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EFFECT OF AGE AND SEX ON ACENOCOUMAROL BLOOD LEVELS IN MECHANICAL HEART VALVE PATIENTS

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ABSTRACT

Acenocoumarol is a commonly used vitamin K antagonist. Its effect is is monitored by INR. But in many situations effectiveness and adverse effects do not correlate with INR. In this study we aimed to find out the effect of age and sex on the trough and peak levels of 2 mg of Acenocoumarol. After ethics approvals and Patients who were satisfying the inclusion and exclusion criteria, were recruited after written informed consent either in English or Tamil. Age, and sex of the participants were noted. 2 ml of blood samples were collected for measuring trough and Cmax levels. By using High performance liquid chromatography Concentration of Acenocoumarol was measured. student t test was used to find out the relation between Sex and Plasma concentration of trough and Cmax of Acenocoumarol, One way analysis of variance (ANOVA) was used to compare trough and Cmax plasma concentration of Acenocoumarol of patients with Age groups, Pearson correlation was done to find out the correlation between age and trough and Cmax concentrations of Acenocoumarol. Totally 56 patients were recruited, In that 50% were males and 50% were females, At 5 % level of significance there were no difference between males and female with trough levels of Acenocoumarol, At 5 % level of significance there were no difference between males and female with Cmax levles of Acenocoumarol. Patients were divided into three categories based on age 19-45 years, 46-52 years, 53 to 88 years. At 5 % level of significance there were no difference between different age groups and trough values. At 5 % level of significance there were no difference between different age groups and Cmax values. There were no correlation between different age groups and trough values. There were no correlation between different age groups and Cmax values. Our study indicated that there is no significant difference in the trough and Cmax concentration of Acenocoumarol between Sex and different age groups. However it has to be confirmed with larger samples.

Key words: Significance, Acenocoumarol, Concentration.

INTRODUCTION

Acenocoumarol is the most commonly used drug after valve replacement surgery for the prevention of thromboembolic disorders [1]. Acenocoumarol is given by once daily dosing. Effect of Acenocoumarol is monitored by International normalized ratio (INR). INR is maintained in the range of 2-3.5 [2]. Adequate dosing of Acenocoumarol is difficult to achieve, due to widespread inter-individual variability and low safety margin. Various factors contribute to the response to vitamin K antagonists including age, gender, weight, height, drug interactions and variations in the VKORC1 and CYP2C9 genes [3]. Age and sex are important parameters which can affect the dosing of acenocoumarol [4]. So in the current study we planned to find out the effect of age and sex on blood levels of Acenocoumarol in patients taking 2mg of Acenocoumarol after valve replacement surgery

Aim and Objectives

To find out the effect of age and sex on the trough and peak levels of Acenocoumarol.

Ethics

Institutional human ethics committee approval was obtained for the conduct of the study. After written informed consent from the participants the study was carried out.

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METHOD

Study Population

Outpatients attending Cardiothoracic and Vascular surgery

Inclusion Criteria

• Patients above 18 years and both sex,

• Patients who underwent mechanical heart value replacement. Taking Acenocoumarol 2mg, Once daily dose. INR of 1.5 - 4.5 [5,6].

- Patient's with normal liver function
- Vitamin-K restricted diet.

• Patients who have completed 3 Months of post operation convalescent period.

Exclusion Criteria

• Known Major illness which lead to coagulation disturbance. (Hemophilia, Factor 5 Leiden mutation, Protein C deficiency, Protein S deficiency, Von Willebrand's disease (VWD), cirrhosis, Shock, Sepsis, Malignancy, Renal disease, Prolonged steroid use, Anti-phospholipid antibody syndrome (APLAS), Systemic Lupus Erythematosus (SLE) [7].

Patients on drugs which are known to produce interactions with Acenocoumarol (Allopurinol, Amiodarone, Azathioprine, Betamethasone, Carbamazepine, Cefoxitin , Cholestyramine, Cimetidine, Dexmethasone, Doxycycline, Erythromycin, Fenofibrate, Fluvostatin, Gingko biloba, Ibuprofen, Ketoconazole, Lovastatin, Orlistat, Quinine, Zafirlukast) [8].

Study Design

Cross sectional study

Timing Of The Blood Sample

2ml of blood was collected from the patients at the trough (just before taking drug) and Cmax levels (Two hours after taking drug) [9].

METHODLOGY

Table 1. Comparison of Sex with Trough and Cmax levels

After ethics approvals and Patients who were satisfying the inclusion and exclusion criteria, were recruited after written informed consent either in English or Tamil. Age and sex of the participants were noted. 2 ml of blood samples were collected for measuring trough and Cmax levels. By using High performance liquid chromatography Concentration of Acenocoumarol was measured [10,11].

STATISTICAL ANALYSIS

The collected data were entered into SPSS version 19 for statistical analysis.

• Student t test was used to find out the relation between Sex and Plasma concentration of trough and Cmax of Acenocoumarol, A P Value of <0.05 was considered statistically significant.

• One way analysis of variance (ANOVA) was used to compare trough and Cmax plasma concentration of Acenocoumarol of patients with Age groups. A P Value of <0.05 was considered statistically significant.

• Pearson correlation was done to find out the correlation between age and trough and Cmax concentrations of Acenocoumarol, Value of r closer to 1 or -1 considered as having positive or negative correlation

RESULT

Totally 56 patients were recruited, In that 50% were males and 50% were females, At 5 % level of significance there were no difference between males and female with trough levels of Acenocoumarol, At 5 % level of significance there were no difference between males and female with Cmax levles of Acenocoumarol. Patients were divided into three categories based on age 19-45years, 46-52 years, 53 to 88 years. At 5 % level of significance there were no different age groups and trough values. At 5 % level of significance there were no difference between different age groups and Cmax values. There were no correlation between different age groups and trough values. There were no correlation between different age groups and trough values.

	Mean (ng/ml)		Standard Error		Standard Deviation		Minimum (ng/ml)		Maximum (ng/ml)	
Plasma Concentration of Acenocoumarol	Trough	Cmax	Trough	Cmax	Trough	Cmax	Trough	Cmax	Trough	Cmax
Male (n=28)	15.22	66.55	0.85	3.86	4.51	20.43	10.12	33.22	29.18	116.74
Female (n=28)	14.73	60.82	0.53	3.36	2.82	17.81	10.17	25.1	19.97	112.3

 Table 2. Comparison of Age groups with Trough and Cmax levels

	Mean (ng/ml)		Standard Error		Standard Deviation		Minimum (ng/ml)		Maximum(ng/ml)	
PlasmaConcentration of Acenocoumarol	Trough	Cmax	Trough	Cmax	Trough	Cmax	Trough	Cmax	Trough	Cmax
19-45 years (n=19)	15.24	64.67	0.67	3.77	2.92	16.43	11.74	33.22	20.67	90.36

46-52 years (n=23)	14.55	64.21	0.75	4.00	3.59	19.19	10.17	33.09	23.73	116.74
53-88 years (n=14)	15.32	61.49	1.33	6.30	4.99	23.58	10.12	25.1	29.18	112.3

DISCUSSION

It was thought that there will be influence of Age and sex on trough and Cmax levels of Acenocoumarol. This study showed that mean trough plasma concentration of Males were more compared to females. Minimum trough concentration of 10.17 ng/ml was found out with female patient and 10.12 ng/ml was found with male. Maximum trough concentration of 29.18 ng/ml was observed in male patient and 19.97 ng/ml was seen in female patient. But at 5 % level of significance there were no difference between males and female with trough levels of Acenocoumarol, Mean Cmax plasma concentration of Males were more compared to females. Minimum Cmax concentration of 33.22 ng/ml was found out with male patient and 25.1 ng/ml was found with female. Maximum Cmax concentration of 116.74 ng/ml was observed in male patient and 112.3 ng/ml was seen in female patient. At 5 % level of significance there were no difference between males and female with Cmax levles of Acenocoumarol (Table 1).

Our study results correlates with study done in North India, which has proved that there is no significant difference between sex and dose requirements of Acenocoumarol [4]. Minimum trough concentration of 10.17 ng/ml was found out with 52 year old female patient and 10.12 ng/ml was found with 55 years male. Maximum trough concentration of 29.18 was observed in 88 year old male patient. Mean trough concentration was more in 53 -88 years and low with 46-52 years

At 5 % level of significance there were no difference between different age groups and trough values. Minimum Cmax of 25.1ng/ml was noticed in 60 year old female patient. Maximum Cmax concentration of 116.74 was seen in 49 year old male patient. Mean Cmax was more in 19-45 years and low with 53-88 years. But at 5 % level of significance there were no difference between different age groups and Cmax values. There were no correlation between different age groups and trough values. There were no correlation between different age groups and Cmax values (Table 2).

It has been noticed in a study on Acenocoumarol dosing requirement that influence of age on dosing of Acenocoumarol is varied. Activity of cytochrome (P450) enzyme in body reduces with advancement of age which resulted decrease in Acenocoumarol dose in elder patients. Decreases in 0.5 to 0.7 mg per 10 yrs [12]. In another study done in North India showed that the dose requirement is decreasing with age. But there was no significant difference [4].

In our study we had maximum number of participants in age group 40-60 (70%). In the age of 20-40 yrs, the percentage of participants were 23%. Above 60yrs of age we had only 5% of participants. While below 20 yrs, there were only 2% of participants. There is a study done in Australia which reveals maximum number of participants with rheumatic heart disease between 50.9 - 71.4. In our study we have maximum number of participants in age group of 40 - 60 yrs [13].

CONCLUSION

Our study indicated that there is no significant difference in the trough and Cmax Concentration of Acenocoumarol between Sex and different age groups. However there are various factors other than age and sex that can affect plasma concentration of Acenocoumarol, it has to be confirmed with larger samples.

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CONFLICT OF INTEREST No interest

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