Inter-centre and inter-observer agreement of determination of DOACs in urine samples of patients by means of DOAC Dipstick test

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INTRODUCTION

In emergency situations, detection of direct oral anticoagulants (DOACs) needs to be fast, but this is not always feasible. With the recent availability of a accurate dipstick point-of-care device, DOACs can be rapidly detected in urine. However, the inter-observer agreement of this visual analysis requires evaluation.

AIM

This study aims to define
(ad 1) the inter-centre and
 (ad 2) inter-observer agreement of the analysis of DOACs in urine samples of patients treated with factor Xa inhibitors or thrombin inhibitor dabigatran by means of DOAC Dipstick test.

METHOD

Ad 1
The inter-centre agreement was analysed from the results of a prospective, open-label, controlled, non-randomized, multicentre study performed in Germany including subjects treated with an oral direct factor Xa inhibitor (DXI) or the oral thrombin inhibitor (DTI) dabigatran.
The true positive and true negative rate of the factor Xa inhibitor and thrombin inhibitor DOAC Dipstick test was compared with the results obtained by liquid chromatography tandem mass spectrometry (LC-MS/MS) from urine samples of subjects.
Ad 2
The inter-rater reliability was analysed from data obtained from an international laboratory study including 13 centres and 10 DOAC samples of patients treated with apixaban, rivaroxaban and dabigatran and controls without anticoagulants.

REFERENCES

1. Harenberg J, et al. Thromb Haemost 2020;120(1):132-140.
2. Harenberg J, et al. Clin Chem Lab Med 2016;54(2):275-283.

RESULTS

Ad 1: Eight hundred and eighty of 904 included subjects were evaluable from 18 German centres for analysis.

➢ The rate of false results for the specific DXI and DTI pads were 2.8% and 0.7%, respectively (Ref.1).

➢ The difference between centres was not significant for DXA and the number of false results with DTI pads was insufficient to perform statistical analyses.

➢ Concentration of DOACs in urine, false negative and false positive visual evaluations of pads for DXI and DTI of DOAC Dipstick (tables 1 to 4)

	n	Median (ng/mL)	5th percentile (ng/mL)	95th percentile (ng/mL)
Apixaban	170	648	89	3213
Edoxaban	131	8785	417	71203
Rivaroxaban	150	1903	248	8160
Dabigatran	429	4206	515	21642

Table 1: Median values (with 5th and 95th percentile) of the concentrations of apixaban, edoxaban, rivaroxaban, and dabigatran in patient urine samples (from reference. 1).

Visual evaluation	LC-MS/MS				
	Apixaban (ng/mL)	Edoxaban (ng/mL)	Rivaroxaban (ng/mL)	n	sum (n)
false negative			86, 89, 98	3	
		83, 108, 965, 4012		4	
	34, 40, 51, 59, 66, 83, 93, 95, 110, 195			10	17
false positive	< 30 (n=7)	< 30 (n=7)	< 30 (n=7)	7	24

Table 2: False visual evaluation of the factor Xa inhibitor pad of urine samples from subjects treated with a DXI and DOAC concentrations determined by LC-MS/MS (cut-off: 30 ng/mL) (per-protocol evaluation). "False positive" results were defined as all three factor Xa inhibitor DOACs being < 30 ng/mL by LC-MS/MS (from reference.1).

Visual evaluation	LC-MS/MS Dabigatran (ng/mL)	sum (n)
false negative	35, 10013	2
false positive	< 30	5

Table 3: False visual evaluation of thrombin inhibitor pad after incubation in urine samples from subjects of the oral thrombin inhibitor (DTI) group revealed by comparison with the dabigatran concentrations determined by LC-MS/MS (cut-off: 30 ng/mL) of the per-protocol evaluation (from reference 1).

	Factor Xa inhibitor pad		Thrombin inhibitor pad	
	Mean	95% CI	Mean	95% CI
Kappa	0.945	0.924; 0.967	0.987	0.976; 0.997

Table 4: Kappa values (mean and 95% confidence interval (CI) of visual evaluation of DOAC Dipsticks from urine samples of patients versus LC-MS/MS results from urine (given as negative and positive output at a cut off of 30 ng/mL) (from reference 1).

Ad 2

➢ The international study showed an inter-observer agreement with kappa values of 0.94 for apixaban and rivaroxaban and of > 0.95 for dabigatran (table5).

Kappa index was calculated from all samples that were judged locally by the naked eye as being either positive (DOAC present) or negative (DOAC absent); data were objectively documented by digital photography.

Apixaban (n=260): 122 and 129 samples were judged correctly as negative or positive and 8 and 1 samples as false-positive or false-negative, respectively

Rivaroxaban (n=259): 98 and 155 samples were identified correctly as negative or positive and 5 and 1 samples as false-positive or false-negative.

Dabigatran (n=259) 108 and 153 samples were judged correctly as negative or positive and 0 and 2 samples as false-positive or false-negative (table 5).

Kappa Index*	Apixaban	Rivaroxaban	Dabigatran
Mean	0.93	0.95	0.98
CI	0.89-0.98	0.91-0.99	0.96-1.00

Table 5: Kappa index (agreement) between observers of the DOAC Dipstick from urine samples of patients treated with DXI or DTI (mean,95%. CI = confidence interval, from reference 2).*

CONFLICT OF INTEREST

JH, FL: Managing director DOASENSE; RB, JBW, CW: consultancy fee DOASENSE; JD, IE, MC, PV, SH: none

CONCLUSIONS

The present study shows that DOAC Dipstick test is determined with a very high agreement between centres and between observers encouraging further multinational evaluation.

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