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Temocillin plasma and pancreatic tissue concentrations in a critically-ill patient with septic shock.

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1 Sir,

2 Resistance of Gram-negative pathogens to current antibiotics has revived interest for earlier and
3 often disused molecules for which resistance is still low. Yet, detailed
4 pharmacokinetic/pharmacodynamic data are scarce for these drugs. A typical example is
5 temocillin (6- α -methoxy-ticarclillin), active against most Gram-negative bacteria, which shows
6 stability against a variety of β -lactamases, including most ESBLs, AmpC and some
7 carbapenemases. Temocillin represents a strategic sparing alternative to carbapenems.¹ There
8 is no EUCAST breakpoint set for temocillin but in recent surveys, MIC₉₀ of 8-16 mg/L were
9 reported for ESBL and AmpC producers.^{2,3} The main driver of efficacy of β -lactams is the
10 fraction of time between successive administrations during which their free concentration
11 remains above the MIC of the offending organism. For penicillins, it is generally accepted that
12 this fraction must reach 40% of the dosing interval. However, more demanding targets (such as
13 maintaining unbound concentrations > 4 times the MIC of the offending organism) have been
14 advocated for severe infections in critically-ill patients⁴ and for preventing the emergence of
15 resistance.⁵ This may require the use of large doses as well as implementing continuous
16 infusion as done routinely for temocillin in our ICU.⁶ Yet, many infections are located deep in
17 tissues, questioning the importance of antibiotic tissue penetration in the final outcome of the
18 treatment. In this context, we report here the case of a critically-ill patient in whom we could
19 measure temocillin concentration in the pancreatic tissue. Written informed consent was
20 obtained from the patient's relatives for collecting samples.

21 A 51 year-old female was transferred to our ICU from another institution because of severe
22 necrotizing pancreatitis secondary to duodenal perforation after endoscopic retrograde
23 cholangiopancreatography. She received meropenem for more than 2 weeks for suspicion of a
24 pancreatic infection. On the third week after admission, her condition deteriorated with
25 development of septic shock. A duodenal fistula was documented and blood cultures grew for

26 *Klebsiella pneumoniae* with MICs (Etest) of 12 mg/L for meropenem (categorized as resistant)
27 and 16 mg/L for temocillin. Temocillin was given for 10 days by continuous infusion at a daily
28 dose of 6 g due to the low susceptibility of the pathogen, even though the patient was under
29 continuous hemofiltration (due to acute renal failure; GFR: 20 mL/min). Temocillin total and
30 unbound concentrations were quantified in plasma samples collected every 24 h from day 5 to
31 day 9, using a validated liquid chromatography–tandem mass spectrometry method.⁷
32 Bacteraemia had resolved after 10 days of treatment, but surgical debridement was required to
33 remove infected pancreatic tissue, giving us the opportunity to collect a necrotic sample at day 8
34 and to measure its temocillin content. In brief, the sample was washed in saline, dried at 40°C
35 during 24 h (temocillin stability was >90% in these conditions), homogenized in saline,
36 reconstituted in ethyl acetate containing internal standard (ticarcillin) and phosphate buffer pH
37 9.2, and centrifuged at 4°C during 5 minutes at 11,000 g. The organic phase was collected,
38 evaporated and reconstituted in 20 µL of mobile phase for assay as described for plasma
39 samples,⁷ with a calibration curve using a fragment of porcine pancreas spiked with temocillin
40 and treated by the same procedure.

41 Mean unbound and total temocillin concentrations in plasma remained stable over time during
42 the sampling period (69.8 ± 5.2 mg/L and 112.5 ± 2.9 mg/L, respectively; see Figure 1). These
43 high levels are likely explained by the patient's renal insufficiency. Notably, the unbound
44 concentrations, which were high probably due to the low plasma protein level (44.6 ± 1.6 g/L;
45 see discussion in refs.^{3,6}), was continuously above 4-times the MIC of the offending organism.

46 Temocillin content in the tissue homogenate was 186 µg/g, which could be approximated to 186
47 mg/L.⁸ Such a high concentration was unexpected, because β-lactams show a low distribution
48 volume (denoting a lack of tissue accumulation), and because necrotic tissue is poorly
49 vascularised. It could be related to the long-lasting exposure of the tissue to stable, elevated
50 serum levels afforded by the continuous infusion, the high unbound plasma concentrations in

51 this patient, and the low perfusion of the organ, which could reduce the clearance of the drug if
52 bound to tissue constituents. As we used whole tissue homogenate, this value represents an
53 average for drug found extra- or intracellularly. In most publications, the temocillin
54 concentrations in tissues and body fluids represent 8-65% of the total serum concentrations (³
55 for review), but these may not represent values at equilibrium since temocillin was given by
56 discontinuous infusion. Moreover, these studies were not performed in critically-ill patients.
57 Finally, total tissue levels could be high due to low serum protein concentration, resulting in a
58 temocillin equilibrium shift in favour of the tissue. This is of particular importance for drugs with
59 non-linear protein binding⁹ as temocillin. Thus, although limited to a single case, these data
60 suggests that temocillin may reach therapeutic levels in some tissues and encourages further
61 studies in this area.

62

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67

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69

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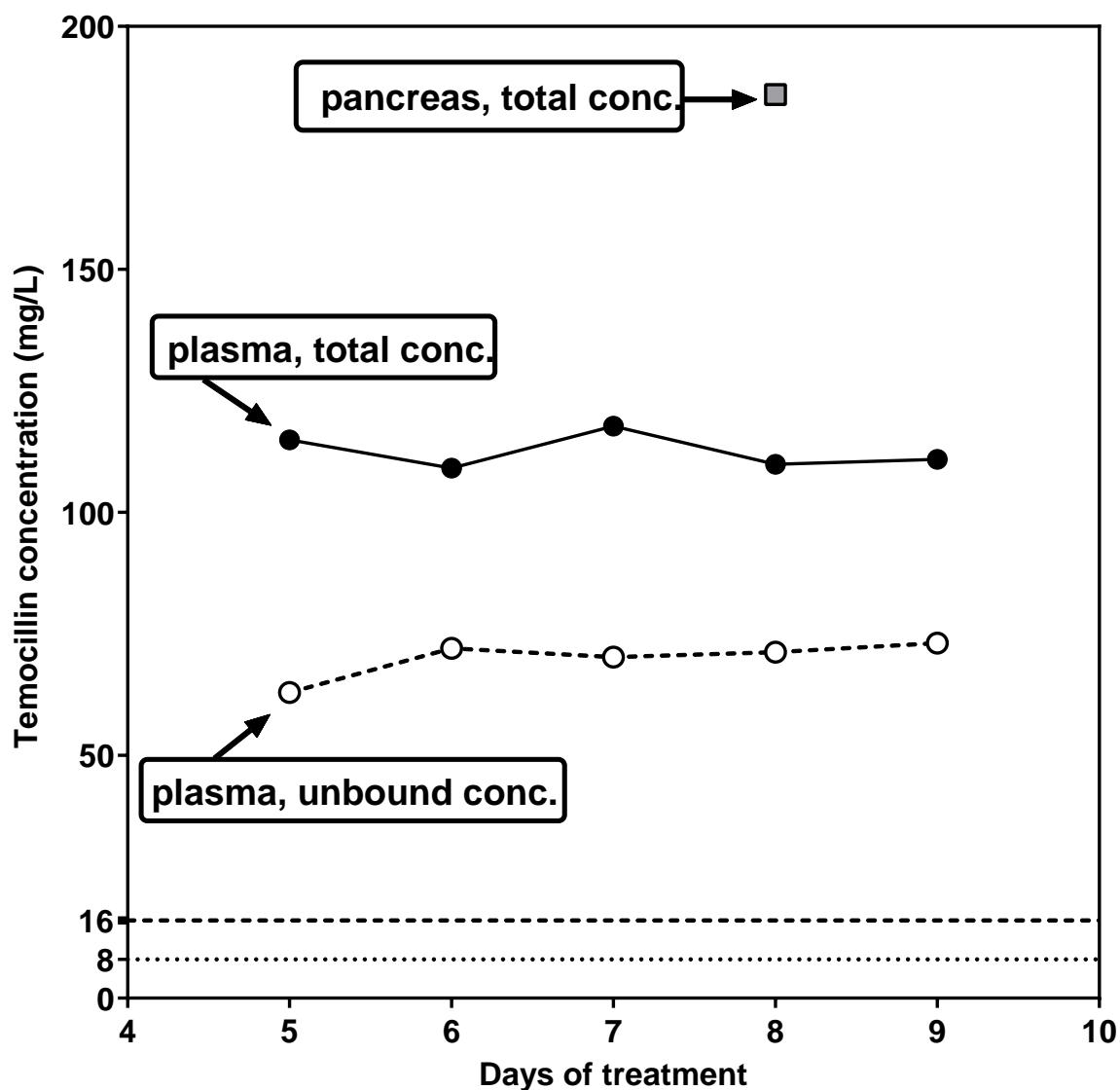


Figure 1: Concentration of total (closed circles) and unbound (open circles) temocillin in plasma samples and of total temocillin in homogenate of pancreas (grey squares) collected from a critically-ill patient receiving 6 g per day by continuous infusion. Plasma samples were collected from day 5 to day 9 of treatment and pancreatic biopsy, at day 8. The horizontal dotted lines correspond to typical MIC₉₀ reported in recent surveys for Enterobacteriaceae producing ESBLs (8 or 16 mg/L).