Exceptional Case

Risk of underdosing of ampicillin/sulbactam in patients with acute kidney injury undergoing extended daily dialysis—a single case

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Abstract
The fixed antibacterial combination of ampicillin and sulbactam is frequently used for various infections. The normal kidneys eliminate ∼60% of ampicillin (371.39 Da) and sulbactam (255.22 Da). Concomitant with the decline in renal function, the terminal elimination half-life increases from 1 up to 24 h in patients with ESRD. Patients on three times weekly low flux haemodialysis exhibit a half-life of 2.3 h on and 17.4 h off dialysis. In contrast, in the present observation the elimination half-life in a single patient with acute kidney injury undergoing extended daily dialysis (EDD) with a polysulphone membrane was 1.5 h, indicating that the current dosing regimen for haemodialysis patients (ampicillin/sulbactam 2.0/1.0 g/day) would result in a significant underdosing for patients undergoing EDD.

Keywords: beta-lactamase inhibitor; dialysis; Genius-dialysis; pharmacokinetics

Background
In December 1986, the Food and Drug Administration approved Unasyn®, a fixed antibacterial combination of the beta-lactam ampicillin and the beta-lactamase inhibitor sulbactam. The continuous use of this combination is fostered by recent national and international guidelines, many of which recommend ampicillin/sulbactam as first-line therapy for various respiratory and skin infections [1]. In individuals with normal renal function ∼60% of both, ampicillin (371.39 Da) and sulbactam (255.22 Da) are excreted unchanged in the urine with an elimination half-life for both ampicillin and sulbactam of ∼1 h [1]. Concomitant with the decline in renal function, the terminal elimination half-life increases up to 24 h in patients with end-stage renal disease. Although ampicillin/sulbactam is frequently used in patients on dialysis, the world literature consists of pharmacokinetic data on four chronic haemodialysis patients [2]. Using a cuprophane low-flux dialyzer with a surface of 1.0 m² (C-DAK model 3500, CD-Medical, Inc., Miami Lakes, FL, USA), a 4-h dialysis session (blood flow 200 mL/min, dialysate flow 500 mL/min) removed ∼35% of ampicillin (28% protein binding) and 45% of sulbactam (38% protein binding), given 2 h before the start of the dialysis session. Over the last 20 years since this publication, many characteristics of dialysis have changed. Aside from the almost ubiquitous use of high-flux dialysis membranes with higher surface areas, prolonged dialysis hours in the setting of extended daily dialysis (EDD) have been introduced. This method is increasingly used in intensive care units (ICUs) throughout the world [3]. EDD removes various antibiotics more efficiently compared with standard intermittent haemodialysis (IHD) three times a week or continuous renal replacement therapy [4–8]. As there are no data on ampicillin/sulbactam using EDD, we determined single-dose pharmacokinetics of both substances in a renal transplant patient with enterococcal urinary tract infection and acute kidney injury undergoing EDD.

Case presentation
A 69-year-old white male was admitted with acute upper GI bleed from a duodenal ulcer. The patient’s past medical history includes status post-renal transplantation due to end-stage renal disease caused by a chronic glomerulonephritis. He had coronary heart disease and underwent coronary artery stenting. Six months prior to this episode of upper GI bleed, he survived a respirator therapy requiring pneumococcal pneumonia. Shortly after the GI bleed, the patient developed increased inflammation markers (Leukocyte count 12.9 Tsd/µL; CRP 64 mg/L) and went into acute kidney injury. EDD was initiated using the GENIUS® dialysis system (Fresenius Medical Care, Germany) with a polysulphone high-flux dialyser (F60S,
Table 1. PK-parameter after a single-dose ampicillin 2.0 g and sulbactam 1.0 g. Data of the presented case compared to data from healthy controls and patients on chronic haemodialysis reported in the literature

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Ampicillin</th>
<th>Sulbactam</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Case IHD²</td>
<td>Controls²</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (mg/L)</td>
<td>73.0</td>
<td>35.0</td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt; (h)</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;last&lt;/sub&gt; (mg/h/L)</td>
<td>187.2</td>
<td>106.0</td>
</tr>
<tr>
<td>T&lt;sub&gt;1/2&lt;/sub&gt; (h)</td>
<td>1.5</td>
<td>1.9</td>
</tr>
<tr>
<td>MRT (h)</td>
<td>1.4</td>
<td>2.0</td>
</tr>
<tr>
<td>V&lt;sub&gt;z&lt;/sub&gt; (L/kg)</td>
<td>0.31</td>
<td>0.34</td>
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<tr>
<td>Cl&lt;sub&gt;tot&lt;/sub&gt; (mL/min)</td>
<td>173.3</td>
<td>151.7</td>
</tr>
<tr>
<td>Cl&lt;sub&gt;dial&lt;/sub&gt; (mL/min)</td>
<td>121.1</td>
<td>147.8</td>
</tr>
</tbody>
</table>

Parameters were peak plasma concentration (C<sub>max</sub>), area under the curve (AUC), time of maximal plasma concentration (T<sub>max</sub>), half-life (T<sub>1/2</sub>), mean residence time (MRT), volume of distribution (V<sub>z</sub>), drug clearance (Cl<sub>tot</sub>), dialyzer clearance (Cl<sub>dial</sub>), IHD (intermittent haemodialysis).

The determination of a dosing regimen in the renal failure population receiving modern means of renal replacement therapy is a challenging task [9]. As pointed out by Mueller and colleagues, the growth of higher delivered doses of renal replacement therapies in critically ill patients with acute kidney injury has rendered old dosing guidelines ineffectual and potentially dangerous [10].

To our knowledge, this is the first report on the pharmacokinetics of ampicillin and sulbactam given as fixed combination in a patient undergoing EDD. Our data indicate that the current dosing regimen for haemodialysis outpatients (ampicillin/sulbactam 2.0/1.0 g/day) would result in a significant underdosing for patients undergoing EDD as AUC and half-life, as well as total body clearance are almost comparable to healthy controls. Like other antibiotics with time-dependent kill activity, the main pharmacokinetic/pharmacodynamic parameter for ampicillin/
Ampicillin/sulbactam and EDD

sulbactam is the proportion of time of the dose interval during which the drug concentration exceeds the MIC (T > MIC). For penicillin, a T > MIC of ~50% of the dose interval has been previously suggested to be effective [1]. In our case, however, ampicillin/sulbactam concentrations exceeded MIC90 values of Enterobacteriaceae, such as *E. coli* or *Klebsiella pneumoniae* (MIC90 ≤ 2.0 mg/L) or *E. faecalis* (MIC90 = 2.0 mg/L), only for 8 h (~30% of the dosing interval) after start of infusion. The slight rebound after EDD, more pronounced for ampicillin than for sulbactam, which is in line with data from chronic haemodialysis patients [2], is probably not clinically relevant. In our view, prospective studies have to elaborate dosing recommendations for ampicillin/sulbactam especially for patients with acute kidney injury treated with effective modes of renal replacement therapy to avoid excess mortality due to underdosing of life-saving medication.

Conflict of interest statements. J.T.K. has received funds for speaking at symposia organized on behalf of Fresenius Medical Care and has also received funds for research from Fresenius Medical Care. O.B. has received research grants from Pfizer Pharma GmbH. Other authors have nothing to declare.

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