

THE EFFECT OF AMODIAQUINE ON SOME AUTONOMICALLY
INNERVATED ORGANS

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DEDICATION

To my parents, whose ideals for my life I have always tried, not always successfully to fulfil, and whose strength and support is with me today.

To my dear younger brothers and sisters, and to My Son Karuri Junior.

A C K N O W L E D G E M E N T

First and foremost, I would like to extend my sincerel gratitude to my Supervisor Mrs. A.N. Guantai who originally gave me the incentive and courage to undertake this piece of work.

Her constant criticism, patience and moral support is greatly appreciated.

I would also like to extend my thanks to the Department of Pharmacy technical staff and in particular Mrs. Munenge and Mr. Ochieng for their total devotion and assistance in setting-up of the tissues. Nothing would have been possible without their participation. Mr. Njoroge D.K. for arranging the supply of Laboratory Chemicals and drugs.

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CONTENTS:

	<u>Page</u>
1. Abstract	1
2. Literature Review	2
3. Introduction	3
4. Experimental	6
. Drugs/Chemicals	6
. Materials & Instruments	6
. Physiological salt solutions	7
. Methods	8
5. Results	12
6. Discussion	28
7. References	31

ABSTRACT

Amodiaquine is a 4-aminoquinoline used in treatment of Malaria. In the present work, the drug was observed to cause myocardial depression on an isolated rabbit heart even in presence of cardiostimulatory doses of adrenaline. The heart rate decreased whereas the coronary flow rate was slightly affected. These effects were shown to be antagonised by adrenaline which is a known antidote to chloroquine poisoning.

A similar experiment was done where amodiaquine was observed to antagonise Ba^{2+} induced guinea-pig ileum contraction. The action of amodiaquine was dose-dependent and could be due to an overall non-specific spasmolytic activity on the membranes.

On the phrenic nerve-diaphragm preparation, the drug had a concentration-dependent dual action. The action of amodiaquine was antagonised by physostigmine in this case.

Various drugs known to induce parturition and which act on an isolated rat uterus were observed to be antagonised by amodiaquine. The drug caused contractions which depending on the drug, required various doses of amodiaquine to abolish.

LITERATURE REVIEW

Amodiaquine is a 4-aminoquine which is used as an antimalarial at a dose of 400 to 600 mg daily for 3 days. Suppressive cure is 400 mg weekly

It is occasionally associated with gastrointestinal symptoms which include nausea, vomiting and diarrhoea. The specific mechanism of action on the smooth muscles or the autonomic nervous system to explain this is not known (5).

Chloroquine like mepacrine and quinine exert non-specific antagonism on prostaglandin induced contractions in the guinea-pig isolated ileum and behaves as an overall spasmolytic agent. It is likely that the overall inhibitions observed in the study with quinine and mepacrine are also related to non-specific membrane properties which might affect the smooth muscles reactivity rather than to any specific antagonism (6).

The enhanced Ca^{2+} uptake by infected cells suggests that the erythrocyte membrane of infected cells may be more permeable to Ca^{2+} or that the Ca^{2+} - Mg^{2+} ATPase that gates efflux from the erythrocytes may be inoperative. Rat erythrocytes infected with plasmodium ch chalaudi contain elevated levels of Ca^{2+} relative to normal erythrocytes.

It has also been demonstrated with $^{45}\text{Ca}^{2+}$, that both increased Ca^{2+} influx, and decreased efflux contribute to the elevated Ca^{2+} levels of infected erythrocytes (9).

In rheumatoid arthritis, the tissue demand for adenosine triphosphate is increased and that amodiaquine inhibits adenosine triphosphatase (10).

Ephedrine has been observed to have two opposite actions on the neuromuscular junction, facilitation and or depression depending on the dose and frequency of stimulation. It could act by altering the C-AMP in nerve or muscle via the adenylate cyclase system.

Amphetamine, an indirectly acting amine also had this concentration dependant dual action (7).

Chloroquine and propranolol can oppose the positive chronotropic and inotropic effect of the isolated rat muscle diminishing also the aminophylline cardiostimulant action, but not the Ca^{2+} Chloroquine may block β -adrenergic receptors of the myocardium (3).

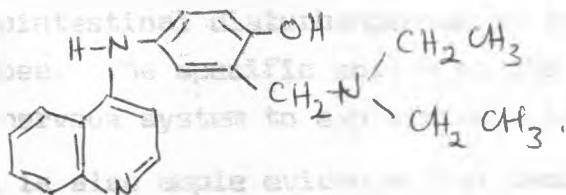
Amodiaquine and chloroquine have received trials as antitremulatory agents but are considered too toxic for this purpose due to excessive of nodal tissue (5).

There is also ample evidence that amodiaquine has effect on the excitable process of nerve and muscle tissue (ibid). Even though the aminoquinolines interact with the DNA, there is no evidence that they are carcinogenic. However the possibility should be borne in mind. In very high doses, amodiaquine is teratogenic (2).

It has been found that amodiaquine is more effective than chloroquine against chloroquine resistant plasmodium falciparum. (13).

INTRODUCTION

STRUCTURE:



Amodiaquine Hydrochloride; Camoquin is 4-(7-chloro-4-quinolylamino) - (diethylamino) - O - cresol.

It occurs as a yellow, odourless crystalline powder being bitter taste. It is soluble in water sparingly soluble in alcohol and very slightly soluble in Ether, chloroform and benzene (12).

It is known to possess some antiinflammatory activity. The actual mechanism of action is not known although in rheumatoid arthritis, it is known that tissue demand for adenosine triphosphate is increased and that amodiaquine inhibits adenosine triphosphatase.

It is also used in the treatment of hepatic amoebiasis and due to its low toxicity, it is preferred to emitine. Its specificity to *entamoeba histolytica* in the liver is due to the fact that it is concentrated in this organ.

It is capable of eradicating malaria from the erythrocyte and hence it is used in the clinical cure of *plasmodium falciparum* malaria, whereas it will only cure the acute attacks in the other types of malaria.

Chloroquine is known to possess quinidine like effects on the heart. Amodiaquine also a 4-amino-quinoline may possess this effect. The two drugs have received trials as antifibrillatory agents but are considered too toxic to be useful for this purpose; since the doses required are higher than those required for malaria.

Orally administered amodiaquine has been observed to have some gastrointestinal disturbances which include nausea, vomiting and diarrhoea. The specific action on the smooth muscles or the autonomic nervous system to explain this is not known.

There is also ample evidence that amodiaquine has effect on the excitable process of nerve and muscle tissue (5). In many cases there may be difficulty in accommodation, headache and dizziness. These are not very serious side effects especially if the drug is used in its usual dosage for malaria.

However, even at this dosage level the skin may be affected as shown by pruritus, bleaching of hair, and various rashes. Dryness, itching, urticaria, maculopapular eruption, pigmentation, desquamation and even exfoliation could occur. Alopecia with or without bleaching of the hair has been reported. (5.).

Though amodiaquine was thought at first to be more toxic, many field trials have shown the drug to be no more toxic than chloroquine.

With the widespread use of the drug in rheumatoid arthritis discoid lupus Erythematosus, and amoebiasis, serious toxicity has been evidenced on the skin, eye, and blood.

On prolonged therapy, leukopenia may be observed. This is not severe and complete bone marrow depression has not been reported.

The aim of the present work is to try and observe whether and how amodiaquine acts on some of the anatomically innervated organs. These include, the ileum, heart, diaphragm and the uterus in-vitro.

This is in line with the findings that amodiaquine side effects and toxicity is usually manifested in these organs.

However this work is only done with these organs in-vitro, and hence the results are not necessarily to mean that the results obtained can be extrapolated to say that the drug will have the same effects in-vivo. This is because the drug could be metabolised, and the metabolites might be the ones to bring about these effects.

EXPERIMENTAL:Drugs and Chemicals:

<u>Name of drug/chemical</u>	<u>Grade</u>	<u>Manufacturer</u>
Amodiaquine Hydrochloride	Biochemicals	Parke - Davis
Acetylcholine	Biochemicals	BDH McGeorge Ltd.
Barium chloride	Laboratory Chemicals	Howse & McGeorge Ltd.
Carbachol	Laboratory chemicals	Howse & McGeorge Ltd.
Adrenaline	Biochemicals	BDH chemicals Ltd.
Histamine	Biochemicals	BDH chemicals Ltd.
Physostigmine	-	Sigma Products
Oxytolin	-	Richter
Tubocurarine	-	Asta
Prostaglandin F2x	-	UpJohn
.Sodium Chloride	Analar	May and Baker
.Potassium chloride	General purpose	Hopkin Willram
.Calcium chloride	Analar	Aldrich Chemical Co.L
.Magnesium chloride	Analar	BDH chemicals Ltd.
.Magnesium sulphate	Analar	BDH chemicals Ltd.
.Sodium dihydrogen phosphate	Analar	May and Baker
.Potassium cdihydrogen phaeophate	Laboratory chemicals	Howse & McGeorge Ltd.
.Sodium bicarbonate	Analar	BDH chemicals Ltd.
.Glucose	Analar	BDH chemicals Ltd.

MATERIALS & INSTRUMENTS:

Needles and thread, Petri-dishes, Scissors, Liquid paraffin, Scales, Measuring cylinders, beakers, Syringes and needles, Gas-95% O₂ and 5% CO₂, Rats, Guinea Pigs, Rabbits, Crocodile crips, Kymograph paper, bottles, Havard recorder, stop clock.

PHYSIOLOGICAL SALT SOLUTIONS USED

	TYRODE SOLUTION	LOCKE SOLUTION	KREB'S HENSELIE	DEJALON SOLUTION
Sodium chloride	8.0	9.0	6.87	9.0
Potassium chloride	0.2	0.42	0.40	0.42
Calcium chloride	0.2	0.24	0.28	0.06
Magnesium chloride	0.1	-	-	-
Magnesium sulphate	-	-	0.44	-
Sodium dihydrogen phosphate	0.05	-	-	-
Potassium dihydrogen phosphate	-	-	0.46	-
Sodium bicarbonate	1.0	0.2	2.10	0.5
Glucose	1.0	0.1	2.00	0.5

The amounts indicated are in grams/litre.

All the solutions used in this work were freshly prepared. The calcium chloride was dissolved separately and added slowly to the rest of the solution; otherwise the solution turned cloudy due to formation of calcium carbonate.

METHODS:1. EFFECT OF AMODIAQUINE ON THE ISOLATED GUINEA PIG ILEUM:

Amodiaquine has been observed to cause nausea, vomiting and diarrhoea. Adult guinea pigs were sacrificed by a blow on the back of the head. Segments of the ileum 3-cm long, and approximately 5-10cm below the stomach were cut shortly after killing and washed with warm Tyrode physiological salt solution in petri dishes.

The segments were then suspended in either 10 or 20 ml tissue baths with Tyrode solution. These were gassed with 95% Oxygen and 5% Carbon dioxide and maintained at 37°C.

Isometric recordings of the longitudinal contractions or changes in tension were recorded on a Kymograph using pen and paper.

The time allowed for each drug to act was until maximum effect was obtained. Amodiaquine and Barium chloride were used in this experiment. The experimental set up is as shown in Plate 1.

The results obtained are shown in the Figure 1 and Table 1.

2. EFFECT OF AMODIAQUINE OF THE ISOLATED MAMMALIAN HEART (LANDENDORFF PREPARATION)

Chloroquine, a 4-aminoquinoline like amodiaquine has caused deaths which have been attributed to myocardial depression. In a few of the cases, adrenoline has been found to be an effective antidote. In this experiment, amodiaquine is used on an isolated mammalian heart to observe its effects.

In this experiment adult rabbits were killed by a blow on the back of the head. The rib cage was then opened quickly but with caution so that the heart was not damaged.

The heart was then removed with at least 1 cm of aorta attached and washed with warm Locke solution, squeezing gently to remove all blood that would otherwise clot. With the heart still pumping, it was then mounted in the Langendorff apparatus. The heart was lubricated with liquid paraffin and maintained at 36 - 37°C with warm Locke solution. Drugs were then injected into the heart and their effects observed.

The change in myocardial contractility was recorded on paper using a Harvard recorder.

The coronary flow rate /30 seconds was determined according to the volume of liquid collected within 30 seconds.

The Locke solution which was freshly prepared was kept flowing to the heart continuously.

The concentration of amodiaquine was varied and the resting period was 3 minutes. The Langendorff apparatus used are shown in Plate 2.

The results obtained are shown in Fig 2 and Table 2.

3. EFFECTS OF AMODIAQUINE ON THE NEUROMUSCULAR JUNCTION (PHRENIC NERVE - DIAPHRAGM PREPARATION)

Amodiaquine is known to have an effect on the excitable process of nerve and muscle tissue (5). However its mechanism of action on the diaphragm and the phrenic nerve is not known, and this formed the basis of this experiment.

Preliminary experiment was done using the rat diaphragm. A rat weighing roughly 300gms. was killed by a blow on the back of the head, the carotid arteries cut and left to bleed as much as possible to ensure the thorax was free of blood.

The skin over the chest and pectoral muscles was removed and the thorax opened along one side. The ribs were cut close to the thoracic vertebrae, while the areus costalis was left intact.

The phrenic nerve was then removed making sure that it was not pulled hard. The preparation had a fan-like shape with about 2.5cm of phrenic nerve attached to it. The costal margin was fastened to the electrode holder and thread tied around the tendinous end was attached to a light lever writing on a Kymograph drum.

In response to electrical stimulation, the contractions of the diaphragm were recorded. The response of the diaphragm to Tuborurarine, physostigmine and amodiaquine were investigated. Each drug was given maximum time to produce the required effect (approximately 3 - 5 minutes); and the recovery period was also adequate and depended on the particular drug.

Repeating the same procedure outline above an experiment was done to investigate whether amodiaquine had concentration-dependent dual action. In this case the frequency was varied between 2 - 4 pulse per second at various concentrations of amodiaquine.

Thorough washing was done before any drug was added to ensure that the contractions had gone back to the original size.

The set of apparatus used in this case is shown in Figure 3. The physiological solution used in this case is the Kreb's-Henseket solution which was kept at 35°C.

The results are shown in Figure 3a, 3b and 3c.

4. EFFECT OF AMODIAQUINE ON THE RAT UTERUS

The 4-aminoquinoline antimalarials are said to be used locally to induce abortion. An attempt to verify this claim was made in this experiment by conducting a series of experiments to establish the effect of amodiaquine on an isolated rat uterus.

Young origin rats (female) weighing 120-200gms. were used. The sensitivity of the uterus was increased by subcutaneous injection of stilboestrol - 0.1mg/kg body weight, 24-48 hours before the rats were killed.

The animals were killed by a blow on the head and the uterine horns located and carefully dissected out into a petri dish of deJalon Ringers solution freshly prepared and warm.

The horns were cleaned and any extraneous fat and connective tissue removed. The horns were separated at the bifurcation to yield two preparation.

The tissue was set up in a 10ml organ bath containing de-Jalon solution maintained at 32°C and aerated with 95% O₂ and 5% CO₂.

After stabilising for a period of up to 2 hours to minimise the spontaneous activity, drugs were added adhering to a 5 minute time cycle, with a 30 - 60 seconds contact time.

After each drug addition and subsequent recording, the tissue was washed three times with warm de-Jalon solution; and contractions allowed to go back to normal.

The concentration of amodiaquine that caused approximately 75% inhibition of the contractions induced by Prostaglandin F₂ , and Oxytocin was investigated.

The set of apparatus used in this experiment is shown in Plate 1.

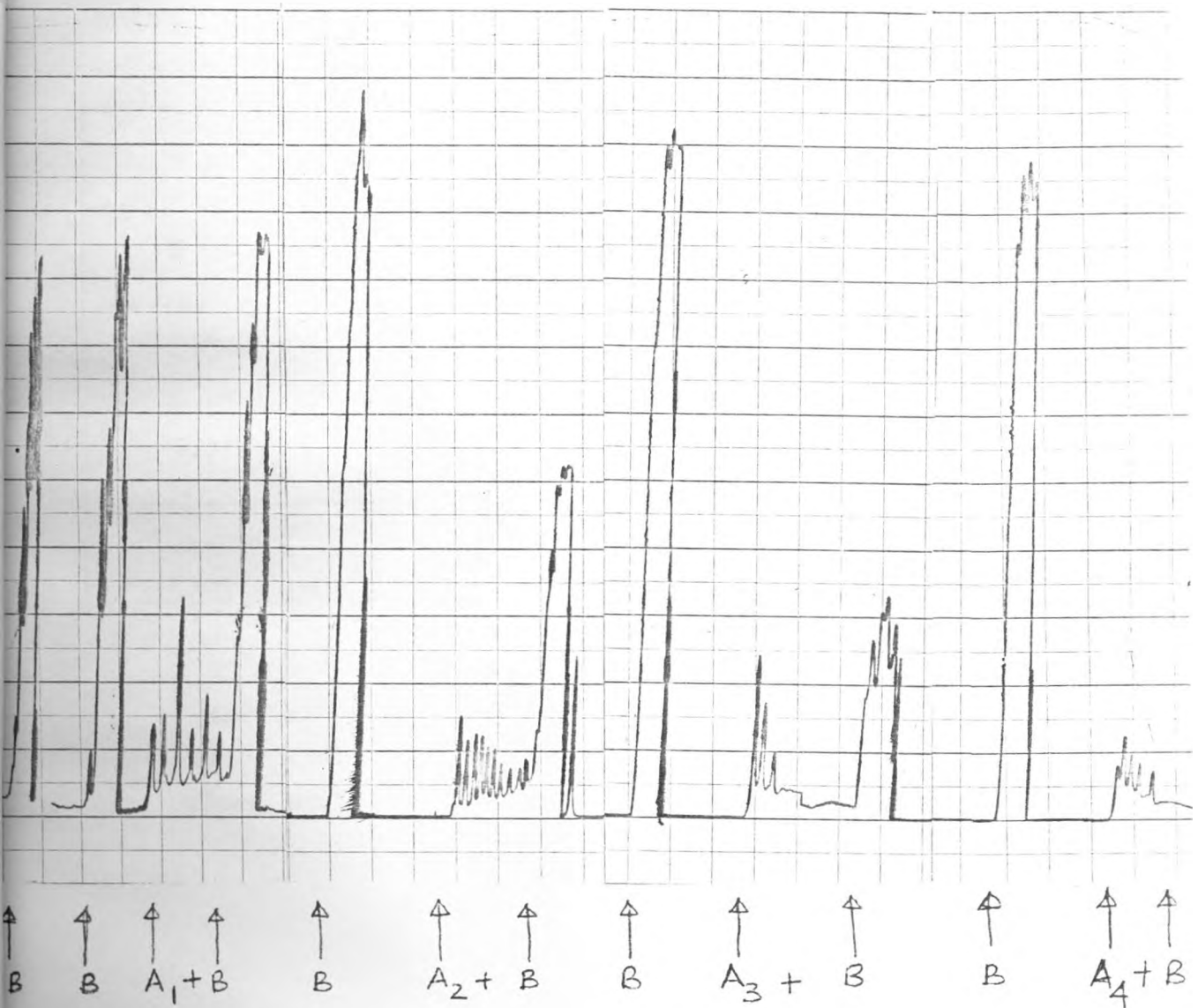
The results are shown in Figure 4a and 4b.

RESULTS:

- . Figure 1 - The Effect of amodiaquine on contractions induced by Barium chloride on isolated guinea-Pig ileum.
- . Figure 2 - Effect of amodiaquine on the isolated mammalian heart.
- . Figure 3a - Effect of amodiaquine on the isolated Rat diaphragm
- Figure 3b - Concentration-dependent dual action of amodiaquine on the Neuromuscular function.
- . Figure 3c - Effect of varying frequency of stimulation while concentration of amodiaquine remains constant.
- . Figure 4a - Effect of amodiaquine on the isolated rat uterus.
- . Figure 4b - as in 4a.
- . TABLE 1 - The percentage inhibition of Barium chloride induced contractions by Amodiaquine on the Guinea-pig ileum.
- . TABLE II - Effect of amodiaquine on the coronary flow rate per 30 seconds.
- . TABLE III + IV - Percentage inhibitions caused by amodiaquine on Drug induced contractions on isolated rat uterus.
- . PLATES: 1 - Apparatus used to investigate Effect of amodiaquine on isolated guinea-pig ileum and isolated rat uterus.
 - 2 - Apparatus used to investigate the effect of amodiaquine on the isolated mammalian heart - (The Langendorff preparation).
 - 3 - Apparatus used to investigate the Effect of amodiaquine on the isolated rat diaphragm (Phrenic nerve - Diaphragm preparation).
 - 4 - Author is seen injecting a drug into an organ in one of the Experiments.

RESULTS:Effect of amodiaquine on contractions induced by Barium chloride on isolated guinea pig ileum

Fig. 1



B = Barium chloride, Concentration 0.2mg/ml

A₁ = Amodiaquine 0.006mg/ml

A₂ = Amodiaquine 0.012mg/ml

A₃ = Amodiaquine 0.018mg/ml

A₄ = Amodiaquine 0.024mg/ml

TABLE 1

INHIBITION BY AMODIAQUINE ON CONTRACTIONS INDUCED BY BARIUM CHLORIDE ON GUINEA PIG ILEUM

AMODIAQUINE DOSE (mg/ml)	HEIGHT DUE TO BARIUM CHLORIDE	HEIGHT DUE TO AMODIAQUINE	PERCENTAGE INHIBITION
0.006	9.00 cm.	7.50 cm.	16.7%
0.012	10.25 cm.	5.00 cm.	52.0%
0.018	10.00 cm.	3.00 cm	70.0%
0.024	10.50 cm.	1.80 cm.	82.90%
0.030	10.00 cm.	0.25 cm.	100.0%

Concentration of Barium chloride is 0.2 mg/ml.

The concentrations of amodiaquine and Barium chloride given, are the bath concentrations.

ADRENALINE 4ug

AMODIAQUINE 0.48 mg

ADRENALINE 4ug

AMODIAQUINE 0.48 mg

(b) EFFECT OF AMODIAQUINE ON THE ISOLATED MAMMALIAN HEART: (RABBIT)

Fig. 2.

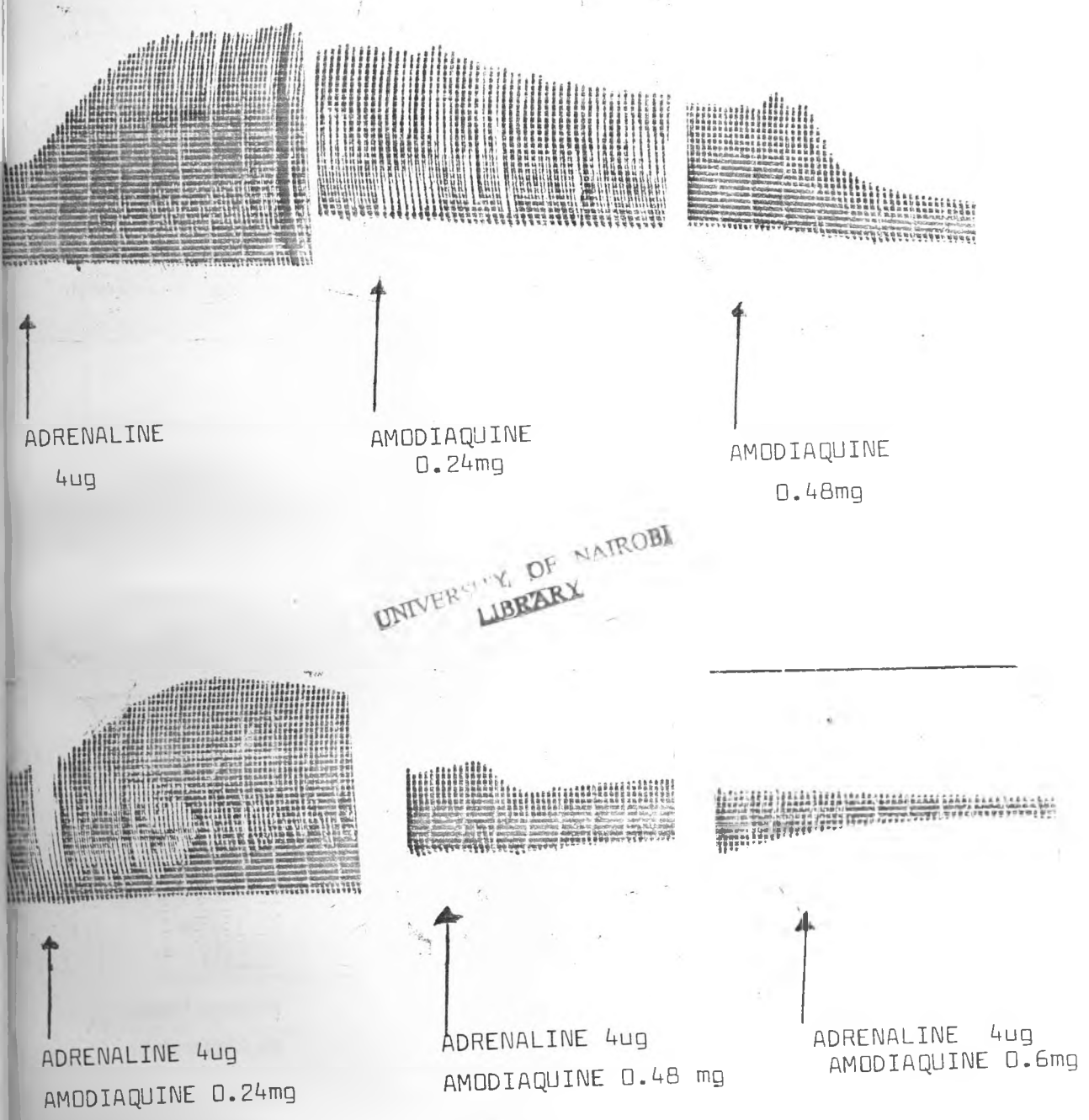


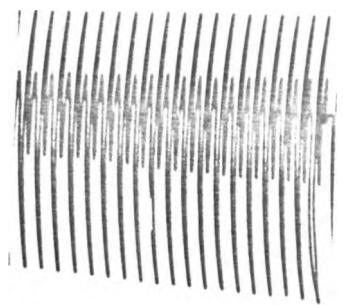
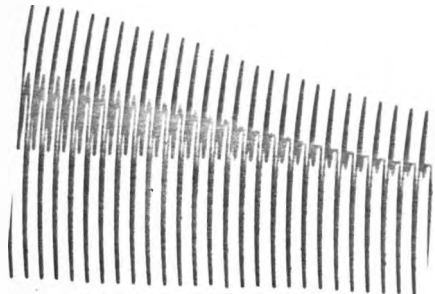
TABLE IIEFFECT OF AMODIAQUINE ON THE CORONARY FLOW RATE PER 30 SECONDS

DRUG(S)	DOSE	CORONARY FLOW RATE (mls/30 seconds)
-	-	23
-	-	22
Adrenaline	4 ug	14
"	"	13
Amodiaquine	0.24 mg	21
"	"	21
-	-	21
Amodiaquine + Adrenaline	0.24 mg 4.0 ug	} 14)
-	-	18
Amodiaquine +Adrenaline	0.36 mg 4.0 ug	} 18)
-	-	16
Amodiaquine + Adrenaline	0.48 mg 4.0 ug	} 16)

(-).....Means Control.

EFFECT OF AMODIAQUINE ON THE ISOLATED RAT DIAPHRAGM:

Fig. 3a



BOCURARINE
1.05mg/ml

↑
AMODIAQUINE
1.2mg/ml

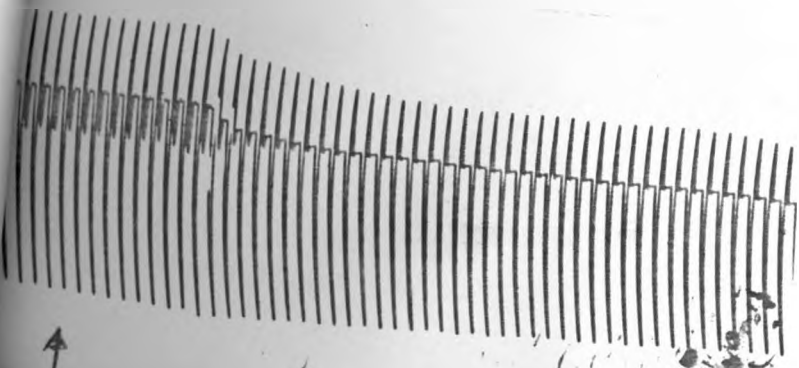
↑
PHYSOSTIGMINE
(0.5ug/ml)

X = Amodiaquine 1.2mg,
Physostigmine 0.5
0.5 ug/ml



↑
X

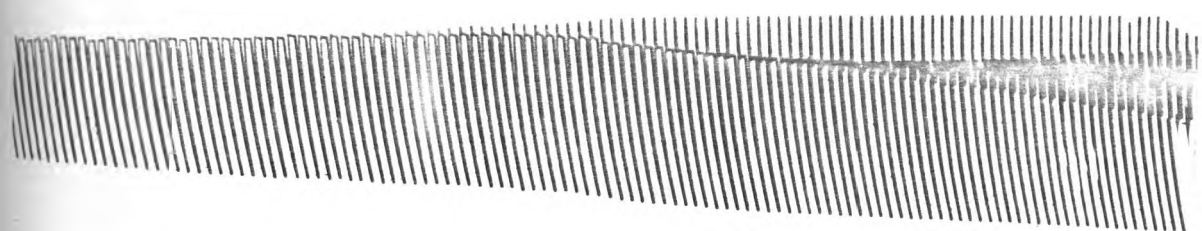
Y = Amodiaquine 1.2mg/ml
Physostigmine 1.0ug/ml



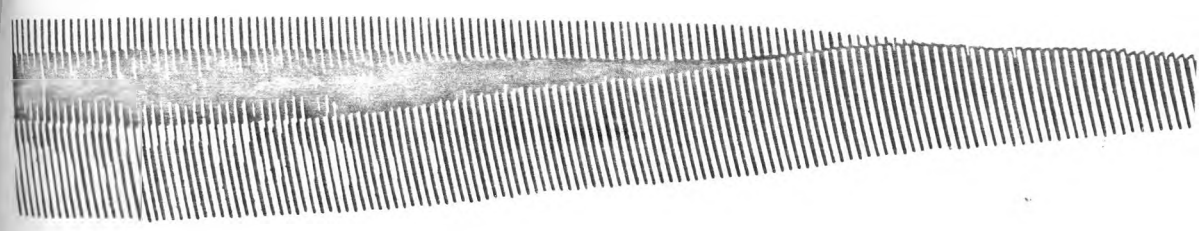
↑

CONCENTRATION-DEPENDENT DUAL ACTION OF AMODIAQUINE ON THE NEUROMUSCULAR JUNCTION:

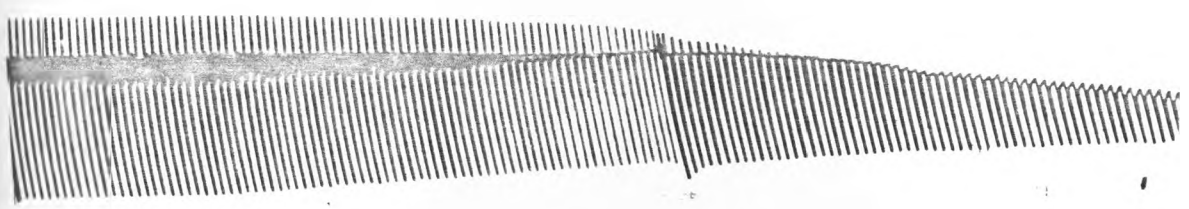
(i) Increasing the concentration while frequency of stimulation remains constant (2 pulse per second)



↑
Amodiaquine 30 ug/ml

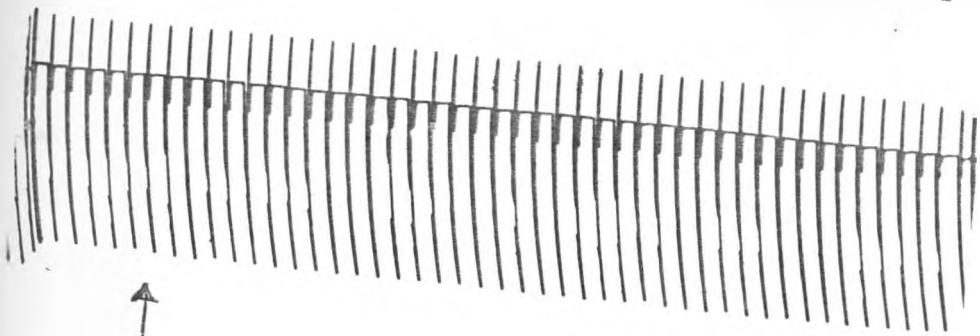


↑
Amodiaquine 60 ug/ml

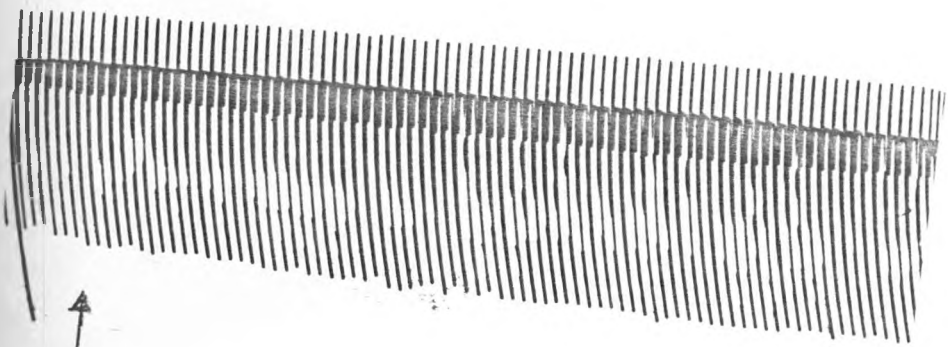


↑
Amodiaquine 90 ug/ml

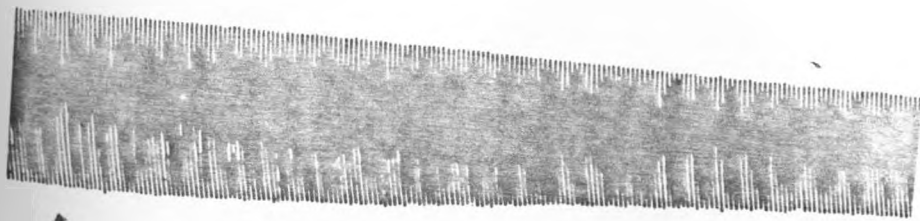
(ii) Varying the frequency of stimulation while concentration of amodiaquine remains constant. (30 ug/ml) Fig. 3c.



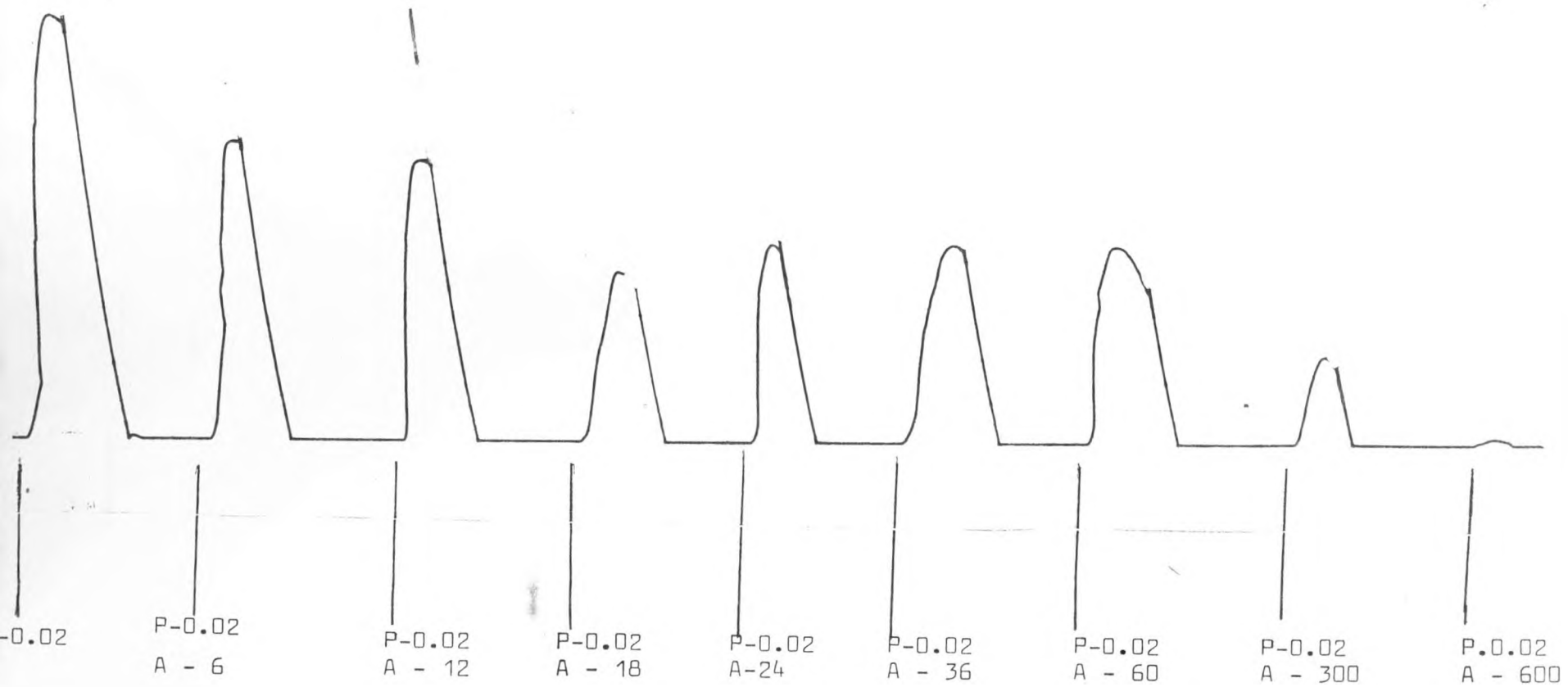
↑
1 pulse per second



↑
2 pulse per second



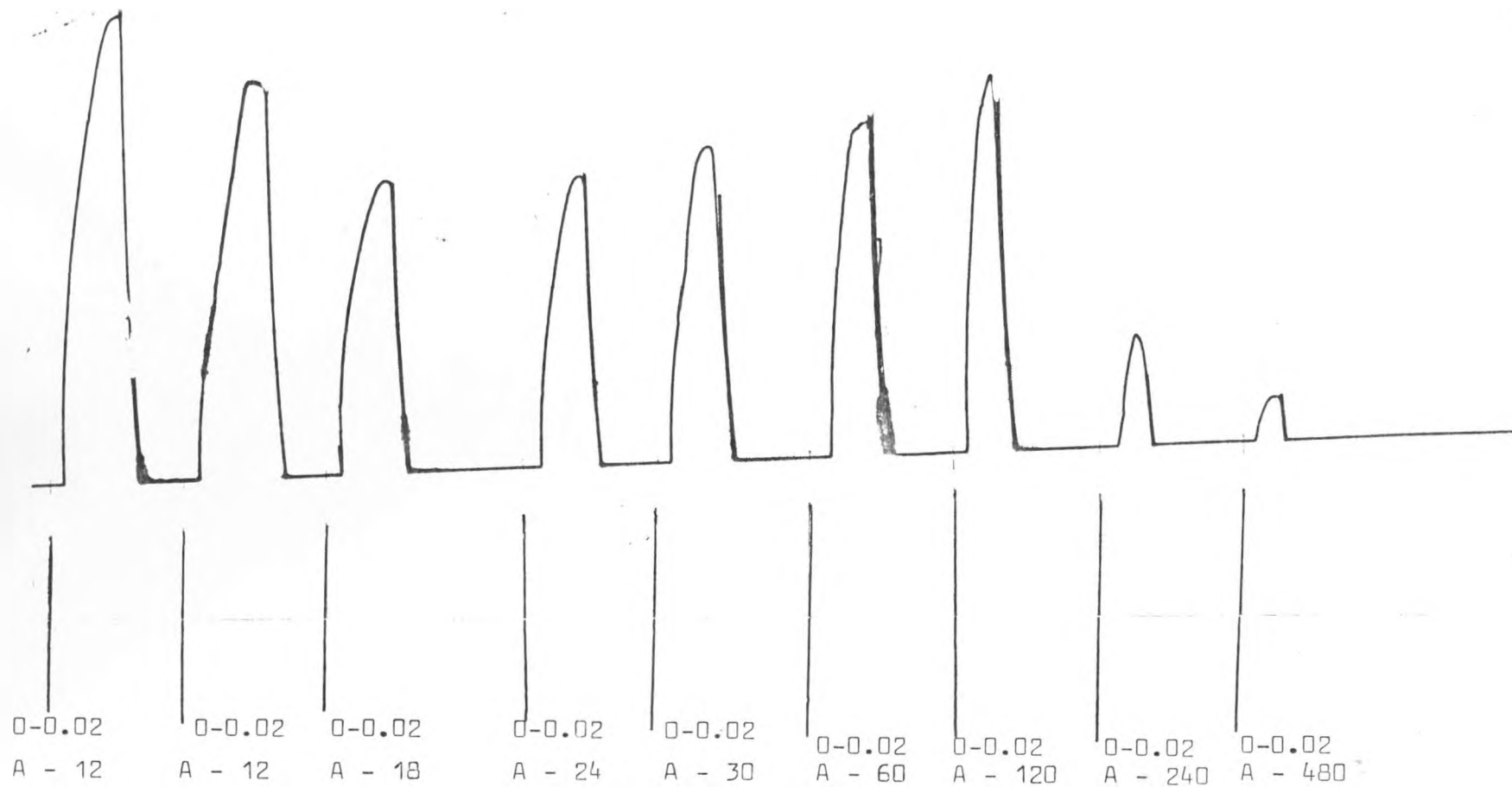
↑
4 pulse per second

Fig. 4a: EFFECT OF AMODIAQUINE ON THE ISOLATED RAT UTERUS

P.....PROSTAGLADIN F2

A.....AMODIAQUINE

For P amounts stated are in Micrograms/ml)
 For A amounts stated are in Micrograms/ml) BATH CONCENTRATIONS

FIG. 4b: EFFECT OF AMODIAQUINE ON THE ISOLATED RAT UTERUS

O..... OXYTOCIN

A..... AMODIAQUINE

Amounts given are in international Units per Millilitre Bath Concentration for Oxytocin
 Amounts given for Amodiaquine are in micrograms per Millilitre Bath Concentration.

TABLE IIIINHIBITIONS CAUSED BY AMODIAQUINE ON DRUG INDUCED CONTRACTIONS
ON ISOLATED RAT UTERUS

AMODIAQUINE DOSE (ug/ml)	HEIGHT DUE TO PGF2 (cm)	HEIGHT DUE TO TO PGF + AMODIAQUINE (cm)	% INHIBITION
6	6.8	4.8	29.4
12	6.8	4.4	35.3
18	6.8	2.7	63.0
24	6.8	3.2	53.0
36	6.8	3.0	56.0
60	6.8	3.0	56.0
300	6.8	1.4	79.40
600	6.8	0.2	97.1

PGF2 - Prostagladin F2

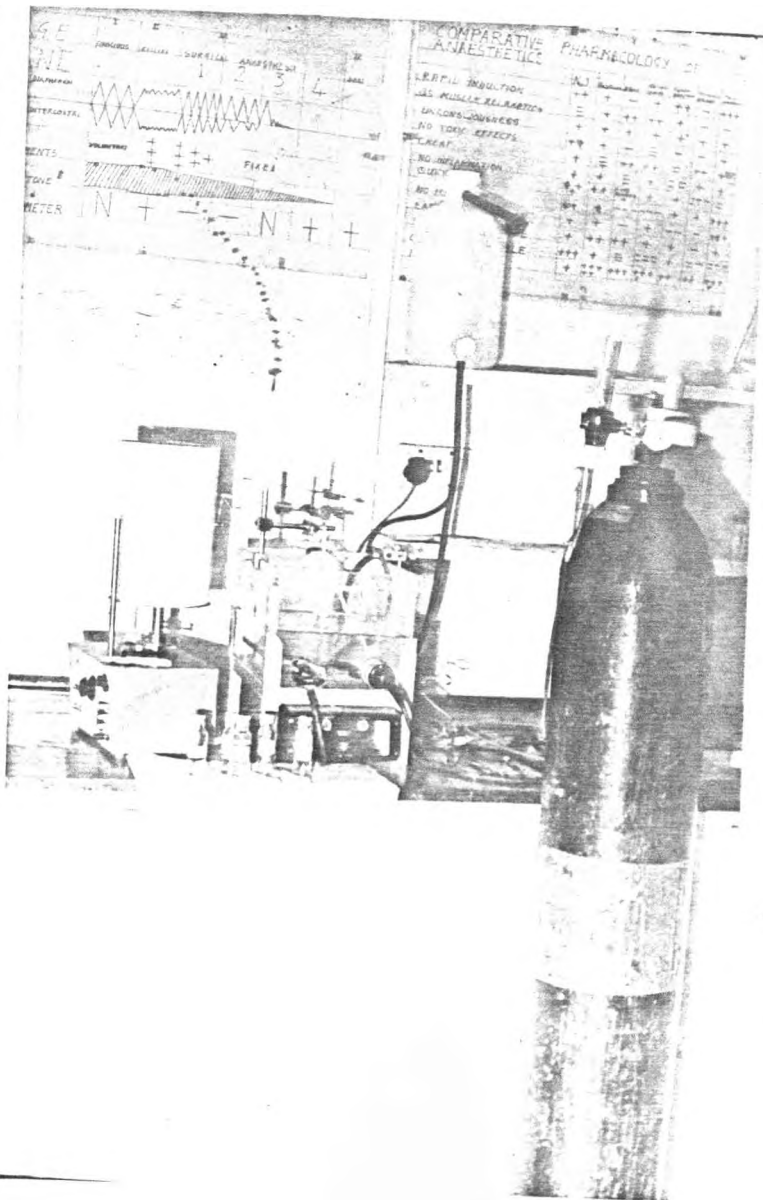
The concentration of PGF2 is in ug/ml.

TABLE IV

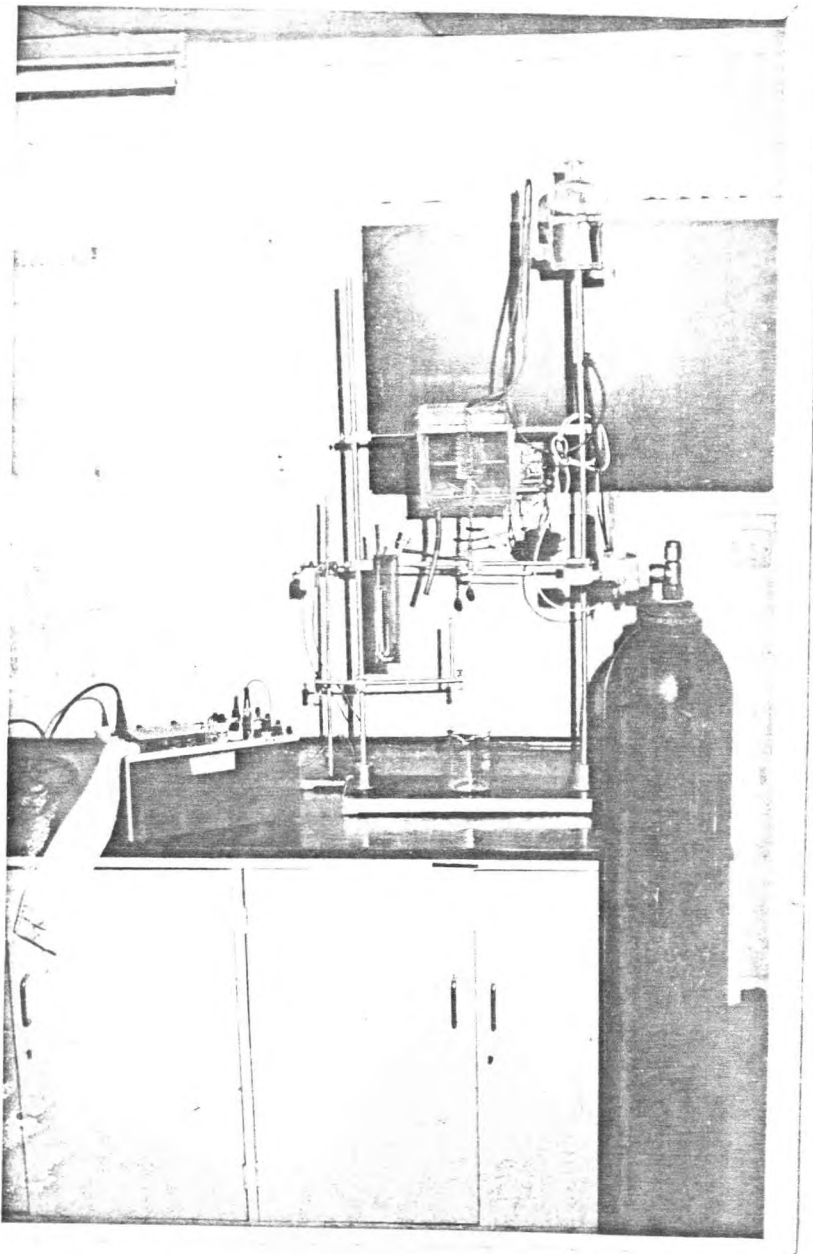
INHIBITIONS CAUSED BY AMODIAQUINE ON DRUG INDUCED CONTRACTIONS
ON ISOLATED RAT UTERUS:

AMODIAQUINE DOSE ug/ml	HEIGHT DUE TO OXYTOCIN (cm)	HEIGHT DUE TO OXYTOCIN + AMODIAQUINE	% INHIBITION
12	7.0	6.0	14.2
18	7.0	4.4	37.0
24	7.0	4.4	37.0
30	7.0	4.7	31.0
60	7.0	5.0	28.5
120	7.0	5.6	20.0
240	7.0	1.6	77.0
480	7.0	0.6	91.0

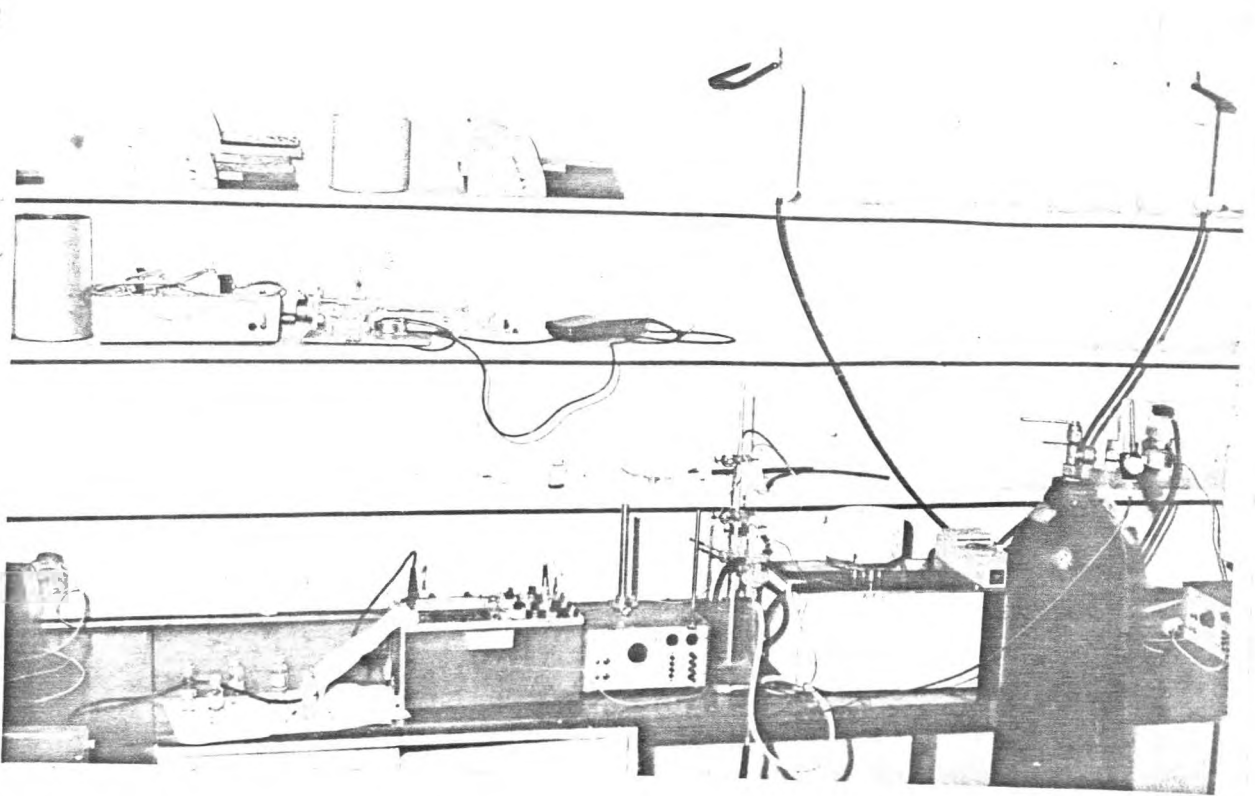
The concentration of Oxytocin is in 1.u/ml, bath concentration.

PLATE 1

ABOVE: This is the setup of apparatus used for investigating the effect of amodiaquine on the isolated Guinea Pig ileum, as well as the isolated rat uterus.

PLATE 2

ABOVE: The above apparatus is the Langendorff heart preparation used for investigating the effect of Amodiaquine on the isolated rabbit heart.

PLATE 3

The figure shows the set-up of apparatus used for investigating the effect of amodiaquine on the isolated rat diaphragm. - Phrenic nerve-Diaphragm preparation.



The author is seen injecting a drug into an organ bath in one of the experiments.

DISCUSSION:

Amodiaquine was observed to inhibit the contractions on the isolated guinea pig ileum caused by Barium chloride. The inhibition was dose dependent and a concentration of 0.03mg/ml (bath contraction) of amodiaquine was observed to cause approximately 100% inhibition to contractions induced by Barium chloride, bath concentration of 0.2mg/ml.

It could have done this by exerting a non-specific overall spasmytic activity on the membranes. It is also known that Ca^{2+} is an essential component of many cellular secretory processes, and is essential for muscle contraction. Since it has been observed that in plasmodium chabandi - infected erythrocytes there is relatively higher concentrations of Ca^{2+} , then it could be said that the antimalarials could either act by causing increased Ca^{2+} extension or inhibiting the influx of Ca^{2+} (9). By doing either of these, they are able to reduce the gastrointestinal motility.

Amodiaquine was observed to cause myocardial depression. Fig 2b, Table 2. Thus it reduced the excitability and conductivity of the cardiac muscles.

Chloroquine acts as a potent myocardial poison, reducing the output of the heart and causing disturbances of conduction, bradycardia and arrhythmias (1).

Amodiaquine also decreased the heart rate which was reversed by adrenaline. The myocardial depression was also antagonised by adrenaline. This makes adrenaline an effective antidote to amodiaquine poisoning.

This would mean that the two drugs could be acting on the same receptors but have antagonistic effects.

Chloroquine poisoning could be attributed to failure of myocardium contraction and aggravated bradycardia. Antidotal therapy with adrenaline and atropine was highly effective (1).

A dose of 0.6mg Amodiaquine injected into the heart caused irreversible myocardial depression, and attempts to antagonise the effect with adrenaline were fruitless. It would hence appear that the amount of amodiaquine which can cause poisoning is rather high. It could also be causing β -adrenergic blockade so as to reduce the heart rate.

Tubocurarine and amodiaquine were observed to have similar action on the isolated rat diaphragm (Fig. 3a). They caused relaxation of the diaphragm, and physostigmine caused contractions.

Amodiaquine and physostigmine were antagonistic in their action and this was shown to be dose dependent (Fig. 3a).

Amodiaquine was also observed to have a concentration dependent dual-action on the Neuromuscular Transmission in-vitro, a concentration of 30ug/ml at a frequency of 2 pulse per second caused contractions of the diaphragm.

When the concentration was increased to 60 and 90mg/ml at a frequency of 2 pulse per second, depression was observed (Fig. 3b).

When the frequency of stimulation was varied and the concentration remained constant, reversal of effect was observed (Fig 3c). A concentration of 30ug/ml was used in this case.

Frequency of 1 and 2 pulse per second was observed to cause facilitation (contraction). Whereas when the frequency of stimulation was increased to 4 pulse per second, there was depression.

Amodiaquine has structural resemblance with anare. Its interaction with end-plate of skeletal muscle involves polar and non-polar interatomic bonds.

It has cationic bonds which means that the interaction with the acetylcholine receptor is more stable. Other types of bonds supplement this ion - ion bonding. These include the hydrogen-bonding due to the presence of oxygen and nitrogen atoms in amodiaquine and the Vander Waals bonds.

The onset of effect of amodiaquine is slow and this could be attributed to the degree of approachment of the compound with the receptor as well as their complementarity.

The effect of amodiaquine was also compared against that of Prostaglandin F2 and Oxytocin on an isolated rat uterus.

Amodiaquine was generally observed to have an inhibitory effect on the contractions induced by prostaglandin F2 and Oxytocin. However amodiaquine had a biphasic trend of action on the effect of the two drugs.

The concentrations used to antagonise the contractions induced by the two drugs varied.

Prostaglandin F2 was used at a concentration of 0.02 ug/ml. The contractions induced on the isolated uterus by Prostaglandin F2 were almost completely abolished by a concentration of 600ug/ml of amodiaquine (bath concentration).

Oxytocin (0.02 i.u/ml bath concentration) induced contractions which were observed, to be antagonised by amodiaquine. These contractions were abolished by a concentration greater than 480 ug/ml of amodiaquine.

The results in (Fig 4a) and (4b) indicate a biphasic response with these two drugs.

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