Validity of CoaguChek S for home monitoring of anticoagulant therapy in pediatrics

James Hill MSc¹, Sébastien Perreault MSc², Michel Dorval PhD³

J Hill, M Dorval, S Perreault. Validity of CoaguChek S for home monitoring of anticoagulant therapy in pediatrics. *Can J Cardiol* 2007;23(1):47-50.

BACKGROUND: CoaguChek S (Roche Diagnostics, Canada) is a portable device designed to monitor international normalized ratio (INR) by capillary puncture. Although the device is used in pediatrics, no study has evaluated its validity in patients of this population.

OBJECTIVE: To evaluate the validity of CoaguChek S as an in-home INR monitor in patients younger than 18 years of age.

METHODS: Data were based on 129 INR pairs collected from nine patients younger than 18 years of age followed up at an anticoagulation clinic between March 1, 2000, and January 19, 2004. The INRs from both the laboratory and CoaguChek S were used to evaluate concordance between the two methods using the intraclass correlation coefficient.

RESULTS: The overall intraclass correlation coefficient between the CoaguChek S and the laboratory was 0.75 (95% CI 0.66 to 0.82). On average, CoaguChek S underestimated INRs by 0.11 ± 0.54 units compared with those of the laboratory. INRs of 3.5 units and higher obtained with CoaguChek S were, on average, 0.49 ± 1.09 units higher than those obtained in the laboratory.

CONCLUSIONS: CoaguChek S appears to be a valid instrument for in-home INR monitoring for most patients younger than 18 years of age, with INR targets of 2.0 to 3.0 followed up by an anticoagulant therapy clinic's program. However, caution must be used when interpreting INRs higher than 3.5. Parents should perform a second test to confirm all CoaguChek S INR results higher than 4.0.

Key Words: Anticoagulants; Home monitoring; International normalized ratio; Pediatrics; Patient self-testing

Intensity of anticoagulant therapy and time spent within the therapeutic range are important, both in terms of treatment efficacy and reduction of risk for thrombosis or hemorrhage (1,2). It is difficult to maintain constant values within a therapeutic range. Unfortunately, children undergoing anticoagulant therapy must be tested more often than adults to ensure adequate treatment monitoring (3). Most children require weekly monitoring, and monthly tests are sufficient only in an estimated 10% to 20% (4).

Portable devices allow measurement of international normalized ratios (INRs) by taking capillary samples and, thus, avoiding venipunctures in children who often have poor venous access. Other advantages include less parental and patient anxiety, fewer visits, less time waiting in the laboratory and possible improved INR testing compliance (1,4,5). There does not appear to be any significant difference between INRs

La validité du CoaguChek S pour le monitoring à domicile d'une anticoagulothérapie en pédiatrie

CONTEXTE : Le CoaguChek S (Roche Diagnostics, Canada) est un appareil portable permettant d'obtenir le rapport normalisé international (RNI) par ponction capillaire. Bien que cet appareil soit utilisé en pédiatrie, aucune étude n'a été effectuée pour évaluer sa validité chez cette population.

OBJECTIF : Évaluer la validité du CoaguChek S utilisé à domicile pour monitorer le RNI chez les patients de moins de 18 ans.

MÉTHODOLOGIE : Les données proviennent de 129 paires de RNI colligés chez neuf patients de moins de 18 ans, suivis par une clinique d'anticoagulothérapie entre le 1^{er} mars 2000 et le 19 janvier 2004. Toutes les paires de RNI obtenus par laboratoire et CoaguChek S ont été retenues pour évaluer la concordance entre les deux méthodes, au moyen du coefficient de corrélation intraclass.

RÉSULTAT : Le coefficient de corrélation intraclass global entre le CoaguChek S et le laboratoire est de 0,75 (intervalle de confiance à 95 % = 0,66–0,82). En moyenne, le CoaguChek S sous-estime le RNI de $0,11 \pm 0,54$ unité par rapport au laboratoire. Les RNI de 3,5 et plus obtenus par CoaguChek S sont en moyenne $0,49 \pm 1,09$ unité plus élevés que ceux obtenus en laboratoire.

CONCLUSION : En somme, le CoaguChek S semble être un instrument valide pour le suivi des RNI à domicile de la plupart des patients de moins de 18 ans suivis dans le cadre d'un programme de clinique d'anticoagulothérapie pour qui un RNI visé se situe entre 2.0 et 3.0. Toutefois, il faut être vigilant dans l'interprétation des RNI supérieurs à 3,5. Les parents devraient refaire un deuxième test si le RNI obtenu est supérieur à 4,0, afin de confirmer le résultat.

obtained by capillary puncture and those from venipuncture when using the same portable monitor (6,7). Many models, such as the CoaguChek S (Roche Diagnostics Canada), have been studied for adult use (5-14). Although a few studies have assessed the validity of these devices among children, no study has yet evaluated the validity of in-home CoaguChek S use among pediatric patients (1,4,5,15,16). Thus, it is difficult to determine whether children may use this device safely and effectively at home.

The main objective of the present study was to evaluate the validity of CoaguChek S as an in-home capillary puncture INR monitor in patients younger than 18 years of age.

METHODS

The present study was a retrospective, longitudinal study. In the pharmacist-managed anticoagulation clinic of the Centre hospitalier

¹Centre de santé et de services sociaux de Rimouski-Neigette, Rimouski; ²Centre hospitalier de l'Université Laval du Centre hospitalier universitaire de Québec, Ste-Foy; ³Faculty of Pharmacy, Université Laval, Unité de recherche en santé des populations, Québec City, Québec

Correspondence and reprints: James Hill, Centre de santé et de services sociaux de Rimouski-Neigette, 150, avenue Rouleau, Rimouski, Québec G5L 5T1. Telephone 418-724-8451, fax 418-724-8646, e-mail james.hill.crsssr@ssss.gouv.qc.ca

Received for publication October 26, 2005. Accepted March 28, 2006

TABLE 1
Selected characteristics of participants

Subject	Sex	Age*	Target INR	Number of INRs	ICC	95% CI
1	F	8	2.5–3.5	4	0.42	–0.66–0.93
2	F	10	2.0–3.0 (3 months) [†] 1.8–2.5	13	0.86	0.63–0.96
3	F	9	2.5–3.5 (5 months) [†] 3.0–4.0 (15 months) [†] 2.5–3.0	61	0.71	0.56–0.81
4	F	9	2.5–3.5	16	0.72	0.37–0.89
5	M	10	2.5–3.5	4	0.83	–0.04–0.98
6	F	14	2.0–3.0	3	0.89	–0.18–1.00
7	F	8	2.5–3.5	11	0.66	0.15–0.89
8	M	9	1.8–2.5	12	0.90	0.70–0.97
9	F	1	2.0–2.5	5	0.83	0.15–0.98

*Age in years at the start of use of the device; [†]International normalized ratio (INR)-targeted, with time limit for follow-up. F Female; ICC Intraclass correlation coefficient; M Male

de l'Université Laval du centre Hospitalier universitaire de Québec (Ste-Foy, Québec), a tertiary pediatric centre, all patients younger than 18 years of age were trained to use the CoaguChek S to monitor their INRs. A consecutive series of patients using the CoaguChek S from March 1, 2000, to January 19, 2004, were identified. Eligible participants were required to have a baseline hematocrit between 23% and 54%, because the CoaguChek S may be less reliable at extreme hematocrit values (13). Patients who were noncompliant with the clinical protocol for testing at the times stipulated by pharmacists were excluded.

The portable device used in the present study was CoaguChek S. Using the Softclix lancet device (Roche Diagnostics Canada), a parent or a nurse took the 10 µL capillary puncture. The international sensitivity index (ISI) of the thromboplastin used was 2.00. Patients and their parents initially met with a pharmacist (SP), trained by the Roche Diagnostics company, for a training session on the proper use of CoaguChek S. Written instructions were also given to the family. Technique verification was performed before leaving the hospital. According to the anticoagulation clinic's protocol, control venipunctures are to be performed more frequently when beginning to use the portable device. One venipuncture is then required each time a new box of 12 strips is opened. A contact pharmacist was on-call after the child returned home. The ISIs of each thromboplastin value from the eight referral laboratories varied between 0.95 and 1.34.

The present study was based on INR pairs (one generated by CoaguChek S and the other by the laboratory), for which the samples were taken the same day, usually within 6 h of one another.

CoaguChek S validity was evaluated using the Pearson correlation coefficient and the intraclass correlation coefficient (ICC) with a 95% CI (17). The Pearson correlation coefficient and the ICC were determined for all patients, and a correlation plot was used to illustrate the distribution of INR values obtained with CoaguChek S and in the laboratory. Statistical analyses were performed using SAS (version 8.2, SAS Institute, USA).

The Centre hospitalier universitaire de Québec research ethics board approved the project.

RESULTS

Ten patients were identified during the study period. All patients used CoaguChek S from the outset of anticoagulation

Figure 1 Relationship between international normalized ratios (INRs) obtained by CoaguChek S (Roche Diagnostics, Canada) and the laboratory

therapy, and one patient was disqualified for noncompliance with treatment protocol (INRs were not performed at the times stipulated by the pharmacists). Therefore, INRs of nine patients were available for analysis. These patients' characteristics are shown in Table 1.

Patients were one to 14 years of age (median nine years), and two were male. Baseline hematocrits varied from 27% to 40%. Five patients had mechanical valves, two had Kawasaki disease, one had Ivemark syndrome and one suffered from primary pulmonary hypertension. No bleeding events were reported during the study period. In total, 129 INR pairs were obtained from these nine patients (three to 61 pairs per patient). Individual ICCs varied from 0.42 to 0.90.

CoaguChek S validity

The overall Pearson correlation coefficient was 0.77 ($P < 0.0001$), and the overall ICC was 0.75 (95% CI 0.66 to 0.82). Figure 1 illustrates the correlation between INRs obtained with CoaguChek S and in the laboratory.

The mean INRs obtained with CoaguChek S and the laboratory are shown in Table 2.

On average, CoaguChek S underestimated INR by 0.11 ± 0.54 units compared with laboratory values. INRs higher than 3.5 obtained with CoaguChek S were, on average, 0.49 ± 1.09 units higher than laboratory values. INRs 4.0 and higher obtained with CoaguChek S were, on average, 1.04 ± 1.17 units higher than laboratory values.

The ICC was 0.90 (95% CI 0.82 to 0.95) among patients with an INR range of 2.0 to 3.0, and was significantly lower among patients with INR targets of 2.5 to 3.5 (0.64 [95% CI 0.50 to 0.74]).

DISCUSSION

The results of present study suggest that the in-home use of CoaguChek S by pediatric patients generally provides valid

results compared with devices used in the hemostasis laboratory. A slight underestimation can be observed among all INRs; however, elevated INRs obtained with CoaguChek S appear to be significantly overestimated, particularly those higher than 3.5.

The in-home use of CoaguChek S by pediatric patients has an acceptable validity, with an overall ICC of 0.75. Nevertheless, the ICC obtained in the present study was lower than that reported by Lizotte et al (0.93 [14]). However, the context for CoaguChek S use in that study was different than ours. In the study by Lizotte et al, all patients were 18 years of age and older, capillary punctures were always performed by the same persons in an anticoagulant therapy clinic and all results were analyzed by the same laboratory.

The correlation coefficients of INRs obtained with portable devices among adults in a clinic varied from 0.86 to 0.96 (6,8-10). One study of adults using the Coumatrak (DuPont, USA) device at home showed lower concordance ($r=0.80$) (11). In pediatrics, there also appears to be a difference between clinical and in-home validity. In an outpatient clinic, the correlation coefficients obtained using an older version of CoaguChek were 0.96 and 0.92, while in-home values were 0.76 and 0.74 (15), which are similar to those observed in our population (0.77).

Overall, the CoaguChek S underestimated INRs by only 0.11 units, which is generally not clinically significant. The most acceptable INRs deviations are those under 2.0 (-0.14 units) or between 2.0 and 3.5 (-0.19 units). However, caution must be used when interpreting INRs higher than 3.5. These results were overestimated, with an average deviation of 0.49 units between laboratory and portable device values. This deviation increased proportionally with the CoaguChek S INR value. For instance, an INR of 4.0 or higher was overestimated by 1.04 units, on average. This tendency for overestimation is consistent with that of previous reports on portable devices (10,12-14).

For this reason, adjusting therapy on the basis of a very high value from CoaguChek S may be unnecessary. In our anticoagulant therapy clinic, a second CoaguChek S test is required for all initial values higher than 4.0 to confirm the result. If the second test result is also higher than 4.0, the child is automatically redirected to a blood test centre for a venipuncture INR. Overall, nearly 77% of INR pairs have 0.5 units or fewer of difference, which is acceptable. However, we admit that deviations higher than 0.5 units could lead to different clinical decisions or dose adjustments by pharmacists.

The fact that the CoaguChek S tends to overestimate results when the same INRs are high may be partly due to the thromboplastin sensitivity of the test strips (ISI of 2.00). Hemostasis laboratory devices use more sensitive thromboplastins (ISI of 0.95 to 1.34). However, we know that the lower the sensitivity level of the thromboplastin, the greater the variability between INRs when the same INRs are elevated (7). This may contribute to the difference between CoaguChek S and laboratory values when INRs are more than 3.5.

In our study, five of nine (56%) patients required an INR target of between 2.5 and 3.5. These patients had a lower ICC (0.64 [95% CI 0.50 to 0.74]), whereas patients with INR targets lower than 3.0 had a higher ICC (0.90 [95% CI 0.82 to 0.95]). According to these results, when an INR is higher than the INR target, the result obtained by the portable device is more hazardous. Therefore, we believe that a safer option is

TABLE 2
Comparison of CoaguChek S with laboratory international normalized ratio (INR) results

Parameter	CoaguChek S	Laboratory
All INR values, n (%)	129 (100)	129 (100)
INR (mean $\pm$ SD)	2.75 $\pm$ 0.85	2.86 $\pm$ 0.71
Mean difference $\pm$ SD	-0.11 ± 0.54	
Percentage within 0.5 INR units	76.7	
INR ≤ 1.99 , n (%)	19 (14.7)	11 (8.5)
Mean INR $\pm$ SD	1.72 $\pm$ 0.18	1.65 $\pm$ 0.19
Mean difference $\pm$ SD	-0.14 ± 0.26	
Percentage within 0.5 INR units	94.7	
INR 2.0–3.5, n (%)	96 (74.4)	92 (71.3)
Mean INR $\pm$ SD	2.72 $\pm$ 0.44	2.71 $\pm$ 0.41
Mean difference $\pm$ SD	-0.19 ± 0.40	
Percentage within 0.5 INR units	75.0	
INR ≥ 3.51 , n (%)	14 (10.9)	26 (20.2)
Mean INR $\pm$ SD	4.37 $\pm$ 1.10	3.91 $\pm$ 0.25
Mean difference $\pm$ SD	0.49 $\pm$ 1.09	
Percentage within 0.5 INR units	64.3	
INR ≥ 4.0 , n (%)	8 (6.2)	7 (5.4)
Mean INR $\pm$ SD	4.84 $\pm$ 1.29	4.25 $\pm$ 0.18
Mean difference $\pm$ SD	1.04 $\pm$ 1.17	
Percentage within 0.5 INR units	50.0	

in-home use of CoaguChek S by children with INR targets of between 2.0 and 3.0.

The present study had certain limitations. First, only nine patients participated in the study, and only 129 pairs of INRs were analyzed. However, the study sample was only slightly smaller than those in three other studies (1,15,16) carried out among children using an in-home portable device. A prospective study among a larger patient cohort would be pertinent. Second, one subject was disqualified from the analysis. The three INR pairs obtained by the two methods always differed by more than one unit for this patient. This anomaly was likely due to the improper use of the device by the patient, despite operating instructions given at the hospital. This demonstrates the importance of close follow-up of patients when first using the device. Third, it was unknown who actually performed each test. Parents or nurses performing INR tests received formal training on CoaguChek S use, but these data were not recorded by the clinic at each test. Fourth, only three parents received systematic review of user technique. We suggest a technique review at least one per year (during a patient's annual consult with a cardiologist) to ensure every testing step is respected. Fifth, it was impossible to determine whether the two tests were actually performed within 6 h of one another. However, because parents always called the clinic when going to the laboratory with their child after using the CoaguChek S, it is reasonable to assume that this delay was usually respected and that the elapsed time between tests did not exceed 24 h. Nevertheless, given the absence of this verification, the level of concordance between the two results was quite high.

Finally, because most of the children lived 50 km or farther from our hospital, many different devices were used in the various hemostasis laboratories to calculate INR. This

factor clearly diminished the quality of possible comparisons with CoaguChek S. However, it reflects reality because in many anticoagulation clinics, patients often use multiple laboratories for venipuncture tests. These limitations underscore the necessity of a proper prospective study of this population, particularly among patients with INR ranges of 2.5 to 3.5.

CONCLUSIONS

The results of the present study suggest that the CoaguChek S device is a valid means for in-home INR monitoring of most children with INR targets of 2.0 to 3.0 followed up at by anticoagulant therapy clinic's program. However, caution must be used when interpreting results of 3.5 or higher. We suggest a second INR measure with CoaguChek S for all results higher than 4.0. In this context, appropriate support from an experienced anticoagulant therapy clinic is recommended. A proper prospective study is required to ensure safe use of CoaguChek S in this population, particularly among children with INR targets of 2.5 to 3.5 or higher.

ACKNOWLEDGEMENTS AND DISCLOSURE: The authors thank Michel Gaudet, MSc, for his help with statistical analysis. Sébastien Perreault received training from Roche Diagnostics on instructing patients and other pharmacists in the use of CoaguChek S.

REFERENCES

- Massicotte P, Marzinotto V, Vegh P, Adams M, Andrew M. Home monitoring of warfarin therapy in children with a whole blood prothrombin time monitor. *J Pediatr* 1995;127:389-94.
- Ansell J, Hirsh J, Poller L, Bussey H, Jacobson A, Hylek E. The pharmacology and management of the vitamin K antagonists: The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004;126:204S-33S. (Erratum in 2005;127:415-6).
- Streif W, Andrew M, Marzinotto V, et al. Analysis of warfarin therapy in pediatric patients: A prospective cohort study of 319 patients. *Blood* 1999;94:3007-14.
- Nowatzke WL, Landt M, Smith C, Wilhite T, Canter C, Luchtman-Jones L. Whole blood international normalization ratio measurements in children using near-patient monitors. *J Pediatr Hematol Oncol* 2003;25:33-7.
- Ignjatovic V, Barnes C, Newall F, Hamilton S, Burgess J, Monagle P. Point of care monitoring of oral anticoagulant therapy in children: Comparison of CoaguChek Plus and Thrombotest methods with venous international normalised ratio. *Thromb Haemost* 2004;92:734-7.
- Lucas FV, Duncan A, Jay R, et al. A novel whole blood capillary technique for measuring the prothrombin time. *Am J Clin Pathol* 1987;88:442-6.
- Kaatz SS, White RH, Hill J, Mascha E, Humphries JE, Becker DM. Accuracy of laboratory and portable monitor international normalized ratio determinations. Comparison with a criterion standard. *Arch Intern Med* 1995;155:1861-7.
- Havrdá DE, Hawk TL, Marvin CM. Accuracy and precision of the CoaguChek S versus laboratory INRs in a clinic. *Ann Pharmacother* 2002;36:769-75.
- Jackson SL, Bereznicki LR, Peterson GM, et al. Accuracy, reproducibility and clinical utility of the CoaguChek S portable international normalized ratio monitor in an outpatient anticoagulant clinic. *Clin Lab Haematol* 2004;26:49-55.
- Hobbs FDR, Fitzmaurice DA, Murray ET, Holder R, Rose PE, Roper JL. Is the international normalised ratio (INR) reliable? A trial of comparative measurements in hospital laboratory and primary care settings. *J Clin Pathol* 1999;52:494-7.
- White RH, McCurdy SA, von Marensdorff H, Woodruff DE, Leftgoff L. Home prothrombin time monitoring after the initiation of warfarin therapy. A randomized, prospective study. *Ann Intern Med* 1989;111:730-7.
- Cosmi B, Palareti G, Moia M, et al. Accuracy of a portable prothrombin time monitor (CoaguChek) in patients on chronic oral anticoagulant therapy: A prospective multicenter study. *Thromb Res* 2000;100:279-86.
- Murray ET, Fitzmaurice DA, Allan TF, Hobbs FDR. A primary care evaluation of three near patient coagulometers. *J Clin Pathol* 1999;52:842-5.
- Lizotte A, Quessy I, Vanier MC, et al. Reliability, validity and ease of use of a portable point-of-care coagulation device in a pharmacist-managed anticoagulation clinic. *J Thromb Thrombolysis* 2002;14:247-54.
- Marzinotto V, Monagle P, Chan A, et al. Capillary whole blood monitoring of oral anticoagulants in children in outpatient clinics and the home setting. *Pediatr Cardiol* 2000;21:347-52.
- Mähönen S, Riikonen P, Väättäin RL, Tikanoja T. Oral anticoagulant treatment in children based on monitoring at home. *Acta Paediatr* 2004;93:687-91.
- Shrout PE, Fleiss JL. Intraclass correlations: Uses in assessing rater reliability. *Psychol Bull* 1979;86:420-8.