is also little doubt that technological and human capabilities will continue to improve and that improvements in patients' outcomes will follow. The point of our editorial was not to argue against research and innovation, quite to the contrary. Our view is simply that the lessons of the worldwide 2009 influenza A(H1N1) epidemic do not support a costly, nationwide investment in new ECMO programs. We believe that the physiologic boundaries that define current treatment space do warrant more careful examination and that ECMO has a place as a research tool in that endeavor.

Rolf D. Hubmayr, MD, FCCP
J. Christopher Farmer, MD, FCCP
Rochester, MN

Affiliations: From the Department of Medicine (Dr Hubmayr) and the Department of Internal Medicine (Dr Farmer), Mayo Clinic.

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Correspondence to: Rolf D. Hubmayr, MD, FCCP, Department of Medicine, Room 8-62, Stabile Bldg, Mayo Clinic, 200 First St SW, Rochester, MN 55905-0001.

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REFERENCES


Colistin Penetration in the Alveolar Lining Fluid of Critically Ill Patients Treated With IV Colistimethate Sodium

To the Editor:

We read with great interest the study by Imberti et al1 in CHEST (December 2010). This is the first study on colistin penetration in the alveolar lining fluid (ALF) after IV administration of colistimethate sodium (CMS) in humans; the writers report that after 2 days of treatment, colistin was undetectable in the ALF. Interestingly, their conclusion seems to be supported by the findings of a recent study in piglets with experimental pneumonia: colistin was undetectable in lung tissue after three IV doses of CMS.2 However, we believe that colistin penetration in the ALF after systemic administration of CMS may not be negligible.

Some previous experimental data from animals and humans suggest that at least some colistin penetrates the lung after IV infusion of CMS. Aoki et al3 using a bioassay, found that after IV administration of a single very high dose of CMS in mice, colistin penetration evaluated as a ratio of area under the curve from end of infusion to two hours in homogenized lungs and serum was 61%. Reed et al4 using a high performance liquid chromatography (HPLC) assay of colistin in patients with cystic fibrosis, found that colistin concentrations in sputum after at least 3 days of CMS IV exceeded observed plasma concentrations.

We recently measured colistin concentrations in the serum and the ALF of two mechanically ventilated multitrauma patients treated with CMS IV (225 mg tid) for sepsis. Collection of data was approved by the hospital’s ethics committee. Patient 1 was a 40-year-old man with a blood stream infection. Patient 2 was a 50-year-old woman with ventilator-associated pneumonia. Both patients underwent fiberoptic bronchoscopy and BAL for bacterial sampling. Two aliquots of 50 mL normal saline (N/S) were infused. The alveolar sample (retrieved from the second aliquot) was strained through a single-layer gauze and then cold-centrifuged. Paired samples of BAL supernatant and serum were assayed for colistin using an HPLC assay, as described previously.5 Colistin concentrations in the ALF were calculated by determining the amount of urea in BAL and serum, to account for the dilutional effect of instilled N/S. Results are shown in Table 1. In both patients, concentrations of colistin in the ALF greatly exceeded concentrations in the serum. Because colistin has a high molecular weight and relatively poor lipid solubility, high colistin levels in the ALF can probably be attributed to avid tissue binding or to some as-yet-unknown mechanism of active drug transport through the alveolar-capillary membrane. The much higher drug penetration in patient 2 may be due to the presence of active bacterial infection (pneumonia) or possibly to a time lag between the serum concentration curve and the ALF concentration curve for colistin, as is the case for many other antibiotics.6

How can we explain the discrepancy between our data and the findings of Imberti et al2 As Imberti et al1 observe, antibiotic levels in BAL can be very low because of the dilutional effects of N/S infusion. Thus, despite the high sensitivity of the assay for colistin they used in their study, the colistin levels in ALF might have been lower than the limit of detection of their assay (50 ng/mL). An additional factor that may have contributed to low colistin levels in their study was the administration of a relatively low dose of colistin. Given the important clinical implications of the findings of Imberti et al1 and the questions that linger on the subject of colistin penetration in the ALF, we believe that further study is needed to clarify colistin pharmacokinetics in the ALF, preferably with newer and more reliable approaches (such as bronchoscopic microsampling7).

Table 1—Colistin Penetration in Alveolar Lining Fluid After Colistimethate Sodium IV Infusion

<table>
<thead>
<tr>
<th>Patient</th>
<th>Day of CMS Treatment</th>
<th>Sampling Time From End of Infusion, h</th>
<th>Colistin BAL, μg/mL</th>
<th>Colistin ALF, μg/mL</th>
<th>Colistin Serum, μg/mL</th>
<th>ALF to Serum Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12</td>
<td>1.5</td>
<td>0.36</td>
<td>4.84</td>
<td>2.85</td>
<td>1.70</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>4.0</td>
<td>0.42</td>
<td>25.82</td>
<td>3.48</td>
<td>7.42</td>
</tr>
</tbody>
</table>

Dose was 225 mg tid. ALF = alveolar lining fluid; CMS = colistimethate sodium.

Correspondence

Nikolaos Markou, MD
Ag Paraskevi, Greece
Marizsa Fousteri, MSc
Sophia L. Markantonis, PhD
Eleni Boutzouka, MD
Evdokia Tsigou, MD
George Baltzopoulo, MD, PhD
Athens, Greece

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The issue raised by Markou et al is extremely important: Does colistin penetrate significantly into lung tissue? The clinical implications are evident, but at the moment, there is not a definitive therapeutic strategy to use. Nebulized CMS has the advantage of not causing any serious systemic adverse events, but colistin lung deposition decreases with the volume of precipitating agents used are critical for CMS and colistin recovery. In our study, we showed that colistin was undetectable in BAL 2 h after the start of an IV CMS infusion (Fig 1A), but it was present at a relevant concentration in the BAL of a patient who received CMS by aerosol (Fig 1B), suggesting significant distal lung deposition. Our findings can be interpreted as indicating either low tissue penetration or colistin tissue binding. In fact, as the result of its chemical properties, colistin (which is a polycation, while CMS is a polyanion) can bind to lung tissue, thus hindering its recovery during BAL.

Animal studies have shown that direct administration of colistin (intranasal or nebulized) to the lung is superior to IV administration in the treatment of experimental pneumonia. Nebulized CMS has the advantage of not causing any serious systemic adverse events, but colistin lung deposition decreases with the severity of pneumonia and aeration loss, a problem shared by all types of nebulized antibiotics. The association of IV and nebulized CMS could raise the lung tissue concentrations of colistin and, it is hoped, favor the cure of pneumonia. Randomized clinical trials comparing nebulized colistin with combination therapy (IV plus nebulization) should be able to determine which is the better therapeutic strategy to use.

Response

To the Editor:

The issue raised by Markou et al is extremely important: Does colistin penetrate significantly into lung tissue? The clinical implications are evident, but at the moment, there is not a definitive answer to this question. Li et al1 cited several studies in humans showing that IV colistin methanesulfonate (CMS) (also called colistimethate) is effective in the treatment of experimental pneumonia caused by multidrug-resistant, gram-negative bacteria that indicate that colistin does indeed penetrate into lung tissue in contrast, studies in animals and humans evaluating the concentrations of colistin or CMS in lung tissue have produced conflicting results. Albeit with methodologic weaknesses in the quantification of CMS and colistin, the pioneer studies performed by Ziv et al2 and Kunin and Bugg3 showed that after IV administration colistin penetrates and accumulates in lung tissue, with the concentration of the bound form being considerably higher than that of the free form. By contrast, Lu et al4 were unable to detect colistin in lung tissue after IV administration of CMS in their experimental model of pneumonia. The reasons for these conflicting results may lie in the different methods used for protein precipitation and CMS and colistin extraction from body tissues. Indeed, it has recently been demonstrated that the type of the bound form being considerably higher than that of the free form. By contrast, Lu et al were unable to detect colistin in lung tissue after IV administration of CMS in their experimental model of pneumonia. The reasons for these conflicting results may lie in the different methods used for protein precipitation and CMS and colistin extraction from body tissues. Indeed, it has recently been demonstrated that the type...