

EFFECT OF AGE ON WARFARIN DOSE REQUIREMENT IN PAKISTANI POPULATION

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Contribution

All the authors contributed significantly to the research that resulted in the submitted manuscript.

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ABSTRACT

Objective: The study was conducted to determine the effect of age on warfarin dose requirement in Pakistani population.

Methodology: This cross-sectional study was carried out at Armed Forces Institute of Cardiology (AFIC) Rawalpindi, Military Hospital Rawalpindi and National Institute of Cardiovascular Diseases (NICVD), Karachi from October 2010 to March 2012. Stable patients receiving warfarin were recruited after detailed medical history, physical examination and laboratory tests. The demographic and clinical data of individuals was recorded in a pre-structured proforma. Data was analyzed using SPSS version 20.0. Pearson correlation coefficient was calculated to study the relationship of dose with age. A p-value of less than 0.05 was taken as statistically significant.

Results: A total of six hundred and seven (607) stable patients fulfilling the eligibility criteria, participated in the study. The mean age of patients was 37.93 ± 12.23 years (range 18-65 years). Mean daily dose of warfarin calculated in 607 patients was 5.62 ± 1.98 mg with the range of 0.36-15 mg whereas mean weekly dose was 39.36 ± 13.8 mg with the range of 2.5-105 mg. There was negative correlation between age and warfarin (correlation coefficient $r = -0.091$) which was statistically significant as p-value was less than 0.05 ($p = 0.026$).

Conclusion: It is concluded that with increasing age, lesser dose of warfarin is required in Pakistani population to produce the same therapeutic anticoagulant response.

Key Words: Warfarin, Age, Dose Requirement, INR

INTRODUCTION

Thromboembolic disorders are among the major health problems. These disorders lead to not only higher rates of morbidity and mortality but also there is substantial financial burden on health care systems associated with these disorders. By administering effective prophylaxis and treatment in such conditions, the incidence or recurrence of thromboembolic events can be reduced to great extent.¹

Warfarin has been the most commonly prescribed anticoagulant. In some parts of the world data collection of patients on anticoagulation therapy has been done. Around one million individuals in United Kingdom and more than two millions in United States of America (USA) are taking warfarin. Each year more than 30,000 new patients are placed on warfarin therapy in USA.^{2,3} It has been used for prophylaxis and treatment of various thromboembolic disorders like valvular heart diseases, prosthetic heart valves, atrial fibrillation, myocardial infarction, pulmonary embolism, deep vein thrombosis and recurrent strokes.

The occurrence of significant intra-and inter-individual variability, variable pharmacokinetics and low therapeutic index leads to difficulty in warfarin therapy management.^{4,5}

Warfarin dose requirement varies considerably among individuals and also in the same person at different time spans. Many food and drug interactions as well as other environmental factors are important for intra-individual variations. Demographic factors like age, gender, weight, height and genetic factors have been reported to affect the warfarin dose requirements. Inadequate or supra-therapeutic anticoagulation may result in substantial morbidity and mortality due to failure to prevent thromboembolism or bleeding complications respectively. The fear of the complications often causes clinicians to avoid prescribing warfarin to patients who are likely to benefit from such therapy.⁵⁻⁷

Age has been considered most important demographic factor affecting warfarin therapy. The elderly population has been found to be at the highest risk of developing thromboembolism and at the same time more susceptible to bleeding complications. The presence of co-morbid diseases, concurrent medications, reduced body mass and functions especially hepatic and renal, make them vulnerable to altered pharmacokinetics and pharmacodynamics of different drugs. There is often tendency to under-treat this group of patients with warfarin and it has been noted that with advancing age the warfarin dose requirement is reduced.⁸⁻¹⁰

The present study was carried out in Pakistani population to demonstrate the effect of age on warfarin dose requirement.

METHODOLOGY

It was a cross-sectional study. The clinical data collection and laboratory investigations were done at Armed Forces Institute of Cardiology (AFIC) Rawalpindi, Military Hospital Rawalpindi and National Institute of Cardiovascular Diseases (NICVD), Karachi. The study was carried out from October 2010 to March 2012. The study was conducted in accordance with the current Good Clinical Practices and the Declaration of Helsinki.^{11,12} The study protocol was approved by ethical committees of Centre for Research in Experimental and Applied Medicine, Army Medical College and National Institute of Cardiovascular Diseases.

Study subjects were adults of either sex between the age of 18 to 65 years who were receiving warfarin as anticoagulation therapy. Stable patients taking warfarin were recruited in the study after informed consent. A stable patient was defined as the one whose warfarin dose had been constant for at least three previous clinic visits over a minimum period of three months, and had an international normalized ratio (INR) of the prothrombin time (PT) within the range of 1.5-3.5.¹³⁻¹⁶ The patients suffering from hepatic and renal disease, any co-morbid disease or taking any concurrent medication or diet which would have affected warfarin therapy, were excluded.

All participants were Pakistani citizens belonging to different regions of Pakistan to provide representation from all areas. Each subject was evaluated by detailed medical history, physical examination and laboratory tests. The demographic and clinical data of individuals was entered in a pre-structured proforma. Demographic data included age, gender and ethnicity whereas clinical data included warfarin dose, present and previous INR values. Data had been analyzed using SPSS version 20.0 (IBM Corporation, USA). Descriptive statistics was used to describe the data. Mean and standard deviation (SD) were calculated for quantitative variables like age, warfarin dose, present and previous INR values. Frequency and percentages were calculated for qualitative variables like gender. Pearson correlation coefficient was calculated to study the relationship of dose with age. A p-value of less than 0.05 was taken as statistically significant.

RESULTS

A total of six hundred and seven (607) stable patients fulfilling the eligibility criteria, participated in the study. The baseline characteristics of the patients in study group are summarized in Table 1. There was negative correlation between age and warfarin dose as depicted in Figure 1. The effect demonstrated was small (correlation coefficient $r = -0.091$) but statistically significant as p-value was less than 0.05 ($p = 0.026$).

Table 1: Baseline Characteristics of Study Population (N = 607)

Characteristics	Values
Age in years	
Mean \pm SD	37.93 \pm 12.23
Range	18-65
Gender	
Male	297 (48.9%)
Female	310 (51.1%)
INR	
Mean \pm SD	2.3 \pm 0.8
Range	1.5-3.5
Warfarin daily dose in mg	
Mean \pm SD	5.62 \pm 1.98
Range	0.36-15
Warfarin weekly dose in mg	
Mean \pm SD	39.36 \pm 13.8
Range	2.5-105

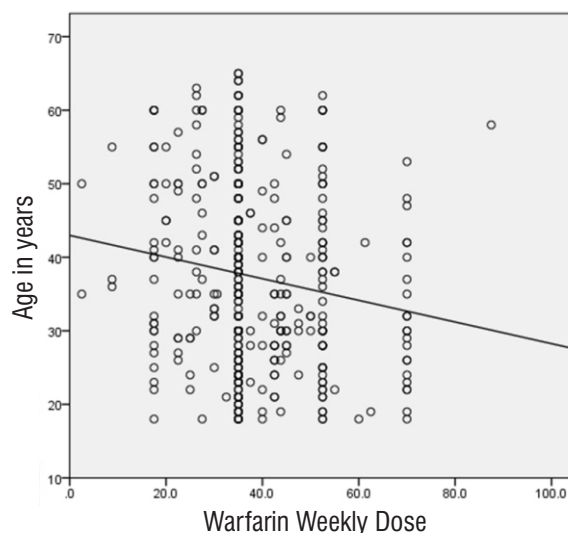
DISCUSSION

It is important to carry out the studies in local population in indigenous environment, especially for drugs affected by environmental, demographic and genetic factors. Warfarin is one of those drugs. In our study population age was found to be a significant factor affecting warfarin dose requirement. A significant negative correlation between age and warfarin dose indicated that with an increase in age, lesser dose of the drug was required. Variations in warfarin sensitivity in elderly patients have been attributed to many factors like reduced hepatic and renal functions, co-morbid diseases and concurrent use of other drugs.^{5,7,8} Different studies have given some postulates regarding less dose requirement in elderly. Some studies identified the pharmacokinetic variables responsible for such effect like age related changes in warfarin clearance whereas others have favored increased warfarin sensitivity to advancing age being due to pharmacodynamic factors. A study done on population pharmacokinetics of warfarin by Mungall et al, demonstrated that oral clearance of warfarin decreases by 1 percent with each year over the age range of 20-70 years.¹⁷ A recent study also reported the decrease in metabolic drug clearance with advancing age responsible for lesser warfarin dose requirement in elderly patients. The study predicted 20-40 percent lower drug clearance in elderly as compared to younger adults.¹⁸ A study comparing the pharmacokinetic profile of warfarin in young (27-37 years)

and older (62-89 years) patients showed that although warfarin clearance was lower in older group but it was not statistically significant.¹⁹ Another study not only reported the significant negative correlation of old age with warfarin dose attributable to slower clearance of S-warfarin but also gave a concept related to pharmacodynamics involving VKOR enzyme. Their findings suggested that decrease in functional hepatic mass contributes to increase in warfarin sensitivity which in turn may be due to reduction in content or activity of vitamin K epoxide reductase enzyme.²⁰ Other studies have supported the concept of increased intrinsic sensitivity of warfarin with advancing age either due to declining body functions or decreased ability to metabolize warfarin.^{21,22}

Most of the studies taking into account the effect of age on warfarin therapy have reported similar results as this study. They have demonstrated an inverse relationship pointing out that increasing age requires lesser dose to produce therapeutic anticoagulant response. Majority of studies conducted in Caucasians have reported decrease in warfarin dose requirement with increasing age.^{21,23,24} A recent study in USA has reported a significant negative correlation of age with warfarin dose not only during initiation phase of therapy ($r=-0.298$, $p < 0.001$) but also during long-term therapy ($r=-0.398$, $p < 0.001$).²⁵ A number of studies conducted in other populations like Thai, Korean, Brazilian, Malaysian, Indonesian, Israeli and Turkish have demonstrated the same results as our study.²⁶⁻³² Studies conducted in Egyptian population gave different results. Two studies reported the same effect of age on warfarin dose as shown by our study whereas another study demonstrated a small variation (1.5%) in dose requirement with age but it was not statistically significant.³³⁻³⁵ Same is

Figure 1: Relationship Between Age and Warfarin Dose in Patients Undergoing Warfarin Therapy



the case in Japanese. Some studies demonstrated significant effect of age on warfarin dose requirement, but one study reported no significant effect.^{16,36,37} Not much of the studies have been carried out in the neighboring countries except in China. Studies conducted in Chinese population have reported the results similar to ours but one recent study did not show any significant correlation of age with warfarin dose requirement.³⁸⁻⁴⁰ One study in the neighborhood is from Iran and another from India which have demonstrated the similar significant effect of age on warfarin dose.^{41,42} Our study is the first one reporting effect of age on warfarin dose requirement in Pakistani population.

CONCLUSION

It is concluded that with increasing age, lesser dose of warfarin is required in Pakistani population to produce the same therapeutic anticoagulant response.

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