Factors affecting the precision of warfarin treatment

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Abstract

Aim: To determine what factors influence the precision of anticoagulant control using warfarin by examining the computerised records of 2207 patients.

Methods: Records from seven district general hospitals were combined and analysed. The precision of anticoagulant control was taken as the absolute deviation of International Normalised Ratio (INR) from target at the most recent determination. This quantity was examined using univariate and multiple regression analyses.

Results: Deviation of INR from target was continuously distributed, almost symmetrically about a mean of zero. The patients' age and sex had little bearing on control. Patients with a high target INR were more likely to be undertreated, and patients taking higher doses of warfarin were more likely to be overtreated. Previous over- or undertreatment were strongly related to poorer current control. The control of treatment varied substantially among the seven hospitals. One possible cause of this variation was the dose adjustment coefficient: the greater the dose adjustment for a given deviation from target INR, the better was the control achieved.

Conclusion: Several groups of patients were identified whose control was less satisfactory and in whom anticoagulant treatment needs particular scrutiny: these include patients with a record of previous over- or undertreatment, but not elderly patients in general. The variation in control among hospitals is a source of concern that merits further attention to achieve better uniformity of anticoagulant treatment.

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assisted by the use of computer systems with records of uniform structure.

Methods

The data were obtained from seven of the district general hospitals which use the AC software system³ to assist in the outpatient management of warfarin treatment, and refer to the most recent visit of patients who had already received some previous treatment.¹ All of the 2356 records contained a target INR, but in 149 (6%) no observed INR was available. Results are based on the remaining 2207 patients for whom the difference between target and observed INRs could be calculated, this difference being used as a measure of the extent to which the prothrombin time was under control. The diagnostic labels recorded by the hospitals were not identical, but permitted classification of most cases into one of seven groups. The duration of treatment before the present visit was also recorded, and the number of times that the patient had, on former occasions, been over- or under-treated. The criteria for over- or under-treatment are set by the system manager, and varied between 1.0 and 1.5 INR units over target for over-treatment, and 0.5 and 1.0 INR units under target for undertreatment.

Control of prothrombin time may also be affected by the options chosen in running the AC system, which were different in the various hospitals. These include the dose adjustment coefficient (DAC), the percentage deviation (or tolerance) from target allowed without dose change, and the maximum permissible interval between visits. No change in dose is recommended by the system if the observed INR is within the percentage tolerance limits; otherwise the new dose is calculated as:

$$\text{old dose} \times (1 + \text{DAC} \times \log_e \frac{\text{target INR}}{\text{observed INR}}).$$

This formula is not allowed to operate in cases of extreme over- or under-treatment, for which other provision is made.

Factors related to either under- or over-treatment (or both) were identified by studying their relation with the absolute difference between observed and target INR. Investigations for each factor separately (univariate analyses) were followed by a multiple regression analysis which considered all the factors simultaneously. Because a few very high observed INRs gave rise to large observed minus target INR differences, those observed INRs greater than 8.0 were set to 8.0 to reduce

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This paper describes a further study of the amalgamated computerised data relating to anticoagulant control which were used in a previous investigation,¹ and is concerned with adequacy of prothrombin control. By adequacy is meant how close the achieved INR is to that intended. The standardisation of thromboplastin preparations has improved uniformity of treatment in recent years,² but there is room for further improvement. Progress in audit of anticoagulant performance will require the study and demonstration of the accuracy of control. Such investigations will be

Figure 1 Distribution of observed minus target INR differences in 2207 patients from seven hospitals.

their influence on statistical analyses: this affected only 7 out of 2207 observations. Since the distribution of absolute differences between target and observed INRs was positively skewed we also performed an analysis using a square-root transformation and checked that our conclusions were not altered.

Results

INR ACHIEVED IN RELATION TO TARGET

Figure 1 shows the distribution of the differences between observed and target INRs. The distribution has a mean value (0.01) very close to zero, showing that observed INRs were, on average, on target. However, 36% of patients had observed INRs more than 0.5 from target, and 12% more than 1.0 from target. The continuous variation of INR differences shown in fig 1 implies that definition of over- or undertreatment is arbitrary. Hence, although the INR minus target differences are categorised for the purposes of presentation in the tables, all statistical analyses are based on the INR differences considered as a continuous variable.

AGE, SEX AND DOSE

The age and sex of the patients were not strongly related to the control of prothrombin times (table 1) but the low mean age in the

undertreated group nearly achieves significance. Considered by itself, the dose of warfarin given at the previous visit was not related to control (table 1): however, after adjusting for target INR in a multiple regression, higher doses (for a given target INR) were significantly related to overtreatment ($p = 0.002$).

TARGET INR: DURATION AND CONTROL OF PREVIOUS TREATMENT

Patients with a high target INR were more likely to be undertreated (table 1). This is depicted in more detail in table 2: the proportion of patients with observed INRs more than 0.5 below target increased as the target INR increased. Those patients who had been treated for more than one year were under similar anticoagulant control compared with patients who had been treated for a shorter time (table 1). However, patients treated for less than 15 weeks showed a higher degree of undertreatment (table 2); 15 weeks was chosen because many patients being treated for less serious conditions were limited to 12–14 weeks of treatment. Current undertreatment was strongly associated with previous episodes of both over- and undertreatment, whereas current overtreatment was associated only with previous overtreatment (tables 1 and 2).

There were differences among hospitals in the degree of anticoagulant control ($p < 0.0001$) (table 3). The mean absolute deviation of observed INR from target ranged from 0.44 in hospital 6 to 0.77 in hospital 3. The differences between the hospitals remained highly significant ($p < 0.0001$) even when the factors listed in table 1 were taken into account. The mean deviations adjusted for these factors were apparently related to the dose adjustment coefficients (DAC) used in the different hospitals (fig 2); higher DACs were being used in the hospitals achieving better control. There was no clear correlation between mean absolute INR deviations in the different hospitals with the percentage tolerance figures being used (which ranged from 16% to 23%); nor was there such a correlation with the maximum interval allowed between visits (range six to 12 weeks).

Table 3 also shows the degree of anticoagulant control achieved in different diagnostic groups. Although there were, apparently, some diagnoses in which control was less good, these differences were no longer significant ($p = 0.51$) after adjusting for hospital and for the factors in table 1; target INR in particular

Table 1 Correlations with extent of under- or overtreatment

Observed minus target INR	Undertreated		Satisfactory	Overtreated		P value*
	< -1	< -0.5 and ≥ -1	≤ 0.5 and ≥ -0.5	> 0.5 and ≤ 1	> 1	
Number of patients	123	281	1402	259	142	
Percentage of men	55%	50%	57%	50%	50%	0.09
Mean age (years)	60.1	62.0	64.7	63.0	63.5	0.07
Mean previous warfarin dose (mg)†	4.92	4.48	4.53	4.72	4.78	> 0.2
Mean target INR	3.15	2.94	2.84	2.85	2.86	< 0.0001
Percentage of patients with > 1 year of treatment	58%	55%	63%	63%	58%	0.11
Percentage of patients previously undertreated	62%	37%	27%	30%	35%	< 0.0001
Percentage of patients previously overtreated	52%	39%	30%	33%	53%	< 0.0001

*P value for univariate relationship with the absolute difference between target and observed INRs.
†Geometric means.

Table 2 Extent of under- or overtreatment according to target INR, duration of treatment and previous under- or overtreatment: percentage of patients with observed INR more than 0.5 from target

	Number of patients	Percentage of patients	
		Undertreated	Overtreated
Observed minus target INR		< -0.5	> +0.5
Target INR:			
< 2.8	761	12%	18%
2.8-3.0	1004	18%	20%
> 3.0	442	30%	15%
Duration of treatment (weeks):			
1-14	235	30%	19%
15-52	618	17%	18%
> 52	1354	17%	18%
Previous undertreatment:			
Yes	1522	26%	18%
No	685	15%	18%
Previous overtreatment:			
Yes	1446	23%	21%
No	761	16%	16%

Table 3 Extent of under- or overtreatment by hospital and diagnostic group: percentage of patients with observed INR more than 0.5 from target, and mean absolute deviation of observed INRs from target

	Numbers of patients	Percentage of patients		Mean absolute deviation†
		undertreated	overtreated	
Observed minus target INR		< -0.5	> +0.5	
Hospital:*				
6	114	12%	21%	0.44
1	658	13%	17%	0.45
5	334	15%	16%	0.48
7	403	22%	21%	0.56
4	304	19%	17%	0.57
0	159	23%	24%	0.65
3	235	31%	14%	0.77
Diagnostic group:*				
Coronary disease	78	13%	18%	0.43
Deep vein thrombosis	377	20%	17%	0.48
Heart disease ± AF**	505	15%	18%	0.50
Pulmonary embolism	297	13%	19%	0.55
Prosthetic heart valve	461	25%	17%	0.59
Arterial disease	247	23%	17%	0.61
Prophylaxis	20	10%	30%	0.61

*Hospitals (and diagnostic groups) in order of increasing mean absolute deviation of observed INR from target: 222 patients had missing or unclassified diagnostic information.

**AF = atrial fibrillation.

†P < 0.0001 for differences between hospitals; P = 0.001 for differences between diagnostic groups.

seemed to account for most of the inequality of control between diagnoses.

Discussion

The relation of age to adequacy of treatment is unexpected: in our series there was a slight

Figure 2 Mean absolute deviation of observed INR from target in seven hospitals according to dose adjustment coefficients. (The absolute deviations of INR are adjusted by multiple regression for the factors listed in table 1.)

tendency for younger patients to be undertreated. It has been suggested that anticoagulation is more difficult in the elderly, and possibly not worth the greater risk.⁴ Our data directly conflict with this view; there seems to have been more difficulty in controlling the younger patients. Increasing target INR increased the proportion of undertreated patients. It is reassuring that there was not a similar increase in overtreatment in patients set a higher target. Patients treated for less than 15 weeks were more likely to be undertreated. This is, perhaps, not surprising because of the difficulties sometimes encountered soon after treatment is started.

Table 1 shows that both under- and overtreated patients differed in their previous treatment experience. Undertreatment was associated with previous divergences in both directions, but overtreatment only in one, that of overtreatment. There therefore may be a difference between irregular response to treatment and a tendency to become overtreated.

Although we cannot entirely account for the differences between hospitals in control of treatment, there is one factor—the dose adjustment coefficient (DAC)—which does so in part. The DAC is under the control of the system manager and was set differently in our hospitals. There is some evidence that the DAC should not be less than 0.5. It may even be that selection of a higher figure than 0.58, the system default, would be beneficial. Although the choice of a DAC as such is relevant only for those using automatic computation of dose adjustment, the coefficient represents the judgement which any prescriber must form in adjusting dosage upwards or downwards in the light of an observed INR. Indeed, the DAC, part of the formula proposed by Wilson and James,³ originally resulted from a study by questionnaire of prescribing habits. The figure for the DAC obtained in that study was 0.66, and this figure was used at Hillingdon Hospital when the system was first used in 1983. It was subsequently lowered to 0.58 on no very secure basis. Another computer system⁷ proposes a different formula which gives a much lesser degree of correction of dose for a given deviation of INR from target: our data do not support the proposal.

We have no evidence that a longer interval between visits worsens anticoagulant control; also the tolerance limits of deviation from target without dose change did not seem to be important. The convenience of patients and avoidance of overburdened clinics require that the interval between visits be as long as possible, but no one will wish to jeopardise effective anticoagulation.

In this study we have taken advantage of the potential for clinical audit and for multicentre research that computerised anticoagulant records offer. However, we have made no use of the facility available under AC to keep records of all visits during the whole period of anticoagulation, and to file free text comments. This feature would, however, make possible a prospective study in which uniformly coded information about clinical events as well as

other factors such as concomitant drug treatment would be available. It would then be possible to assess efficacy in clinical and therapeutic rather than in solely laboratory terms.

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