International Normalized Ratio

Dear Madam, The P.T. assay, first described in 1935 by Quick et al. soon became the monitoring of oral anticoagulant therapy. The P.T. measures the affect of reduction in the Vit. K dependent coagulant factors II, VII and X. Because the Prothrombin Time Ratio (P.T.R.) is markedly affected by the activity of thromboplastin, the W.H.O. in 1982 has adapted I.N.R. and is used to standardize the reporting of P.T with international reference standard, the I.S.I. (International Sensitivity Index). Indeed it is now recommended that I.S.I. values be instrument specific. The I.S.I. is used as a correction factor in calculation of I.N.R. by formula.

I.N.R.= (P.T.R.)I.S.I

The I.N.R. is the P.T. ratio that would be obtained if the W.H.O. reference thromboplastin which is by definition has an 1.S.l. of 1.0.

I.N.R,

It helps to determine the intensity of anti-coagulation therapy based on results of prothrombin time tests performed by laboratories using different normal ranges. In many coutries, laboratories report I.N.R. as if the prothrombin time (P.T.) had been determined with WHO. Reference thromboplastin (I.S.I). Many manufacturers now calibrate their thromboplastin reagent against W.H.O. reference standard and provide the user with an I.S.I. value enabling hospital laboratories to report result as I.N.R. in standardized manner instead of P.T.R. The difference in responsiveness of thromboplastin is a major potential cause of variability of "Prothrombin Time" test-results. Because of the variability in the commercial thromboplastin used to determine P.T. and consequent uncertainty about the actual intensity of anti-coagulation. may reduce the potential gain in life expectancy.

Table I. Relationship between Prothrombin time ratio and International Normalized Ratio for Thrombo-plastin with different International Sensitivity Index.

Observed P.T. ratio	Hospital A ISI= 1.2	Hospital B ISI=1.8	Hospital C ISI=2.6	
1.3	$INR=1.3^{1.2}$ $=1.4$	$INR=1.3^{1.8}$ $=1.6$	$INR=1.3^{2.6}$ $=2.0$	
1.5	$INR=1.5^{1.2}$ $=1.6$	$INR=1.5^{1.8}$ $=2.1$	$INR=1.5^{2.6}$ $=2.9$	Formula
2.0	$INR=2^{1.2}$ $=2.3$	$INR=2^{1.8}$ $=3.5$	$INR=2^{2.6}$ $=6.1$	$NR=(PTR)^{ISI}$

Observed PT ratio of 1.3, 1.5 and 2.0 reflect different anti- coagulation intensities as represented by the INR depending upon the sensitivity index (ISI).

Paller reported in 1987 that l.S.l. value for the commercial Rabbit Brain Thromboplastins widely used in North America vaiy between 2.0 and 2.6, while LS.I. of most throinboplastins used in USA vary between 1.8 and 2.8. It is better to use the more responsive reagents, those with low 1.S.I. (1.0 to 1.2) particularly when low intensity Warfarin is given.

Table II. The INR and combined risk of major bleeding thromboembolism.

INR	All bleeding	Major bleeding	Thrombo-embolism	Major bleeding +embolism
		Percentage of group		
1.0	2.8	0.6	18.1	18.7
1.5	5.3	1.1	11.9	13.0
2.0	10.0	2.0	8.1	10.1
2.3	14.6	2.9	6.4	9.3
2.4	16.6	3.3	6.0	9.3
2.5	18.8	3.8	5.6	9.4
2.6	21.4	4.3	5.2	9.5
2.7	24.3	4.9	4.9	9.8
2.8	27.5	5.5	4.6	10.1
2.9	31.3	6.3	4.3	10.6
3.0	35.5	7.1	4.1	11.2
3.5	66.8	13.4	3.1	16.5
4.0	125.9	25.2	2.5	27.7

The risk of bleeding is a function of change in the INR rather than in the ratio of prothrombin time for each unit increase in INR the relative risk of any type of bleeding was 3.5 Landefeld et al.

There were marked disparities in the sensitivity index (I.S.I.) of thromboplastin used by 53 laboratories involved in Stroke Prevention Atrial Fibrillation Study (S.P.A.F.). This means that although two laboratories report the same P.T.R. the intensity of anti-coagulation may differ substantially. Put another way, for the same specimen analyzed at two different laboratories, a markedly different P.TR. could be reported. if such variability is not recognised it can create uncertainty about the actual intensity of anti-coagulation achieved with any prescribed P.T.R. If this uncertainty leads to insufficient anti-coagulation patients are exposed to increased risk of thrombo-embolic events. Alternatively if the uncertainty leads to excessive anti- coagulation, patients are at high risk for haemorrhagic events.

I.N.R. and Heparin

Eckman and his co authors recommend that the 1.N.R. may be reported instead of P.T.R. However, both the 1.N.R. and P.T.R. are unsuitable if thromboplastin reagents are sensitive to heparin. After an acute M.I. or implantation of artificial prosthetic materials patients often receive anticoagulation therapy with heparin followed by oral anti-coagulants in an overlapping fashion. It is, therefore,

important that anti-coagulation be monitored with thromboplastin that is insensitive to heparin, since false values of prothrombin time ratio and I.N.R. may suggest sufficient anti-coagulation and heparin therapy stopped prematurely.

References

1. Bussey HI, Force RW, Bianco TM, et al, Reliance on prothrombin time ratios causes significant errors in anticoagulation therapy, Arch. Intern. Med, 1992; 152:278-82.
2. Poller L. Progress in standardization in anticoagulant control. Hematol. Rev. Commun., 1987; :225-41.
3. Hirsh 3, Poller L, Deykin D,. et al. Optimal therapeutic range for oral anticoagulants. Chest. 1 989;95 :(Suppl) 55-115 (Erratum, Chest, 1 989;96:962)
4. Helistem P. Anders CU, Oberfrank, et al. Heparin sensitivity of throniboplastins for the determination of the prothrombin time. Klin Lab., 1 992;38: 183-8

Syed Azhar Hussain Sherazi, Cardiologist DHQ Hospital, Dera ismail Khan, NWFP.