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THE STUDY OF PLATELETS ACTIVATION IN HYPERTENSION PATIENTS

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ABSTRACT

Introduction

Platelet function occurs in vivo in human essential hypertension by comparing hypertensive patients and appropriate healthy controls. Then we analyzed which of the clinical investigations and patient variables was independently correlated with the diagnosis of hypertension and for the identification of cardiovascular risk and to confirm the effect of atenolol compared to placebo in patients with essential hypertension. Of particular interest was the effect of the drug on platelet function since any antihypertensive drug possessing also 'anti-platelet' properties would be advantageous.

Methods

One hundred seventy -two patients with established hypertension were included to study the effects of day atenolol compared to placebo on platelet function compared to 20 healthy individual control groups.

Results

Atenolol was found to be an effective antihypertensive agent, reducing blood pressure. Hypertensive patients appear to have increased in vitro platelet activation. Atenolol significantly reduced platelet adhesion, but had little effect on aggregation. This may be important in contributing towards the now-recognised cardio-protective effect of the B adrenoceptor blocking agents.

Conclusion

Platelet activation is associated with the presence of hypertension-related microvascular changes. In this setting, the findings might help identify hypertensive patients who are at increased risk for cardiovascular events and who might benefit from long-term treatment with antiplatelet agents.

Key words: Sea level, Tamilnadu, Beachridges, Pagodas, Kaveripatinam

INTRODUCTION

The medical treatment of hypertension has been substantial progress. Among the medications, drugs with properties of anti-,3-adrenoceptor activity have become the first-line choice in the majority of patients with hypertension (Laragh, 1976; Conway, 1977). The original, B-adrenoceptor blocking drugs (propranolol and others) were not cardio-selective; that is, their blocking effect applied to both the ,81 and f2 receptors. Much attention has been given to the development of a specific f 31-adrenoceptor blocker. Such a drug is atenolol, which does not have the serious side effects that were attributed to the initial selective, 8-adrenoceptor blocker practolol (Simpson, 1977; Zacharias, 1977). Previous studies with /8-adrenoceptor blocking drugs have yielded contradictory results in terms of the effects on platelet function (Frishman *et al.*, 1976; Keber *et al.*, 1979; Leon *et al.*, 1978; Vlachakis and Aledort, 1980). To the best of our knowledge the effect of atenolol on platelet functions has not been reported.

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Large observational studies indicate that in human essential hypertension, cardiovascular morbidity and mortality are related to the severity of the hypertensive state and to the development of cardiac and vascular changes. However, the signals that allow alterations in blood pressure control to be translated into atherothrombotic complications have only partially been characterized. Increased oxidative stress might be implicated. This hypothesis is based on data from animal models of genetic hypertension, showing increased generation of oxygen free radicals within the vascular wall, associated with worsening of blood pressure control, alterations in vascular function, and progression of vascular lesions.1–3 Experimental data suggest that oxidative stress might be increased in human essential hypertension and could be responsible for altered endothelial function Taddei *et al*, 1998; Guzik *et al*, 200). Different risk factors for atherothrombosis, such as hypercholesterolemia, (Davi *et al.*, 1997) severe hyperhomocysteinemia, (Di Minno *et al.*, 2001) visceral obesity, (Guagnano *et al.*, 2008) and diabetes mellitus, (Ciabattoni *et al.*, 1999) have been shown to be

associated with biochemical evidence of platelet function (Patrono *et al*., 1997).

We tested the hypothesis that platelet function occurs in vivo in human essential hypertension by comparing hypertensive patients and appropriate healthy controls. Then we analyzed which of the clinical investigations and patient variables was independently correlated with the diagnosis of hypertension and for the identification of cardiovascular risk and to confirm the effect of atenolol compared to placebo in patients with essential hypertension. Of particular interest was the effect of the drug on platelet function since any antihypertensive drug possessing also 'anti-platelet' properties would be advantageous.

MATERIALS METHODS

Subjects and Study Protocol

This study was done during the period of time March 2005 to August 2008 in Khartoum state teaching hospitals. We retrospectively analysed 172 patients fulfilling the clinical definition of essential hypertension (male and female), above 40 years(target disease age) on treatment or off treatment. while, patients with previous history of venous or arterial thrombosis, diabetes mellitus, received antiplatelets or anticoagulants drugs in past 15 days were excluded from the study and 20 healthy individual males and females above 40 years setting as control groups. Data of all patients and control group were collected using questionnaire included the information of age, sex, duration of the disease, and laboratory investigations.

Clinical Investigations

Platelet-rich plasma was prepared from citrated blood by low-speed centrifugation (200 g, 10 min,room temperature). Platelet aggregation was determined according to the method of Born (1962) using a Chronalog aggregometer. The aggregating agents were adrenaline (10 AM), ADP (10 AM), collagen (1,ug/ml) and 5-hydroxytryptamine (10 Mm). The extent of aggregation was determined as the area under the aggregation curve. Blood was also taken for determination of blood platelets count and Bleeding time.

Statistical analysis

The obtained data analzyed using Student's paired t-test and the Wilcoxon rank test were employed in each group.

RESULTS

Platelet function

The result showed that the distribution incidence of age related sex among hypertension patients, includes three age groups ,in age group (40-50)years 10%were males and 12.5% were females , group(51-60) years 15% were males and 15%were females, the age related to sex showed highly incidence in males(32.5%) compared to females(15%) in age group (>60)years(Table 1). 63% of pateints showed normal platelets count as in Table 4. bleeding time in hypertensive patient prolonged in 59% of patients and the rest within normal value in compared to control groups(Table 5). The hypertensive patients revealed both increased platelet adhesion and increased platelet aggregation in comparison with normotensive controls (Table 2). The effect of atenolol is demonstrated in Table 3. There was a reduction in platelet adhesion subsequent to treatment, but atenolol evoked little effect on platelet aggregation. The placebo had no effect on either platelet adhesion or platelet aggregation. No further changes in these parameters were noted.

DISCUSSION

Platelets appear to play an important role in the pathogenesis of atherosclerosis (Mustard and Packham, 1975); and in conditions such as hyperlipidaemia (Aviram and Brook, 1982), diabetes (Kwaan *et al*., 1972) and chronic renal failure (Viener *et al*., 1982), in which accelerated atherosclerosis is a feature, enhanced platelet activity has been described. Hypertension is another important risk factor for atherosclerosis. Platelet function in hypertensive individuals has rarely been studied. We report here that our hypertensive patients appear to have increased in vitro platelet activation, as evidenced by increased adhesion and increased aggregation in response to ADP. The effect of j3-adrenoceptor blockers on platelet aggregation has been determined by others. In most instances propranolol was the (3-adrenoceptor blocker tested (Nathan *et al*., 1977; Frishman *et al*., 1976, 1978; Vlachakis & Aledort, 1980; Weksler *et al*., 1977; Leon *et al*., 1978; Keber *et al*., 1979), but pindolol (Nathan *et a*l., 1977) and more recently timolol (Thaulow *et al*., 1981) and carteolol (Small *et al*., 1982) have been examined. The in vitro addition of the 3-adrenoceptor blocker invariably resulted in inhibition of platelet aggregation (Nathan *etal*., 1977; Weksler *et al*., 1977; Thaulow *et al*., 1981). However, contradictory results were reported in patients taking f3-adrenoceptor blockers. Propranolol induced decreased in vitro platelet aggregation in patients with angina pectoris (Frishman *et al*., 1976, 1978) and hypertension (Vlachakis & Aledort, 1980) in whom a hyperaggregability state had been diagnosed before the onset of 8-adrenoceptor blocker therapy. In contrast, propranolol failed to decrease in vitro platelet aggregation in either ischaemic heart disease patients (Keber *et al*., 1970) or healthy volunteers (Leon *et al*.,1978) who did not demonstrate any underlying hyperaggregability. In patients taking timolol on a long term basis there was no effect on platelet aggregation (Thaulow *et al*., 1981).

To the best of our knowledge the effect of atenolol on platelet function has not been reported. Certainly the modality of platelet adhesion has not been investigated. Interestingly, in our patients atenolol significantly reduced platelet adhesion, but there was little effect on platelet aggregation as measured in vitro. Most workers consider the anti-aggregatory properties of the 83-adrenoceptor

blockers to be related to the membrane stabilizing activity (MSA) of the drug (Nathan *et al.*, 1977; Weksler *et al.*, 1977; Keber *et al.*, 1979) Propanolol which possesses

function in human essential hypertension is available so far. In fact, although no statistically significant differences were found in platelets count between healthy

Table 1. The age related to sex incidences in Essential hypertension patients and control

	Patients	*Control*
40-50 years	10% male 12.5% female	19% male 26% female
51-60 years	15% male 15% female	10% male 10% female
> 60 years	32.5% males 15% female	25%male 10% female

Table 2 Platelet function in normal and hypertensive subjects.

	Normals	*Hypertensives*
Platelet adhesion (platelets/2500 M²)	8.2 ± 3.9	10.6 ± 3.5 ($P < 0.01$)
ADP-induced platelet aggregation (area weight in mg)	2.38 ± 0.88	3.35 ± 0.61 ($P < 0.01$)

Table 3 The effect of atenolol treatment on platelet function in hypertensive patients.

	Platelet adhesion (platelet/2500 m²)	*Platelet aggregation (area in mg) ADP*	*Adrenaline*	*Collagen*	*5-HT*
Before treatment	9.4 ± 3.2	3.85 ± 0.48	0.76 ± 0.70	1.39 ± 1.20	0.31 ± 0.11
After treatment	7.9 ± 3.8 ($P < 0.02$)	3.67 ± 1.31 NS	0.79 ± 0.88 NS	1.71 ± 1.62 NS	0.34 ± 0.26 NS

NS not significant.

Table 4. The platelets count distribution among patients and control

platelets count/L	*(1.5 - 4.5)X10⁹/L*	*< 1.5X10⁹/L*	*>4.5X10⁹/L*
patients %	63%	25%	12%
Control%	96%	3%	1%

Table 5. The bleeding time distribution among patients and control

bleeding time	*normal*	*Prolonged*
patients %	41%	59%
Control%	98%	2%

therapeutic application and importance of atenolol. It also indicates a possible mechanism for the cardio-protective effect of the f8-adrenoceptor blocking drugs. Abundant evidence indicates that platelet functions, as assessed by measuring bleeding time can be detected in clinical conditions associated with increased cardiovascular disease or thrombosis risk and cerebrovascular syndromes. However, relatively limited evidence concerning platelet

normotensive controls and patients with mild to moderate essential hypertension. Data from the present study indicate that the median of normal platelet count is significantly normal in hypertensive patients when compared with pair-matched, normotensive controls. Our findings, demonstrating that patients with more severe microvascular alterations have enhanced activation, offer a plausible explanation for the apparent

inconsistency of previously published data. It is interesting to note that advanced hypertensive retinopathy is usually observed in a small percentage of patients with more severe hypertension and is associated with increased risk of thromboembolic events. We also observed that platelet activation was lower when blood pressure was normal or in the presence of antihypertensive treatment, consistent with the well-defined relations between hypertension and its treatment with cardiovascular events. independent of blood pressure levels, thus suggesting that specific antihypertensive drugs might have favorable effects on platelet activation in vivo. However, a properly designed intervention study is necessary to test this hypothesis. In conclusion, we obtained some platelets function investigations in essential hypertensive patients and observed that platelet activation is associated with the presence of hypertension-related microvascular changes. In this setting, the findings might help identify hypertensive patients who are at increased risk for cardiovascular events and who might benefit from long-term treatment with antiplatelet agents. hypertension patients should be introduced a program of regular reviewing of platelets functions during different period of ages requlary to minimize the risk factor of thrombosis.

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