilla y León for a Ph.D. grant (Orden EDU/1490/2003).

REFERENCES