

RECENT TRENDS IN CARDIAC THERAPY WITH ATARAXIC AGENTS

By

R. B. ARORA

Department of Pharmacology, All India Institute of Medical Sciences, New Delhi.

Very recently with the advent of ataraxic agents there has been a tremendous upsurge of interest in Psychopharmacology and the tranquillising compounds have been employed not only in the treatment of mentally ill persons but also in a multiplicity of other ailments. However in spite of the fact that heart is referred as the "Specific organ of anxiety comparable to the eyes as the sense organ of sight" little attention has been given to the use of these agents in cardiac disorders. We have shown that in experimental cardiac arrhythmias the normal action of the heart can be restored by some of the tranquillising agents. The 14 tranquillisers which form part of today's talk belong to 5 chemical groups.

1. Alkanediol dicarbamate.
2. Alkamine ester of diphenylacetic acid.
3. Indole ethylamine derivatives.
4. Phenothiazines.
5. Ketonic substituted Decalin derivative.

The experimental techniques used were selected with a view to satisfy the existing theories of Cardiac Arrhythmias.

Over the years, three aetiological concepts have found widespread support.

1. Multiple heterotopic impulse formation which assumes a complete functional independence of small areas each responding to its own abnormal pacemaker (Herring, 1900; Lewis, 1909; Engelman, 1895; Kisch, 1950).

2. Single heterotopic tachysystole, by which a single ectopic auricular focus inherent frequency will discharge repetitively and therefore act as auricular pacemaker (Trendelenberg, 1903; Rothberger and Winterberg, 1916; Scherf and Terranova, 1949; Prinzmetal *et al.*, 1952).

3. Circus movement theory (Mines, 1913; Lewis, 1918; Carrey, 1914, 1924; DeBoer, 1920; Rosenblueth and Garcia Ramos, 1947 a, b; Samojloff, 1952), where either one impulse traverses auricular tissue in a circular fashion with tangential off-shoots or where multiple small circuits may be established.

Much less work has been done on the mechanism of ventricular arrhythmias. Different workers have stressed the importance of ectopic focus (Harris and Guevara Rojas, 1943; Harris and Matlock, 1947; Harris, 1950; Kennamer and Prinzmetal, 1954; Osborne *et al.*, 1951) and multiple reentry mechanisms (Katz and Pick, 1953, 1956). The presence of circus waves have not been demonstrated (Kennamer and Prinzmetal, 1954).

In view of this disagreement as to the mechanism of cardiac arrhythmias, in the present study use was made of only those experimental procedures which are representative of each theory (Dick and McCawley, 1955), auricular fibrillation produced by acetylcholine (Multiple foci), by aconitine (Single ectopic focus) and injury stimulation induced auricular flutter (Circus movement).

4. The methods selected for the production of ventricular arrhythmias, i.e. ventricular tachycardia resulting from experimental acute myocardial infarction and ouabain induced ventricular arrhythmias, in the unanesthetised dog, bear a close aetiological semblance to similar arrhythmias encountered a clinical practice (Harris *et al.*, 1951; Winbury and Hemmer, 1956; Clark and Cumming, 1956).

OBSERVATIONS AND RESULTS

In our experiments both quinidine-benactyzine and quinidine-alseroxylon mixtures were found to show potentiative synergism, while a mixture of quinidine and meprobamate showed an additive synergism. No untoward side-effects of the drugs were noticeable in the unanesthetised dog. A quinidine-chlorpromazine mixture, however, did not show significant synergistic response, and reserpine actually antagonised the effect of quinidine.

In view of the fact that quinidine-chlorpromazine mixture did not offer much hope 10 other phenothiazine derivatives known to possess ataractic activity were tried.

Taking into consideration both potency and the systemic toxicity, it is felt that promethazine, promazine, prochlorperazine and perphenazine are very promising drugs and that the clinical trials of these compounds in selected cases of cardiac arrhythmias, may yield a therapeutically superior quinidine substitute.

The individual dosages of these drugs when used in combination were much less than their toxic dosages, and we may hope that their synergistic action will prove useful in the treatment of cardiac arrhythmias. On the other hand, we cannot yet offer any information on drug mixtures in man.

It might be worth mentioning that some of the indigenous Indian tranquillising agents have shown the same type of cardiac activity as the synthetic ones, e.g. Jatamansone, (pure ketonic principle isolated from Jatamansi by Govindachari) which we have recently shown to possess tranquillising properties was also found to possess puissant antiarrhythmic activity. It may be interesting to mention here that general pharmacological and toxicological investigation on this indigenous tranquilliser have shown it to be very safe substance in therapeutic dosages. Similarly volatile oil from *Acorus Calamus* on which one of my colleagues Dr. Dandiya has published a number of papers on its potential tranquillising properties has been shown by us to be effective in Cardiac Arrhythmias. These 2 drugs are awaiting clinical trial. The especial advantage that the use of tranquillising drugs offers in cardiac arrhythmias are two (1) They allay the anxiety states, stress and emotional upheaval which are prone to be associated with cardiac arrhythmias, especially tachycardia and extrasystole (2) Secondly by possessing a *per se* antiarrhythmic action they can revert the irregular rhythm to the normal sinus one.