Removal of Dabigatran Is Superior by Sustained Low Efficient Dialysis (SLED) Compared to Intermittent Hemodialysis

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Dear Editor,

Here is a report on a 90-year old female patient with chronic heart failure who was admitted with spontaneous vaginal bleeding due to endometrium carcinoma [1]. Oral medication included candesartan, to-rasemide, spironolactone, digitoxin and a beta blocker. In the past three weeks, she had been put on treatment with dabigatran 2 × 110 mg for atrial fibrillation. On physical examination it was found that uremic fetor was present as well as signs of dehydration. Blood pressure was low at 100/55 mm Hg and heart rate was 60/min. Laboratory analysis revealed plasma creatinine concentration of 4.5 mg/dl and plasma urea concentration of 347 mg/dl, both consistent with acute kidney injury. Coagulation parameters were deranged with an international normalized ratio (INR) of 7.8 (Quick value 8%) and a prolonged activated partial thromboplastin time (aPTT) of 140 s (upper limit <40 s). Hemoglobin concentration was 9.0 g/dl, Dabigatran plasma concentration measured with the calibrated Hemoclot® Thrombin Inhibitor assay (HYPHEN BioMed) was massively increased at 2,230 ng/ml (expected through levels <143 ng/ml).

Vaginal bleeding was treated with external tamponades. Due to uremia, life-threatening dabigatran accumulation and the uncertainty whether kidney function could be

restored, hemodialysis treatment was started in addition to volume resuscitation. Prior to placement of the dialysis catheter 2,000 IE of prothrombin complex and 2 mg of activated factor VII were given. Overnight, the patient was dialysed with an SLED (sustained low efficiency dialysis) regimen and an intermittent hemodialysis session after another 10 h. Renal function promptly ensued after volume substitution indicating prerenal azotemia as a cause of renal failure (diuretic use and heart failure). After a third

hemodialysis session, dabigatran concentration was no longer detectable; this was paralleled by the normalization of coagulation tests. The patient was transfused with five units of erythrocyte concentrates.

Measurements of dabigatran concentrations in the spent dialysate by ultra-performance liquid chromatography tandem mass-spectrometry (UPLC-MS/MS) allowed the comparison of the efficacy of both hemodialysis modalities [2]. As shown in table 1, SLED removed more

Table 1. Comparison of SLED and HD for removal of dabigatran in the patient

	SLED	iHD
<i>Dialysis settings</i>		
Dialysis machine	FMC Genius	FMC 4008
Blood pump speed, ml/min	150	300
Dialysate flow, ml/min	150	500
Duration, h	10	3
Dialyzer	high flux (F _x 60)	high flux (F _x 60)
Cumulative blood volume, l	90	54
<i>Dialysis efficacy</i>		
Predialysis dabigatran concentration, ng/ml	1,710	471
Dabigatran reduction rate, %	72	56
Rebound after 10 h, %	–2.2	+19.9
Total removed dabigatran, mg	26.5	6.1
Hourly removed amount of dabigatran, mg/h	2.65	2.04
Dialyzer clearance, ml/min	40	101

dabigatran (molecular weight 627 g/mol) per hour than intermittent HD despite lower dialyzer clearance. This can be explained by the high distribution volume of dabigatran reaching 60–70 l [3], which requires the redistribution for effective removal during hemodialysis. Our data showed that an SLED approach is advantageous to clear dabigatran from body stores, whereas a short intermittent he-

modialysis session is followed by rebound. Renal dabigatran clearance measured after the regeneration of diuresis in a 24-h collected urine was 16 ml/min and similar to the glomerular filtration rate of 24 ml/min, as determined from the mean of creatinine and urea clearance. However, urinary dabigatran excretion amounted to only 0.18 mg per hour compared to 2.65 mg/h and 2.04 mg/h during SLED or

iHD, respectively. Hence, dabigatran can be effectively and quickly removed by hemodialysis.

In conclusion, dabigatran can accumulate massively during acute renal failure and evoke a life-threatening bleeding diathesis. Until Fab-based dabigatran antidotes are available, SLED offers a highly efficient modality to remove excess dabigatran.

References

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