

Primary care



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Reliability of international normalised ratios from two point of care test systems: comparison with conventional methods

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Editorial by Murray and Greaves

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Abstract

Objective To find out how accurately two point of care test systems—CoaguChek Mini and TAS PT-NC (RapidPointCoag)—display international normalised ratios (INRs).

Design Comparison of the INRs from the two systems with a “true” INR on a conventional manual test from the same sample of blood.

Setting 10 European Concerted Action on Anticoagulation centres.

Participants 600 patients on long term dosage of warfarin.

Main outcome measures Comparable results between the different methods.

Results The mean displayed INR differed by 21.3% between the two point of care test monitoring systems. The INR on one system was 15.2% higher, on average, than the true INR, but on the other system the INR was 7.1% lower. The percentage difference between the mean displayed INR and the true INR at individual centres varied considerably with both systems.

Conclusions Improved international sensitivity index calibration of point of care test monitors by their manufacturers is needed, and better methods of quality control of individual instruments by their users are also needed.

Introduction

Demands for warfarin have greatly increased in recent years for a range of clinical states including atrial fibrillation.¹ As a consequence, anticoagulant facilities throughout the world are overwhelmed by demands for monitoring; many patients may not receive this treatment because of limited facilities.²

Innovative testing procedures at the point of care have been introduced to determine the prothrombin time for samples of whole blood. These procedures do not need the technical expertise of traditional methods because the tests use unmeasured samples of blood.³

One of two monitors—CoaguChek (Roche Diagnostics, Basel)—which we studied is being introduced throughout the United Kingdom with widespread promotion in the national media. Most large centres in the United Kingdom have limited but increasing numbers

of patients using CoaguChek. In Germany, 50 000 to 60 000 patients are already in self testing or self dosage programmes using CoaguChek.¹

Point of care test monitors must give dependable international normalised ratios (INR) because the safety and effectiveness of warfarin depends on keeping patients within target INR ranges. Thrombotic events increase at INRs less than 2.0 and bleeding complications increase at INRs greater than 4.5.⁴

We evaluated two point of care test monitoring systems which are widely marketed in the European Union—CoaguChek Mini, and TAS PT-NC (Rapid-PointCoag). We compared INRs displayed on the two types of monitors with “true” INRs determined by conventional manual prothrombin time testing with World Health Organization (WHO) species specific thromboplastin standards on the same samples of blood. We coded our results because we assessed only two of several systems currently marketed.

Materials and methods

The manufacturers of the two systems (CoaguChek Mini and TAS PT-NC, described in detail elsewhere) provided their systems to each of the 10 European Concerted Action on Anticoagulation centres.^{5 6}

We took non-citrated venous whole blood from 60 patients stabilised on long term oral anticoagulants at each centre. We tested each sample on both monitor systems within 15 seconds of collection and recorded the INRs that the systems displayed.

We tested plasmas to determine the true INR within six hours of collecting blood.⁶ We classified an absolute deviation of INR of more than 50% from the true INR as “aberrant” and recorded the number of tests at each centre which gave aberrant results for both systems.

Results

Of the 600 samples of blood tested by the two point of care test systems (coded A and B), we excluded 64 according to WHO protocol because the INRs were outside the 1.5 to 4.5 range with the relevant WHO thromboplastin standard.⁷

The overall mean INR displayed by the monitors of the 536 samples remaining after exclusions was

considerably higher with system A than with system B (overall mean difference 21.3%).

With system A, the difference between the mean displayed INR and the true INR of the local samples varied between 0% and 34.6% at the 10 centres. At nine centres, the mean displayed INR on system A was significantly higher than the true INR, for the same samples of blood ($P < 0.001$). The overall difference between the mean displayed INR and the true INR was 15.2%. At seven of the 10 centres, mean differences in INRs were more than 10%, which is clinically relevant according to WHO's guidelines.⁷ The limits of agreement, which give a measure of the variability of individual INR results, ranged from -0.70 to 1.47 units (see fig 1).

The difference between the displayed mean and true INR was less with system B. Mean displayed INRs were, however, 7.1% lower than true INRs. Six of the 10 centres gave statistically significant differences in mean displayed INR—between 19.0% lower to 3.5% higher—compared with the true INR, and at four centres mean results exceeded the 10% limit.⁷ The limits of agreement (fig 1) ranged from -1.24 to 0.87 units.

Relation to intensity of anticoagulation

Although the Bland-Altman plots (fig 1) show greater deviation with higher INRs, the percentage difference from the true INR is not simply related to the INR.⁸ The individual differences varied between displayed INRs and true INRs within centres with the two monitor systems (see tables on bmj.com).

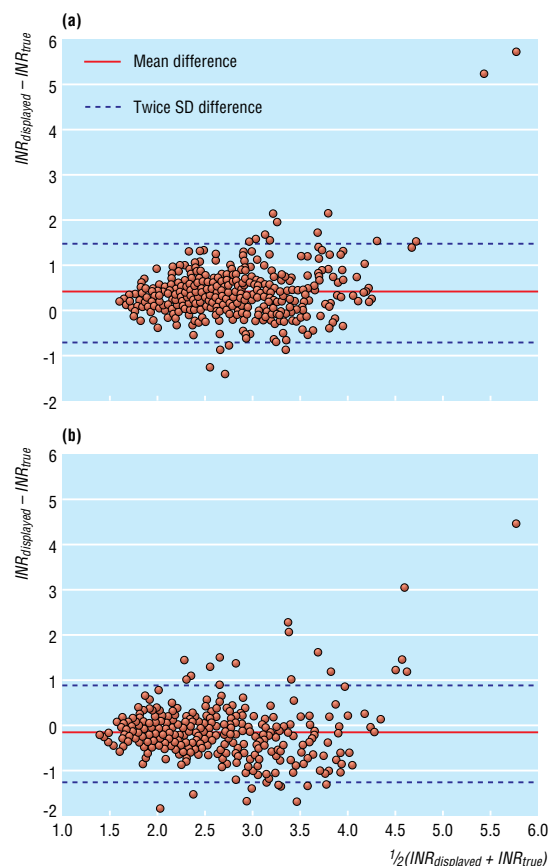


Fig 1 Bland-Altman plots of differences in INR plotted against the mean INR displayed by (a) monitoring system A and (b) monitoring system B and "true" INRs for the 536 samples

Aberrant results

With system A, monitors at eight of the 10 centres gave at least one aberrant result (more than 50% deviation from the true INR), with a total incidence of 28 (5%). A single instrument at one centre accounted for 10 of these. With system B, 12 (2%) results were aberrant. In all, four of the aberrant results, from different samples, differed by more than 2.0 units (fig 1).

Discussion

The two whole blood point of care test monitoring systems gave INRs which differed by 21.3%—a considerable clinical discrepancy. The systems were tested on the 536 patients treated with warfarin remaining in the analysis after exclusions at 10 centres.⁷

The second concern is the considerable disagreement between the overall displayed INR with system A and the true INR, and this occurred to a lesser extent with system B. Even with system B, however, the percentage difference in mean INR at four of the centres exceeded WHO's 10% limit for clinical relevance.⁷ With system A, displayed results of INR from nine of the 10 centres were greater than the true INR, but the results of system B showed the opposite trend with most mean displayed INRs less than the true INRs. Another problem is the inconsistency of variations between centres between the mean displayed INR and the true INR.

The clinical relevance in warfarin dosage of these discrepancies is important (fig 2). The effect on dosage of warfarin may be that with system A less warfarin is prescribed than with system B to achieve target INRs. This might result in a tendency to increased bleeding with system B or alternatively less protection from thrombosis with system A as it is necessary to maintain patients within target INR intervals to minimise bleeding and further thrombosis.⁴

Monitors of whole blood at the point of care are convenient and simple, and claims have been made that they are more reliable than laboratories performing conventional INR testing.^{9–13} Only two randomised cross over studies of such systems have been reported, but none of the clinical studies compared the results displayed by the monitor with true INR on the same blood samples tested with the WHO thromboplastin standard and the manual technique.^{14 15}

Van den Besselaar previously reported, in a single monitor study, a statistically but not clinically significant difference in mean INR from reference values with a WHO thromboplastin standard using the manual technique with the CoaguChek Mini system.¹⁶

The manufacturers of the two systems make considerable efforts to ensure the reliability and safety of their monitors. Nevertheless the results indicate that additional steps in international sensitivity index calibration and quality control are essential to ensure the reliability of displayed INR of these systems. Several other types of point of care test monitors are currently marketed, and they may share similar problems.

As users cannot adjust the INR displayed by the monitors, calibration of the international sensitivity index of a monitor to derive INRs has to be the responsibility of the manufacturer. Because of the large numbers of monitors in use and the complexity of the recommended procedure, calibration of international sensitivity index for all individual instruments would

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What is already known on this topic

Whole blood point of care test prothrombin time monitors are convenient and simple and claims have been made that they are more reliable than laboratories doing conventional international normalised ratio (INR) monitoring

What this study adds

The INRs obtained using manual tests with two thromboplastin standards gave better agreement than the INRs from the monitoring systems despite the thromboplastins coming from different species

Manufacturers need a more practical way of calibrating the international sensitivity index of their systems but better methods of quality control are needed to check performance of individual monitors and operators

not be possible.¹⁷ Furthermore, to be reliable, such calibrations need to be on a multicentre basis. A minimum of three centres is required to calibrate the TAS PT-NC and five for the CoaguChek Mini.¹⁸

Manufacturers of monitors therefore need a less complex and demanding procedure for calibrating international sensitivity index. We have developed such a system using lyophilised plasmas certified by European Concerted Action on Anticoagulation, which has been validated in a multicentre exercise and needs to be used with each of the two point of care test monitor systems studied in this report.^{5 19 20} Nevertheless, even with the simplified procedure, calibrating all instruments will still not be feasible and since calibration does not check performance of operators, quality control of individual monitors and their users is also necessary. Recommendations for such quality control have been made by the European Concerted Action on Anticoagulation as existing national or regional systems of external quality control could not be expected to cope with the massive numbers of point of care test monitors in use.²¹

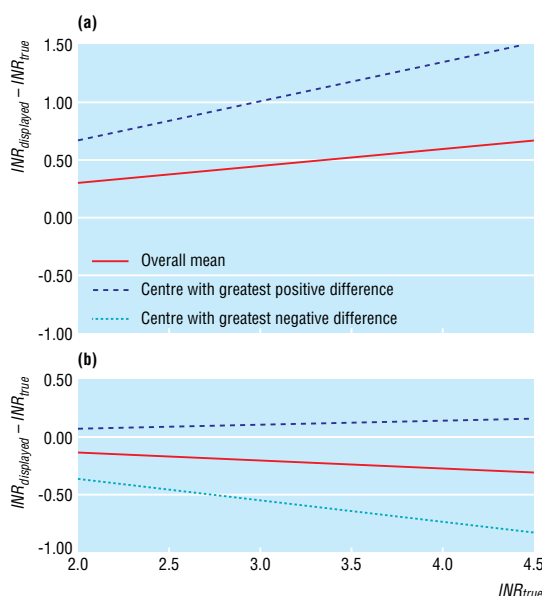


Fig 2 Differences in mean INR plotted against "true" INR; (a) monitoring system A, (b) monitoring system B

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