Comparative Study of a Portable Prothrombin Time Monitor Employing Three Different Systems in Oral Anticoagulant Units

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Key Words

Prothrombin time · Portable monitor · Anticoagulant treatment, oral

Abstract

The aim of this study was to evaluate the accuracy of the portable coagulometer CoaguChek® (Roche Diagnostics) as a prothrombin time (PT) monitor, and to correlate capillary blood results with those of three different routine methods used for monitoring oral anticoagulant therapy (OAT): capillary, plasma and whole blood samples. Three hospitals participated in the study with a total of 235 patients on OAT. The international normalized ratio (INR) results obtained with Coa-

guChek were compared with those obtained using each of the routine methods. The study presents a good correlation between the PT monitor and the three methods studied: $r = 0.9745$ (hospital A), $r = 0.9283$ (hospital B), $r = 0.9136$ (hospital C). A simplified concordance test of the methods results in a nine-field comparison table showing concordances of 87.2, 85.7 and 68.4%, respectively. The absolute difference (mean $\pm$ SD) between laboratory A and CoaguChek INRs was 0.0571 ± 0.2042 , with values of 0.04286 ± 0.3906 for laboratory B and 0.6986 ± 0.6170 for laboratory C. These results confirm that CoaguChek could be used as a new method for oral anticoagulant monitoring, and is in best agreement with the capillary blood PT system.

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Introduction

Laboratory control of oral anticoagulant therapy (OAT) is based on prothrombin time (PT) [1]. Different combinations of thromboplastin reagents and techniques used in performing the PT test can introduce great variations in results despite the existence of the international normalized ratio (INR) [2]. The recent advent of portable coagulation monitors that measure PT from capillary whole blood samples has introduced new possibilities for oral anticoagulant monitoring [3–5]. The possibility of instantaneous results and the improvement in the quality of life of anticoagulated patients [6, 7] make it advisable to evaluate the accuracy and correlation of these devices with three routine laboratory systems used in oral anticoagulation units.

Patients and Methods

Patients

The study was performed in three hospitals: Ciudad Sanitaria de Bellvitge (Hospital A), Hospital de Basurto (Hospital B) and Hospital La Fe (Hospital C), with a similar number of patients undergoing OAT and stabilized over 6 weeks in an INR range between 2.0 and 4.0. The total number of patients was 235, broken down as 77, 84 and 74 patients, respectively. In the three hospitals, all patients gave their oral consent to participate in the study.

Methods

PT Measurement

Hospital A: Thrombotest in Capillary Blood Method. 77 patients on OAT with different therapeutic ranges of hypocoagulability underwent a simultaneous collection of capillary blood samples using a Micro-lance Long Point (Becton Dickinson, France) and rejecting the first drop. With an automatic pipette, 40 μ l of capillary blood were collected and put on the CoaguChek® PT test carrier to determine INR with CoaguChek. Another drop was put in a cuvette with bovine thromboplastin, ISI = 1.04 (Thrombotest, Immuno), and INR was determined with the mechanical

coagulometer Thrombotrak (Nicomed, Norway) as in the case of AMAX CS-190.

Hospital B: Plasma Sample. 84 patients on OAT with a therapeutic range between 2 and 4 were included in the study. The blood was extracted by venipuncture and placed in siliconized vacuum glass tubes (Becton Dickinson), previously filled to 1/10 volume with 0.129 M trisodium citrate and centrifuged to 1,500 g for 15 min at 4 °C. The clinical laboratory methodology for INR measurements employed an STA coagulometer (Diagnostics Stago, Barcelona, Spain), and the rabbit thromboplastin STA Neoplastine Plus (Diagnostics Stago) with an ISI = 1.29 supplied by the manufacturer. The mean normal PT was determined by the geometrical mean of 20 fresh normal plasmas.

Hospital C: Thrombotest in Venous Whole Blood. 74 patients on OAT with different intensities of hypocoagulability and different diagnoses participated in the study. The samples were obtained from venipuncture in siliconized and vacuum tubes containing 0.129 M sodium citrate (Vacutainer, Sumilab) (1/10) and tested immediately in the coagulometer AMAX CS-190 (Grifols, Barcelona, Spain), ISI = 0.92. AMAX is a mechanical coagulometer that measures the time from the addition of the starting reagent up to the beginning of fibrin formation. The sample of whole blood and the reagent are put into a special cuvette which is inserted into one of the mechanical measuring wells. A stainless steel ball is placed on the bottom of the cuvette. Upon addition of the starting reagent, the cuvette starts to rotate around its longitudinal axis, while the steel ball is kept exactly in place by a magnet. When coagulation starts, the fibrin filaments drag the ball away from the original site. This change in position releases an impulse in the magnetic sensor which automatically stops the time recording. All samples were analyzed in duplicate. To check the perfect reconstitution of the lyophilized material and the functioning of the coagulometer we used a control plasma (Control Plasma AK-R from Immuno).

Method of CoaguChek. The portable coagulometer to be evaluated was a CoaguChek (Roche Diagnostics, Barcelona, Spain). One drop of capillary whole blood was collected from the patient's finger using the lancet device Softclix (Boehringer-Mannheim, Germany) containing iron oxide particles and reagent which mix by an oscillating electromagnetic field when the whole blood sample is applied. At the start of coagulation, the iron particles stop their movement. This change is detected by reflectance photometry. A code chip for each lot of CoaguChek PT test provides all necessary calibration information: the ISI value and the mean

Fig. 1. Comparison between CoaguChek and Thrombotest (TT) in capillary blood. Coefficient of correlation: $r = 0.974$; regression analysis: $y = 0.0709 + 0.995x$. $R^2 = 0.9489$.

normal PT. The code used was lot 031 and the ISI = 1.5.

Statistical Analysis

The statistical methodology for comparing the INR results obtained with the three methods included determination of the mean, standard deviation (SD), interval of confidence to 95% (IC), regression analysis and the plot of the average value of a pair of measurements versus their difference applying the Bland and Altman method [8].

A test of simple concordance was performed as a method of analyzing the accuracy of the technique and the kappa index to avoid a chance agreement [9, 10]. Values were classified in three ranges: $INR < 2.0$, INR between 2.0 and 4.0 and $INR > 4.0$. Agreement is established to describe the number of tests that overlap in the different fields created corresponding to the therapeutic ranges.

$$K = \frac{P_0 - P_e}{100 - P_e}$$

where P_0 = % total concordance and P_e = % concordance due to chance related to concordance due to observed reliability ($P_0 - P_e$) with the maximum value obtained in case both observers agree, ruling out chance ($100 - P_e$).

Results

The mean and standard deviation of the INR obtained with the four methods are given in table 1.

Figures 1–3 graphically represent the regression lines obtained comparing the CoaguChek monitor with the three systems studied. In all cases a good correlation is observed: $r = 0.974$ (Hospital A), $r = 0.928$ (Hospital B) and $r = 0.914$ (Hospital C).

Regarding the test of simple concordance, tables 2–4 present the comparison of CoaguChek with each of the other systems, showing 87.2% agreement with the Thrombotest/KC-1 system, 85.7% with the Neoplastine/STA system and 68.4% with Thrombotest/AMAX. If the kappa index is applied, these values are 0.719, 0.656 and 0.358, respectively.

Figures 4–6 represent the plotting of the average INR value of a pair of measurements versus their difference. The absolute difference (mean $\pm$ SD) in laboratory A and Coa-

Fig. 2. Comparison between the CoaguChek and the Neoplastine/STA system. Coefficient of correlation: $r = 0.928$; regression analysis: $y = 0.485 + 0.839x$, $R^2 = 0.8609$.

Fig. 3. Comparison between CoaguChek and Thrombotest in whole blood (AMAX). Coefficient of correlation: $r = 0.914$; regression analysis: $y = 0.631 + 0.617x$, $R^2 = 0.8347$.

Table 1. INR mean and SD with CoaguChek and the three studied systems

Lab	Patients	Routine system	INR routine system	INR CoaguChek
A	77	Thrombotest/KC-1	2.83 ± 0.88	2.89 ± 0.90
B	84	Neoplastine/STA	2.78 ± 0.95	2.74 ± 1.05
C	74	Thrombotest/AMAX	3.47 ± 1.31	2.77 ± 0.88

Table 2. Comparison between CoaguChek PT test and Thrombotest in capillary blood: frequency distribution of measured values (n = 77)

Thrombotest/ KC-1 system	CoaguChek PT system		
	INR <2	INR 2–4	INR >4
INR <2	10 (13.0)	5 (6.5)	
INR 2–4	4 (5.2)	49 (63.6)	1 (1.3)
INR >4			8 (10.4)

Figures in parentheses represent percentage. Concordance = 87%; kappa index = 71.8%

Table 3. Comparison between CoaguChek PT test and the Neoplastine/STA system. Frequency distribution of measured values (n = 84)

Neoplastine/ STA system	CoaguChek PT system		
	INR <2	INR 2–4	INR >4
INR <2	14 (16.7)	1 (1.2)	
INR 2–4	4 (4.8)	52 (61.9)	4 (4.8)
INR >4		3 (3.6)	6 (7.1)

Figures in parentheses represent percentage. Concordance = 85.7%, kappa index = 65.6%.

Table 4. Comparison between CoaguChek PT test and Thrombotest in whole blood: frequency distribution of measured values (n = 74)

Thrombotest/ AMAX system	CoaguChek PT system		
	INR <2	INR 2–4	INR >4
INR <2	5 (6.8)	9 (12.2)	
INR 2–4		40 (54.1)	13 (17.6)
INR >4			7 (9.5)

Figures in parentheses represent percentage. Concordance = 70.4%; kappa index = 39.0%.

guChek INRs was 0.0571 ± 0.2042 , 0.04286 ± 0.3906 in laboratory B and 0.6986 ± 0.6170 in laboratory C. The 95% limits of agreement of INR difference versus the average were $0.0106 \div 0.1037$ (laboratory A), $-0.1490 \div 0.1276$ (laboratory B) and $0.5557 \div 0.8416$ (laboratory C). The coefficients of correlation between the INR average value of a pair of measurements versus their difference in the studied systems were 0.0089, 0.069 and 0.4942, respectively.

Discussion

Although Thrombotest in KC-1 has already been compared with CoaguChek [11, 12], we were interested in the results of testing Thrombotest with two different blood samples, capillary and whole venous blood. When we compared the INR results, the monitor showed a good correlation with capillary blood sample, yielding a figure (0.974) which is similar to the values obtained in other studies (0.910, 0.997). With Thrombotest in whole venous blood we found a coefficient of correlation of 0.914, which is the same as in the study of Kapiotis et al. [11] with capillary blood.

The laboratory that determined PT using the Neoplastine/STA system in citrated venous plasma obtained a similar correlation as that in other studies [13].

In the comparison of absolute differences (mean $\pm$ SD), Thrombotest in whole venous blood data presented the greatest variability (0.6986, IC: $0.5557 \div 0.8416$) evidenced by a larger coefficient of correlation, $r = 0.4942$, compared to the other two laboratories (0.0571, IC: $0.0106 \div 0.1037$, $r = 0.0089$ for laboratory A and 0.04286 , IC: $-0.1490 \div 0.1276$, $r = 0.0690$ for laboratory B). This variability was confirmed when the 95% limits of agreement of the INR difference versus

Fig. 4. INR differences for patients by CoaguChek and Thrombotest (TT) in capillary blood. INR differences (DCOAG-TT) and mean INR (XCOAG-TT) are shown.

Fig. 5. INR differences for patients by CoaguChek and the Neoplastine/STA system. INR differences (DCOAG-STA) and mean INR (XCOAG-STA) are shown.

the average were calculated: -0.35134 to 0.4654 , -0.8214 to 0.7383 and -1.9326 to 0.5354 . The increase in the variability of the results corresponded to an increase in the magnitude of the measurements. The system of laboratory A with Thrombotest in KC-1

had a coefficient of correlation close to zero, showing a lower dispersion.

In the simple concordance studies, CoaguChek tended to exceed Thrombotest whole venous blood INR results, since 18.9% of the INR values were incremented (12.2% in INR

Fig. 6. INR differences for patients by CoaguChek and Thrombotest in whole blood. INR differences (DCOAG-AMAX) and mean (XCOAG-AMAX) are shown.

< 2 and 16.6% in INR = 24). The percentage of concordance with this method was lower (70.4%, kappa index = 0.39) than when using the other systems: 87% and kappa index = 0.718 for laboratory A and 85.7% and kappa index = 0.656 for laboratory B.

This study showed that CoaguChek INR results are in better agreement with Thrombotest capillary blood results than in Thrombotest venous whole blood results. The use of high sensitivity thromboplastin in the two methods would seem to indicate that the dif-

ference in the results may be caused by differences in preanalytical conditions [3].

On the basis of our experience with the use of this kind of monitor, we feel it is a viable alternative to laboratory testing and an optional method for monitoring anticoagulated patients. To this end, the sensitivity of the thromboplastins used in these devices must first be calibrated against international reference preparations, and a correlation study should be done with the routine method used as a reference.

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