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Performance Characteristics of DOAC Dipstick in Determining Direct Oral Anticoagulants in Urine

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Abstract

Testing for direct oral anticoagulants (DOACs) in patient urine may facilitate medical treatment decisions. The aim of this study was to investigate interobserver variability by 2 independent observers compared to laboratory staff in the visual interpretation of factor Xa (DXI) and thrombin inhibitors (DTI) using the DOAC Dipstick test. We also examined whether test pads reacted to other anticoagulants and abnormal urine colors. The colors of the DOAC Dipstick direct factor Xa inhibitor and thrombin inhibitor pads were interpreted with 100% accuracy (95% confidence interval 0.862 to 1.000) for urine samples from persons treated with apixaban (n = 26), rivaroxaban (n = 24), and dabigatran (n = 29) and without anticoagulant therapy (n = 29). The factor Xa and thrombin inhibitor pads did not interact with heparin, nadroparin, fondaparinux, or coumadin. One μg/mL r-Hirudin and 6 μg/mL argatroban interacted with the DTI pad; however, this is unlikely to cause clinical problems because dabigatran is unlikely to be administered together with r-Hirudin and argatroban in clinical circumstances. Abnormal urine color was reliably detected by the urine color pad, so can prevent false interpretation of the DOAC Dipstick pad colors. In conclusion, we have demonstrated that interobserver variability when interpreting the DOAC Dipstick test strip is low and that factor Xa and thrombin inhibitor pads do not react to other anticoagulants such as heparins and coumadin. R-Hirudin and argatroban can be detected by the thrombin inhibitor pad and abnormal urine colors can be detected by the urine color pad to prevent false interpretation of the results in patient urine samples.

Keywords

direct oral anticoagulants, apixaban, edoxaban, rivaroxaban, dabigatran, point of care test

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Introduction

In medical emergency situations, direct oral anticoagulants (DOACs) may need to be detected quickly; however, this is not always feasible and remains a major challenge.[1-3] Several coagulation tests have been developed to support medical decision making in cases where the presence of DOACs needs to be tested.[4-6] The in vitro diagnostic DOAC Dipstick test was developed[7] to detect DOACs in urine samples.[8] Testing urine samples rather than plasma avoids potential confounding of the test results by plasma proteins and blood cells. The DOAC Dipstick detects direct factor Xa inhibitors (DXI) and thrombin inhibitors (DTI) in one test. Test pads contain reagents that react specifically with DXI and DTI and do not interact with each other. Specific colors develop on the pads within 10 min depending on whether the DOAC is present or not, and these colors can be identified by eye.[9] The accuracy of the CE-labeled DOAC Dipstick test in detecting oral apixaban, edoxaban, rivaroxaban, and dabigatran in urine samples has been described in a large multicenter trial. The visually interpreted pad color is compared with a color scale on the DOAC Dipstick label. In the multicenter clinical study, color interpretation of the factor Xa and thrombin inhibitor pads was false negative in 2.8% of cases and false positive in 0.7% of cases.[10]

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However, interobserver variability was not analyzed in this study. Heparins may interact with the DOAC Dipstick pads when individuals switch from DOAC to heparin treatment and vice versa.[10,11] However, in the multicenter study, not enough participants switched from DOAC to heparin therapy or vice versa to evaluate the effect of heparin on DOAC Dipstick results.[10] Other anticoagulants may also interact with the factor Xa and thrombin inhibitor test strip pads. Urine color can be altered by diseases and by intake of specific food and drugs[12] and may affect the colors of both pads. This was also reported too infrequently in the multicenter study to draw firm conclusions. In the present study, we examined the effect of these factors on DOAC Dipstick test results.

Subjects and Methods

Preparation of Urine Samples

Urine samples were obtained from persons treated with apixaban, rivaroxaban, and dabigatran and from individuals without anticoagulant therapy (controls). Participants did not take any other anticoagulant or antiplatelet medication for at least 1 week before sample collection. Urine samples were collected in 100-ml propylene containers with integrated units for closed transfer of urine to a V-urine vacuum system (Saarstedt, Nuermbrecht, Germany). Urine samples (4 ml) were transferred into polyethylene terephthalate tubes (V-Monovette urine Z4 ml, Sarstedt AG, Nuermbrecht, Germany) using plastic syringes and were frozen immediately at −25°C until analysis. All samples were analyzed within 1 month. Permission to perform the study was granted by the university ethical board and all participants gave written informed consent prior to participation.

Interobserver Variability

Urine samples were obtained from individuals treated with apixaban 5 mg bid (n = 26), rivaroxaban 20 mg od (n = 24), and dabigatran 110 mg or 150 mg bid (n = 29) and from individuals without anticoagulant therapy (controls, n = 29). Participants did not take any other anticoagulant or an antiplatelet medication for at least 1 week before examination. Test strips contained reagents to detect DXI and DTI and were incubated in urine samples for 2 to 3 seconds and processed as described below. Two independent observers adjudicated the colors of the test pads to assess interobserver variability.

Interaction with Anticoagulants

Urine samples were obtained from persons treated with 10 mg od rivaroxaban, 110 mg or 150 mg bid dabigatran, and nadroparin (a low-molecular weight heparin) (each group n = 6), and from controls (n = 5).

Urine samples from controls and patients treated with rivaroxaban were not spiked or spiked with 0.1, 0.3 and 1.0 IU unfractionated heparin (UFH) and nadroparin, 0.1, 0.3 and 1.0 μg/ml fondaparinux. Urine samples of patients treated with dabigatran were not spiked with an anticoagulant and were spiked with the same concentrations of UFH and r-hirudin and argatroban up to 6 μg/ml. Samples were gently mixed at room temperature. DOAC Dipsticks were immersed in the urine samples and processed as described below.

Urine samples of patients (n = 10) taking stable oral anticoagulants with the vitamin K antagonist coumadin (international normalized ratio between 2.0 and 2.8) were tested with the test strips to assess whether coumadin interacts with the DXI and DTI pads.

Influence of Colored Components on Pads of Test Strip

Three urine samples from healthy controls and 14 urine samples from patients with normal (n = 10) and abnormal urine color (n = 4) were spiked with 0 ng/ml, 150 ng/ml, and 800 ng/ml rivaroxaban and 0 ng/ml, 100 ng/ml, and 800 ng/ml dabigatran in triplicates (total n = 144). Test strips were incubated in the urine samples as described below.

Analysis of DOAC Dipstick Test Strip

The test procedure has been described in detail previously using prototypes of DOAC dipsticks.[9] In short, the test strip is dipped into urine samples for 2 to 3 seconds before being placed on a flat surface at room temperature with the pads facing upward. Test strips are left undisturbed for 10 minutes to allow the chemical reaction to take place on the pads. The pads show specific colors depending on the presence or absence of the 2 DOAC types: white and rose in the presence of DXIs and DTI (a positive result) and yellow and ochre in the absence of DXIs and DTI (a negative result). The urine color pad determined whether the urine color was normal (white) or abnormal (not white). Two independent observers interpreted the pad colors visually. If the interpreted color did not match a color on the label, the test was deemed not evaluable. Digital photos were taken of test strips of urine with normal urine color from patients treated with a DXI and a DTI and from a patient with abnormal urine color under treatment with a DXI.

Statistics

All statistical calculations were performed using SAS software, release 9.4 (SAS Institute Inc., Cary, NC, USA). The qualitative data were presented as absolute and relative frequencies. Sensitivity, specificity, and accuracy positive predictive value (PPV) and negative predictive value (NPV) were evaluated for results of factor Xa and thrombin inhibitor pads of DOAC Dipstick for 2 independent trained observers compared to results of laboratory staff. The kappa-index of the observers was calculated as a measure of interindividual agreement. The association of the evaluation of factor Xa and thrombin inhibitor pads for normal and abnormal urine color pads between observers was tested by Chi-square of Fishers exact test at a level $p < 0.05$. The 95% confidence intervals (CI) limits were calculated for parameters.

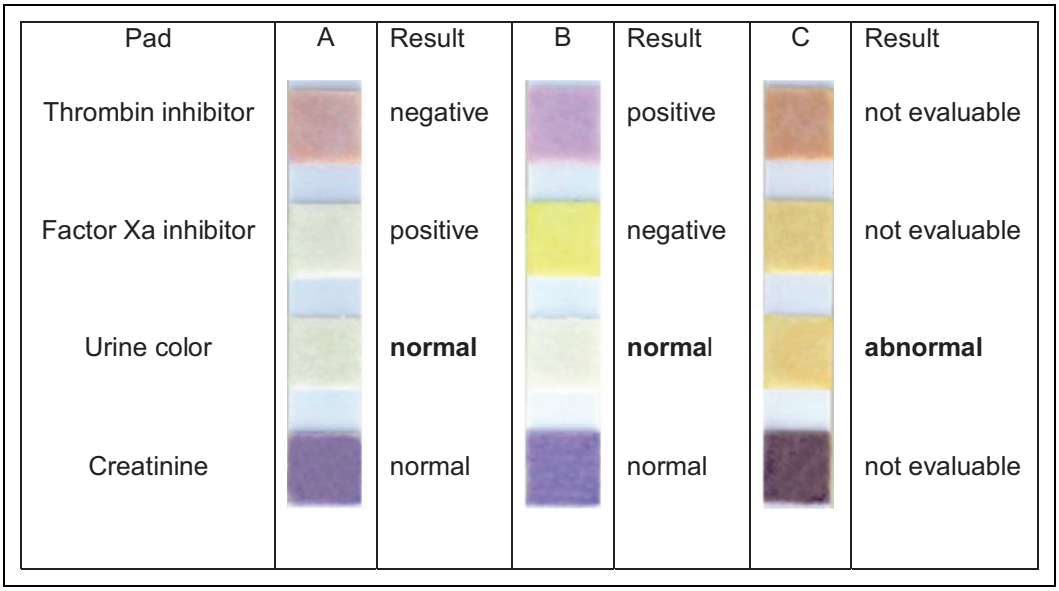

Figure 1. Digital photos of strips of patients' urine samples of patients treated with the result "normal" of urine color pad (A: treated with a DXI, B: treated with a DTI) and "abnormal" (C: treated with a DXI). Columns 3 and 5 describe the result of the colors of the pads compared to the color scale of DOAC Dipstick. Column 7 "not evaluable": not in accordance with the color scale of DOAC Dipstick label.

Results

Figures 1A and 1B show digital photos of the test strips from patients' urine samples under treatment with a DXI (1A) and a DTI (1B) with the result "normal" of urine color pad. The colors of the pads correspond to those of the color scale of DOAC Dipstick.[9,10] Figure 1C shows a photo of a test strip from a patient's urine sample treated with a DXI with the result "abnormal" of urine color pad of the test strips. These colors cannot be assigned to those of colors of the scale of DOAC Dipstick.[9,10]

Interobserver Variability

The factor Xa and thrombin inhibitor pads that were incubated in control urine samples (n = 29) were all correctly identified as negative by both observers compared to the results of the laboratory staff. The sensitivity and PPV could not be analyzed because controls were not treated with anticoagulants (Table 1). The factor Xa and thrombin inhibitor pads that were incubated in urine samples from persons treated with apixaban (n = 26), rivaroxaban (n = 24), and dabigatran (n = 29) were all correctly interpreted as positive. Thus, the numerical values for sensitivity, specificity, accuracy, NPV, PPV and Kappa index were equal 1. The corresponding 95% CIs are given in Tables 1 and 2.

Interaction of Factor Xa and Thrombin Inhibitor Pads With Other Anticoagulants

The factor Xa and thrombin inhibitor pads were negative after being incubated in control urine samples that were not spiked with an anticoagulant. Factor Xa inhibitor pads were all

Table 1. Sensitivity, specificity, accuracy, negative predictive values (NPV), positive predictive values (PPV), and kappa index of the visual evaluation of factor Xa and thrombin inhibitor pads after incubation in urine from patients treated with dabigatran (n = 29) and from control participants without anticoagulation (n = 29).[a]

	Dabigatran		Control	
	Value	95% CI	Value	95% CI
Sensitivity	1.000	0.881; 1.000	n.c.	n.c.
Specificity	1.000	0.881; 1.000	1.000	0.938; 1.000
Accuracy	1.000	0.938; 1.000	1.000	0.938; 1.000
NPV	1.000	0.881; 1.000	1.000	0.938; 1.000
PPV	1.000	0.881; 1.000	n.c.	n.c.
Kappa	1.000	n.c.	n.c.	n.c.

[a]Values are given with 95% confidence interval. Sensitivity, PPV, and kappa values could not be determined for controls because patients were not treated in this group. (n.c. = not calculable).

Table 2. Sensitivity, specificity, accuracy, negative predictive values (NPV), positive predictive values (PPV), and kappa index of the visual evaluation of factor Xa and thrombin inhibitor pads after incubation in urine from patients treated with apixaban (n = 26) and rivaroxaban (n = 24).

	Apixaban		Rivaroxaban	
	Value	95% CI	Value	95% CI
Sensitivity	1.000	0.868; 1.000	1.000	0.858; 1.000
Specificity	1.000	0.881; 1.000	1.000	0.881; 1.000
Accuracy	1.000	0.935; 1.000	1.000	0.933; 1.000
NPV	1.000	0.881; 1.000	1.000	0.881; 1.000
PPV	1.000	0.868; 1.000	1.000	0.858; 1.000
Kappa	1.000	n.c.	1.000	n.c.

[a]Values are given with 95% confidence interval.

interpreted as negative after incubation in control urine samples spiked with 0.3 and 1.0 IU/ml heparin and nadroparin and 0.3 and 1.0 μg/mL fondaparinux. Thrombin inhibitor pads were negative after being incubated in control urine samples spiked with 0.1 and 0.3 μg/ml r-hirudin and argatroban and positive after being incubated in urine samples spiked with 1 μg/ml r-hirudin and 6 μg/ml argatroban.

The factor Xa inhibitor pad was interpreted as positive and the thrombin inhibitor pad as negative after incubation in urine samples from persons treated with apixaban and rivaroxaban. The factor Xa inhibitor pads were interpreted as positive after incubation in urine samples from apixaban and rivaroxaban-treated patients that were spiked with UFH, nadroparin, and fondaparinux and thrombin inhibitor pads were all interpreted as negative. The thrombin inhibitor pads were interpreted as positive after incubation in urine samples from dabigatran-treated patients that were spiked with r-hirudin and argatroban (see above). The factor Xa inhibitors pads were all interpreted as negative.

The factor Xa and thrombin inhibitor pads were interpreted as negative after incubation in urine samples from patients on stable coumadin therapy (n = 10) within a therapeutic range of 2.0 to 2.8 international normalized ratio.

Influence of Colored Components on DOAC Dipstick Results

The urine color pad was interpreted as normal in 117/144 cases and abnormal in 27/144 cases.

Observers correctly interpreted the colors of the factor Xa inhibitor pad incubated in urine samples spiked with rivaroxaban (n = 117). The urine color pads were normal in these samples. The color of the pad could not be interpreted after incubation in rivaroxaban-spiked urine samples with an abnormal color (n = 27).

The thrombin inhibitor pad was correctly interpreted by the observers in 126 samples containing dabigatran. In 18 pads, the identified colors did not match the standard colors on the DOAC Dipstick label so could not be interpreted.

Urine color pad was interpreted as abnormal in 3/10 urine samples. Visual interpretation of the factor Xa and thrombin inhibitor pads of these 3 samples did not correspond to colors of the color scale of DOAC Dipstick. Results of interpretation of factor Xa inhibitor and thrombin inhibitor pads were significantly different comparing urine samples with normal versus abnormal color (all $p < 0.0001$, chi-square test).

Normal urine color did not affect the observers' interpretations of the DOAC Dipstick pads. In addition, there was no difference in interpretation of the control pad and factor Xa inhibitor pad colors. The thrombin inhibitor pad was interpreted correctly in a few urine samples despite detection of an abnormal urine color. However, this does not modify the importance of an interpretation of the urine color pad.

Discussion

In this study, we have shown that there is low interindividual variability in visual interpretation of the factor Xa and thrombin inhibitor pads of the DOAC Dipstick test strip in the absence and presence of DXIs and the DTI dabigatran. This finding suggests that the low variability in correct negative and correct positive DOAC Dipstick results observed in a previous multicenter study was not affected by interindividual variability.[10]

The reagents that are immobilized onto DOAC Dipstick pads specifically detect DXIs or DTI and do not interact with one another.[9] Here, we showed that UFH, low molecular weight heparin, and fondaparinux do not react with the factor Xa and thrombin inhibitor pads of the test strip either. This suggests that the DOAC Dipstick can specifically detect DOACs in urine even when therapy is switched from DOAC to heparin and vice versa. This contrasts with coagulation tests using blood samples, which detect both categories of anticoagulants.[13] The amount of active heparin in urine is 30% or less [14] and the concentrations of heparin cofactors are too low in urine to activate heparin; this may explain why heparin was not detected in urine samples. Thus, the possibility of interaction of UFH and LMWH in urine by DOAC Dipstick is extremely low. Elevated levels of heparin-cofactors were reported in patients with nephrotic syndrome [15,16] and would require specific investigations.

Forty percent of the direct thrombin inhibitor r-hirudin is excreted into urine by the kidney[17] while argatroban is not excreted into urine.[18] Argatroban was added to the experiments because its synthetic origin and similar molecular weight as dabigatran. In the present study, spiking control and patient urine samples with r-hirudin and argatroban led to a positive result on the thrombin inhibitor pad. The interference of hirudin and presumably of bivalirudin may be detected, when a patient with heparin induced thrombocytopenia is treated with any of these drugs during an unstable clinical situation and is switched to dabigatran. However, simultaneous therapy of DOACs with these DTIs is highly unlikely to be administered simultaneously in patients.

Ninety percent of vitamin K antagonists are excreted as inactive glucuronide metabolites[19] and only 2% are excreted as active compounds.[20] As expected, coumadin did not react with any DOAC Dipstick pads.

Hematuria and blood components such as urobilinogen alter the color of urine[12] and may compromise the interpretation of factor Xa and thrombin inhibitor pad colors. To address this, the DOAC Dipstick contains a pad that detects abnormal urine color. The normal yellow color of urine does not influence the white color of this pad, probably because a low volume of urine is absorbed. In this study, we showed that the color of factor Xa and thrombin inhibitor pads is affected by abnormal urine color. Diseases, food, drugs, and drug metabolites can all change the color of urine[21-24] so the urine color pad is an important control for accurate DOAC Dipstick results.[9,25]

There are some limitations to this study. The number of participants was low to determine the interindividual variability; however, the results are similar to those obtained in another study including 18 centers. It may be necessary to test urine samples from more patients to investigate whether other drugs and anticoagulants interact with factor Xa and thrombin inhibitor pads. However, the chemical reactions on the pads are specific. Patients with reduced renal function and other severe organ dysfunctions were not included in the present study but could be included in future clinical studies.[26] Another limitation is that we only investigated abnormal urine colors in a few patients only; however, pathological color occurs rarely as seen in the previous multicenter study.[10] Case reports or small cohort studies may provide more information.

In summary, the present study shows that interindividual variation in interpretation of the DOAC Dipstick factor Xa and thrombin inhibitor pads is low. The DOAC Dipstick test strip is specific and does not interact with other anticoagulants such as heparin and coumadin. Furthermore, potential confounding by abnormal urine color is controlled by a specific urine color pad.

Authors' Note

JH: study designs, interpretation of data, drafting of manuscript. CW: study protocols, statistical analysis, reviewing of manuscript. SH: statistical analysis, review of manuscript. CD: visual analysis, data collection, drafting of method section, reviewing of manuscript. AM: drafting of results section, review of manuscript. SK: visual analysis, data collection, reviewing of manuscript. JH: managing director and founder of DOASENSE. Not related to this work: a patent US 9,133,501 licensed, a patent EU 2643475 licensed, a patent US 9,944,971 licensed, and a patent EU 2723886 licensed. All authors approved the final version of the manuscript. Ethical approval was obtained from *Medical Ethics Committee II, Medical Faculty y Mannheim, University of Heidelberg, Germany (Approval numbers 2011-356N-MA, 2012-226N-MA, 2013-510N-MA). Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article. Research materials can be provided up to 10 years following submission of the manuscript. Shanshan Du is also affiliated to Qingdao University of Science and Technology, School of Chemical Engineering, State Key Laboratory Base for Eco-Chemical Engineering, Qingdao, China.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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