Evaluation Of The Efficacy Of β-Blockers Administered Early In Acute Myocardial Infarction

Thesis
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By

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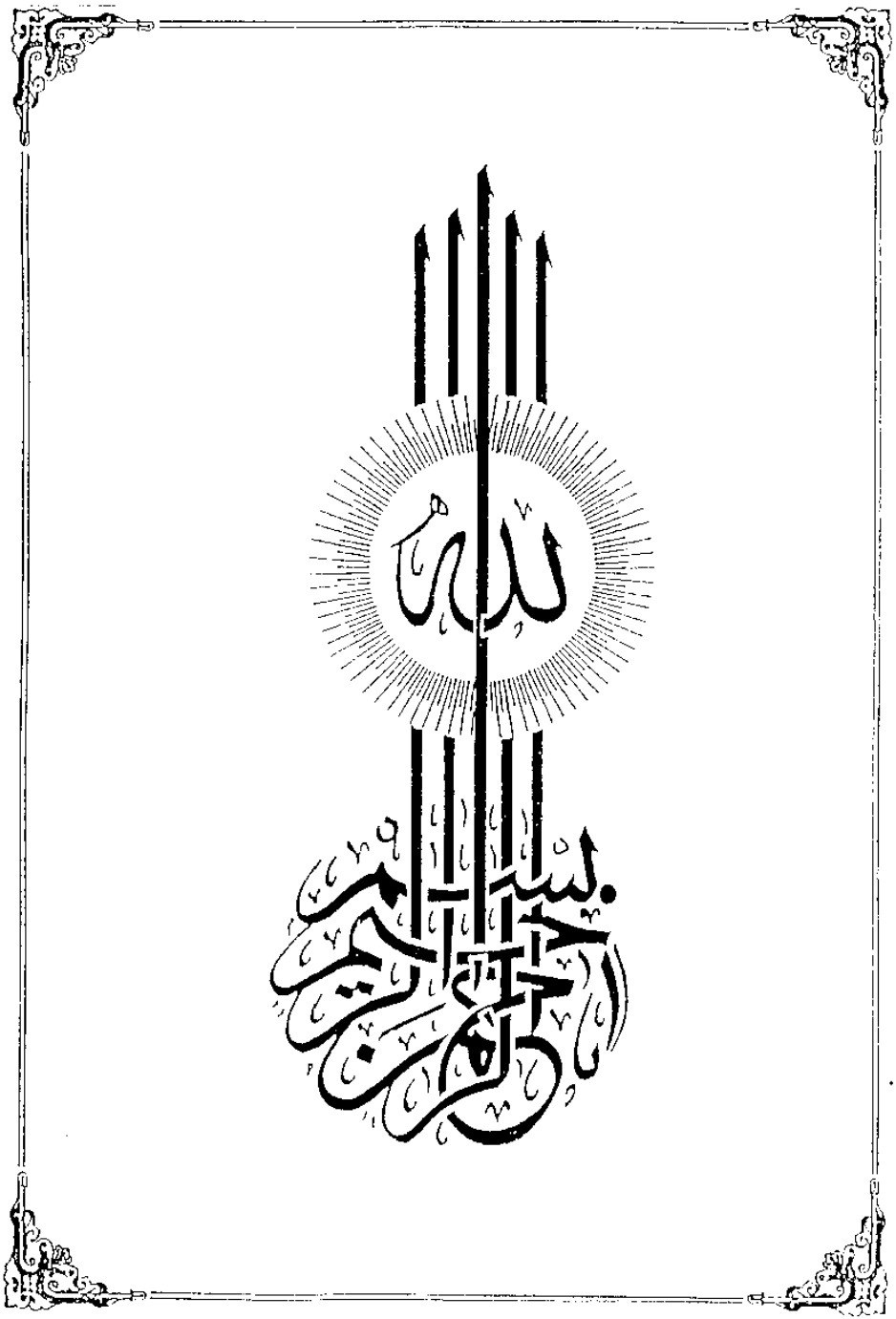
To My Beloved Family



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Introduction

Introduction

The effect of β-blockers in the setting of acute myocardial infarction has been extensively studied. Over fifty randomized clinical trials involving more than 50,000 patients have been carried out to evaluate either β-blockers begun intravenously after myocardial infarction or their long-term oral use as secondary prevention. Pooled data from trials in which therapy was initiated before hospital discharge and maintained at least for one year indicate that mortality can be reduced by an average of 21% and reinfarction by 24% ***(Hjalmarson, 1988)***.

Trials of the early use of intravenous β-blockers in the prethrombolytic era have been less impressive. Pooled data from 27 trials involving 27,000 patients revealed only 13% reduction in mortality ***(Yusuf et al., 1988)***. The use of β-blockers early in acute myocardial infarction after thrombolytic therapy was studied in the TIMI IIB trial which concluded that the use of β-blockers is safe when given early after thrombolytic therapy and is associated with decreased myocardial ischaemia and reinfarction in the first week but offers no benefit over late administration in improving ventricular function or reducing mortality ***(Roberts et al., 1991)***.

Metoprolol was a subject of most of the previously mentioned studies. Propranolol has also been studied in acute myocardial infarction

with a conclusion that it reduces infarct size, arrhythmias and chest pain ***(Yusuf et al., 1983)***. The comparative effect of metoprolol and propranolol in the setting of acute myocardial infarction, on the in-hospital complications and left ventricular function has not yet been clarified.

Aim Of The Work

Aim Of The Study

The aim of our study is to evaluate the effect of early intravenous β-blockers in acute myocardial infarction on the in-hospital complications, mortality and global left ventricular function. Also, we will compare the effect of selective "metoprolol" versus non-selective "propranolol" β-blockers in the setting of acute myocardial infarction.

Review Of Literature

Pharmacology Of β-Adrenergic Receptor Antagonists

Introduction:

β-adrenergic receptor antagonists have received enormous clinical attention because of their efficacy in the treatment of hypertension, ischaemic heart disease and certain arrhythmias.

The first β-adrenergic blocking agent discovered was dichloroproterenol. However, this compound is a partial agonist, and this property was thought to preclude its safe clinical use ***(Pawell and Slato, 1958)***.

Sir James Black and his colleagues initiated a program in the late 1950s to develop additional agents of β-blockers. Although the usefulness of their first antagonist, promethalol, was limited by the production of thymic tumours in mice, propranolol soon followed ***(Black and Stephenson, 1962)***.

Propranolol is a competitive β-adrenergic antagonist that is devoid of agonistic activity and it remains the prototype with which other β-blockers are compared.

Subsequent efforts to generate additional compound have resulted in compounds that can be distinguished by the following properties: relative

affinity for B_1 and B_2 receptors, intrinsic sympathomimetic activity, blockade of β-adrenergic receptors, differences in lipid solubility and general pharmacokinetic properties.

Some of these distinguishing characteristics have clinical significance and they help to guide the appropriate choice of β-adrenergic antagonist for individual patients ***(Goodman and Gilman's, 1992)***.

Pharmacological Properties Of β-Adrenergic Receptor Antagonists

1- Potency:

β-adrenergic receptor antagonists are competitive inhibitors of catecholamine binding at B-adrenoceptor sites. The dose response curve of the agonist is shifted to the right. That is, a given tissue response requires a higher concentration of agonist in the presence of β-blocking drugs ***(Frishman, 1981)***.

β-blocking potency can be assessed by inhibition of tachycardia produced by isoproterenol or exercise. Potency varies from compound to compound but it is of no therapeutic relevance. However, it explains the different drug dosages needed to achieve effective β-adrenergic blockade when initiating therapy in patients or when switching from one agent to another ***(Frishman et al. 1979)***.

2- Structure-activity relationship:

The chemical structure of most adrenergic blockers have several features in common with the agonist isoproterenol; aromatic ring with a substituted ethanolamine side chain linked to it by - OCH_2 group ***(Conolly et al., 1976)***. Substitution of the isopropyl group or more bulky subsitituent on the amino nitrogen favor interaction with β-adrenergic receptors ***(Goodman and Gilman's, 1992)***.