Experimental Study of Betaxolol.A new Cardioselective β-Adrenergic Antagonist

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By

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بسم الله الرحمن الرحيم

"قالوا سبحانك لا علم لنا إلا ما علمتنا
إنك أنت العليم الحكيم"

صدق الله العظيم

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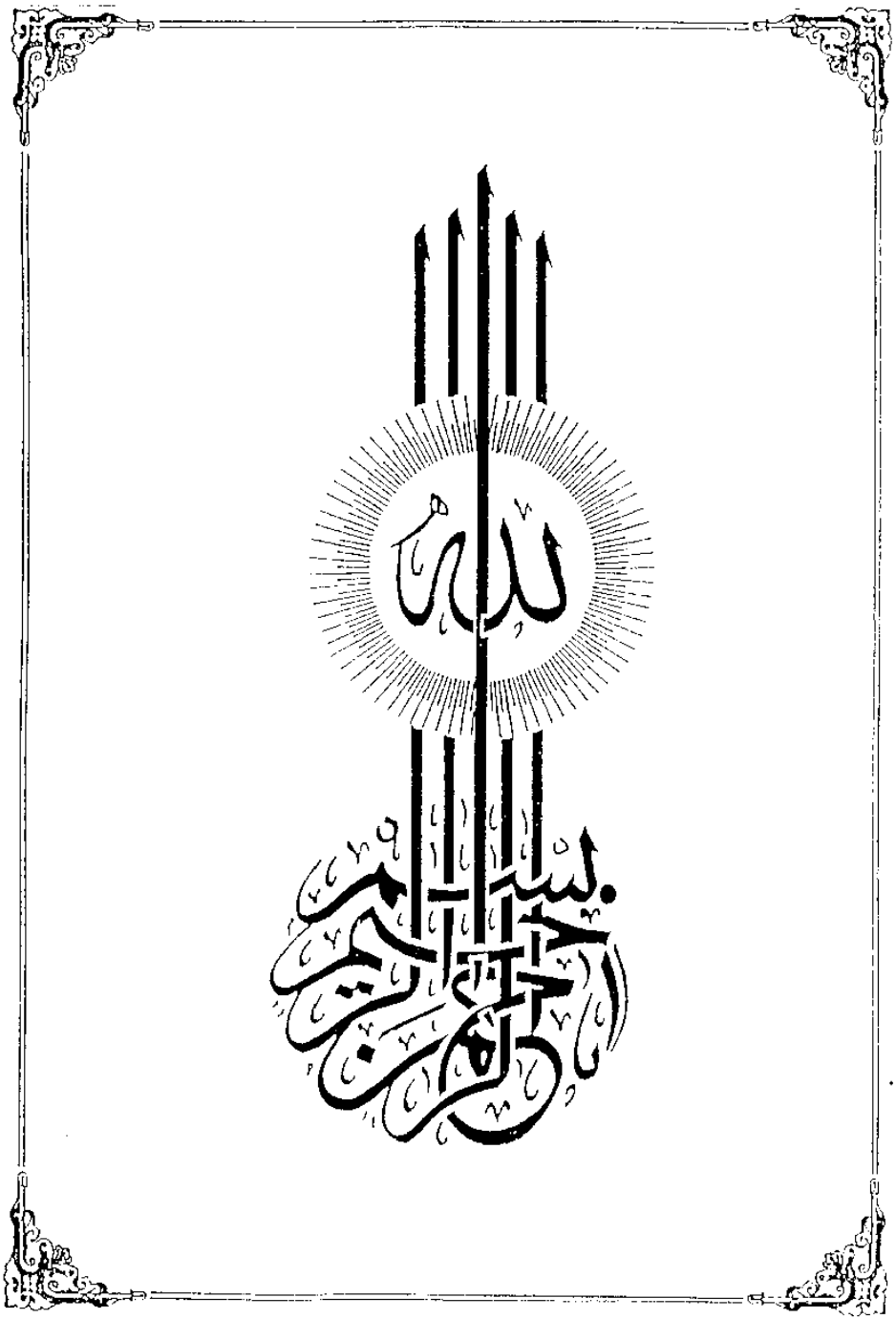

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INTRODUCTION

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The advent of β-adrenergic blocking agents may prove to be the single most important development in cardiovascular therapeutics in the past 20 years(*McMahon,1990*).They still enjoy a continuously increasing use after a relatively slow startin the treatment of tachycardic dysrhythmia and angina;the extraordinary boost occurred when their anti-hypertensive potential was discovered(*Gross,1983*).The subclassification of β-adrenoceptor blockers into selective β_1 and β_2 adrenoceptor blockers,based on their abilities to antagonize the effects of sympathomimetic amines in some tissues at lower doses than the others, has proven to be useful and now generally accepted.Certain β-adrenergic blockers have greater affinity for the innervated β_1 receptors;e.g. metoprolol,atenolol & acebutolol than for the β_2 receptors e.g. butoxamine,while other drugs block β_1 and β_2 receptors equally and are called non-selective β-blockers; e.g. propranolol, nadolol, timolol and others (*Gross,1983*).

Drugs that primarily block β_1-receptors are called cardioselective.With regard to this property;two important qualifications must be kept in mind;first,cardioselectivity is only relative.Thus,when the concentration of any β_1-blocking is sufficiently high,the compound will block β_2-receptors as well.Second,most tissues contain β_1 and β_2 receptors but the relative amount vary in different tissues.For example,the heart

contains mainly β_1 receptors but also some β_2 receptors,while the bronchioles contain mainly β_2 receptors but also some β_1 receptors(*Sullivan,1990*)The latter may explain why even low doses of β_1-blockers decrease the forced expiratory volume (FEV) immediately at rest,because β_1-receptors of the bronchioles are blocked.Higher doses block the bronchial β_2 receptors causing a still greater decrease in FEV.That's why many clinicians avoid using β-blockers(βBs)in treatment of patients with asthma,largely because alternative agents are available to treat associated conditions(e.g. calcium channel blockers for treatment of angina,hypertension,supraventricular dysrhythmia *(Sullivan,1990)*.

Blockade of both β_1 and β_2 receptors leaves α_1-receptors unopposed when they are stimulated by epinephrine.Thus patients with peripheral vascular diseases sometimes have diminution in tissue perfusion when non-selective agents are used. However,decreased perfusion can occur with low doses of selective agents because of the fall in cardiac output (*Sullivan,1990*).Differences in selectivity have clinical implications in diabetic patients in two aspects.First,during hypoglycemia epinephrine is released, which, by stimulating unopposed α receptors during non-selective β-blockade,can cause hypertension and subsequent reflex bradycardia,potentially hazardous in diabetics with coronary artery disease. Second, epinephrine increases glycogenolysis and gluconeogenisis in the liver and skeletal muscles by stimulating β_2 receptors.Thus,

the use of non-selective βB agents has the potential of prolonging the recovery from hypoglycemia in insulin dependent diabetic patients.Further because the tachycardia induced by sympathetic discharge is blocked,the patient loses one of the warning signs of hypoglycemia(*Sullivan,1990*).

One further important aspect of relative β_1 selectivity,is the fact that such agents,even when given in doses high enough to affect β_2 receptors,don't bind to these receptors with the same avidity as do non-selective βBs.Therefore,they can be displaced by lower levels of β_2 agonists.Thus patients with bronchospastic diseases who encounter difficulties while receiving β_1 selective agents can be more easily treated with β_2 agonists such as terbutaline(*Ellis et al.,1981*).

All β receptors contain both binding and activating sites.A pure agonist such as isoproterenol is bound avidly to binding and activation sites.In contrast,a pure antagonist such as atenolol and most other βBs interact avidly with attachment sites but not with activation sites.Certain βBs attach avidly to attachment sites but have relatively low affinity for the activation sites.Therefore,they stimulate the receptor mildly while blocking the effect of released catecholamines.These blockers are called partial agonists or βBs with intrinsic sympathomimetic activity (ISA) (*Svensson et al.,1981*).The partial agonist activity is competitive and can be blocked by non-selective βBs(*Haeuster,1990*).These agents

offer advantages in patients with effort angina,low basal cardiac rate or with minor AV conduction problems.Also βBs with this property cause a reduction in peripheral vascular resistance with little change in cardiac output which may be due to activation of peripheral β_2 receptors by ISA.These agents could be preferable in treatment of patients with peripheral vascular diseases or obstructive airway diseases(*Svensson et al.,1981*).

Some β-adrenoceptor blocking drugs,notably propranolol have quinidine-like action in that it impairs the capacity of excitable tissues to undergo depolarization.This effect is due to the capacity of these compounds to interact with sodium channels in cell membranes.This effect is called membrane stabilizing or local anaesthetic action.With clinically available compounds this property becomes apparent only at doses much higher than those required for maximal β-adrenoceptor blockade.Certain βBs have only a weak membrane stabilizing activity;e.g. pindolol while others including atenolol have no membrane stabilizing activity (*Sullivan,1990*).There is no evidence that membrane stabilizing activity is responsible for any direct negative effects of these agents since both drugs with and without this property equally depress left ventricular function.Membrane stabilizing activity can manifest itself clinically during massive βBs intoxication(*Frishman,1983*).

All β-adrenoceptor blocking agents are competitive antagonists,that is,they can be displaced from binding sites on the β-receptors by increasing the concentration of the agonist.For example,the degree of blockade imposed by a β-blocking agent is usually estimated by determining how much the dose of isoproterenol must be increased to raise the heart rate by a certain amount before and after β-blockade.One explanation for the wide variation in doses of different βB required to obtain a desired clinical result is the difference in their efficacy of blockade(*Sullivan,1990*). In general,β-adrenoceptor blockade is indicated in those clinical situations where sympathetic activity exceeds the level appropriate to the maintenance of internal hemostasis(*Barrett,1983*).Thus,there appears to be a maximum blood concentration of βBs or plateau,beyond which further increases in dosages do not result in more blockade,possibly because sympathetic activation cannot be increased beyond certain limits.

A group of β-adrenoceptor blocking agents can act as competitive antagonists at both α and β- adrenoceptors(*Frishman and Halpin,1970*).The prototype of which is labetalol .In addition,labetalol is the prototype of a β-blocker possessing vasodilatory properties either direct or mediated via β-agonist activity.Labetalol appears to combine the advantages of α and β blockers while minimizing the unwanted effects of both types of agents(*Walter and Allan,1990*).

Labetalol contains two asymmetric centers and thus is a racemic mixture of four stereoisomers.These optical isomers have different activities directed at β and α- adrenoceptors. Dilevalol,the R.R.isomer,differs in effect from the racemic mixture in that,it is much stronger selective β2 agonist than labetalol(7:1).It is a stronger competitive antagonist for both β_1 & β_2 receptors (4:1) and it is a much weaker competitive antagonist for α1 receptors than labetalol(1:7).The first property is responsible for the comparable vasodilator activity of dilevalol to labetalol*(Wallin,1990)*.

The blockade of vasodilator action of β_2 adrenoceptors by non-cardioselective βBs,induce vascular spasm with Raynaud's phenomenon, intermittent claudications and even coronary spasm.In addition,this vascular spasm could limit the effectiveness of βBs in the cardiovascular diseases making the cardioselective βBs clinically preferable *(Dunlop and Shanks, 1968)*.Addition of vasodilator drugs such as nitrites or nifedipine to the βBs increases there effectiveness and minimizes their vascular side effects*(Ablad et al.,1975)*.

As regards the pharmacokinetic properties of βBs., most β-adrenoceptor blocking drugs are lipid soluble such as propranolol,acebutolol and metoprolol.A few such as atenolol and nadolol are more soluble in water.Lipid soluble agents penetrate membranes easily and cross the blood-brain barrier rapidly.They tend to have larger volume of distribution.These

agents are highly bound to plasma proteins and are relatively rapidly metabolized by the liver.In contrast,water soluble βBs are excreted by the kidney without metabolic change.Although water and lipid soluble βBs don't appear to differ in clinical efficacy,the difference in their solubility has clinical implications(*Taylor et al.,1981*).Lipophilic βBs have been found to have higher ratios of brain-plasma concentrations,to which the side effects of fatigue,insomnia,night mares and depression have been attributed(*Kostis and Rosen,1987*).In general,water soluble agents are absorbed from the GIT at variable rates and are excreted by the kidney without undergoing hepatic metabolism.Their rate of excretion depends on renal function and is diminished as glomerular filtration falls.Water soluble βBs tend to have relatively longer half-lives.Lipid soluble βBs are rapidly absorbed from the GIT and metabolized by the liver at varying rates during their first pass.Drugs such as metoprolol and propranolol are rapidly cleared from the liver whereas agents such as timolol and pindolol are cleared less quickly.Considerable variation exists between individuals also with regard to the amount of a βB that is metabolized during the first pass through the liver;thus,a greater dose titration is required.Because of the rapid hepatic clearance of these drugs,their half-lives tend to be short.In addition,there is also the possibility of drug interaction with other drugs such as pentobarbitone and cimetidine which affect hepatic enzymes (*Frishman,1987*).

The clinical implications of the differing pharmacokinetics of the βBs are reflected in the required dose intervals.Because the water soluble agents are excreted slowly,they need to be given only once daily,whereas the lipid soluble agents are metabolized more rapidly and must be given two or three times daily to maintain clinically efficacious β_2-blockade*(Sullivan,1990)*.

Important breakthrough in hypertension research during the past two decades have soundly demonstrated that the sources of hypertension occupy a long spectrum between two relatively opposed mechanisms ;renin-mediated and non-renin-mediated (*Laragh,1973,Laragh et al.,1979;1982*).The most likely endocrine agents of these antagonist roles are the vasoconstrictors angiotensinII and norepinephrine ,either of which is capable of producing the exalted peripheral resistance,that is the common characteristic of all hypertension(*Ames et al.,1965*).However, the similarity ends there,for the conditions imposed by these two agents are radically different in their implications for risk,survival and treatment.

The vasoconstriction ordered by angiotensinII,the active component evoked from renin secretion,results in "dry hypertension" which is characterized by a peripheral resistance generally higher than that imposed by other forms(*Laragh et al.,1979*).Angiotensin stimulates aldosterone production which is correspondingly high.Plasma volume is relatively low (given

a reasonable renal capacity for diuresis),as is cardiac output.A by-product of this relative diuresis is greatly elevated blood viscosity,blood urea and hematocrit value,with low tissue perfusion and the patient is susceptible to postural hypotension(*Laragh,1981*).

Non renin-mediated hypertension ,on the other hand,a category in which peripheral resistance,in general is less dramatically elevated.Plasma renin activity is low or absent,while aldosterone secretion is ranging from low to high.This type can be called a "wet hypertension".This type is associated with comparatively higher plasma volume,cardiac output and low blood urea,hematocrit and viscosity values. Tissue perfusion is comparatively high and postural hypotension is absent(*Laragh,1986*).

Renin-induced vasoconstriction in dry hypertension can be reversed by renin system blockade using angiotensin converting enzyme (ACE) inhibitors(*Case et al.,1977*).On the other hand,in primary hyperaldosteronism,wet hypertension finds its way:the induced sodium retention builds up massive fluid accumulation and causes a reactive shut down of the renin system. Pharmacologic blockade of the renin system is ineffective here;verifying that the source of vasoconstriction must be sought in other mechanisms.Temporary relief of the situation can be achieved with diuretics and permanent cure by surgically