Original articles

Effect of age upon the induction and maintenance of anticoagulation with warfarin

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Summary

We aimed to examine the effect of age upon the control of anticoagulation with warfarin in ordinary clinical practice, using a retrospective examination of routine anticoagulation clinic records from the University Hospital, Nottingham.

Considerable over-anticoagulation (international normalisation ratio (INR) >6.0) during induction occurred in 54 (11%) of 495 patients and was more likely in older patients ($p<0.05$). Lesser degrees of over-anticoagulation during induction (INR >4.0) were also more common in older patients, occurring in 58% of those aged 75 or above. Loading doses of warfarin were not reduced in older patients. INR in the maintenance phase rose with age ($p<0.001$) despite lower maintenance doses of warfarin ($p<0.001$). An INR >6.0 in the maintenance phase was noted in 24 (3%) of 739 patients and again was more likely in older patients ($p<0.05$). Patients using ambulance transport to the clinic were older than those who did not ($p<0.01$) and those aged over 75 had shorter intervals between clinic visits ($p<0.01$).

We conclude that doctors using warfarin therapy do not take sufficient account of the increased sensitivity of older people to warfarin. Hospital anticoagulant policies need implementation and evaluation.

Keywords: warfarin, anticoagulation, elderly

Introduction

Controversy remains among clinicians about the safety of anticoagulation with warfarin in old age,^{1–4} yet older people are increasingly likely to be considered for anticoagulation now it has been shown that it reduces stroke risk in patients with atrial fibrillation.⁵ The risks of bleeding whilst on warfarin rise with international normalisation ratio (INR)⁶ and since evidence suggests that older people are more sensitive to warfarin in the maintenance phase,^{7–10} and possibly during induction, they may be at greater risk unless due correction for this sensitivity is made. To find out what happens in ordinary clinical practice, we examined the records of patients attending a hospital anticoagulant clinic to investigate the

relationship between age and anticoagulant usage and control.

Methods

The anticoagulant clinic records were examined of patients attending an anticoagulant clinic at the University Hospital, Nottingham (UHN). Longitudinal and cross-sectional samples were drawn so that short- and long-term indications for anticoagulation would be represented. The cross-sectional sample examined the records of all patients taking warfarin attending four consecutive anticoagulant clinics over two weeks in September 1992. The longitudinal sample examined a random 20% of the anticoagulant records of patients who had been discharged from the clinic or who died while under supervision of the clinic between October 1987 and September 1992.

Details recorded were age, sex, indication for and duration of anticoagulation, most recent INR (or last INR before tailing off) and the preceding week's warfarin dose, interval between the last two clinic visits and use of ambulance transport. Where available, initial dosing schedules and INRs over the induction period (which we defined as the first two weeks) were recorded in patients who started warfarin at the UHN. Since there was no hospital policy for the induction of warfarin there was no uniformity in the use of INR estimations. INRs >4 or >6 during the first two weeks were used as indicators of poor control during induction.

Results

PATIENT CHARACTERISTICS

In the cross-sectional sample, 453 patients attended the four anticoagulant clinics of whom 11 were taking anticoagulants other than warfarin and the records of nine patients were inadequate, leaving 433 for analysis. In the longitudinal sample, 636 (20%) of 3180 records were examined. Records of 306 (48%) of these 636 were suitable for analysis, because data were not available in 268 (42%) who had either started warfarin elsewhere or had their warfarin control transferred elsewhere and the records in 62 (10%) were inadequate for analysis. Overall, 419/739 (57%) were aged over 65 and 178/739 (24%) were aged 75 years or more. The mean age of those using the ambulance was 71 years compared to 63 years in those who did not (t-test, $p<0.01$). Patients aged 75 or above were seen more frequently (median six weeks to

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the next appointment) than patients aged <75 (median eight weeks) (MannWhitney, $p<0.01$).

INDUCTION

Details of the induction stage were available in 189 (44%) of those in the cross-sectional sample and in all 306 of those in the longitudinal sample. There were no significant differences in the age at induction or the induction doses or schedules used in the two samples and so data on all 495 patients were analysed together. The mean age of the combined sample when warfarin was started was 64 years (standard deviation 14). Table 1 shows details of the warfarin induction stage and the effect of age, and table 2 shows the indications for warfarin in these patients.

Table 1 shows that the chance of the INR being above 4.0 or 6.0 during the first two weeks increased with age yet that there was no significant reduction in the loading dose of warfarin with age. Table 2 shows that the largest group being anticoagulated was younger patients with venous thromboembolism.

MAINTENANCE

The relationships between age and last recorded clinic INR, warfarin dose, indication for warfarin and duration of therapy for the combined sample are illustrated in table 3. Table 4 shows the indications for warfarin in this sample of patients in the maintenance phase, where there was a greater proportion of patients with longterm indications for anticoagulation such as valvular heart disease. The mean weekly dose of warfarin in patients aged 75 or above (23.9 mg) was 29% lower than that used in patients aged <65 (33.5 mg).

An INR > 6.0 in the maintenance phase was noted in 24 (3%) of 739 patients. There was a small significant positive correlation between age and clinic INR (Pearson, $r=0.13$, $p<0.001$), despite a stronger negative correlation between age and weekly dose (Pearson, $r=-0.32$, $p<0.001$). As might be expected from guidelines already given to clinicians,¹¹ another factor related to the clinic INR was the

indication for warfarin: an INR >4 was more common in those anticoagulated for valvular heart disease (18%) or ischaemic heart disease (19%) than in those with venous thromboembolism (9%) or atrial fibrillation (11%) (Chi square, $p<0.05$). To identify whether the predictive effect of age on the clinic INR was independent of warfarin dose, duration of anticoagulation or indication for anticoagulation a multiple logistic regression model was developed using these factors: the positive relationship between age and clinic INR remained significant ($p<0.05$).

Discussion

The majority of people being anticoagulated with warfarin and of those attending clinic in Nottingham were over the age of 65 and 24% were aged over 75. Although one report showed no difference with age in the initial response to warfarin,⁷ an earlier report showed older subjects to be more sensitive to warfarin during induction.⁹ The much larger study reported here supports the latter findings. In the patients being anticoagulated aged 75 or over, more than half (58%) had an INR >4.0 during the first two weeks and yet there was no reduction with age in the initial loading doses of warfarin. Although this unintended over-anticoagulation could also have been due to inadequate monitoring and dosing after the third day, clinicians, in particular the junior doctors initiating warfarin, need to be made aware that older people are particularly sensitive to warfarin during this phase.

From our results we would conclude that the introduction and evaluation of hospital guidelines is needed. A previous report suggests that junior doctors would welcome one.¹² One proposal could be a flexible anticoagulation schedule that takes the special needs of elderly patients into account. One schedule¹³ has been evaluated in older subjects,¹⁴ but it is not clear from the published results whether the particular sensitivity of elderly patients as demonstrated in our unselected series would be taken fully into account.

Table 1 Warfarin induction details and age (years)

	Age <65	Age 65–74	Age 75 or above	All
No patients	241	148	106	495
No with INR >4 during induction*	57 (24%)	59 (40%)	61 (58%)	177 (36%)
No with INR >6 during induction*	18 (8%)	18 (12%)	18 (17%)	54 (11%)
Mean warfarin dose over first 3 days (mg)**	24.1 (SD 3.7)	22.6 (SD 4.4)	23.0 (SD 8.0)	23.4 (SD 5.1)
Induction schedule:*				
9 mg day 1, 9 mg day 2, check INR & dose day 3	173 (72%)	78 (53%)	50 (47%)	301 (61%)
9 mg day 1, 6 mg day 2, check INR & dose day 3	30 (13%)	37 (25%)	27 (26%)	94 (19%)
15–30 mg day 1, none day 2, check INR & dose day 3	30 (13%)	21 (14%)	13 (12%)	64 (13%)
other	7 (3%)	12 (8%)	16 (15%)	35 (7%)

*Significant difference between age groups, Chi-square, $p<0.05$. **Significant difference between age groups, ANOVA, $p<0.01$.

Table 2 Indications for warfarin induction and age (years)

Indication	Age <65	Age 65–74	Age 75 and above	All
Venous thromboembolism	115 (48%)	43 (29%)	40 (38%)	198 (40%)
Atrial fibrillation	61 (25%)	52 (35%)	34 (32%)	147 (30%)
Valvular heart disease	12 (5%)	18 (12%)	4 (4%)	34 (7%)
Ischaemic heart disease	29 (12%)	17 (12%)	9 (9%)	55 (11%)
Other	24 (10%)	18 (12%)	19 (18%)	61 (12%)
Total	241	148	106	495

Table 3 Relationship between clinic INR, dose of warfarin in maintenance phase and age (years)

	Age <65	Age 65–74	Age 75 and above
Number	320	241	178
Mean clinic INR (SD)	2.98 (1.1)	3.20 (1.2)	3.29 (1.6)
Number (%) with INR >4.0	34 (11%)	32 (13%)	29 (16%)
Number (%) with INR >6.0*	5 (2%)	8 (3%)	11 (6%)
Mean weekly dose (SD) (mg)	33.5 (14)	28.4 (14)	23.9 (11)
Median duration (IQR)	9 (3–46)	20 (4–64)	8 (3–58)

* Significant difference between age groups, Chi-square, $p<0.05$; IQR = inter-quartile range.

Table 4 Indications for anticoagulation in the maintenance phase sample according to age (years)

Indication	Age <65	Age 65–74	Age 75 and above
Venous thromboembolism	121 (38%)	52 (22%)	49 (28%)
Atrial fibrillation	69 (22%)	89 (37%)	62 (35%)
Valvular heart disease	65 (20%)	55 (23%)	31 (17%)
Ischaemic heart disease	35 (11%)	26 (11%)	11 (6%)
Other	30 (9%)	19 (8%)	25 (14%)

Summary/learning points

- older people are more sensitive to warfarin, in both the induction and maintenance phase
- in ordinary clinical practice, due recognition of this is not made
- as a result older people are more likely to be over-anticoagulated
- appropriate anticoagulation policies might reduce this problem
- hospital control of anticoagulation in older people is more costly and inconvenient
- community-based anticoagulation control needs evaluation

Despite previous reports over two decades^{7,8,10} older people continue to be more likely to be over-anticoagulated during the maintenance phase. The proportion who were markedly over-anticoagulated (INR>6.0) was low (3%), although rather more (16%) had lesser degrees of over-anticoagulation (INR>4.0). It should be possible to develop more effective maintenance guidelines to take the sensitivity of older patients fully into account, thus allowing elderly people to be safely anticoagulated in an ordinary clinical setting without the need for a specialised geriatric clinic.¹⁵

Older patients are likely to be more expensive to keep anticoagulated than younger patients since they use more ambulance journeys and more clinic appointments. Because of this they are more likely to be inconvenienced by anticoagulation than younger patients. Methods of controlling anticoagulation at home, which might be cheaper and more convenient, require evaluation.

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