Medical Liability Risk Avoidance: A Case for Adopting the International Normalized Ratio (INR) System

Sandra S. Kline, PharmD, JD; and Maureen O. Atkins, JD

Abstract

Since bleeding is a common adverse effect associated with the oral anticoagulant warfarin, maximizing the therapeutic potential of this drug requires close laboratory monitoring. The International Normalized Ratio (INR) is a system that has been developed to improve and standardize the assessment of the intensity of oral anticoagulation therapy. Clinical information and medicolegal arguments supporting the adoption of this system are reviewed. The potential for improvement in patient outcomes and minimization of medical liability favors the adoption of the INR system.

(Am J Man Care 1997;3:59-63)

Warfarin is an anticoagulant indicated for the prophylaxis or treatment of venous thrombosis, pulmonary embolism, and thromboembolic complications associated with atrial fibrillation or cardiac valve replacement. It is also used to reduce the risk of death, recurrent myocardial infarction, and thromboembolic events such as stroke or systemic embolization after myocardial infarction.[1]

Warfarin has a narrow therapeutic range with a low therapeutic index. Therapeutic index is a measure of a drug safety. It is determined by the ratio between a dose that results in toxicity and a dose that results in a therapeutic benefit. Those drugs with a narrow therapeutic index have values near 1; that is, their effective therapeutic dosages are near the dosages that cause toxicity.

From (at the time of this writing) the Medical College Hospitals, Toledo, OH, and (currently) Fujisawa USA, Inc, Deerfield, IL (S.S.K.); and Doyle, Lewis & Warner, Toledo, OH (M.O.A.)

This study was supported by an unrestricted educational grant from DuPont Pharma.

Address correspondence to: Sandra S. Kline, Senior Medical Information Associate, Fujisawa USA, Inc, Three Parkway North, Deerfield, IL 60015.

The most common adverse effect of warfarin therapy is bleeding. Although it is difficult to determine if a specific incident of bleeding is related to warfarin therapy, bleeding risk correlates with the intensity of anticoagulation therapy.[2] Hence, it is understandable why warfarin requires close monitoring to maximize the drug's therapeutic potential while at the same time minimizing adverse patient outcomes.

The therapeutic effect of warfarin is not determined by measuring serum concentrations of the drug. Rather, it is assessed by measuring the indirect anticoagulant effect caused by warfarin's inhibition of the production of vitamin K–dependent clotting factors II, VII, IX, and X. This effect is measured by determining a patient's prothrombin time (PT). Quick et al. introduced the PT or "protime" in 1935 as a means of measuring the activity of the vitamin K–dependent factors II, VII, and X.[3] The test is performed by adding a tissue thromboplastin and calcium to citrated plasma, which in turn activates the clotting cascade. The PT, measured in seconds, is the time it takes for clotting to commence.

The PT and the prothrombin time ratio (PTR) (the patient's PT divided by a mean normal PT) have been the national standard in the United States for monitoring oral anticoagulation therapy since the 1940s.[4] However, in recent years the results of these tests have become less reliable because of the introduction of thromboplastin reagents that vary substantially in their sensitivity to warfarin-induced effects on the prothrombin. Hence the international normalized ratio (INR) system was introduced by the World Health Organization (WHO) in 1983 to adjust for the variability among thromboplastin reagents and to standardize the reporting of PT test results in the monitoring of anticoagulation therapy.[5]

The INR is calculated as follows: INR = (observed PT ratio)^{ISI}. The observed PT ratio is the patient's PT divided by a mean normal PT, and the ISI (international sensitivity index) is the correction factor in the equation that relates the PT ratio of the laboratory thromboplastin to the reference standard thromboplastin.

The following factitious example is presented to illustrate the need for a standardized system to evaluate the intensity of anticoagulation therapy. Assume a patient has been well maintained on warfarin therapy for many years. The patient's physician only evaluates the patient's PT value to assess the intensity of anticoagulation therapy and has established a target PT range of 15 to 19 seconds. The laboratory that the patient has been going to for these PT assessments has been using the same source of thromboplastin throughout this patient's warfarin therapy, and it has had an ISI value of 2.8. The laboratory mean normal prothrombin time is 12 seconds. Hence the patient's INR range over the years can be calculated to be 1.9 to 3.6.

Now, assume that the laboratory changes the source of thromboplastin. This new thromboplastin has a ISI value of 1.0. As a means of simplification, assume the laboratory mean normal PT remains at 12 seconds. Thus, in order to achieve the same level or intensity of anticoagulation as the patient has been achieving over the previous years (INR range = 1.9–3.6), the new targeted PT range would need to be 23 to 43 seconds.

Imagine the response of the treating physician who has only been evaluating this patient's warfarin therapy by assessing the PT result if he received a report of 40 seconds! It is very likely that a warfarin dosage reduction would be ordered, especially since the physician is expecting a PT result for this patient between 15 and 19 seconds. Unfortunately, a dosage reduction—if based solely on the comparison of this patient's prior PT values (15–19 seconds) to the current value (40 seconds) without taking into consideration the sensitivity of the thromboplastin used—would result in a lower level of anticoagulation intensity than the patient's previous maintenance level and would put the patient at risk for developing a thromboembolism or clot. Hence educating clinicians such as the physician in this example about the INR system is essential to minimize unnecessary poor patient outcomes.

In addition to the WHO, the International Committee on Thrombosis and Hemostasis, the International Committee for Standardization in Haematology, the American College of Chest Physicians, and the American Society of Health-System Pharmacists have recommended the adoption of the INR system.[6–8]

Although the INR system has gained the endorsement of many professional committees and organizations, it has also been criticized.[9–11] Some problems that have been reported include lack of reliability of the INR system when used at the onset of warfarin therapy, loss of accuracy and precision of the INR system when thromboplastin reagents with high ISI values are used, lack of reliability of the ISI result provided by the manufacturer, incorrect calculation of the INR resulting from use of inappropriate control plasma, and high INR values in overanticoagulated patients, which can produce unnecessary alarm.[10] Despite the problems and limitations associated with the INR system, it appears to be more accurate than the traditional manner of assessing the intensity of oral anticoagulation therapy by using PTs in seconds or uncorrected PTRs. This paper will assess the clinical and medicolegal support for the adoption of the INR system in the United States.

INR Adoption: Clinical Support

In 1982 Hull et al. published the results of a clinical trial in which 96 patients with proximal deep-vein thrombosis were treated with oral warfarin therapy and were randomly assigned to have their anticoagulation therapy monitored by thromboplastin from one of two sources, each thromboplastin with a significantly different degree of sensitivity.[12] Although the therapy in both groups was equally effective in preventing thromboembolism, a significant difference in bleeding complications was reported between the two thromboplastin reagents. This was the first trial to indicate that targeting anticoagulation therapy to a defined PTR may be an inaccurate means of assessing the intensity of anticoagulation when thromboplastin reagents with different sensitivities are used.

A more widespread concern with assessment of anticoagulation therapy was revealed in the results of a survey conducted in the early 1990s of nearly 200 laboratories located throughout the United States.[13] It was found that thromboplastin reagents with a wide range of sensitivity were being used, and few institutions were reporting INR results. The authors concluded that based on these results, a potential for warfarin therapy mismanagement existed if the uncorrected PTR is relied on solely to assess anticoagulation therapy.[13]

More recently, Andrews and colleagues used an unblinded, retrospective time-series design to assess the thromboembolic events and bleeding complications of all patients receiving anticoagulation therapy who were monitored in an anticoagulation clinic.[14] Complication rates for patients monitored with uncorrected PTRs were compared with those for patients monitored with the INR system of reporting PT results. The groups had similar patient-years of follow-up: 403 patient-years for those monitored by PTRs and 418 patient-years for those monitored with

the INR system. The two groups had similar indications for anticoagulation therapy. There were significantly fewer total bleeding complications (major and minor) in the INR-monitored group. The rate of complications associated with using the PTR to guide therapy was 6.7% versus 2.9% with the INR system ($P = .02$). However, even though fewer thromboembolic events occurred in the INR group (0.2% versus 1.0%), no statistically significant difference existed with respect to these events. Although the authors noted limitations in the study, the data suggest that oral anticoagulation therapy monitored with the INR system compared with the uncorrected PTR is associated with fewer bleeding complications and a trend toward a lower rate of thromboembolic events.

INR Adoption: Medicolegal Support

Medical malpractice is based on the theory of liability called negligence. Negligence is founded on the principle that professionals are required to use the same degree of care that a reasonable professional in a similar situation would use. The elements of negligence based on medical malpractice are (1) the existence of the healthcare provider's duty to a patient usually based on the provider-patient relationship, (2) violation of the applicable standard of care, (3) a compensable injury, and (4) a causal connection between the violation of the standard of care and the injury.[15]

To establish a standard of care the courts are increasingly looking to a national standard of practice versus a local standard of practice. Therefore, professionals need to be aware of the nationally accepted standards of practice in their particular specialty area. The following case excerpts reflect the trend in the legal community of supporting a national standard of care over a local practice standard.

In *McCormack v Lindberg*, the court found error in the failure of the trial court to instruct the jury that the standard of care applicable to a specialist is a national one (not a local one) and that a specialist must be held to the same standard of care as other specialists in the field.[16] Likewise, in *DeHerrera v Memorial Hospital of Carbon County*, Justice Rooney wrote in a separate opinion that negligence cannot be excused on the ground that others in the same locality practiced the same kind of negligence.[17]

Position statements by various professional organizations and committees, clinical literature, medical textbooks, published results of clinical trials, professional practice guidelines, and pharmaceutical manufacturers' product information may be used as presumptive evidence of the standard of care. However, expert testimony will still be required to introduce the standard and establish its sources and relevancy.

There is an increasing amount of support for the INR system compared with the PT or uncorrected PTR to assess the intensity of oral anticoagulation therapy. Therefore, the INR can be construed as the accepted national standard of practice for monitoring warfarin therapy. Thus, failure to adopt the INR system may have some serious medicolegal consequences in an oral anticoagulation medical malpractice case.

The following section will illustrate cases that could be used to establish a legal basis in support of adopting the INR system as a means of reducing the risk of medical liability of healthcare institutions and individuals.

Pharmaceutical manufacturers consistently update and supply product information to healthcare providers. The manufacturer's product information may be used to establish the standard of care for the use of a particular drug. For example, a package insert may be used as evidence in support of a purported standard of care, as in the case of *Thompson v Carter*.[18] Although such evidence is not conclusive in and of itself, the weight of the evidence will be reviewed by the trier of fact. Information contained in the package insert and admitted as evidence as to the proper use or indication of a drug may be rebutted. Such rebuttal is ordinarily brought forward by physicians, who will advance a theory for a deviation from the manufacturer's recommendations.

The current package information for Coumadin (warfarin) DuPont Pharma, Wilmington, Delaware recommends that the INR system be used to assess the level of anticoagulation.[1] Thus, if the healthcare provider who is responsible for monitoring the patient's warfarin therapy fails to assess the therapy based on the INR system, it would be the burden of this provider to explain why he or she deviated from the manufacturer's recommendations.

The opinion of the court in *Thompson v Carter* can be further used to establish who can testify as an expert on the issue of a physician's standard of care. In this case, a pharmacologist-toxicologist was called as an expert to testify regarding a patient's allergic reaction. The court held that the expert was allowed to testify not only concerning the effect of a drug on the human body, but also to the physician's medical standard of care in prescribing the drug. This testimony was allowed over the objection that the expert could not testify since he did not hold a medical degree. Specifically, the court found that the expert does not have to hold a medical degree, but rather that he or she possesses medical knowledge, however obtained.[18]

Therefore, since many anticoagulation clinics throughout the United States are staffed by nonphysicians (nurses, nurse-practitioners, and pharmacists), these individuals could be called to testify as experts as to the standard of care in prescribing warfarin.

All providers of healthcare to a patient, including the hospital, may be potentially liable for improper monitoring of a patient receiving anticoagulation therapy. The case of *Thompson v Nason Hospital* is an example.[19] In this instance, a patient came to the hospital after an automobile accident and was treated at the emergency room. Anticoagulation prophylaxis therapy with heparin and warfarin was administered. The patient subsequently died because of improper monitoring of this particular therapy. The implication of this case is that the physician was clearly liable for the failure to monitor, but the plaintiff also was successful in establishing liability against the hospital. Therefore, since the INR system is considered to be more reliable than the PT or PTR, failure to use the INR system when assessing oral anticoagulation therapy could be deemed improper monitoring of the anticoagulation and the healthcare provider responsible for such monitoring could be deemed liable, as in this particular case.

Likewise, liability may be found if one applies the court's holding in this case to the reverse situation. For example, consider a physician who uses the INR system as his standard of practice, but treats his patients in a hospital that does not routinely report the INR. If an adverse patient outcome occurs with respect to the oral anticoagulation therapy because of the hospital's failure to report the INR, the physician could be found liable.

Finally, the burden and costs involved in adopting the INR system are minimal. Setting aside the debate as to whether the INR system should be deemed the standard of care over the traditional PTR, the potential clinical benefits of instituting the INR system clearly outweigh the burden of ignoring the system. Courts have found liability in the absence of a recognized standard of care. In the case of *Helling v Carey*, a glaucoma test was not normally administered in a routine eye examination to patients under the age of 40 years because the incidence of glaucoma at younger ages was so rare.[20] However, when a patient in her twenties developed glaucoma, the court found the ophthalmologists negligent as a matter of law, in the absence of a previously established standard of care. The reasoning for this finding was that the test was simple to perform, it was an inexpensive procedure, it was not harmful to the patient, and the benefit of early detection of glaucoma outweighed any associated burden of this glaucoma test. Such testing is now considered the standard of practice.

In light of such case law, the INR system can be argued to be of a similar nature. Manufacturers of thromboplastin routinely assign a sensitivity measurement, the ISI value, to their product. The INR system involves a mathematical calculation utilizing the traditional PTR and this sensitivity measurement.[5] Using the INR adds an additional mathematical calculation in the assessment of a patient's oral anticoagulation therapy. This calculation is automatically performed by many PT measuring instruments used to monitor anticoagulant. Thus, a minute burden, if any, is imposed on the healthcare institution or provider responsible for testing and monitoring patients receiving this therapy. On the other hand, the burden of not adopting this system is great.

Summary

In summary, warfarin is an agent that offers vast clinical utility in minimizing the morbidity and mortality associated with thromboembolic events. However, due to its narrow therapeutic range and low therapeutic index, it warrants close monitoring to lessen the risk of bleeding complications. With the introduction of thromboplastin reagents that have varying degrees of sensitivity, the assessment of the intensity of anticoagulation therapy has forced modification of the traditional PT system. The INR system improves the reliability of these PT assessments, thus improving patient outcomes. Legally, but more important clinically, literature supports the adoption of this system. Failure to utilize the INR in assessing anticoagulation therapy may be perilous to the patient as well as the healthcare provider.

··· REFERENCES ···

1. Du Pont Pharma. Coumadin (crystalline warfarin sodium) product information. Wilmington, DE; August 1996.
2. Saour JN, Sieck JO, Mamo LAR, et al. Trial of different intensities of anticoagulation in patients with prosthetic heart valves. *N Engl J Med* 1990;322:428–432.
3. Quick AJ, Stanley-Brown M, Bancroft FW. A study of the coagulation defect in hemophilia and in jaundice. *Am J Med Sci* 1935;190:501–511.
4. Pollock BE. Clinical experience with warfarin (Coumadin) sodium, a new anticoagulant. *JAMA* 1955;159:1094–1097.
5. WHO Expert Committee on Biological Standardization 33rd report. *World Health Organ Tech Rep Ser* 1983;687:33, 81–105.
6. Hirsh J, Dalen JE, Deykin D, Poller L, Bussey H. Oral anticoagulants: Mechanism of action, clinical effectiveness, and optimal therapeutic range. *Chest* 1995;108 (suppl): 231S–246S.

7. ICSH/ICTH. ICSH/ICTH recommendations for reporting prothrombin time in oral anticoagulant control. *J Clin Pathol* 1985;38:133–134.
8. American Society of Health-System Pharmacists. ASHP therapeutic position statement on the use of the international normalized ratio system to monitor oral anticoagulant therapy. *Am J Health Syst Pharm* 1995;52:529–531.
9. Ts'ao C, Neofotistos D. The use and limitations of the INR system. *Am J Hematol* 1994;47:21–26.
10. Hirsh J, Poller L. The international normalized ratio: A guide to understanding and correcting its problems. *Arch Intern Med* 1994;154:282–288.
11. Ng VL, Levin J, Corash L, Gottfried EL. Failure of the international normalized ratio to generate consistent results within a local medical community. *Am J Clin Pathol* 1993;99:689–694.
12. Hull R, Hirsh J, Jay R, et al. Different intensities of oral anticoagulation therapy in the treatment of proximal-vein thrombosis. *N Engl J Med* 1982;307:1676–1681.
13. Bussey HI, Force RW, Bianco TM, Leonard AD. Reliance on prothrombin time ratios causes significant errors in anticoagulation therapy. *Arch Intern Med* 1992;152:278–282.
14. Andrews TC, Peterson DW, Doeppenschmidt D, et al. Complications of warfarin therapy monitored by the international normalized ratio versus the prothrombin time ratio. *Clin Cardiol* 1995;18:80–82.
15. Black HC. *Black's Law Dictionary*. 6th ed. St. Paul, MN: West Publishing Co; 1990.
16. *McCormack v Lindberg*, 352 NW2d 30 (Minn App, Jun 12, 1984) (No. C5-83–1448).
17. *DeHerrera v Memorial Hospital of Carbon County*, 590 P2d 1342 (Wyo, Mar 5, 1979) (No. 4996).
18. *Thompson v Carter*, 518 So2d 609, 56 USLW 2278 (Miss, Oct 7, 1987) (No. 56, 874).
19. *Thompson v Nason Hospital*, 527 Pa 330, 591 A2d 703, 59 USLW 2734 (Pa, May 20, 1991) (No. 50 WD App 1988).
20. *Helling v Carey*, 83 Wash2d 514, 519 P2d 981, 67 ALR3d 175 (Wash, Mar 14, 1974) (No. 42775).