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A COMPARISON OF ANTIFIBRILLATORY DRUGS IN THE HEART-LUNG PREPARATION

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Quinidine, amethocaine, Trasentin and atropine have been tested for their ability to stop atrial fibrillation produced in the heart-lung preparation of the dog by stimulating the right atrium in the presence of acetylcholine. The results suggest that atropine acts by specifically antagonizing acetylcholine, but that amethocaine and Trasentin act chiefly by virtue of their quinidine-like properties.

The method of producing atrial fibrillation in the heart-lung preparation of the dog, as described by Burn, Vaughan-Williams and Walker (1955), provides a preparation in which atrial fibrillation can be initiated and continued at will. It therefore offers suitable conditions for evaluating antifibrillatory drugs. However, this fibrillation requires the continuous infusion of acetylcholine and is abolished by atropine.

Few studies have been carried out in which antifibrillatory drugs have been tested directly for their efficacy in preventing or stopping experimentally induced atrial fibrillation. More frequently, a less direct technique has been used. Thus Dawes (1946) described a method of determining the maximum rate at which rabbit atria would respond to electrical stimuli, and suggested that drugs which reduced this rate might prove useful in treating atrial fibrillation in man.

We have investigated the relative activity of a series of drugs in abolishing atrial fibrillation in the dog heart-lung preparation. The drugs to be tested were chosen because they had very dissimilar relative potencies when tested on electrically stimulated rabbit atria (Dawes, 1946) and when tested for their action in inhibiting the effect of acetylcholine on the isolated rabbit atria (Elio, 1948). It was of interest to find out how far the ability of these substances to stop fibrillation maintained by infusion of acetylcholine was due to their atropine-like (anti-acetylcholine) action and how far it was related to their quinidine-like property as measured by Dawes.

METHODS

Fibrillation in the Heart-lung Preparation.—The preparation was set up and atrial fibrillation was established as described by Burn *et al.* (1955). The minimal rate of infusion of acetylcholine at which fibrillation would persist for at least 15 min. after stopping the stimulation was determined. This rate was continued for the rest of the experiment.

The drug to be tested was dissolved in 0.9% NaCl solution and infused from a burette into the blood flowing into the superior vena cava. As soon as fibrillation was abolished the drug was stopped and the amount infused was recorded. Attempts were then made to re-establish fibrillation by electrical stimulation in the usual way. If it was re-established and persisted for more than 1 min. after the end of stimulation the drug was again infused until normal rhythm returned. The preparation was tested once more to see if fibrillation would persist. The final reading was therefore the least amount of drug required to abolish fibrillation and to prevent its being effectively re-established.

The presence or absence of atrial fibrillation was determined from the blood pressure record, from the electrocardiogram and by direct observation.

Quinidine-like Action on Rabbit Atria.—The method described by Dawes (1946) was followed exactly.

RESULTS

The results of nine experiments on the heart-lung preparation are set out in Table I.

DISCUSSION

By the method described here, it is not possible to control all the variable factors which might affect the amount of drug required to abolish fibrillation. For instance, the amounts of acetylcholine necessary to maintain fibrillation ranged from 1.0 to 12.0 mg./min., and it is possible that preparations differing in sensitivity to acetylcholine might also vary either directly or inversely

TABLE I

AMOUNTS OF DRUGS REQUIRED TO STOP ATRIAL FIBRILLATION

Expt.	Rate of Infusion of Acetylcholine (mg./min.)	Drug	Duration of Infusion of Drug (min.)	Amount of Drug Given (mg.)	Mean Amount (mg.)
1	3·2	Quinidine	10	10·0	
2	1·2	,,	17	12·7	13·9
3	1·0	,,	20	19·0	
4	4·0	Amethocaine	20	14·0	16·6
5	12·0	,,	16	19·2	
6	1·5	Trasentin	36	5·9	4·8
7	2·8	,,	9	3·8	
8	1·2	Atropine	2	0·005	0·005
9	1·2	,,	5	0·005	

in their sensitivity to antifibrillatory drugs. However, the results do not give evidence of any consistent variation of this sort. There is, for instance, a threefold difference in sensitivity to acetylcholine between the two experiments with amethocaine, and the less sensitive preparation required slightly more amethocaine to abolish fibrillation. On the other hand, the results from the experiments with quinidine and Trasentin suggest that those preparations which require most acetylcholine to produce fibrillation require least antifibrillatory drug to abolish fibrillation.

When comparing antifibrillatory potencies it would be desirable to infuse the drugs at such a rate that effective doses were given in equal times. During prolonged infusions, some of the drug might be absorbed by tissues other than the heart or even metabolically inactivated in some way; in either case it would be necessary to give more of the drug at low rates of infusion than at higher rates. Comparison of the doses of drugs required and the durations of the infusions do not suggest that these complications have arisen in these experiments. Indeed, a heart-lung circuit allows only limited possibilities for elimination of added drugs.

The relative potencies of quinidine, amethocaine, Trasentin and atropine in abolishing atrial fibrillation are given in Table II and compared with their relative potencies in reducing the maximum rate at which isolated rabbit atria can be driven (Dawes, 1946) and in antagonizing the action of acetylcholine on isolated rabbit atria (Elio, 1948). It is evident that atropine is very effective in the preparations involving the use of acetylcholine. The ratios of activity of quinidine to atropine in antagonizing acetylcholine and abolishing fibrillation are approximately the same, and it would seem at first sight that quinidine exerted its antifibrillatory action here solely by virtue of its atropine-like activity. However, this cannot be true of Trasentin, which has 1/10 of the activity of atropine in antagonizing acetylcholine, but only 1/1500 of its activity in abolishing fibrillation. Furthermore, since amethocaine is quite devoid of atropine-like activity on atria, its antifibrillatory activity must be due to a "quinidine-like" property. Though on the preparation of Dawes amethocaine has 11.5 times the activity of quinidine, it has only 1/8 the potency of quinidine in abolishing atrial fibrillation induced by acetylcholine. This discrepancy might be due to the fact that it actually potentiates the action of acetylcholine on the atria.

TABLE II

RELATIVE ACTIVITY OF QUINIDINE, AMETHOCAINE, TRASENTIN AND ATROPINE IN VARIOUS PREPARATIONS

The asterisk indicates a value taken from our own results. The numerals in the table are the ratios of activity, on a molar basis, taking quinidine = 1.

Preparation	Quinidine	Amethocaine	Trasentin	Atropine
Driven rabbit atria (Dawes, 1946)	1	11·5	0·59	0·17*
Antagonism of acetylcholine on rabbit atria (Elio, 1948)	1	Potentiation	400	4,000
Abolition of atrial fibrillation in the dog heart-lung preparation	1	0·13	1·6	2,470

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