Individual variability in antibiotic trough concentrations of piperacillin in critically ill patients

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Background

Research has shown that concentrations of β-lactam antibiotics in blood of critically ill patients are very variable and unpredictable, with many patients dosed suboptimally[1], because of the pathophysiological changes occuring in these patients[2].

Objectives

The purpose of this study was to investigate the variability in antibiotic trough concentrations over time both between patients (inter patient variability), as well as within one patient (intra patient variability).

Materials and methods

Eleven adult critically ill patients without renal dysfunction were studied, treated with a 30 minutes loading dose of 4 g piperacillin/tazobactam followed by 4 x 4 g per day, which was administered as a 3-hour extended infusion. One antibiotic trough sample was taken per day for 7 consecutive days and were analysed using ultra high performance liquid chromatography tandem mass spectrometry.

Sample pretreatment consisted of protein denaturation using acetonitrile and subsequent dilution with water. This method was validated according to FDA principles. The method was found to be lineair from 4-250 mg/L with an imprecision < 15 % at all levels.

Results

Patient characteristics are shown in table 1.

Antibiotic trough concentrations vary greatly, both between patients (inter-patient variability), as well as in the same patient (intra-patient variability), as shown in figure 1, which shows the boxplot for the piperacillin trough concentrations. The median coefficient of variation (CV)of the intra-patient variability was 32 % , ranging from 20 to 123%. The mean CV of the inter-patient variability was 30 %, ranging from 18 to 92 %. The trough concentrations over time for each patient are shown in figure 2.

Table 1 : patient characteristics

Patient characteristic	Median (IQR)
Age (years)	67 (51-75)
Sex (% male/female)	82 %/ 18%
Weight (kg)	75 (67-83)
Creatinine clearance on day 1 (ml/min)	93 (88-99)
SOFA day 1	3 (4-6)
APACHE II	24 (18-30)

Conclusion

This report is the first to mention the intra-patient variability of piperacillin trough concentrations. Considering both the wide inter- and intra-patient variability, TDM may be useful. However, the frequency should be high, preferably daily, as antibiotic concentrations within the same patient may vary greatly over time

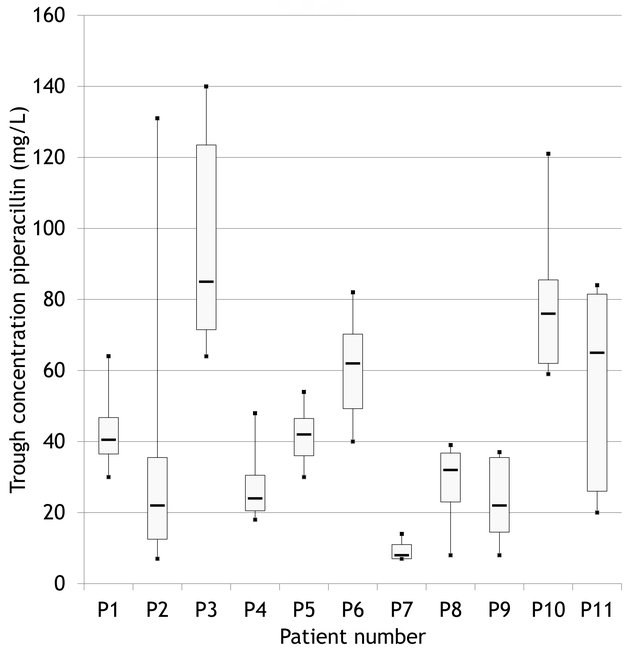

Figure 1 : boxplot of piperacillin trough concentrations over 7 days

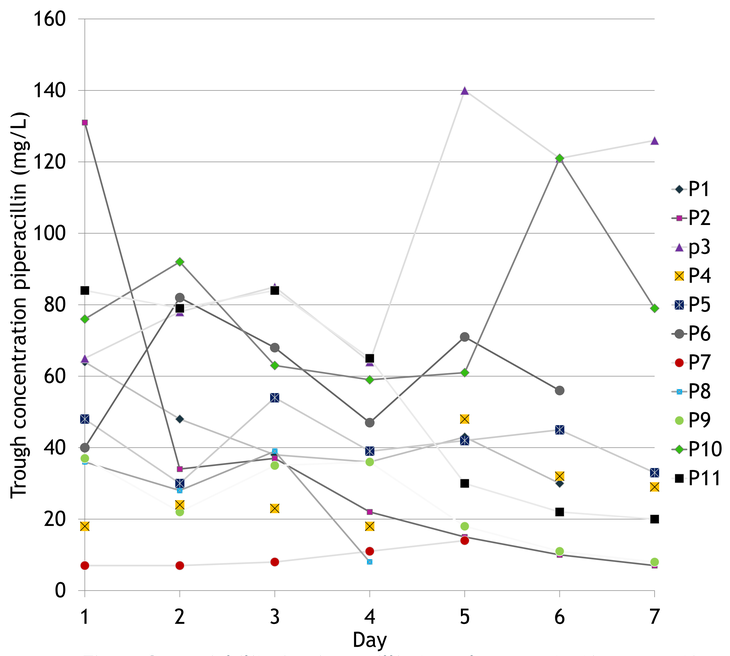

Figure 2 : variability in piperacillin trough concentrations over time for each patient

References and acknowledgment

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1. Roberts JA, Lipman J: **Pharmacokinetic issues for antibiotics in the critically ill patient.** ***Crit Care Med 2009, 37(3):840-851.***

2. Roberts JA, Ulldemolins M, Roberts MS, McWhinney B, Ungerer J, Paterson DL, Lipman J: **Therapeutic drug monitoring of beta-lactams in critically ill patients: proof of concept.** ***Int J Antimicrob Agents 2010, 36(4):332-339.***