Some Antiarrhythmic Actions of Primaquine, Amodiaquin, and Quinidine

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This study concerns (*a*) the antiarrhythmic properties of amodiaquin and primaquine in comparison with those of quinidine and (*b*) the ionic fluxes caused by acetylcholine and the depression of these fluxes by the antiarrhythmic drugs used. Under (*a*) it was found that both amodiaquin and primaquine are as effective as quinidine in halting atrial fibrillation induced by the injection of acetylcholine after pretreatment with neostigmine. Under (*b*) no ion fluxes were demonstrated after the injection of acetylcholine under the conditions of the experiment.

QUINIDINE is an established drug in the treatment of cardiac disorders. It is the dextroisomer of quinine and is the most active of the cinchona alkaloids in antiarrhythmic activity (1). Quinidine has been reported by Lewis (2) to have the following effects on heart muscle: it depresses excitability, slows conduction, slows the rate, increases the refractory period, and causes a decrease in vagal tone. It has no effect on the contractility of the heart in normal doses.

A search of the literature revealed two synthetic antimalarials that had been studied only a very little for their antiarrhythmic activity. In the few studies that have been done on these drugs it was shown that they are more effective than quinidine in halting atrial fibrillation; these two drugs are amodiaquin and primaquine (3–5).

Arora, *et al.* (3), have shown that amodiaquin is more effective than quinidine in reversing aconitine-induced auricular fibrillation in cats. In another report, Arora, *et al.* (4), have shown that amodiaquin possesses a quinidine-like action on the refractory period of isolated rabbit atria and has a stronger antifibrillatory action on acetylcholine-induced atrial fibrillation in dogs than quinidine. Arora (4) has also reported that amodiaquin differs from quinidine in not protecting against epinephrine-induced ventricular arrhythmias and causing a greater slowing of conduction rate and less prolongation of the refractory period.

Primaquine has been reported by Arora, *et al.* (5), to be more effective than quinidine in protecting dogs against atrial fibrillation induced by the topical application of aconitine and atrial flutter caused by crush stimulation of the atria, but did not show protective action against epinephrine-hydrocarbon-induced ventricular arrhythmias. It has been shown (5) by the electrocardiograph that primaquine increases the refractory period and conduction time of the heart more than did quinidine.

Several authors have also shown that acetylcholine stimulates the efflux of potassium and the influx of sodium in myocardial tissue (6–12). It has also been reported that quinidine depresses this ionic flux (8–10).

EXPERIMENTAL

Antiarrhythmic Study.—One object of these studies was to compare the action of amodiaquin and primaquine with quinidine as to relative effectiveness in halting atrial fibrillation induced by the injection of acetylcholine after the animal had been pretreated with neostigmine.

Five mongrel dogs weighing from 15 to 24 Kg. were used in these studies. Each animal was anesthetized with pentobarbital sodium solution, 35 mg./Kg. intraperitoneally. The anesthetic was supplemented, if necessary, by pentobarbital sodium solution intravenously.

Control electrocardiograms were taken on all animals to determine if any cardiac abnormalities were present. If the animal exhibited any it was rejected.

All electrocardiograms were taken on a Sanborn model 150 four-channel recorder and monitored visually at all times with a Sanborn Visoscope oscilloscope. Standard limb lead II was used and the lead wires were connected to the animal by means of subcutaneous electrode needles.

All injections were made through an indwelling 21-gauge needle placed in either the right or left saphenous vein. To keep the needle from plugging, a very slow (3 to 5 drops/minute) infusion of isotonic sodium chloride was allowed to infuse. The animals were placed in the prone position with the posterior elevated to facilitate the drainage of the copious salivary secretions caused by the acetylcholine.

A method of initiating atrial fibrillation of sufficient duration and predictability to determine the effectiveness of the three drugs was adapted from the following. Leveque (13) produced atrial fibrillation averaging about 25 seconds in dogs by thyroid administration and acetylcholine injection. Loomis and Krop (14) reported that atrial fibrillation could be induced in dogs by the injection of acetylcholine

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after the animal had been pretreated with an anticholinesterase agent.

The latter method was found to be the most reliable for inducing atrial fibrillation of extended duration. The cholinesterase agent chosen was neostigmine bromide which was given in a dose of 0.05 mg./Kg. A dose of 0.15 mg./Kg. of acetylcholine 30 minutes after neostigmine was found to produce an atrial fibrillation of long duration with nonfatal respiratory embarrassment.

To summarize, the atrial fibrillation was induced four times by the injection of acetylcholine, after pretreatment with prostigmine, for each treatment with each drug. The average time of the first and second fibrillation served as the control time, and the average time of the third and fourth fibrillation served as the treatment time. Each animal was used three times at random intervals and was treated with each of the antiarrhythmic drugs, fibrillation being produced 12 different times in each.

Drugs and dosages used in the antiarrhythmic study were as follows

Drug[1]	Dose, mg./Kg.
Neostigmine bromide	0.05
Acetylcholine chloride	0.15
Quinidine gluconate	5.00
Amodiaquin hydrochloride	4.00
Primaquine dihydrochloride	4.00

Ion Studies.—The purpose of these studies was to determine the extent to which acetylcholine causes a sodium and potassium flux and to determine whether the three antiarrhythmic drugs studied would depress it.

Serum sodium and potassium were determined using a Beckman model DU spectrophotometer with a flame attachment according to the method of Hawk, *et al.* (15).

All blood samples were drawn from either the right or left saphenous vein or the right or left radial vein in the following order: control (no drug administered except the anesthetic), 20 minutes after prostigmine, immediately after acetylcholine, and shortly after the antiarrhythmic drug. The 5-ml. samples of blood were allowed to coagulate in a refrigerator and then were centrifuged and the clear supernatant serum was drawn off. The serum was diluted 1:250 for the determination of sodium and 1:100 for the determination of potassium. This method is described in Hawk, *et al.* (15).

In this series each dog was used three times as in the antiarrhythmic studies. Blood samples were taken in the order indicated each time the dog was used in the antiarrhythmic study and analyzed for sodium and potassium.

RESULTS AND DISCUSSION

Antiarrhythmic Study.—Each figure of Table I expresses time as minutes:seconds, and is the average of two determinations, showing the average duration of an atrial fibrillation.

The columns labeled "before" show the duration of control fibrillations and the columns labeled "after" are the fibrillatory periods after treatment with the antiarrhythmic drug.

[1] These drugs were kindly furnished by the respective manufacturers: neostigmine bromide, Roche Laboratories; acetylcholine chloride, Merck & Co.; quinidine gluconate, Eli Lilly and Co.; amodiaquin HCl, Parke Davis; primaquine diHCl, Winthrop Laboratories.

It can be seen from Table I that all of the drugs are effective in shortening the duration of the acetylcholine-induced atrial fibrillation. To determine if the three drugs are equally effective, a statistical analysis of the results was done. This is a randomized block experiment with three treatments (drugs) and five replications (dogs).

The difference between the control (before) times and the treatment (after) times was used in the statistical analysis. These differences appear in Table II, the differences being expressed as seconds.

The statistical analysis shows that the three drugs are effective in shortening the duration of the acetylcholine-induced atrial fibrillation, $F = 86.19$.

It also indicates that the dogs are not a variable in this experiment, $F = 0.556$.

And finally the statistical analysis shows that the three drugs in the doses used are equally effective in shortening the duration of the acetylcholine-induced atrial fibrillation. These results do not support those of Arora, *et al.* (3–5), who state that both amodiaquin and primaquine at a dosage level of 4 mg./Kg. are more effective than quinidine at a dosage level of 5 mg./Kg. Our work shows an equal effect of the three drugs at a dosage of 4 mg./Kg. for amodiaquin and primaquine compared to 5 mg./Kg. for quinidine, thus indicating a stronger effect for the two experimental drugs. This difference in results can probably be explained by the different experimental techniques. In their work the heart was exposed and the atrial fibrillation was induced by the direct application of acetylcholine or aconitine. This extensive surgical manipulation may have caused a general weakening of the animal or an altered ionic concentration and have affected their results.

Ion Studies.—At no point in these studies is there any indication of a statistically significant ion flux. The ranges for the ion values obtained are presented in Table III.

These findings do not agree with those of the authors cited previously (6–12), however the methods used are probably not comparable.

Most work done previously was done on an isolated perfused preparation. Holland used an isolated perfused amphibian heart. The differences in experimental techniques and the differences between an isolated perfused amphibian heart and an intact mammalian heart are probably responsible for the differences between this work and his. Conn and Wood (8) used a dog's heart as an isolated perfused preparation. Again wide variations in experimental techniques are probably responsible for the difference in results.

There is a strong possibility that these ionic fluxes occur so rapidly that it is difficult to collect a blood sample at the exact peak of the flux. There is also a possibility that these ion changes are of such magnitude that the instrument used in this study would not be sensitive to them. Still another possibility for the discrepancy in these results and those of other workers is that the red blood cells may play a role in adjusting these fluxes. As the blood is coagulating, the red blood cells may tend to adjust the ionic imbalances back toward normal. Still another possibility for the inability to demonstrate these fluxes is that the kidney may make a rapid readjustment.

TABLE I.—FIBRILLATORY DURATION TIME

Dog No.	Quinidine, 5 mg./Kg. Before	Quinidine, 5 mg./Kg. After	Amodiaquin, 4 mg./Kg. Before	Amodiaquin, 4 mg./Kg. After	Primaquine, 4 mg./Kg. Before	Primaquine, 4 mg./Kg. After
1	5:20	2:20	4:45	4:15	5:20	3:10
2	3.47	2:27	2:25	1:35	4:07	1:56
3	3:28	1:34	2:30	1:10	2:25	1:10
4	6:00	3:05	5:25	3:10	2:30	1:07
5	4:12	2:19	3:51	2:00	4:03	3:00

TABLE II.—DIFFERENCE BETWEEN AVERAGE TIMES OF TABLE I

Dogs	Quinidine	Amodiaquin	Primaquine	Replication Totals
1	180	30	130	340
2	80	50	131	261
3	114	80	75	269
4	175	135	83	393
5	113	111	63	287
Total	662	406	482	1,550

Calculation of F Value

Source of Variation	Sum of Squares	Degrees of Freedom	Mean Square	F
Replication	4,113.5	4	1,033.35	0.556
Grand mean	160,166.6	1	160,166,66	86.19
Treatment	6,914.2	2	3,457.10	1.86
Error	14,865.8	8	1,858.23	
Total	186,080.0	15		

TABLE III.—RANGE OF ION VALUES IN MEQ./L.

	Low	High
Sodium		
Control	154.0	185.5
Neostigmine	137.5	187.0
Acetylcholine	130.0	215.0
Quinidine	125.0	182.2
Amodiaquin	142.0	170.5
Primaquine	145.0	186.5
Potassium		
Control	4.8	8.5
Neostigmine	4.9	9.9
Acetylcholine	4.2	10.2
Quinidine	5.4	7.6
Amodiaquin	6.13	9.0
Primaquine	4.4	6.5

SUMMARY AND CONCLUSIONS

An investigation of the antiarrhythmic properties of amodiaquin and primaquine has shown them to be as effective as quinidine in shortening the duration of experimentally induced atrial fibrillation but of stronger antiarrhythmic activity. The atrial fibrillation was induced by the injection of acetylcholine after the animal had been pretreated with the anticholinesterase agent, prostigmine.

This study has attempted to show the ionic changes caused by acetylcholine. Further, this study has attempted to show that these ionic fluxes are depressed by the antiarrhythmic drugs studied. No ionic fluxes are demonstrated at any point in this study so it could not be said that quinidine or related drugs had any demonstrable effect on the ionic concentration or ionic fluxes of the myocardial tissue.

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