A COMPARISON OF THE ANTIARRHYTHMIC ACTIVITIES OF AMODIAQUIN, PRIMAQUINE, AND QUINIDINE

by

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A Comparison of the Antiarrhythmic Activities of Amodiaquin, Primaquine, and Quinidine

Introduction

Quinidine is an established drug in the treatment of cardiac disorders. Quinidine is the dextroisomer of quinine and is the most active of the cinchona alkaloids in antiarrhythmic activity.[23] Quinidine has been reported by Lewis[15] to have the following effects on the heart muscle. It depresses the 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.

The electrocardiographic changes caused by quinidine are quite characteristic and are related to its effect on the repolarization time which it lengthens. There is broadening of the Q-T interval and a flattening and broadening of the T wave.[20]

Atrial fibrillation is the commonest of all cardiac irregularities making up fifty percent of the total number of rhythm disturbances and is responsible for from sixty to seventy percent of all serious cardiac

failures.[9] In atrial fibrillation the atria do not necessarily beat at the same rate.[20] Quinidine should not be used to treat a long standing atrial fibrillation, atrial fibrillation during heart failure, or atrial fibrillation in the presence of cardiac enlargement.[22] There are three serious dangers in using quinidine in the treatment of atrial fibrillation. They are sudden death, progressive cardiac enlargement with subsequent cardiac failure, and pulmonary insufficiency.[22]

Quinidine has several toxic reactions that limit its usefulness among which are thrombopenia with purpura, skin rashes, nausea, vomiting, shock and vascular collapse, tinnitus, vertigo, intense nervousness, and emotional reactions that may lead to psychosis.[8] These toxic reactions have lead investigators to search several different chemical groups of drugs with a wide variety of pharmacological actions in search of a drug that would be as effective as quinidine in cardiac arrhythmias but less toxic. Among the groups studied are the local anesthetics,[8, p.512] antihistaminics[18] other antimalarials,[1][2][3] and adrenergic blocking agents.[17] While all of the above drugs have some

antiarrhythmic activity they are generally less active than quinidine.

A search of the literature revealed two synthetic antimalarials that had been studied 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 in halting atrial fibrillation than quinidine; these two drugs are amodiaquin and primaquine.

Arora et al.[1] have shown that amodiaquin is more effective than quinidine in reversing aconitine induced auricular fibrillation in cats. In another report Arora et al.[3] 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[3] 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.[2] 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[2] by the electrocardiogram that primaquine increases the refractory period and conduction time of the heart more than did quinidine.

While amodiaquin and primaquine are both synthetic antimalarials they have some chemical similarities to quinidine. Quinidine and primaquine both possess a methoxy group, they all have a basic nitrogen in a side chain, and amodiaquin and primaquine are both aminoquinoline derivatives. Although quinidine does not have a nitrogen attached directly to the quinoline ring it could be viewed as an aminoquinoline derivative. It has been reported by Dawes[7] that compounds with aromatic and basic groups joined by an ester, ether, keto, or carbinol linkage are the most active. It can be seen from Figure I that all of these compounds possess the groups necessary for the greatest activity.

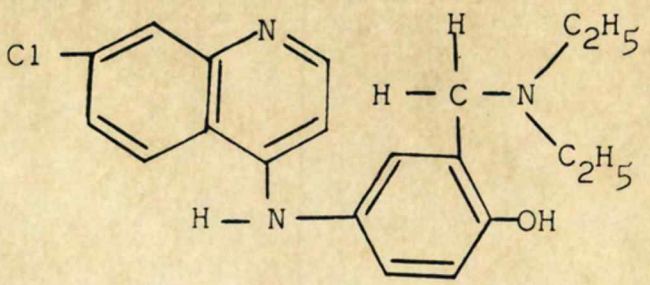
The structures of the three compounds are presented in Figure I.

It has been shown by several authors[4][5][6][11][12][13][21] that acetylcholine stimulates the outflux of potassium and the influx of sodium in the myocardial tissue. It has also been reported by several authors that quinidine depresses this flux.[6][11][12]

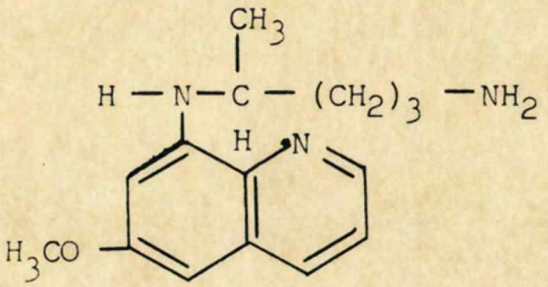
Figure I

Structures of the Antiarrhythmic Drugs

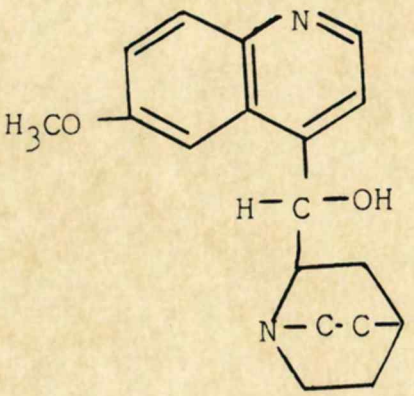
Amodiaquin



Primaquine



Quinidine



Reports by W. C. Holland[11][12] have shown that acetylcholine stimulates the loss of potassium from the isolated frog atria and produces atrial arrhythmias. When quinidine was added with the acetylcholine the rate of potassium loss was considerably depressed and the arrhythmias did not persist after the cessation of the acetylcholine stimulation. He also stated that the myocardial depressant properties of quinidine depend upon the potassium concentration and that quinidine also slows the outflux of potassium from the myocardial tissue and that this is the probable mechanism of action of quinidine.

Conn and Wood[6] using an isolated perfused heart say that quinidine causes an increased influx of potassium into the myocardial cells during the resting phase but during the active phase quinidine causes no increase or demonstrable alteration in the potassium outflux or the total potassium exchange. If any change occurs, a slight decrease in potassium influx takes place.

Johnson and Robertson[13] have reported that quinidine produces cardiac arrest by interfering with the sodium carrier mechanism. They also report that acetylcholine causes an increase in potassium

permeability of the heart and that it stimulates the sodium carrying mechanism.

Bammer[4] states that acetylcholine influences the potassium concentration of the myocardium by changing the membrane potential to sodium.

Burgen and Terroux[5] have reported that the main effect of acetylcholine on the heart is an increase in the passive permeability of the heart to potassium.

Shanes[21, p.125] states that acetylcholine causes a loss in potassium from the mammalian heart and that quinidine reduces the potassium lost from the atrial fibers.

As a result of the questions arising in the above review it was decided to compare the effectiveness of amodiaquin and primaquine with that of quinidine in controlling atrial fibrillation in the dog. It was also decided to test whether acetylcholine causes a sodium and potassium flux and to determine, if this flux is demonstrated, whether quinidine, amodiaquin, and primaquine would depress this flux.

Experimental Methods

Arrhythmic Studies

The object of these studies was to determine if amodiaquin and primaquine were as effective as quinidine in halting atrial fibrillation.

Five mongrel male dogs weighing from 15 to 24 kilograms with an average weight of 20.4 kilograms were used in these studies. Each animal was anesthetized with pentobarbital sodium solution, 35 mgm/kgm intraperitoneally. The anesthetic was supplemented, if needed 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 abnormalities, it was rejected.

All electrocardiograms were taken on a Sanborn Model 150 four channel recorder and monitered visually at all times with a Sanborn Viso-scope 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.

All animals were placed in the ventral position with the posterior end elevated to facilitate the drainage of the copious salivary secretions caused by acetylcholine.

A method of initiating atrial fibrillation of sufficient duration and predictability to determine the effectiveness of the three drugs was adapted from works as discussed below.

Leveque[14] produced atrial fibrillation in dogs by thyroid administration and intravenous injection of acetylcholine. When using acetylcholine alone, atrial fibrillation was produced in 30 percent of his animals and in the thyrotoxic animals he was able to produce atrial fibrillation in 81 percent. The average duration of the atrial fibrillation produced by both methods was about 25 seconds which is not sufficient to permit studies in cardiac arrhythmias. Another problem with this method is the respiratory embarassment due to the bronchiolar constriction and the copious salivary secretion caused by acetylcholine.

Loomis and Krop[17] reported in 1955 that atrial fibrillation could be induced in unanesthetized normal dogs, goats, and monkeys. By the use of the proper

anesthetic drug, and the pretreatment of the dogs with an anticholinesterase agent to prevent rapid degradation of acetylcholine, injected acetylcholine or vagal stimulation produced atrial fibrillation of extended duration. This fibrillation can be extended and sometimes accelerated by the injection of more acetylcholine or further vagal stimulation.

It was decided that the most predictable and reliable method of inducing atrial fibrillation of extended duration would be to administer an acetylcholinesterase inhibiting agent followed by the injection of acetylcholine. The cholinesterase inhibitor chosen was prostigmine bromide which was given in a dose of 0.05 mgm/kgm. The dose of acetylcholine found to produce the atrial fibrillation of the longest duration with nonfatal respiratory embarassement was 0.15 mgm/kgm and this dose was used throughout the experiment.

By adapting the above techniques an attempt was made to develope a relatively safe, dependable method for inducing ventricular fibrillation but none was found and any attempt to study the effects of these drugs on ventricular arrhythmias was discontinued.

To summarize the atrial fibrillation was produced four times by the injection of acetylcholine after the pretreatment of the animal with prostigmine. 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 varying intervals and was treated with each of the antiarrhythmic drugs.

Drugs used in the antiarrhythmic study were:

Drug	Dose	Manufacturer
Prostigmine Bromide *	0.05 mgm/kgm	Roche Laboratories
Acetylcholine Chloride *	0.15 mgm/kgm	Merck & Company
Quinidine Gluconate *	5.00 mgm/kgm	Eli Lilly & Co.
Amodiaquin HCl *	4.00 mgm/kgm	Parke Davis & Co.
Primaquine diHCl *	4.00 mgm/kgm	Sterling-Winthrop

* Generously donated by the respective companies.

Ion Studies

The purpose of these studies was, as stated earlier, 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.

All blood samples were drawn from either the right or left saphenous vein or the right or left radial vein.

Sodium and potassium were determined using a Beckman Model DU Spectrophotometer with a flame attachment. Standard, known solutions of sodium and potassium were made and run concurrently with the determination of the serum potassium and sodium. These serum values were obtained from the standard curve prepared with each determination. This method is described in Hawk et al.(10)

Blood samples were taken in the following order: control (no drug administered except the anesthetic), twenty minutes after prostigmine, immediately after acetylcholine, and shortly after the antiarrhythmic drug. Approximately 5 cc samples of blood were taken and the blood was allowed to coagulate in a refrigerator. After coagulation the blood was 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.

In these studies each dog was used three times as in the antiarrhythmic studies. Blood samples were taken in the order previously given each time the dog was used in an antiarrhythmic study and analyzed for sodium and potassium.

Results and Discussion

Antiarrhythmic Studies

All of the times in Table I are the average of two determinations and are expressed as minutes:seconds.

The columns labeled "before" are the controls. The columns labeled "after" are the times after treatment with the antiarrhythmic drug.

Table I

Results of the Antiarrhythmic Studies

	Quinidine 5 mg/Kgm		Amodiaquin 4 mg/Kgm		Primaquine 4 mg/kgm	
	Before	After	Before	After	Before	After
Dog 1	5:20	2:20	4:45	4:15	5:20	3:10
Dog 2	2:47	2:27	2:25	1:35	4:07	1:56
Dog 3	3:28	1:34	2:30	1:10	2:25	1:10
Dog 4	6:00	3:05	5:25	3:10	2:30	1:07
Dog 5	4:12	2:19	3:51	2:00	4:03	3:00

It can be seen from the table 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.

Table II

Differences Between Average Times of Table I

	Drugs			
Dogs	T_1	T_2	T_3	T_r
R_1	180	30	130	340
R_2	80	50	131	261
R_3	114	80	75	269
R_4	175	135	83	393
R_5	113	111	63	287
T_t	662	406	482	G=1,550

T_1 represents quinidine, T_2 represents amodiaquin, T_3 represents primaquine, T_r represents the replication totals, and T_t is the treatment totals. G is the grand total. The R's are the five dogs used in this experiment.

Table III

Analysis of Variance of Table II

Type of Total	Total of Squares	No. of Items Squared	Observations per Squared Item	Total of Squares Observation
Grand	2,402,500	1	15	160,166.66
Replication	493,900	5	3	164,300.00
Treatment	835,404	3	5	167,080.80
Observation	186,080	15	1	186,080.00

Calculation of F Values

Source of Variation	Sum of Squares	Degrees of Freedom	Mean Square	F.
Replication	4,133.4	4	1,033.35	0.556
Treatment	6,914.2	2	3,457.10	1.86
Grand	160,166.6	1	160,166.66	86.19
Error	14,865.8	8	1,858.23	
Total	186,080.0	15		

If we take as the first hypothesis that the three drugs have no effect on the duration of the acetylcholine-induced atrial fibrillation, the critical region of F at the 5 percent level with 1 and 8 degrees of freedom is F greater than 5.3177. The F value obtained from the analysis of variance calculations is 86.19 which is highly significant and the hypothesis is rejected. This means that the drugs are effective in shortening the duration of the acetylcholine-induced atrial fibrillation.

If as the second hypothesis we assume that the dogs are equal in effect, that is the influence of the dogs on the drugs is equal, the critical region of F at the 5 percent level with 4 and 8 degrees of freedom is F greater than 3.8378. The F value obtained from the analysis of variance calculations is 0.556 which is outside of the critical region and the hypothesis is accepted. This means that the dogs are not a variable in this experiment, that their influence on the drugs is equal.

If the third hypothesis is the assumption that the three drugs are equally effective in shortening the duration of the acetylcholine-induced atrial fibrillation, that is that the three treatment means are

equal, the critical region of F with 2 and 8 degrees of freedom at the 5 percent level is F greater than 4.459. The F value obtained from the calculations is 1.86. This value is outside of the critical region and the hypothesis is accepted. This shows that the three drugs are equally effective in shortening the duration of the acetylcholine-induced atrial fibrillation.

The statistical analysis has shown that amodiaquin and primaquine at a dosage level of 4 mgm/Kgm are as effective as quinidine at a dosage level of 5 mgm/Kgm in reducing the length of the acetylcholine-induced atrial fibrillation. Even though amodiaquin and primaquine have lower absolute total times in the difference between the control times and the treatment times than quinidine, this is not a significant difference and the drugs are equally effective.

The results obtained in this series do not support the results obtained by Arora et al.[1][2][3] who state that both amodiaquin and primaquine are more effective than quinidine in halting experimentally-induced atrial fibrillation. Part of this difference 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 tissue or altered ionic concentration and affected their results.

Ion Studies

These results are presented in the following tables. Tables IV through VIII are the results with quinidine. Tables IX through XIII are the results with amodiaquin and tables XIV through XIX are the results with primaquine.

Table IV

Na^+ meq/l. with Quinidine as the Treatment Drug

Dog	Control	Prostigmine	Acetylcholine	Quinidine	T_r
1	163.0	155.0	215.0	140.0	673.0
2	158.5	149.0	175.0	125.0	607.5
3	185.5	168.2	182.0	182.2	717.9
4	158.0	187.0	165.0	163.0	673.0
5	154.0	148.0	130.0	160.0	592.0
T_t	819.0	807.2	867.0	770.2	G=3263.4

Table V

Analysis of Variance Calculations for Table IV

Source of Variation	SS	DF	MS	F
Replication	2,700.69	4	675.17	1.69
Treatment	956.99	3	318.99	0.82
Error	4,174.92	12	392.91	
Total	8,372.60	19		

If as the first hypothesis we assume that the five replication effects are equal, that is, the five dogs all respond the same way to the drugs, the critical region of F at the 5 percent level with 4 and 12 degrees of freedom is F greater than 3.2592. The F value obtained from the calculations is 1.69 which is outside of the critical region and the hypothesis is accepted.

If we let the second hypothesis be that the four treatment means are equal, the critical region of F at the 5 percent level with 3 and 12 degrees of freedom is F greater than 3.4903. The F value obtained from the analysis of variance calculations is 0.82 which is outside of the critical region and the hypothesis is accepted. This means that there is no ion flux demonstrated. Even though there appears to be a difference in the treatment totals, this is not statistically significant.

Table VI

K^+ meq/l. with Quinidine as the Treatment Drug

Dog	Control	Prostigmine	Acetylcholine	Quinidine	T_r
1	5.5	6.0	6.3	5.4	23.2
2	6.8	7.1	6.8	6.4	27.1
3	6.2	9.9	8.7	6.2	31.0
4	7.8	5.9	6.4	7.6	27.7
5	5.5	6.2	7.1	5.8	24.6
T_t	31.8	35.1	35.3	31.4	G=133.6

Table VII

Analysis of Variance Calculations for Table VI

Source of Variation	SS	DF	MS	F
Replication	10.63	4	2.66	2.89
Treatment	2.57	3	0.86	0.88
Error	11.66	12	0.97	
Total	24.86	19		

If we take as the first hypothesis that the drugs affect all of the dogs in the same way, that is, the five replication effects are equal, the critical region of F at the 5 percent level with 4 and 12 degrees of freedom is F greater than 3.2595. The F value shown in

Table VI is 2.89 which is outside of the critical region and the hypothesis is accepted.

If we let the second hypothesis be that the four treatment means are equal, the critical region of F at the 5 percent level with 3 and 12 degrees of freedom is F greater than 3.4903. The F value obtained from the calculations is 0.88 which is outside of the critical region and the hypothesis is accepted. This means that there is no ion change demonstrated.

The following four tables show the ionic effects of the drugs with amodiaquin as the antiarrhythmic drug.

Table VIII

Na^+ meq/l. with Amodiaquin as the Treatment Drug

Dog	Control	Prostigmine	Acetylcholine	Amodiaquin	T_r
1	140.5	154.0	140.5	170.5	605.5
2	161.0	151.0	148.0	150.0	610.0
3	152.5	139.0	137.0	142.0	570.5
4	155.0	160.0	137.5	155.0	607.5
5	160.0	168.0	152.0	158.0	638.0
T_t	769.0	772.0	715.0	775.5	G=3031.5

Table IX

Analysis of Variance Calculations for Table VIII

Source of Variation	SS	DF	MS	F
Replication	272.87	4	68.22	0.59
Treatment	490.95	3	163.65	1.1
Error	1785.12	12	148.76	
Total	2548.94	19		

If we let the first hypothesis be that the five replication effects are equal, that is, the dogs all respond the same way to the drugs, the critical region of F at the 5 percent level with 4 and 12 degrees of freedom is F greater than 3.2592. The F value obtained from the analysis of variance calculations is 0.59 which is outside of the critical region and the hypothesis is accepted.

If we let the second hypothesis be that the four treatment means are equal, the critical region of F at the 5 percent level with 3 and 12 degrees of freedom is F greater than 3.4903. The F value shown in Table IX is 1.1 which is outside of the critical region and the hypothesis is accepted. This means that there is no ion flux shown. Even though there appears to be a difference in the treatment totals, this is a chance effect and is not statistically significant.

Table X

K^+ meq/l. with Amodiaquin as the Treatment Drug

Dog	Control	Prostigmine	Acetylcholine	Amodiaquin	T_r
1	6.25	7.1	6.6	6.13	26.08
2	6.45	7.25	7.25	6.6	27.55
3	5.75	5.75	5.5	7.15	24.15
4	8.5	8.8	10.2	9.0	36.5
5	7.4	8.6	8.8	7.1	31.9
T_t	34.35	37.5	38.35	35.98	G=147.18

Table XI

Analysis of Variance Calculations for Table X

Source of Variation	SS	DF	MS	F
Replication	2.52	4	0.63	1.77
Treatment	1.86	3	0.62	1.77
Error	4.20	12	0.35	
Total	8.58	19		

If both hypothesis remain the same as they were in the analysis of variance of Table VI they are both accepted and no ion flux is demonstrated.

The following four tables show the results obtained using primaquine as the antiarrhythmic drug.

Table XII

Na^+ meq/l. with Primaquine as the Treatment Drug

Dog	Control	Prostigmine	Acetylcholine	Primaquine	T_r
1	166.5	137.5	186.5	186.5	677.0
2	160.0	150.0	155.0	145.0	610.0
3	155.0	146.0	130.0	150.0	581.0
4	173.0	164.0	158.0	146.0	641.0
5	159.0	138.0	159.0	148.0	604.0
T_t	813.5	735.5	788.5	775.5	G=3113.0

Table XIII

Analysis of Variance Calculation for Table XII

Source of Variation	SS	DF	MS	F
Replication	1383.3	4	345.75	1.96
Treatment	636.5	3	212.18	1.2
Error	2110.7	12	175.89	
Total	4130.55	19		

If both hypotheses remain the same as they were in the analysis of variance of Table VIII, they are both accepted. This shows that no ion flux has occurred in this series of experiments.

Table XIV

K^+ meq/l. with Primaquine as the Treatment Drug

Dog	Control	Prostigmine	Acetylcholine	Primaquine	T_r
1	5.6	6.1	5.75	5.65	23.1
2	5.9	5.56	5.56	6.5	23.5
3	7.4	7.2	5.9	6.4	26.9
4	4.8	4.9	4.2	4.4	18.3
5	5.9	5.6	5.6	5.4	22.5
T_t	29.6	29.36	27.01	28.35	G=114.3

Table XV

Analysis of Variance Calculations for Table XIV

Source of Variation	SS	DF	MS	F
Replication	9.44	4	2.36	2.71
Treatment	2.16	3	0.72	0.90
Error	10.46	12	0.87	
Total	22.06	19		

If both hypotheses remain the same as they were in the analysis of variance of Table VI they are both accepted and no ion flux is demonstrated.

At no point in this study is there any indication of a statistically significant ion flux. These findings do not agree with those of authors cited earlier in this report.(4)(5)(6)(11)(12)(13)(21)

W. C. Holland's work was done on an isolated perfused amphibian heart. The experimental difference between an isolated perfused amphibian heart and an intact mammalian heart may explain the differences in these studies and his published results.

Conn and Wood(6) even though using a dog heart, still used it as an isolated perfused preparation. The experimental difference between an isolated preparation and an intact heart is probably responsible for the differences in these two works.

There is a strong possibility that these ionic changes occur in such a rapid manner that it is difficult to collect a blood sample at the exact peak of the flux. There is also a possibility that these ionic fluxes are of such magnitude that the instrument used in these studies would not be sensitive to them. Still another possibility for the discrepancy in these results and the published results is that the red blood cells may play a role in adjusting these ionic fluxes. As the blood is coagulating the red blood cells may tend to

adjust these ionic imbalances back towards normal. Still another possibility for the inability to demonstrate these ionic fluxes is that the kidney may rapidly readjust them back toward normal.

Summary and Conclusions

An investigation of the antiarrhythmic properties of amodiaquin and primaquine has shown these two drugs to be as effective as quinidine in shortening the duration of acetylcholine-induced atrial fibrillation. Even though the total difference between the control and treatment times is lower with amodiaquin and primaquine this is not statistically significant and the drugs are equally effective.

This study has attempted to show the ionic changes caused by acetylcholine. Further this study has attempted to show that these ionic changes are depressed by the antiarrhythmic drugs used in this study. No ionic fluxes were demonstrated at any point in this work so it could not be said that quinidine or related drugs had an effect that could be demonstrated on the ionic fluxes caused by acetylcholine.

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