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NOTES

RELATIONSHIP OF AGE, WEIGHT AND BODY SURFACE AREA TO WARFARIN MAINTENANCE DOSE REQUIREMENTS

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INTRODUCTION

Multiple factors have been shown to influence the pharmacokinetics, pharmacodynamics and, hence, dosage requirements of the oral anticoagulant, warfarin (1–3). The relationship between patient age in the adult population and warfarin maintenance dose is controversial. Several studies (4–6) have found a significant inverse correlation between age and dose, and it has been reported (5) that the elderly, when compared to a population of relatively younger adults, are more sensitive to the pharmacologic effects of the drug at any given dose. Subsequently, two other research groups (7, 8), however, failed to confirm a significant age-dose relationship.

A recent study by Dobrzanski *et al.* (9) found both an inverse correlation between age and warfarin maintenance dose ($r = -0{\cdot}39$; $P < 0{\cdot}01$) and a positive correlation between patient total body weight and warfarin dosage requirements ($r = 0{\cdot}39$; $P < 0{\cdot}01$). Although the authors acknowledged that additional variables affect warfarin dose, they suggested that patient age and weight may be a useful guide in choosing initial warfarin maintenance doses. It is presently uncommon in clinical practice for warfarin dose to be calculated on the basis of weight (i.e. mg/kg), and the only other study in the literature which reported the relationship between weight and dose (6) failed to find a significant correlation between those parameters.

If a relationship between patient weight and warfarin dose exists, the correlation may be greater if lean body weight (i.e., the lesser of either total body weight minus excess weight due to obesity or, in the case of a lean individual, actual body weight) were utilized instead of total body weight. Such a finding would be expected since warfarin has a low volume of distribution consistent with its high affinity for serum proteins. It partitions poorly into adipose tissue and, therefore, the apparent volume of distribution should not increase linearly with total body weight in the case of an obese patient (1). For the same reasons, a relatively strong correlation between lean body weight-derived body surface area (BSA) and dosage requirements should be found.

The objectives of our study were, therefore, to attempt to verify the findings of Dobrzanski and coworkers, and to determine if measures of lean body weight and BSA will enhance the predictive value of the potential correlation between body weight and warfarin maintenance dose.

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METHODOLOGY

Prescription records were used to identify all patients being monitored for maintenance warfarin therapy at a Veterans Administration Medical Center. The majority of patients identified were followed by a pharmacist-managed anticoagulation surveillance clinic. Patients who had been on therapy for less than 3 months were excluded to allow for stabilization of dosing requirements. Because of the nature of the hospital, all 95 study patients were males. The goal of therapy was to maintain patients at a prothrombin time (PT) of between 1·5 and 2·5 times control, and preferably between 1·5 and 2·0 times control, since more aggressive oral anticoagulant therapy has been shown to increase the risk of bleeding complications but has not been proven to enhance therapeutic effect (10, 11). Prothrombin times were performed using a photo-optical sensor with fibrin clot formation as the endpoint. The reagent used was rabbit brain thromboplastin from Ortho Diagnostics, New Jersey, U.S.A.

Because some variability of dose requirements over time is likely even in a 'well-controlled patient', a mean warfarin dose and mean PT value were calculated for each patient by averaging the values recorded at each visit or for the most recent 2-year period, in the case of long-term therapy. An average of 12·9 warfarin determinations per patient was obtained. Unlike Dobrzanski *et al.*, who evaluated only those patients whose prothrombin times fell within a PT ratio range of between two or three as estimated using Manchester reagent, our results were determined for all patients as well as for the subsample of patients whose mean PT was within our therapeutic range. Pearson product-moment correlation coefficients were determined for mean warfarin maintenance dose and for the following parameters: age, actual body weight, lean body weight, actual BSA and lean body weight-derived BSA. The correlation analyses were conducted for both the entire sample and for the 'therapeutic' subsample.

The following formulae were used for lean body weight and body surface area calculations, respectively:

$$\text{LBW (kg)} = 51{\cdot}7\ \text{kg} + 1{\cdot}85\ \text{kg/inch over 5 feet (or actual body weight, whichever was less)} \tag{12}$$

$$\text{BSA (m}^2\text{)} = \text{weight (kg)}^{0{\cdot}425} \times \text{height (cm)}^{0{\cdot}725} \times 71{\cdot}84 \tag{13}.$$

RESULTS AND DISCUSSION

Mean values of patient characteristics for our overall sample ($n = 95$) and the subsample of patients within the therapeutic range of PT ($n = 82$) (the 'therapeutic subsample') are presented in Table 1. For the overall sample, a significant inverse correlation was found between mean maintenance dose and age ($r = -0{\cdot}32$, $P = 0{\cdot}001$), but not between mean maintenance dose and total body weight ($r = 0{\cdot}10$). No significant correlation was found between dose and either lean body weight, actual BSA, or lean weight-derived BSA ($r = 0{\cdot}17$, $0{\cdot}08$ and $0{\cdot}07$, respectively). Similar correlation coefficients were found for the relationships between dose and age, actual body weight, lean body weight, actual BSA and lean weight-derived BSA for the therapeutic subsample ($r = -0{\cdot}35$ [$P = 0{\cdot}001$], $0{\cdot}12$, $0{\cdot}20$, $0{\cdot}10$ and $0{\cdot}09$, respectively). As expected from these correlations, multiple regressions of age and any of the various body weight and body surface area factors on warfarin dose did not add significantly to the predictive value of age alone.

Table 1. Patient characteristics*

Parameter	Overall sample†	Therapeutic subsample‡
Age (years)	56·2 ± 10·3	55·9 ± 10·2
Actual body weight (kg)	83·3 ± 19·1	83·5 ± 19·8
Lean body weight (kg)§	68·8 ± 6·3	69·1 ± 6·6
Body surface area (BSA) (m^2)	2·0 ± 0·2	2·0 ± 0·2
Lean body weight-derived BSA (m^2)	1·8 ± 1·1	1·8 ± 1·1
Warfarin dose (mg)	6·9 ± 3·0	6·9 ± 3·0
Mean prothrombin ratio	1·73 ± 0·15	1·72 ± 0·24

*Values are means ± SD.

†All patients identified who met study inclusion criteria, regardless of mean PT ratio ($n = 95$).

‡Subsample of overall sample whose mean PT ratio was within the therapeutic range of 1·5–2·5 times control ($n = 82$).

§Lean body weight for each patient was determined as the lesser of either the patient's ideal body weight or actual body weight.

These findings confirm the previously reported (4, 5, 9) correlation between age and warfarin dose. We were unable, however, to corroborate the existence of the weight-warfarin dose relationship reported by Dobrzanski *et al.* even with the use of an enhanced method to estimate warfarin maintenance dose and more pharmacokinetically sound means of expressing body weight (i.e., lean body weight and lean weight-derived body surface area). Reasons for the differences in findings between the two studies are not clear. It is unlikely that the weight-dose relationship reported by Dobrzanski and his colleagues was a byproduct of an age-dose correlation, since they did not find a significant correlation between the age and weight of their patients.

Another difference that was noted between the two studies was that the mean warfarin dose for both our overall patient sample and the subsample of patients with a therapeutic PT ratio was substantially higher than that reported by Dobrzanski (6·89 mg versus 4·24 mg, respectively). This difference may, in part, be due to inter-study variations in the thromboplastin reagent utilized and in the defined therapeutic PT ratio ranges (14, 15). It is difficult to compare PT ratios quantitatively between different institutions and studies (15). However, a therapeutic range of 1·5–2·0 times control (rather than 1·5–2·5 times control) using our rabbit brain thromboplastin reagent would more closely approximate the therapeutic range utilized in the Dobrzanski study (2·0–3·0 times control using Manchester reagent) (15). Of the 82 patients in our therapeutic subpopulation (i.e., those that have a mean PT ratio of 1·5–2·5 times control using rabbit thromboplastin), 76 had PT ratios of less than 2·0 (mean of 1·71 ± 0·12). Yet, the mean warfarin dose required to attain that more conservative degree of anticoagulant control for this subgroup was still 6·9 ± 3·0 mg. It is, therefore, unlikely that the 63% interstudy difference in mean doses is predominantly related to variation in thromboplastin reagent and/or defined therapeutic range. Additional factors are likely to contribute to this dissimilarity.

Although the mean age of the population of Dobrzanski and coworkers was slightly greater than the current study (59·2 years ± 10·9 and 56·2 years ± 10·3), this slight difference is unlikely to account for the relatively large dissimilarity in dose. One difference between the two study populations was that our study was conducted using only males while the other population was presumably comprised of both men and women, although no breakdown of study subjects by gender appears within the Dobrzanski data. It has been reported that women tend to be more prone to warfarin-related bleeding complications and that their dosage requirements tend to be lower than those of the male population (2, 16). These reports, however, fail to cite the source of this information and O'Malley *et al.* (4) found that gender did not affect anticoagulant control. If women are, indeed, more sensitive to the pharmacologic effects of the drug, the apparent difference between the studies in mean warfarin dose required to attain a therapeutic PT ratio might be related to differences in gender composition between the studies. Other potential dissimilarities in the study populations, such as differences in the incidence of liver dysfunction, uraemia, and smoking also have the ability to influence certain study results.

Consideration of patient age, but not patient weight, appears valid when choosing an initial warfarin maintenance dose. However, many additional factors, including hepatic function, diet, and even gender also appear to contribute to variations in warfarin requirements. There is a significant potential for harm when administering the wrong dose of warfarin, and relative difficulty is often experienced in identifying the most appropriate initial maintenance dose. Further research to identify determinants of warfarin dose and to develop dosing guidelines based upon multiple regression should be encouraged.

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