Extended Duration and Continuous Infusions of Antibiotics

Rationale

The importance of pharmacokinetic/pharmacodynamic (PK/PD) indices to maximising the efficacy of antimicrobials was highlighted in Issue 2. Extended duration or continuous infusions for time dependent antibiotics (e.g. beta lactams) are one way of using PK/PD to maximise clinical success.

There is strong evidence that the amount of time in which the free or non-protein bound drug concentration exceeds the Minimum Inhibitory Concentration (MIC) of the organism (T>MIC) is the best predictor of bacterial killing and microbiologic response for beta lactams.¹

Continuous or extended duration infusions increase the time of maintaining serum drug concentrations above the MIC over a 24 hour period. This is particularly important for infections caused by bacteria with increased MICs and/or intermediate resistance. For example, the time required above the MIC for maximal bactericidal effects on Gram-negative bacteria depends on the class of beta-lactam: penicillins require T>MIC of 50%, cephalosporins require 50-70% and carbapenems require a T>MIC of 40%.¹ Required T>MIC exposures for Gram-positive bacteria are usually lower due to a longer post-antibiotic effect of the antimicrobial.¹

Intermittent IV Administration – the infusion is usually given over 30-60 minutes

Continuous IV Infusion - the infusion is given at a fixed rate over a 24 hour period

Extended Duration Infusion (Extended Dosing Interval) – the infusion is extended to 40-50% of the dosing interval (e.g. over 3-4 hours)

In which situations could continuous/extended duration infusions be considered?

<table>
<thead>
<tr>
<th>Bacteria with intermediate susceptibility or high MICs</th>
<th>Patients with altered pharmacokinetics (PK)</th>
<th>Outpatients / Hospital at Home</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Predictive models and small clinical studies have demonstrated the benefits of extended infusions over intermittent dosing for patients with Gram-negative infections with higher MICs.</td>
<td>• Altered PK (seen in critical illness, burns, cystic fibrosis) makes achieving optimal concentrations of antimicrobials challenging due to augmented renal drug clearance, abnormal fluid balance and changes in protein binding</td>
<td>• Continuous infusion devices (e.g. Baxter infusors) can deliver an antibiotic over 24 hours</td>
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<td>• Example: A meta-analysis combining 12 retrospective and prospective studies of critically ill patients with resistant pathogens observed significantly lower mortality among 587 patients treated with extended versus standard infusion of piperacillin/tazobactam or carbapenems.²</td>
<td>• Continuous infusions have been associated with positive clinical outcomes, including increased 30-day patient survival in critically ill patients with infections caused by non-fermenting Gram-negative bacilli.³</td>
<td>• This maximises T&gt;MIC and enables the patient to be discharged from hospital and treated at home</td>
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<td>• Infusors provide convenience for ambulatory patients needing prolonged IV antibiotic courses</td>
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<td>• Example: benzylpenicillin for treating syphilis - daily dose can be given over 24 hours instead of 4-hourly intermittently⁴</td>
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</tbody>
</table>
The Benefits of Extended Duration Infusions

Not all antimicrobials are stable enough to be given as a continuous infusion. One way to overcome stability and optimise dosing according to the PK/PD profile is to administer via an extended duration infusion. For example, a haematology cohort of patients was given meropenem as an extended duration infusion over 3 hours instead of 30 minutes. Results showed a greater 5 day treatment success (as defined by resolution of fever, improvement in symptoms, absence of bacteraemia and no need for additional antibiotics). There were however no differences in length of stay and 100-day mortality between the two groups.

Cefepime is another example of a beta-lactam antibiotic with limited stability once made into solution. Overall mortality was significantly reduced in ICU patients with Pseudomonas aeruginosa infections (bacteraemia and/or pneumonia) when they were given cefepime as an extended duration infusion over 4 hours rather than over the usual 30 minutes (3% vs 20%, p=0.03).

Examples of beta-lactam antibiotics that can be given via continuous or extended duration infusions

<table>
<thead>
<tr>
<th>Continuous Infusion (dose may be dependent on renal function)</th>
<th>Continuous Infusion</th>
<th>Extended Duration Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefazolin (up to 8g/24 hours)</td>
<td>✓</td>
<td>Not practiced</td>
</tr>
<tr>
<td>Cefepime (up to 4.8g/24 hours)</td>
<td>✓</td>
<td>Over 3 to 4 hours</td>
</tr>
<tr>
<td>Ceftazidime (up to 6g over 24hrs)</td>
<td>✓</td>
<td>Over 3 to 4 hours</td>
</tr>
<tr>
<td>Flucloxacillin (up to 12g over 24 hours)</td>
<td>✓</td>
<td>Not practiced</td>
</tr>
<tr>
<td>Meropenem (not stable)</td>
<td>×</td>
<td>Over 3 hours</td>
</tr>
<tr>
<td>Piperacillin/Tazobactam (up to 16g/2g over 24hrs)</td>
<td>✓</td>
<td>Over 4 hours</td>
</tr>
</tbody>
</table>

Logistical barriers

Drug Stability

The type of intravenous fluid used to reconstitute the drug, the concentration of the final solution and the storage temperature all influence the stability of antimicrobials made into solution. The Australian Injectable Drugs Handbook is an excellent resource on drug stability. Pharmaceutical companies (including Baxter or Slade) can also provide advice on antimicrobials that are suitable for infusors.

Mobility

24-hour antibiotic infusors are usually limited to use in the outpatient setting due to cost. Continuous or extended duration infusions prescribed to inpatients are given via infusion pumps. These have a limited battery life and require recharging if the patient wishes to mobilise.

Vascular Access

Continuous infusions must be given using an appropriate access device such as a:
- Peripherally inserted central catheter (PICC)
- Midline catheter
- Tunnelled central venous catheter (CVC)
- Implanted port

Antimicrobial properties should be considered when choosing between inserting a midline catheter or PICC. In general, a PICC is preferred for longer treatment courses (> 1 to 2 weeks) and when giving antimicrobials which have a high or low pH (< 5 or > 9) or are hypertonic.

Examples of antimicrobials recommended to be administered via a central line include aciclovir and ganciclovir (both have a high pH of 9-11), piperacillin/tazobactam (risk of thrombophlebitis) and vancomycin and flucloxacillin (irritant at high concentrations).
Compatibilities

If the patient is on other intravenous medications then the compatibility of the medications and access to other IV lines needs to be considered as the continuous or extended duration infusion will occupy one access point. One way around this is to insert a dual or triple lumen PICC line.

What does this mean clinically?

It is important to note that greatest benefits and outcomes of using continuous or extended duration infusions of antimicrobials has been in critically ill patients (e.g. in ICU) or with altered PK. Patients with high MIC Gram-negative bacteraemia (e.g. severe infections with carbapenemase-producing Enterobacteriaceae, MDR-Pseudomonas spp or MDR-Acinetobacter spp) may also benefit from continuous or extended duration infusions. Evidence is lacking to support clinical success or treatment failure using the different dosing strategies; however continuous infusions given in the outpatient setting do offer many advantages to patients including increased mobility and quality of life as well as decreased healthcare associated infections and costs.

What about vancomycin?

Vancomycin is a glycopeptide and is indicated for infections caused by multi-drug resistant Gram-positive bacteria including methicillin-resistant Staphylococcus aureus (MRSA) and methicillin-resistant Staphylococcus epidermidis. Vancomycin demonstrates slow and time-dependent killing in most patients and unlike beta-lactam antibiotics it has a long post-antibiotic effect (meaning withdrawal of the antibiotic is not immediately followed by bacterial growth).

Some of the benefits gained by giving vancomycin as a continuous infusion are:

- Useful for patients requiring higher or more frequent doses (e.g. obese patients, patients with augmented renal function);
- Less risk of nephrotoxicity when treating infections caused by pathogens with a high vancomycin MIC;
- Target concentrations are achieved faster;
- Less variability of the area under the curve (serum concentrations) over 24 hours;
- Easier therapeutic drug monitoring (level can be taken at any time);
- Reduced cost and convenience (for patients treated at home).

Further reading and references: