

**FREQUENT PROTHROMBIN TIME TESTING REDUCES
INAPPROPRIATE WARFARIN DOSE CHANGES**

Tiffany Gunneman, R.Lynne Ruybalid, Alan K. Jacobson, Betsy Snell,
Jorge Mouro, Marcia L. Zucker, Frank M. LaDuca
Jerry L. Pettis Memorial VA Hospital, Loma Linda, CA,
International Technidyne Corp, Edison, NJ

Presented at
Anticoagulation Forum
May 13-15, 1999
Vancouver, British Columbia, Canada



8 Olsen Avenue • Edison, NJ 08820 USA
tel: 732.548.5700 • fax: 732.248.1928
www.itcmed.com

a subsidiary of Thoratec Corporation

FREQUENT PROTHROMBIN TIME TESTING REDUCES INAPPROPRIATE WARFARIN DOSE CHANGES

Tiffany Gunneman, R.Lynne Ruybalid, Alan K. Jacobson, Betsy Snell, Jorge Mouro, Marcia L. Zucker, Frank M. LaDuca
 Jerry L. Pettis Memorial VA Hospital, Loma Linda, CA, International Technidyne Corp, Edison, NJ.

ABSTRACT

Patient self-testing (PST) for prothrombin time (PT) offers the opportunity to rapidly assess the hemostatic status of patients taking oral anticoagulants. While target INR ranges are defined, patients often require diverse dose regimens to maintain an adequate degree of protection from thrombosis or hemorrhage.

Methods: Twenty-three patients were enrolled in a PST protocol over six months. Testing at a minimum frequency of once per week, patients accumulated 686 PST tests (range of 17-49 tests per patient). A patient management protocol was established in which dose adjustment was withheld in lieu of close monitoring.

Results: Using traditional 1.0 INR range limits, the average percent of tests within the therapeutic range was 57% (range 27 - 91%). Employing an expanded clinical range defined on an indication specific basis, (target range plus a safe limit, e.g. ± 0.5 INR units for DVT patients), the average number of tests within the expanded range rose to 91% (range: 76-100%). In 56% of out of range results, the INR stabilized within a safe range or returned to the therapeutic range within two weeks without dose adjustment. In total, few dose adjustments were made: 43% of patients had no dose adjustment, 43% had 1-2 dose adjustments and 14% had three or more adjustments.

Conclusions: In these studies, an increased PT test frequency allowed patients with INR values outside of the target range, time to demonstrate a stable INR prior to changing the dose without exposing the patient to risk. Furthermore, through close PT monitoring, unnecessary dose changes were avoided which could have led to increased variability in INR values, and the possibility of exposing the patient to dangerously low or high anticoagulation. Ultimately, all patients maintained adequate hemorrhagic and thrombotic reserve in the closely monitored PST setting.

OBJECTIVES

Determine if accessibility to high frequency PT monitoring through the use of patient self testing (PST) could minimize unnecessary dose adjustments.

METHODS

Patient Selection and Training. PST patient candidates were selected from patients enrolled in the Anticoagulation Clinic. Properly selected patients completed a training course in which anticoagulation principles, monitoring goals and lifestyle influences were reviewed. Patients were required to demonstrate proficiency with self-testing prior to acceptance in the PST program. A total of twenty-three patients were selected for this pilot project. The ProTime Microcoagulation Analyzer (ITC, Edison, NJ) was used for INR monitoring.

Anticoagulation Management. A patient management protocol was established in which dose adjustment was withheld in lieu of close monitoring when the patient's INR exceeded the desired therapeutic range. Expanded acceptable ranges were developed based upon the patient's clinical indication for oral anticoagulant therapy.

RESULTS

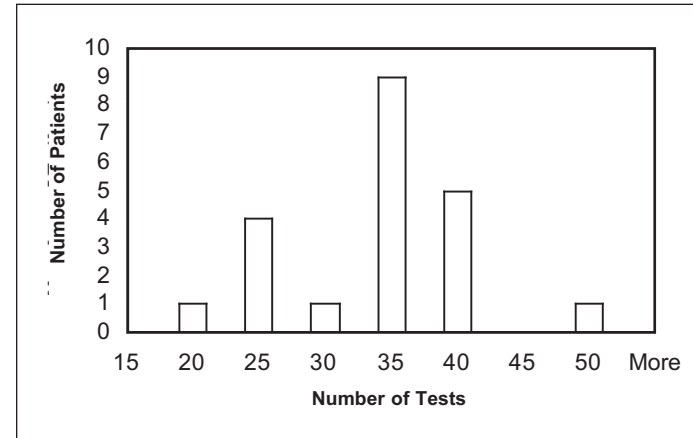
Patient Demographics

Gender	Age (years)		
Male	21	Mean	63
Female	2	Range	40-80

TARGET INR	Indication	# Patients
1.5 - 2.5	S/P MI	1
2.0 - 3.0	A-fib	3
	A-fib / AVR	1
	A-fib / DVT	2
	AVR	2
	CAD / CVA	1
	DVT	7
	S/P MI / CVA	1
	PE	1
2.5 - 3.0	AVR	1
2.5 - 3.5	AVR	1
	DVT / PE	1
3.0 - 4.0	MVR	1

Patient Self-testing

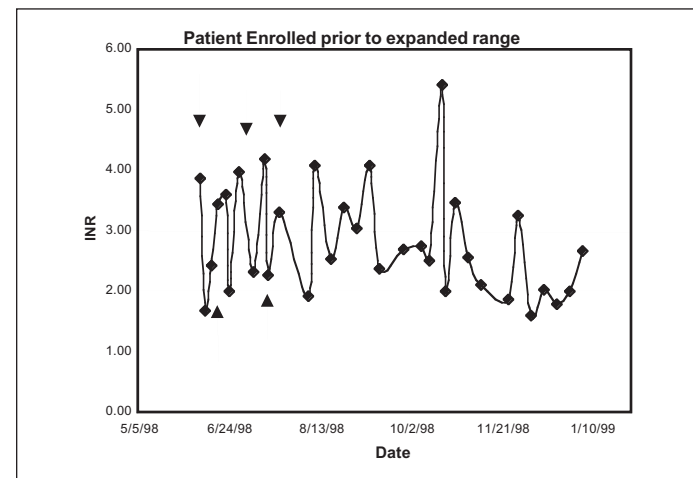
Patients were instructed to test their INR once each week and call the value into the Anticoagulation Clinic. Patients were enrolled on an ongoing basis over the course of six months. The number of tests conducted by each patient was dependent upon the date of enrollment, as well as temporary discontinuations of warfarin therapy due to surgical or dental procedures.



On average, patients tested their INR 33 times (range 17 - 49) in the six-month study period.

"Tight" Therapeutic Range Maintenance and Dose Adjustment

Under a "tight" therapeutic range maintenance protocol, frequent dose adjustments are required whenever patients exceed the desired range.



Frequent dose adjustments caused erratic PT results. Six weeks after enrollment (8/13/99), the management for the above patient was changed to use an expanded clinical range, whereby dose adjustments were only made when the patient exceeded the target range by defined limits.

Clinical Use of the Expanded Therapeutic Ranges and Dose Adjustment

Number of Patients	Number of Dose Adjustments	Range Used to Decide If Adjustment Needed
9	0	Expanded
4	1	Expanded
5	2	4- Expanded 1- Standard
2	3	Expanded
1	5	Standard

Target Ranges were expanded on a patient individualized basis. Expanded ranges represented a defined INR value below the minimum therapeutic range (e.g. 0.5 INR) and a defined INR above the maximum therapeutic range limit (e.g. 0.5-1.0 INR).

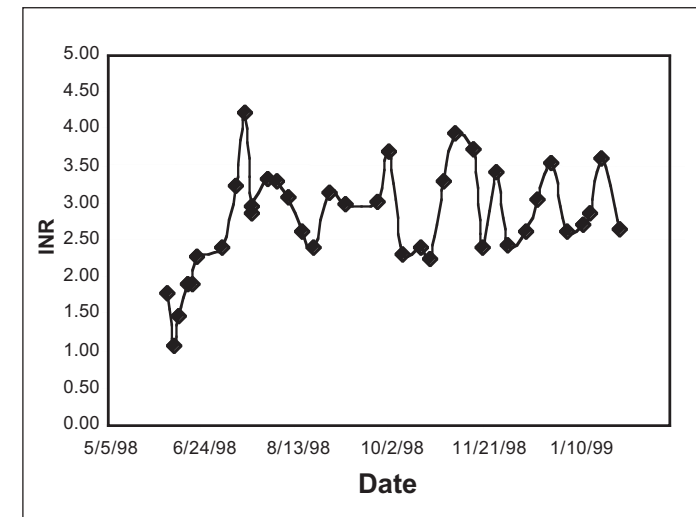
Frequency of INR Maintenance using Standard and Expanded Target Ranges

Total tests: 686	Values Below Therapeutic Range	Values within Therapeutic Range	Values Above Therapeutic Range
Standard	167	393	126
Range	24.3%	57.3%	18.4%
Expanded	37	626	24
Range	5.4%	91.3%	3.5%

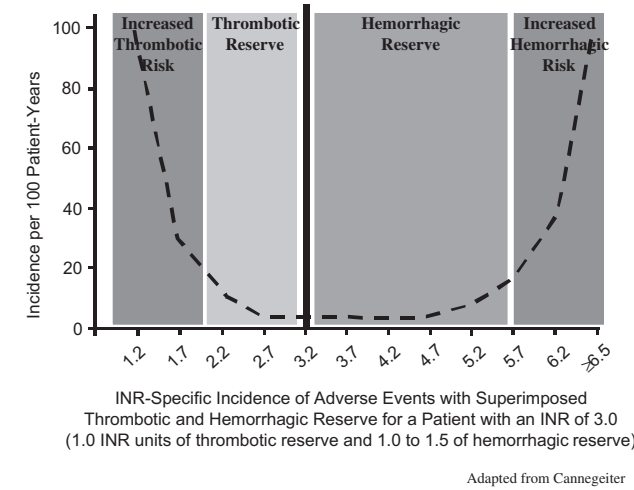
Patients maintained in the expanded range were seen to require very few dose adjustments, with 90% of the test results remaining within the appropriate INR range.

INR profile for a Patient Maintained within the Expanded Clinical Range

The patient's INR was allowed to fluctuate 0.5 INR below and 1.0 INR above the nominal therapeutic range. No dose adjustments were required during the six-month study period.

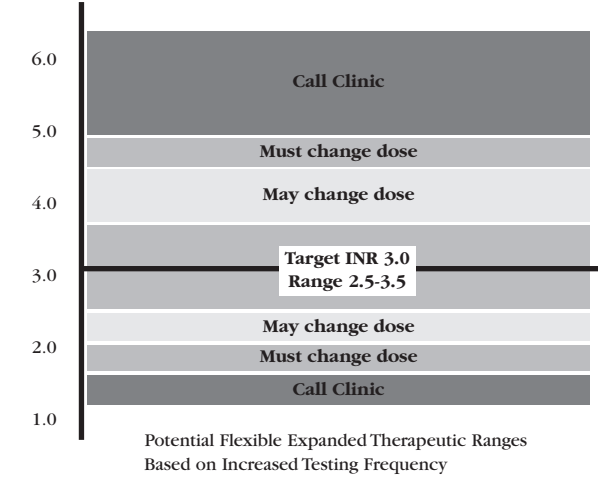


Clinical Application



Adverse events are least likely when the INR is maintained at a consistent level within the therapeutic range. Narrow ranges are appropriate within the limitations of laboratory testing using a four to six week monitoring interval. Within this test interval, a significant drift of INR may occur due to change in patient condition. In such a protocol sufficient thrombotic and hemorrhagic reserve must be maintained to assure patient safety between clinical visits.

Flexible Expanded Therapeutic Range



A change in dose should occur only in response to a change in steady state (i.e. addition of a new drug) or a deviation of the INR into a dangerous range. Weekly testing, practical with PST, affords timely detection of a change in steady state. A temporary increase in test frequency may be necessary to confirm a clinically significant shift which would warrant a dose adjustment. This approach allows for a transitional INR zone where dose adjustment is acceptable, though not mandatory, as well as a zone where adjustment is highly recommended.

RESULTS SUMMARY

- With increased test frequency, expanded therapeutic ranges may be employed safely.
- Patients maintained with frequent PT testing can be allowed to fluctuate outside "tight" target ranges yet within expanded therapeutic ranges without exposing the patient to hemorrhagic or thrombotic risk.
- Patients maintained with frequent testing require less hemorrhagic and thrombotic reserve.

CONCLUSION

- PST for PT (PST-PT) offers a practical method to increase the frequency of PT testing.
- This provides the opportunity to detect a shift in INR stability in a timely manner to determine if that shift will become clinically significant and necessitate a dosage adjustment.
- PST-PT has the potential to decrease the frequency of unnecessary dosage adjustments by minimizing the amount of time that the INR can drift prior to detection, effectively widening the allowable therapeutic range by decreasing the amount of thrombotic and hemorrhagic reserve required.