Standard dosage of piperacillin leads to subtherapeutic plasma concentrations in burn patients

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Background:

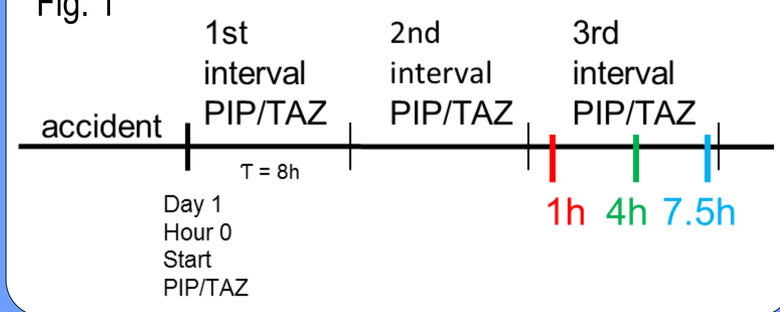
Infections are a major problem in patients with burn diseases (BD). Due to severe injuries of their total body surface area (TBSA), burn patients have altered pharmacokinetic characteristics. Therefore, insufficient plasma concentrations may be achieved, when standard dosing schedules are applied for antibiotics such as piperacillin. For time dependent antibiotics, the duration how long drug concentration exceeds the minimal inhibition concentration (MIC) is crucial for their antibacterial effects. Since Pseudomonas spp. is the main problematic pathophysiological bacterium for BD patients. The aim of the present study was to monitor the plasma concentration of piperacillin during piperacillin/tazobactam (PIP/TAZ) treatment in BD patients. Patients from Intensive Care Units (ICU) served as controls.

Study design and Methods:

13 BD patients and 11 patients from ICU (Tab. 1) were included in this observational study. Blood samples were taken within the 3rd interval of the 8h-lasting dosing period (T) of PIP/TAZ (4/0.5g within 0.5h) at 1, 4 and 7.5h after the end of infusion (Fig. 1). Total and free piperacillin concentrations were determined in plasma using HPLC-UV after deproteinisation with acetonitrile and by ultrafiltration, respectively. Pharmacokinetic parameters and dosing simulations were calculated by TDMx (www.tdmx.eu). Free plasma concentrations of piperacillin exceeding at least 1xMIC but preferably 4xMIC over the whole dosing interval were considered to be sufficient for antibiotic efficacy (MIC 16 mg/L for Pseudomonas spp., www.eucast.org).

Tab. 1	BD	ICU
No. of patients	13	11
Age (y)	47.8±4.7	71.5±3.6
Sex (no. male/ no. female)	8/5	5/6
Weight (kg)	80.3±5.1	69.7±2.8
Height (cm)	175.5±3.2	168.8±2.3
TBSA (%)	36.1±4.3	
Serum Krea (mg/dL)	0.974±0.1	1.073±0.1

Fig. 1



Results:

1.The pharmacokinetic (PK) parameters of total PIP were calculated for each BD or ICU patient.

2.4xMIC and Cmax are lower in BD than in ICU patients (Fig. 4/5, Tab. 2).

3.Clearance (CL) and volume of distribution (VD) are higher in BD than in ICU patients (Fig. 6/7, Tab. 2).

4.Half-life (t1/2) did not differ between both groups (Tab. 2).

5.TDMx simulations predicted that the duration per day for 4xMIC could be enhanced if PIP dosing regime will be increased to 4x8g/d and the infusion duration to 3h (Fig. 8).

Tab. 2	BD	ICU
1xMIC (%)	60.26±6.7	78.4±8.4
4xMIC (%)	13.0±2.2	33.9±4.2
Cmax (mg/L)	66.2±8.3	137.6±25.7
t ½ (h)	1.7±0.2	1.9±1.1
CL (L/h)	14.2±2.6	7.4±1.1
VD (L)	30.9±2.6	20.2±1.5

Fig. 2: time dependent PIP concentration

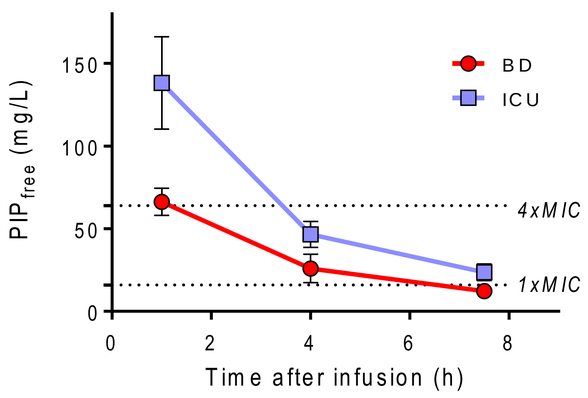


Fig. 3: % above 1xMIC

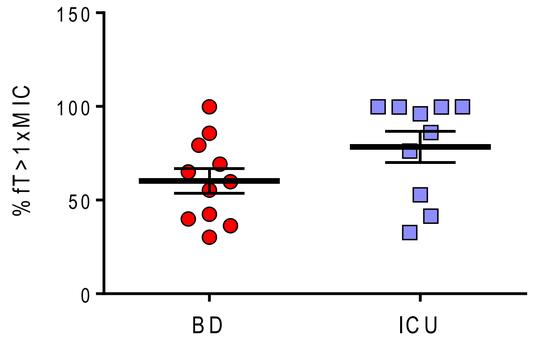


Fig. 4: % above 4xMIC

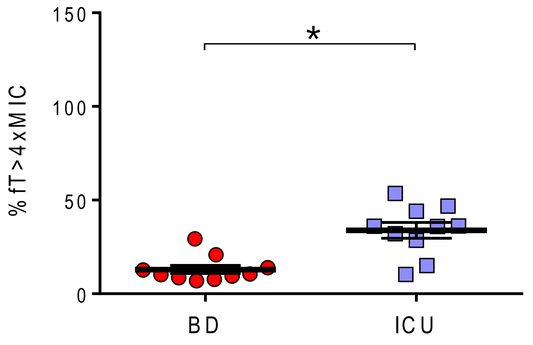


Fig. 5: Cmax

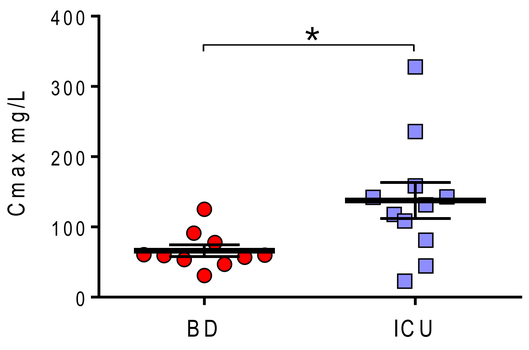


Fig. 6: Clearance

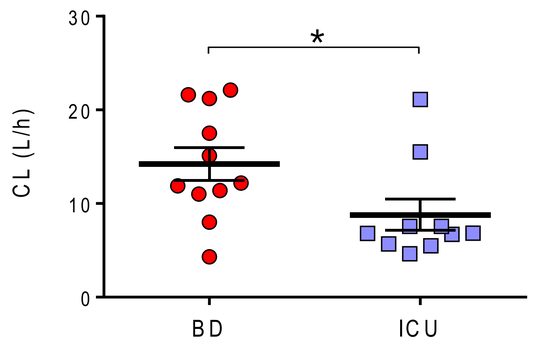
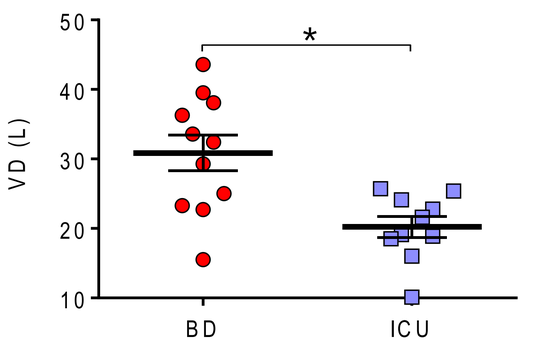


Fig. 7: Volume of Distribution



Conclusions:

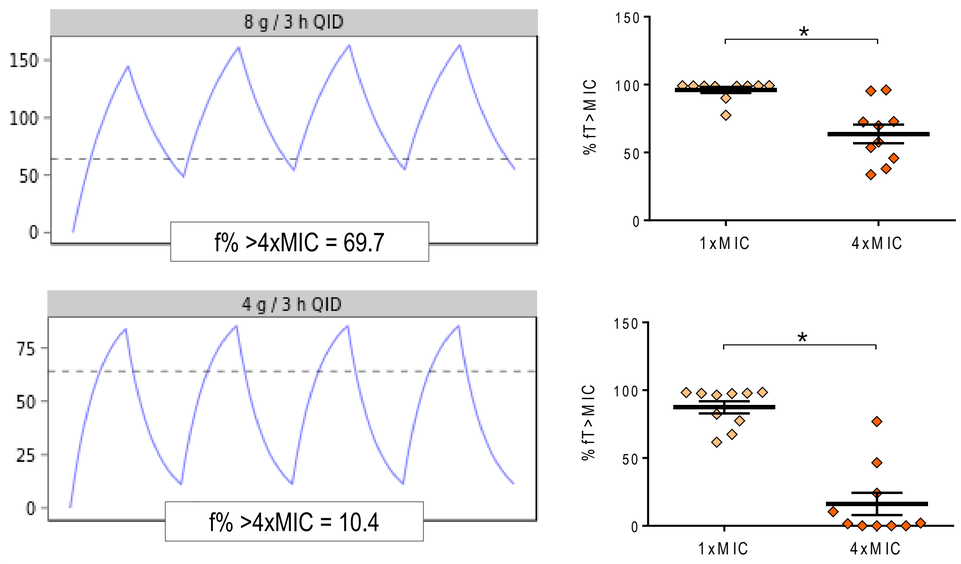
1.Standard dosage regimes of PIP/TAZ resulted in suboptimal plasma concentrations of PIP in BD as well as in ICU patients.

2.Drug monitoring and TDMx simulation of kinetic parameters may easily help to improve PIP treatment in BD patients.

3.TDMx simulation analyses indicate that treating BD patients with maximal allowed PIP doses (4x4g PIP, 3h) did not result in sufficient plasma concentrations (Fig. 8).

4.Plasma concentrations may markedly be increased in BD patients when they were treated with off-label dosages (8x4 g PIP, 3h). We, however, can only speculate, whether the clinical outcome of the BD patients is really improved when PIP dose is enhanced. Thus, pharmacokinetic have to be determined in a pilot study with BD patients to ensure predicted values and clinical parameters should be monitored.

Fig.8 TDMx simulations for BD patients



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