INADEQUATE MONITORING OF WARFARIN DOSAGE

To the Editor:

I would like to bring to attention the results of two recent surveys indicating that there is a serious problem with the control of oral anticoagulant therapy in many centers of the United States. The problem exists because most of the more than 200 laboratories surveyed appeared to be unaware of the variability in responsiveness to the coumarins of commercial thromboplastin reagents used to perform the prothrombin time assay (PT). The "responsiveness" of a given thromboplastin to coumarin-induced reduction in clotting factors mirrors its potential for factor X activation. A "responsive" thromboplastin results in a greater prolongation of the PT for a given reduction in clotting factors because it is more sensitive to reduction in the plasma concentrations of these factors. It has been known for over 30 years that thromboplastins vary markedly in their responsiveness depending on their method of preparation. This difference in responsiveness of thromboplastins to the anticoagulant effect of coumarins was responsible for an inadvertent increase in the therapeutic range in North America in the 1960s when hospitals changed from local preparations of responsive thromboplastins to commercial preparations of less responsive thromboplastin reagents without making a concomitant adjustment in the recommended therapeutic range. To solve the problem of variability in responsiveness of commercial thromboplastins, an international normalized ratio (INR) was established which is a calibration system based on a linear relationship between the logarithm of the PT ratios obtained with the reference and test thromboplastins. This calibration model was adopted by the World Health Organization (WHO) in 1982 and is used to standardize the reporting of the PT by converting the PT ratio observed with any local thromboplastin into an INR, which is calculated as follows: INR = observed PT ratio2, where the PT ratio is patient PT/control PT and "C" is the power value representing the international sensitivity index (ISI) for each thromboplastin. The ISI is a measure of the responsiveness of a given thromboplastin to reduction of the vitamin K-dependent coagulation factors; the lower the ISI, the more "responsive" is the reagent and the closer the derived INR to the observed PT ratio. The INR is, therefore, the PT ratio that would be obtained if the WHO reference thromboplastin itself (ISI = 1.0) had been used to perform the PT.

The results of the two recent surveys performed in the United States are disturbing for three reasons. The first reason is that most of the over 200 participating laboratories were unaware of the ISI of the thromboplastin used in their PT assay and, therefore, reported the PT results without any attempt at standardization. The second reason is that the information provided to Bussey et al from three prominent North American manufacturers indicates that the ISI values of their thromboplastins varies from 1.8 to 2.8, which is an even wider variation than was reported previously. The third reason is that the survey by Ansell of 88 laboratories in Massachusetts indicates that close to 70% of the laboratory supervisors had little or no understanding of the meaning of the terms ISI and INR and that only 5% reported the PT result as an INR.

In practical terms, this magnitude of variability in ISI values means that a targeted PT ratio of 2.0 (which is the upper limit of the therapeutic range used in many centers for patients with mechanical prosthetic heart valves) would be equivalent to an INR of 3.5 for a thromboplastin with an ISI of 1.8 and equivalent to an INR of 7.0 for a thromboplastin with an ISI of 2.8. The lack of standardized reporting by the majority of the laboratories surveyed is exposing patients to an unnecessary risk of bleeding because there is good evidence based on randomized trials that the intensity of the anticoagulant response is a powerful determinant of the risk of clinically important bleeding.

The problem is not trivial, but could be solved with a concerted effort. The first step is to educate laboratory supervisors that a problem exists. The next step would be to fine tune the system in North America by ensuring that each new batch of thromboplastin reagent is calibrated carefully by the manufacturer and that a reliable ISI is provided to the laboratory. Laboratories could then report their PT results as an INR. Because there have been anecdotal reports of inaccurate calibration by manufacturers, laboratories should have ready access to a reference preparation or to a central facility that could check the ISI of new batches when required. Ideally, the quality control of the manufacturers ISI values should be monitored by a national agency because faulty calibration could impair the safety and efficacy of anticoagulant therapy. If these steps were taken, the reliability of PT reporting would be improved greatly. There are, however, other problems that reduce the reliability of the INR system. Thus, the INR system loses precision when poorly responsive thromboplastins are used and when certain automatic clot detection systems are used.

The first problem can be overcome by purchasing one of a number of responsive commercial thromboplastins (ISI values between 1.1 and 1.8) now readily available. The second difficulty can be overcome by requesting that the manufacturer calibrate the thromboplastin for the automatic clot detection system and provide the laboratory with a suitably adjusted ISI value. These latter two technical problems are much less important causes of unreliable warfarin monitoring than the present practice of reporting non-standardized PT results.

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RESPONSE

We agree that the points raised in Dr Hirch's letter are
important and will request that future published manuscripts
dealing with the clinical use of oral anticoagulants include the
calculated INR values in describing the intensity of anticoagula-
tion.

THE EDITORS
Inadequate monitoring of warfarin dosage [letter] [see comments]

J Hirsh