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Can we successfully predict dialysate loss of antimicrobial agents in continuous venovenous haemodialysis?

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Objectives

The purpose of this study was to evaluate the correlation between measured and predicted concentrations of antimicrobial agents in dialysate samples and to investigate stability of the selected drugs in dialysis solution at -21°C.

Methods

232 dialysate samples from intensive care patients under continuous renal replacement therapy were investigated after storage at -21°C for 25-35 month. All samples contained at least one of the following anti-infective drugs: Ceftazidime, Flucloxacillin, Fluconazole, Gentamicin, Levofloxacin, Linezolid, Meropenem, Metronidazole, Penicillin, Piperacillin, Rifampicin, Vancomycin. Samples were analysed by liquid chromatography and an immunologic assay.To calculate the concentrations in the dialysate samples, the algorithm of the CADDy® program w as used w ith regard of actual given drug doses and applied dialysis settings.For stability of measured drugs under storage conditions various concentrations in dialysis solution (Multibic®, Fresenius Medical Care) w ere frozen at -21°C, thawed and measured after one, four and six month with the same analytical methods.

Results

All penicillins, the cephalosporine and the carbapenem were unstable under storage conditions at -21°C with a loss of substance ranging from over 90% after six month for Flucloxacillin, Meropenem and Piperacillin, to over 80% for Ceftazidim and over 50% for Penicillin (s. fig.1). According to this findings concentrations in dialysate samples were mostly lower than the analytical limit of quantification or not detectable at all. No substance loss over 6 month was seen for Fluconazole, Levofloxacin, Gentamicin, Linezolid, Metronidazole and Vancomycin. Predicted and measured mean concentrations (P/M) were 8,7/6,2 mg/l for Fluconazole, 2,1/2,1 mg/l for Gentamicin, 5,4/5,6 mg/l for Linezolid, 12,2/17,0 mg/l for Metronidazole, 5,0/7,7 mg/l for Vancomycin and 2,2/4,8 mg/l for Levofloxacin.

Conclusions

In contrast to drug solutions with sodium chloride or water for injection, the investigated betalactams are not stable in dialysis solution stored at -21°C. As far as w e know this is not published previously and it casts a doubtful glance at the common practice of storing patient samples over longer periods before analytical evaluation. This observation might change the results of other already published studies in the field of haemodialysis and –filtration resulting in a massive underestimation of dialysed drug amount. Further studies addressing stability of drugs during frozen conditions also at -80°C in dialysis or ultrafiltrate solutions are needed. For stable drugs the CADDy® algorithm predicts reliable dialysate concentrations. The difference in predicted and measured values might be mainly due to altered protein binding and altered non renal clearance, both are common phenomenona in the critically ill patient.

Fig. 1: Decomposition of betalactams stored at -21°C in dialysis solution