EFFECTS OF PSYCHOTROPIC DRUGS ON THE ELECTROCARDIOGRAM

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BY

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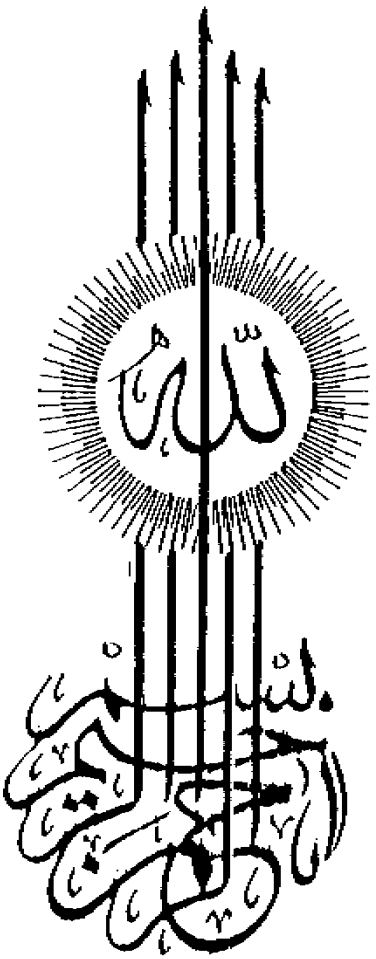

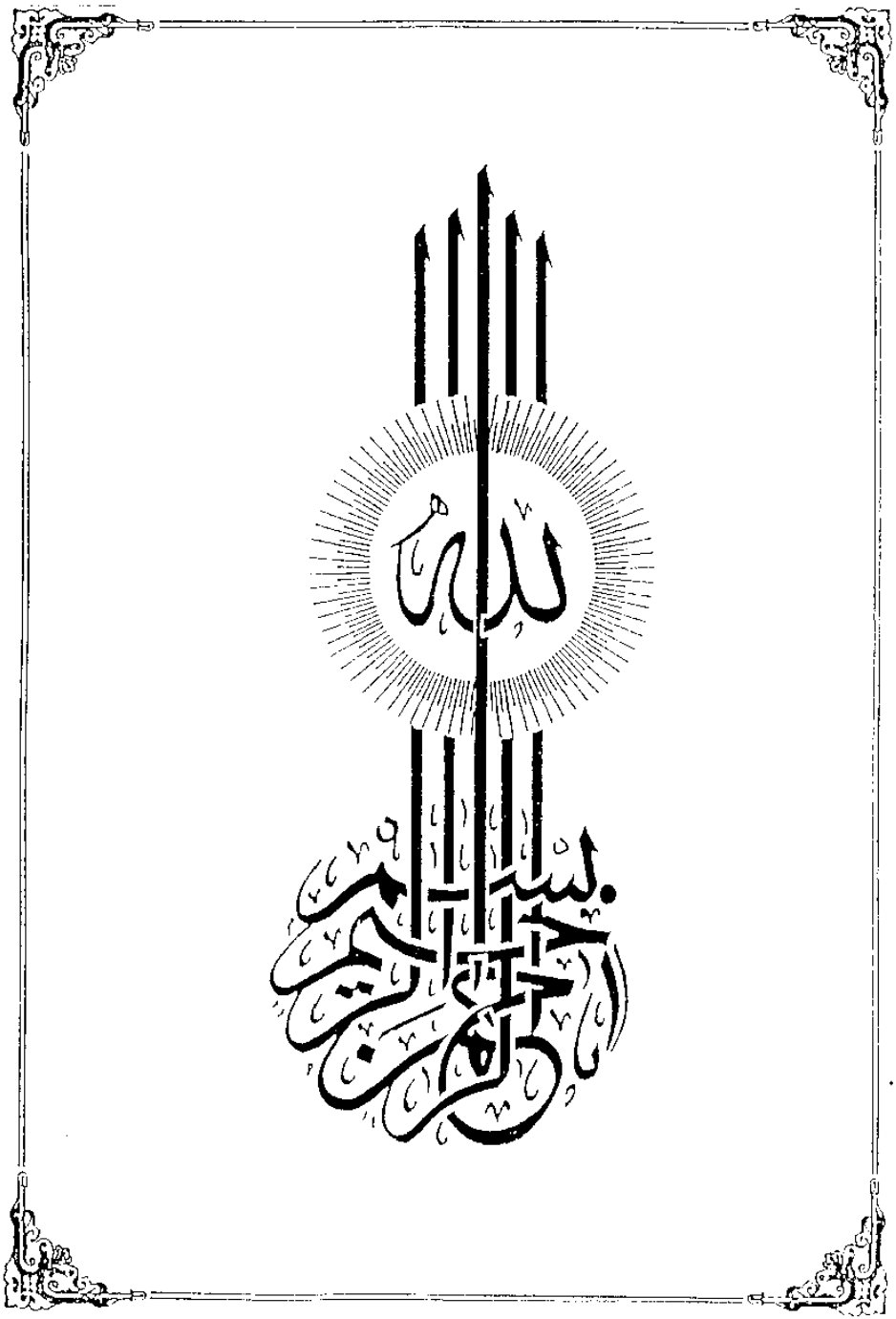

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Acknowledgement

INTRODUCTION

It is known since long that, changes in cardiac functions are an integral part of all emotional reactions [Stevenson, 1949; Wolf, 1952; Friedlander, 1958; Raab, 1966]. In fact the heart has often been referred to as "specific sense organ of anxiety" just as eyes are considered to be the sense organ for sight. That is why the heart may be "sad" or "merry", "fickle" or "Sincere". For centuries it has been recognized that emotional stimuli like apprehension, fear, anxiety, annoyance, depression, compulsiveness and excitement may provoke disturbances of rate and rythm of the heart [Dreifus and Watanabe, 1965; Arora' and Madan, 1960].

Perhaps one of the earliest observations on emotionally induced tachycardia were made by Avicenna in the 10th century. In 1940, Mainzer and Krouse were the first to record electrocardiographic changes produced by anxiety states in man. Bayer et al., in 1947, directed attention to the ralationship of the electrocardiogram and diseases of the central nervous system. Since then many investigators have documented abnormalities of the electrocardiogram and cardiac, arrhythmias in association with emotional disturbances [Duncan et al., 1950; Harvey et al., 1952; Grou, 1956; Sigler, 1959; Lapiccirella, 1960; Bergmoshi and

Logani, 1973) and C.N.S lesions like cerebrovascular accidents, trauma, neurosurgery and infections [Finkelstein and Nigagliona 1961; Levine and White, 1962; Srivastavo and Rabson, 1964; Harrison, and Gibb, 1964; Abildskov et al., 1970] The most frequently encountered electrocardiographic changes where lengthened Q-T. interval, notched or inverted T waves and prominent U waves.

There is also a large body of experimental evidence showing the role of C.N.S in maintaining and modifying cardiac rhythmicity [Notherman et al., 1952; Nakamoto, 1965; James, 1973].

Cardiac arrhythmias of central origin have also been consistently produced following the intracerebroventricular administration of a variety of chemically and pharmacologically unrelated agents; picrotoxim [Bircher et al., 1962, 1963; Varma et al., 1962], caffeine [Dikshit, 1934]; pentylenetrazol [Bircher et al., 1980], quinidine and procainamide [Weinberg and Haley, 1955]; acetylcholine and nicotine [Dikshit, 1934], and aconitine [Bhatgava et al., 1969].

Thus there is both clinical and experimental evidence for the origin of arrhythmogenic impulses from the C.N.S. It is therefore, possible that some of the centrally active drugs may have a supplemental value in the therapy of cardiac

arrhythmias. In fact sedation with barbiturates is a time-honoured adjunctive remedy in cardiac arrythmias [Diploma, 1956].

Hence the use of tranquilizers, which have the hypothalamus as the chief locus of their action, may prove beneficial to the patients of cardiac arrhythmias particularly if such drugs (tranquilizers) have also a direct quindine-like effect on the heart.

Based on the neurogenic and psychosomatic basis of cardiac arrythmias, some agents have been investigated for their anti-arrhythmic activity e.g. phenothiazine. However, their potential clinical value for the treatment of disorders of rate and rhythm of the heart remain questionable because of their arrhythmia-Comboting as well as arrhythmia-provoking activity.

Nowadays increasing numbers of patients are receiving psychotropic drugs, while great number of these patients are benifitting from these drugs, a new spectrum of cardio-vascular diseases has been created, this may come to the attention of the cardiologist when his patient complains of severe headache or fail to respond to a carefully regulated anti-hypertensive regimen. More dramatically cardiac arrhythmias, hypertensive crisis, intracerebral haemorrhage, or sudden death may herald the interaction between anti-

depressant and antihypertensive drugs.

So the association between psychotropic drugs and electrocardiographic changes, cardiac arrhythmias and sudden death has been documented.

Previous communications have been dealt with the risk of major arrhythmias or sudden death in patients who receive a toxic drug overdose or who have an underlying heart disease.

What would be the picture in young adults with no heart lesion and who are receiving the usual therapeutic doses of psychotropic drugs?

PSYCHOTROPIC DRUGS

Psychotropic drugs or psychoactive drugs are pharmachological agents that exert a powerful effect on the higher functions of the C.N.S. They can change mood, thinking, behaviour and emotions.

They can be classified into:

I- Psychotherapeutic agents: used in the treatment of psychatric disorders:

a- Minor tranquilizers or anti-anxiety drugs: used in treatment of anxiety. Benzodiazepines are the most important and widely used as anti-anxiety drugs.

b- Major tranquilizers or anti- psychotic: used in treatment of psychosis.

c- Drugs used in the treatment of disorders of mood [Mania and depression]:

1- Mood stabilizing drugs: Lithium salts.

2- Antidepressant (Mood-elevating drugs) like tri-cyclic antidepressants.

II- Psycho-stimulants: increase the level of alertness and/or motivation e.g. amphetamines.

III- Psycho-dysleptics (hallucinogens) e.g. L.S.D., Cannabis.

ECG Changes Due To Minor And Major Tranquilizers

PHENOTHIAZINES

Phenothiazines can supress as well as provoke the disorders of cardiac rhythm. The pathogenesis of phenothiazine induced rythm disturbances is still unknown.

Antiarrhythmic activity of phenothiazines:

Courvoisier et al., in 1953, were the first to report the ability of chloropromazine to combat cardiac arrhythmia. In the following year, Finkelstien et al. (1954) investigated the influence of chloropromazine on the inotropic action of sympathomimetic amines and described its antiarrhythmic activity. When tested in atrial flutter produced in the anesthetized dog, chloropromazine was found to share the ability of quindine to reduce the atrial rate which was invariably followed by abrupt reversion to normal sinus rhythm [Arora and Madan, 1955]. But since the drug did not prevent the disappearance of p waves, nor did it elevate the fibrillation threshold, Dilalme and Catenacci (1955) suggested that the antiarrhythmic activity was due to its anti-adrenergic activity rather than to any direct quindine-like effect on the myocardium.

Involvement of the adrenergic system in mediating the antiarrhythmic activity of phenothiazines was also suggested by Singh (1968).

The C.N.S. actions of chloropromazine may play a role in mediating its antiarrythmic activity is conceivable in view of the following observations.

1- Arrythmogenic impulses can originate from the hypothalamus [Melville et al., 1963] which is the chief site of action of ataractics.

2- Centrogenic arrhythmias are mediated through enhanced central sympathetic activity [Bhargava et al., 1969].

3- Chloropromazine antagonise adrenergic mechanism in the brain [Gagnon and Melville, 1967]. Against this concept is an observation of Weinberg and Hailey (1950) that centrogenic arrhythmias produced by the administration of tryptamine-strophanthidine into the 4th ventricle of an anesthetized dog were supressed by I.V. injection but not by interacerebroventricular administration of chloropromazine.

4- According to Jarvik (1970). antiarrhythmic activity of chloropromazine is due to its local anesthetic property. Since thioridazine is chemically related to chloropromazine it was investigated for its quindine like activity and it was found to be useful in selected cases of cardiac arrhythmia [Baldev R. et al. 1983].

Electrophysiology of phenothiazine induced E.C.G. abnormalities and arrhythmias:

Experimental evaluations in animals demonstrated a significant effect of phenothiazine on the action potential of isolated atrial and ventricular muscle as well as purkinge fibers [Hollander, P.B., and Cain, R.M. 1971]. Arita and Surawiez showed that phenothiazine reduced membrane responsiveness by decreasing the maximal rate of rise of phase O of the action potential. The psychotropic drugs also cause decrease in the amplitude of phase 2 as well as a reduction in the rate dependent change in the duration of this phase. Phase 3 was found to be prolonged following phenothiazine administration. The electrophysiologic properties of phenothiazine, are similar to those reported for quindine [Hollander, P.B., and Besch, H.R, 1969]. This explain the similar effects of phenothiazines and quindine on the surface E.C.G.

In man, the earliest E.C.G. change produced by phenothiazine is lengthening of the Q-T interval, which is accompanied by widening, blunting and notching of the T wave [Kelly, H.G., and Laverty 1963 and Burda C.D., 1978].

These changes reflect the disturbances in ventricular repolarization and were found by Huston and Bell (1966) in 53 of 106 (50%) hospitalized psychiatric patients receiving