

Comparison of the DOAC Dipstick test from urine to the chromogenic substrate methods from plasma of patients treated with direct oral anticoagulants

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INTRODUCTION

At present, direct oral anticoagulants (DOACs) have become the leading therapeutic choice demonstrating considerable efficacy, safety, and convenience in thromboembolic settings, qualities closely related to DOAC presence in patient's blood, identifying daily treatment adherence as a major factor of efficacy. The in vitro diagnostic DOAC Dipstick is an easy-to-use bedside tool whose development was based on the rationale that DOACs are excreted in urine. Direct oral factor-Xa and thrombin inhibitors are detected on separate DOAC Dipstick pads, each containing immobilized reagents that specifically interact with the respective type of DOAC.

AIM

The aim of the study was to compare the performance DOAC Dipstick device from urine samples to plasma concentration of DOAC treated patients.

METHODS

It consisted of an observational cohort study. Herein presented the results of consecutively enrolled patients on DOAC treatment, followed-up at the Antithrombotic Clinic of Tenon, an academic hospital which forms part of the Assistance Public Hôpitaux de Paris (AP-HP) Sorbonne Université. The study period was conducted from the 1st of December 2019 to the 31st of July 2021, including patients on active treatment or prevention of venous thromboembolism with DOACs.

Dipstick test was performed from patients' urine samples and subsequent visual evaluation of pads' colors for oral direct factor Xa (DXI) and thrombin inhibitors (DTI) by trained staff. DOACs' plasma concentration was assessed STA@-Liquid Anti-Xa and a STA@-Liquid Anti-IIa chromogenic substrate assays. Threshold values of DOACs were compared at ≥ 30 ng/ml and ≥ 20 ng/ml to positive and negative results of DOAC Dipstick, because it was reported that lower concentrations of DOACs in plasma were detected at a higher sensitivity (1). The sensitivity, specificity, negative (NPV) and positive predictive values (PPV) were determined at both threshold levels. Specificity values and NPV were determined despite their low validity due to low number of available values from the DTI group. P-values were calculated by t-test statistics.

RESULTS

Biographic data shows no differences between the DXI and DTI groups (table 1). All patients had a normal renal function and the urine color pad was observed as "normal" in these cases. Based on the plasma threshold of ≥ 30 ng/mL in the DXI group (n= 121), the factor Xa inhibitor pad was evaluated in 103/106 cases as correct positive (sensitivity: 97.1%, CI : 92.0-99.4%) and in 3/15 cases as true negative (specificity 20%, CI : 4.3-48.1%, low validity due to low number of DTI patients). The PPV, NPV and accuracy values were 89.5%, CI: 86.9-91.2%, 50%, CI:18.15-81.85%, and 87.6%, CI: 80.4-92.9%. respectively (Tables 1 and 2).

For the threshold of ≥ 20 ng/mL, sensitivity and accuracy were at 96.7 % and the PPV 100%. Specificity and NPV could not be calculated due to the absence of negative pad results (Table 3).

The results of correct and false visual evaluations of FXA pads at thresholds of ≥ 30 ng/ml and of ≥ 20 ng/ml for patients treated with apixaban and rivaroxaban as well as results of sensitivity, specificity, NPV, PPV and accuracy are given on tables 2 and 3, respectively. The low number of negative results limit the reliability of the calculated specificity and NPV of subgroups.

The agreement of the visual agreement of DOAC Dipstick test results between two observers was 123/123 for FXA and THR pads of the DXI and DTI groups. The kappa value was calculated at 1 (Table 4).

	ALL	ELIQUIS	XARELTO	DABIGATRAN
Male/Female (n/n)	60/63	19/25	41	0/2
Age (years, mean SD)	55.4 ± 16.1	55.8 ± 19.1	55.3 ± 14.5	52 ± 2.8
Dosage (mg/day: n)		10 mg/d: 4 5mg/d: 37 20mg/d: 2	10mg/d: 14 20mg: 60 15mg/d: 3	300 mg: 2 (Apicat study): 2 30mg/d: 1
Indication				
CAT-associated TED	13	8	5	0
Recurrent TED	48	18	40	0
AF	3	1	1	1
APLS	6	2	3	1
PE	18	11	7	0
DVT	22	4	18	0
Ischemic stroke	2	0	2	0
Laboratory values				
AXa /Alia,ng/mL, mean SD	NA	163 ± 130	129 ± 118	184.5 ± 9
Intake interval (h.min)	11 ± 6	13h ± 5.6	9.6 ± 6.	10 ± 10

Table 1: Median age, sex distribution, indications, renal function, DOAC intake interval before sampling

Concomitant medications (n)
Antihypertensives : 7
Antidiabetics : 6
Lipid lowering drugs: 6
Cardiovascular drugs: 1
Diuretics: 3
Anticancer agents: 5
Aspirin: 1
Neurological drugs: 6
Thyroid hormones: 4
Alternative medication: 2
Vitamin D: 2
Other medications: 6

Table 2: Concomitant medication

DOAC Dipstick result at ≥ 30 ng/mL/ ≥ 20 ng/mL plasma, n/n	DOAC present or absent by DOAC Dipstick and plasma threshold at ≥ 30 ng/mL and ≥ 20 ng/ml (n/n)					
	All DXI patients		Rivaroxaban		Apixaban	
	present	absent	present	absent	present	absent
Positive	103/117	12/0	64/75	10/0	39/42	2/0
Negative	3/4	3/0	1/2	2/0	2/2	1/0
Total	106/121	15/0	65/77	12/0	41/44	3/0
	Measures, mean (SD), %					
	≥ 30 ng/mL					
Sensitivity	97.2 (92.0-99.4)		98.4 (91.7 - 100)		95.1 (83.5-99.0)	
Specificity*	20 (4.3-48.1)		16.6 (2.1 - 48)		33.3 (0.84-90.6)	
PPV	89.5 (86.9-91.7)		86.4 (83.22-89.2)		95.1 (89.7-97.7)	
NPV*	50 (18.2-81.9)		66.6 (16.4-95.3)		33.3 (5.8-80.2)	
Accuracy	87.6 (80.4-92.9)		85.7 (75.9-92.7)		90.9 (78.3-97.7)	
	Measures, mean (SD), %					
	≥ 20 ng/mL					
Sensitivity	96.7% (96.7 -96.7)		97.4 (97.4-97.4)		95.4 (95.4-95.4)	
Specificity*	NA		NA		NA	
PPV **	100		100		100	
NPV*	NA		NA		NA	
Accuracy	96.7% (96.7 -96.7)		97.4 (97.4-97.4)		95.4 (95.4-95.4)	

Table 3: Comparison of sensitivity, specificity, PPV, NPV and accuracy at thresholds of ≥ 30 ng/mL and ≥ 20 ng/mL

* Low reliability of calculations due to low number of negative test results

** CI not determined

	Observer 1	Observer 2
True positive	103	103
False positive	12	12
True negative	3	3
False negative	3	3
Kappa value	1.0	1.0

Table 4: Results of interobserver agreement

CONCLUSIONS

- ✓ DOAC Dipstick detects with high sensitivity and PPV plasma concentrations of DXI at ≥ 30 ng/mL plasma.
- ✓ The sensitivity of DOAC Dipstick increases at lower DXI levels thus improving patients safety for medical decision making.
- ✓ Specificity and NPV values are not reliable due to the low number of negative DOAC Dipstick test results. One reason is the decreasing descript of Dabigatran compared to DXI at our medical center.
- ✓ The number of subgroups of DXI and dabigatran is also too low to enable generating robust data on Specificity and PPV for the reason given above.
- ✓ The inter-observer agreement supports earlier data on the strength of the correctness of visual assessment of DOAC Dipstick.
- ✓ The authors believe that the aforementioned results demonstrate the comfort, efficacy and safety of the DOAC Dipstick device for anticoagulant treatment assessment in various clinical settings.

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CONFLICT OF INTEREST

LP, SA, LT, IE, GG: no conflict of interest to declare

JH: founder and managing director of DOA SENSE GMBH, Germany

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