Effect of Ageing upon Warfarin Dose Requirements: A Longitudinal Study

H. A. WYNNE, F. KAMALI, C. EDWARDS, A. LONG, P. KELLY

Summary

This longitudinal study was designed to establish the rate of age-related change in warfarin dose requirements. Warfarin dosage was recorded retrospectively in 104 patients who had been stabilized on warfarin for a median period of 10 years (range 6–24 years) for prophylaxis of thromboembolic disease. There was a significant negative correlation between dosage and age at the start of therapy ($p = 0.002, r = -0.30$). Warfarin requirements fell over time, dosage difference being significantly correlated with age difference ($p = 0.01, r = 0.25$). Use of the regression equation derived from these data suggests a 21% fall in warfarin requirements in this population over a 15-year period. The relationship between change in warfarin dose requirements and ageing established in this longitudinal study is in good agreement with that established by cross-sectional studies, suggesting that no major birth cohort effect is influencing requirements in our warfarin-treated population.

Keywords: Warfarin, Ageing.

Introduction

Cross-sectional studies are consistent in reporting that warfarin requirements to achieve the same degree of anticoagulation are lower in elderly than in younger patients [1–3]. Although it has been inferred from these observations that warfarin requirements fall with ageing, such differences could result from birth cohort effects alone. Only the longitudinal method of study, in which serial measurements are made on the same subjects, can identify true age-related changes. The study described here was designed as a longitudinal study to test the hypothesis, suggested by the results of cross-sectional studies, that there is an age-related fall in warfarin requirements. We set out to investigate the rate of this change in a population of anticoagulated patients.

Methods

Patients who had been attending the anticoagulant clinics at the three Newcastle Hospitals, for a minimum period of 6 years, were invited to take part. The hospitals perform a full range of secondary care, as well as cardiothoracic surgery. One hundred and four community-dwelling patients (47 men) took part. They had been stabilized on warfarin for a median period of 10 years, range 6–24 years. Indications for warfarin were cardiac valve replacement (37), cardiac valve disease and atrial fibrillation (21), atrial fibrillation and cerebral embolism (16), recurrent deep-vein thrombosis or pulmonary embolism (28), and ischaemic cardiomyopathy (2). All patients were clinically stable and none was suffering from acute medical illness such as uncontrolled cardiac failure. Patients taking, or who had taken, drugs known to increase or inhibit warfarin sensitivity were excluded, as were those with abnormal blood tests of renal or hepatic function. Eighty-six patients were taking a range of drugs chronically, including loop diuretics (39), thiazide diuretics (15), amiloride or potassium (8), digoxin (61), beta-blockers (20), calcium channel antagonists (9), nitrates (5) angiotensin converting enzyme inhibitors (11), aspirin (13), thyroxine (4), allopurinol (5), iron (1), quinine (1), cinnarizine (1) and paracetamol (3).

All patients had retained, and provided for data collection, a complete record of their warfarin dosage over time, and degree of anticoagulation, measured before 1984 as the Thrombotest [4] and after 1984 as the International Normalised Ratio [5]. Each patient's age at the start of therapy was recorded, as was the average weekly dose during this and each subsequent year of therapy.

Statistical Methods

The data were evaluated by regression analysis using the MINITAB statistical package. Correlation coefficients ($r$) and the regression equations are reported, along with the $p$ value. Ninety-five per cent prediction intervals for individuals with specified values of an $x$ variable, which is an indication of the variability in the prediction of an individual's $y$ variable using the regression equation in question were calculated.

Results

Median age of the patients at start of therapy was 59 years (range 31–74 years). Median dosage at commencement of therapy was 31 mg/week (range 9–70 mg/week). There was a significant negative correlation between dosage and age at the start of therapy...
Figure 1. The relationship between dose at start of therapy in mg per week and age at start of therapy in years in the study group. The regression line is shown (—) along with the 95% confidence intervals (.....) and the 95% prediction intervals (———) for a given \( x \) value.

\( p = 0.002, \ r = -0.30 \) (Figure 1). The regression equation for this relationship was: dosage at start of therapy (mg/week) = 58.0 - 0.43 age at start of therapy. There was a significant fall in warfarin requirements over time, dosage difference being significantly correlated with age difference (\( p < 0.01, \ r = 0.25 \)) (Figure 2). The regression equation for the change in warfarin requirements over time was: dosage difference = -0.29 + 0.47 age difference. Use of this equation indicates a 21% fall in warfarin requirements in this population over a 15-year period. Estimations of actual fall in warfarin requirements over time, based upon this equation are shown in the Table.

Discussion

Most studies of the effects of ageing have been cross-sectional, examining individuals of all ages under investigation at a specific time. Their results can be confounded by cohort effects exerted, for example, by variations in environmental influences, such as changes in social conditions, education and diet over time. The aged represent a population of survivors and results from studies using this selected population of patients cannot necessarily be extrapolated to the original birth cohort. The apparent fall in aortic diameter in the very elderly is an example of this phenomenon [6]. Cross-sectional studies also frequently merge the separate effects of ageing, disease and medication. Some of these limitations can be minimized or overcome by a longitudinal study in which the same subjects are measured repeatedly. Thus, for example, although in the Baltimore Longitudinal Study, a progressive linear decline in creatinine clearance was noted by cross-sectional study, longitudinal evaluation allowed the establishment of the actual rate of renal ageing, in which an acceleration of the rate of decline with advancing age occurs [7].

The study sample represents a population of survivors, which allowed the identification of age-related effects, without the confounding influence of terminal illness. We included only patients who were clinically stable, without overt acute medical illness, with normal renal and hepatic function, and free of drugs known to affect warfarin pharmacokinetics, to minimize any possible confounding influence of disease or drug alterations. Our results therefore suggest that the fall in warfarin requirements is a true age-related phenomenon and not explainable as a secondary effect. As the relationship between weekly dose requirements and ageing changes established in this longitudinal study (dose start = 58.0 - 0.43 age start) is in good agreement with that established by a cross-sectional study of differences in warfarin requirements according to age in stable patients (dose = 56.6 - 0.50 age) [1], the data suggest that no major birth cohort effect is influencing requirements in our warfarin-treated population.

Meaningful results from long-term studies of warfarin requirements rely upon stability in the degree of anticoagulation achieved. The degree of anticoagulation aimed for in this population had not changed over the time of the study. Quality control of prothrombin-time measurements is rigorously applied in our laboratories to minimize assay variability, which together with the nearly constant International Sensitivity Index between batches of a given prothrombin-time reagent ensures compatibility of the results over time [4].

The results of this longitudinal study support our hypothesis that there is a genuine age-related fall in warfarin requirements but the \( r \) value of 0.25 indicates that the fall in dosage requirement is not fully explained by age alone. Although the mechanism of this observation has not been fully elucidated, it is possibly contributed to by an age-related fall in racemic warfarin clearance [8, 9], although this has been disputed [10]. The 21% fall in warfarin requirements over a 15-year period indicated in our study may be related to the fall
EFFECT OF AGEING ON WARFARIN DOSE REQUIREMENTS

Table. Estimated average weekly reduction in warfarin dosage requirements over a 5–15-year period, using the regression equation of the relationship between dose difference and age difference obtained using data from the 104 subjects studied

<table>
<thead>
<tr>
<th>Age increase (years) (x)</th>
<th>Reduction in mean weekly warfarin dosage (mg)</th>
<th>95% confidence intervals for population age increase (x)</th>
<th>95% prediction intervals for individual age increase (x)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>2.1</td>
<td>0.5–4.6</td>
<td>-12.1–16.3</td>
</tr>
<tr>
<td>6</td>
<td>2.5</td>
<td>0.3–4.8</td>
<td>-11.6–16.7</td>
</tr>
<tr>
<td>7</td>
<td>3.0</td>
<td>1.0–5.0</td>
<td>-11.1–17.1</td>
</tr>
<tr>
<td>8</td>
<td>3.5</td>
<td>1.7–5.2</td>
<td>-10.6–17.6</td>
</tr>
<tr>
<td>9</td>
<td>3.9</td>
<td>2.4–5.5</td>
<td>-10.1–18.0</td>
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<td>10</td>
<td>4.4</td>
<td>3.0–5.8</td>
<td>-9.6–18.5</td>
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<td>11</td>
<td>4.9</td>
<td>3.5–6.3</td>
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<tr>
<td>12</td>
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<tr>
<td>13</td>
<td>5.8</td>
<td>4.3–7.4</td>
<td>-8.2–19.9</td>
</tr>
<tr>
<td>14</td>
<td>6.3</td>
<td>4.6–8.0</td>
<td>-7.8–20.4</td>
</tr>
<tr>
<td>15</td>
<td>6.8</td>
<td>4.8–8.7</td>
<td>-7.3–20.9</td>
</tr>
</tbody>
</table>

in liver size observed with increasing age [1] whilst the contribution of other factors such as changes in enzymes or clotting factor activities cannot be ruled out.

Key Messages

- Only longitudinal studies in which serial measurements are made can identify true age-related changes, as differences observed in cross-sectional studies could result from birth cohort effects alone.
- This longitudinal study set out to determine whether there is an age-related fall in warfarin requirements, as suggested by cross-sectional studies, and to establish the rate of any change.
- Warfarin dosage requirements at start of therapy were significantly negatively correlated with age.
- Patients demonstrated a significant fall in warfarin requirements over time.
- The relationship between warfarin requirements and age established in this longitudinal study is similar to that established by cross-sectional studies and suggests that no major birth cohort effect is influencing requirements in our warfarin-treated population.

References

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