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Letter to the Editor

Recurrent and Drastic Increase in Dabigatran Levels May Be Induced by Therapeutic Plasma Exchange

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Dear Sir:

We present the case of a 76-year-old man, who received plasma exchange (PE) after initially being treated with intravenous immunoglobulins for severe Guillain-Barré-Strohl syndrome. He had been on regular oral anticoagulants with dabigatran 110 mg twice a day for prevention of stroke and systemic embolism because of non-valvular atrial fibrillation.

Dabigatran was paused in the evening before the day of lumbar puncture and continued in the evening of hospital day 3. Table 1 shows the administration scheme for anticoagulants. Shortly before the first PE, partial thromboplastin time (PTT) was 69 seconds, and international normalized ratio (INR) was 1.40. No other anticoagulant was administered after the onset of the first PE (Table 1).

On the first day after PE, coagulation parameters changed to an INR >5.0 and PTT of 166 seconds (Table 1). A control later that day confirmed those values (INR >5.0; PTT >200 seconds). This time, thrombin time (TT) was >200 seconds. Dabigatran levels, derived from the ecarin clotting time, which "provide(s) a direct measure of the activity of direct thrombin inhibitors,"[1] was measured, yielding an elevation beyond the measurable value (>460 ng/mL). Since the patient showed active signs of gastrointestinal bleeding and bleeding from catheter insertion sites, he received idarucizumab (Praxbind®, Boehringer Ingelheim Pharmaceuticals, Ingelheim, Germany) 5 g/100 mL and intravenous vitamin K 10 mg after undergoing a second PE. Later that day, there was no measurable level of dabigatran found, and INR (1.90), PTT (54 seconds), and TT (15.5 seconds) were stable.

After a third PE on the next day, dabigatran levels rapidly increased again to 142 ng/mL, and coagulation parameters changed accordingly (INR, 3.91; PTT, 107 seconds; TT >200 seconds). The next day, dabigatran levels kept increasing (163 ng/mL), and the patient continued showing active signs of bleeding from catheter insertion and gastrointestinal sites. It was decided to provide another infusion of 5 g/100 mL idarucizumab (Praxbind®) and intravenous vitamin K 10 mg. Later that day, no measurable level of dabigatran was found (<15 ng/mL).

Once again, after a fourth PE the next day, the dabigatran level was 32 ng/mL in the evening and increased to 47 ng/mL the next morning. TT was 69.9 and 75.6 seconds in the evening and next morning, respectively. Meanwhile, the patient showed no active signs of bleeding. Therefore, no third dose of idarucizumab was administered. In the following days, dabigatran levels slowly decreased while PE was paused. On hospital day 7, the anticoagulants were discontinued.

To the best of our knowledge, this is the first case of excessive anticoagulation due to dabigatran in a patient undergoing PE, with accordingly altered coagulation parameters, including high dabigatran levels, and repeated clinically relevant bleeding despite drug discontinuation and administration of the specific antidote twice. The close and repeated timely correlation to the PEs and recurrence shortly after being administered with idarucizumab suggests that PE mobilizes dabigatran. Dabigatran generally shows "low (34% to 35%) concentration-independent binding of dabigatran to human plasma proteins" and is mainly stored in body water and moderately in body tissue.[1] Pre-existing accumulation of dabigatran in extravascular compartments may be linked to initially moderate and later severe renal impairment in an elderly patient who is critically ill at the time of PE. Severe renal impairment and old age are associated with significantly elevated dabigatran plasma levels.[1] The patient received no drugs that are known to elevate dabigatran plasma levels.[1]

Since impairment of thrombin activity also affects the endpoints of the intrinsic and extrinsic parts of the blood coagulation cascade, there are unspecific changes to other coagulation parameters. No other cause of significant bleeding, i.e., signifi-

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Table 1. Laboratory findings of patient on days after administration

	INR	PTT	TT	Dab	CrCl	Fib	Plt	Anticoagulant agent	Plasma exchange
Day 0	1.41	51			40		204	Dabigatran per oral 110-0-110 mg	
Day 1								Dabigatran per oral 110-0-0 mg	
Day 2								None	
Day 3								Dabigatran per oral 0-0-110 mg	
Day 4								Dabigatran per oral 110-0-110 mg	
Day 5	1.37	38			44		211	Dabigatran per oral 110-0-0 mg Enoxaparin subcutaneous 0-0-60 mg	
Day 6	1.35	43	47.5		38		179	Enoxaparin subcutaneous 60-0-0 mg	
Day 7	1.40	69			28	404	144	Heparin intravenous	03:30 PM–05:00 PM
Day 8 04:36 AM	>5	166			30	232	152	None	10:30 AM–12:00 AM
Day 8 04:50 PM	>5	>200	>200	>460	28	138	149	None	
Day 8 11:32 PM*	1.90	54	15.5	<15		184	137	None	
Day 9 09:40 AM	2.08	78	15.9	<15	24	248	152	None	09:30 AM–11:00 AM
Day 9 06:14 PM	3.91	107	>200	142		141		None	
Day 10 05:50 AM	2.54	98	>200	163	26	220	121	None	
Day 10 07:05 PM†	1.30	44	14.5	<15				None	
Day 11 06:09 AM	1.24	71	26.1	<15	27	322	121	None	10:30 AM–12:00 AM
Day 11 07:56 PM	1.84	58	69.9	32		158		None	
Day 12	1.65	59	75.6	47	28		138	None	
Day 13	1.49	60	74.2	39	25	271	119	None	
Day 14	1.39	49	55.6	29	26	267	122	None	02:00 PM–03:30 PM
Day 15	1.59	42	37.0	<15	28	158	150	None	
Day 18	1.20	38	30.1	<15	32	304	162	Enoxaparin subcutaneous 0-0-40 mg	

PTT (reference: 29–38 seconds); TT (reference: 16.2–17.2 seconds); Dab levels using STA®-ECA II (ng/mL; reference: <15 ng/mL in dabigatran-naive patient, 120–280 ng/mL 2 hours after administration, 60–140 ng/mL at trough level [12 hours after administration]); CrCl measured by using CKD-EPI-formula (mL/min; reference: 80–140 mL/min); Fib levels, Clauss method (mg/dL; reference: 190–430); Plt (g/L; reference: 150–400); anticoagulant agent, scheme of any anticoagulant agent on the given day; heparin, continuous intravenous unfractionated heparin 25.000 IE/50 mL, infusion rate: 1,6 mL/hr, started 06:00 AM, discontinued: 04:00 PM.
INR, international normalized ratio; PTT, partial thromboplastin time; TT, thrombin time; Dab, dabigatran; CrCl, creatinine clearance; Fib, fibrinogen; Plt, platelets.
*After first administration of idarucizumab 5 g/100 mL intravenous; †After second administration of idarucizumab 5 g/100 mL intravenous.

cantly reduced fibrinogen or platelet levels, liver failure, or other toxic influences on coagulation were identified.

A recent report indicated that patients might benefit from PE when experiencing bleeding at toxic dabigatran levels.[2] The underlying limitations in comparing those cases are the difference in the patient age, difference in drug dosage, and lack of data for coagulation parameters after PE in the previous article.

We concluded that patients with the use of dabigatran with or without underlying risk factors, such as age, renal impairment, or comedication, should be closely monitored for a sudden and lasting elevation of dabigatran levels while undergoing PE.

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