Minocycline in Treatment of Carbenapem-resistant Klebsiella Pneumoniae

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ABSTRACT

Background: The current treatment of carbenapen-resistant (CRE) infections can be challenging with ongoing antibacterial drug shortages, lack of oral options, and poor tolerability of older antibiotics. Evidence supporting the use of minocycline (MIN) for treatment of CRE infections is limited. We present our experience using high dose MIN for treatment of carbenapen resistant Klebsiella pneumoniae (CRE-KP) infections during the period of national shortage of tigecycline and ceftazidime/avibactam.

Methods: This is a single center, retrospective case review of patients who received MIN for treatment of CRE infection at Westchester Medical Center, New York. Minocycline susceptibility was initially predicted by tigecycline (TET) Minimum Inhibitory Concentration (MIC) determined by the MicroScan Neg MIC panel (Beckman) and subsequently confirmed by E-test (bioMérieux). The MLS breakpoints for TET treated strains were applied. Sensitivity (S) for MIN was determined for MIN/CVE: Resistant (R) for MIC ≥16. Concurrent antibiotics were used, as needed, in setting of poly-microbial infection.

Results: During 2015-2016, 4 patients with CRE infections at distinct sites were treated with MIN 200 mg twice a day. MIN was tolerated in all patients without any adverse effects. 4/4 patients had good clinical response. 1/4 patients developed further CRE bacteremia 18 days after initial clinically successful completion of therapy.

Conclusion: In selected patients, high dose MIN was used successfully to treat various non-bacteremic CRE infections. This limited clinical data along with known favorable pharmacokinetics, offers MIN as an oral option for definitive and step-down therapy in treatment of CRE infections.

INTRODUCTION

Optimal antibiotic therapies for treatment of CRE infections are not well defined. From 2015-2016, there was a nationwide shortage of tigecycline and ceftazidime/avibactam, further limiting the treatment options for treatment of CRE infections. This shortage prompted investigation of novel antibiotics for treatment of CRE infections.

In this case series, we report our experience with use of minocycline for treatment of infections caused by carbenapen-resistant Klebsiella pneumoniae (CRE-KP).

MATERIALS AND METHODS

This is a retrospective case review of 4 patients treated with minocycline for CRE-KP infections from January 1, 2015 to December 31, 2016, at Westchester Medical Center (WMC), a tertiary care hospital located in suburban New York.

Clinical data, antimicrobial susceptibility results, and antibiotic treatment regimens for the subjects were collected. Minocycline (MIN) susceptibility was initially predicted by tigecycline (TET) Minimum Inhibitory Concentration (MIC) determined by the MicroScan Neg MIC panel (Beckman) and subsequently confirmed by E-test (bioMérieux). MIC breakpoints were fixed as per CLSI 2017 guidelines: sensitiveMIC ≤4 mg/ml; intermediate 8 mg/ml; resistant ≥16 mg/ml.

RESULTS

Patient Characteristics Infection Sites Other organisms Treatment Concurrent antibiotics

<table>
<thead>
<tr>
<th>Patient</th>
<th>Characteristics</th>
<th>Infection Sites</th>
<th>Other organisms</th>
<th>Tetracycline</th>
<th>MIN/mg/L</th>
<th>Tigecycline</th>
<th>MIN/mg/L</th>
<th>Avibactam</th>
<th>Clinical- \nAvibactam</th>
<th>Treatment Duration</th>
<th>Concurrent antibiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIN 13</td>
<td>Gastric, colon cancer, Lynch syndrome</td>
<td>Cholecystitis, Intestinal to Vespertilion- resistant Enterobacter</td>
<td>24</td>
<td>2</td>
<td>18</td>
<td>2</td>
<td>MIN x 17 days + Piperacillin/tazobactam</td>
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<tr>
<td>MIN 14</td>
<td>Refractory pre-acute lymphoblastic leukemia (ALL)</td>
<td>Peri-renal abscess, Cholecystitis to Vespertilion- resistant Enterobacter</td>
<td>4</td>
<td>1</td>
<td>8</td>
<td>6</td>
<td>Intravenous drainage Minocycline x 10 days + Ceftazidime</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>MIN 15</td>
<td>Ischemic Carotid Stenosis, Coronary artery disease, Cerebrovascular accident</td>
<td>Hospital-acquired pneumonia</td>
<td>None</td>
<td>4</td>
<td>4</td>
<td>16</td>
<td>2</td>
<td>MIN x 17 days + Piperacillin/tazobactam</td>
<td></td>
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<tr>
<td>MIN 16</td>
<td>Hepatitis C, C. Difficile, Type-2 Diabetes Mellitus, Emphysema, End stage renal disease</td>
<td>Pseudomembranous colitis</td>
<td>None</td>
<td>4</td>
<td>4</td>
<td>16</td>
<td>2</td>
<td>MIN x 10 days + Avibactam x 6 days</td>
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</tbody>
</table>

DISCUSSION

Centers for Disease Control and Prevention (CDC) characterized CRE as an urgent threat to public health. These multidrug-resistant organisms cause infections that are associated with high mortality, have limited treatment options, and are an increasing cause of health-care-associated infections.

Minocycline is a semisynthetic derivative of tetracyclines. Compared with other tetracyclines, minocycline has enhanced tetracycline resistance, which results in longer half-life, better oral absorption and improved tissue penetration.

Minocycline is available in intravenous and oral formulations. Minocycline is 90-100% bio-available when given orally. For Klebsiella pneumoniae, minocycline is reported to have a MIC 50 of 4 mg/ml, similar to tetracycline and lesser than that of doxycline (128 mg/ml).

When given at dose of 200 mg twice a day, Minocycline has the highest area under the concentration-time curve (AUC). This offers the highest AUC/MIC ratio among all tetracyclines. Minocycline has a better side-effect profile than colistin and polymixin B.

There is very limited clinical data for use of Minocycline for treatment of infections caused by CRE-KP.

CONCLUSION

In our study, minocycline was used successfully to treat infections caused by CRE-KP in different sites. Minocycline may be used even at higher doses. This limited clinical data along with known favorable pharmacokinetics, offers minocycline as an oral option for definitive and step-down therapy in treatment of select infections caused by certain multi-drug resistant gram negative organisms including CRE.

REFERENCES

Epidemiological, clinical and microbiological data is summarized in the table. Patients with CRE infections at distinct sites received minocycline 200 mg enterally every 12 hours. Concurrent antibiotics were used, as needed, in setting of poly-microbial infection or based on co-morbidities. Treatment duration was based on the clinical and microbiological response to initial antibiotic therapy.

- MIN was tolerated in all patients without any adverse effects.
- 4/4 patients had good clinical response.
- 4/4 patients had an microbiological response. One patient (MIN) developed CRE-KP bacteremia 18 days after initial successful completion of therapy in the setting of prolonged neutropenia and restarting of chemotherapy. The subsequent isolate did not show increased MIC to tigecycline or Minocycline.