

SOME PHARMACOLOGICAL ACTIONS OF OXMNIQUINE
ON WHOLE ANIMAL AND ISOLATED TISSUES

BY

other vessels attached to the heart are trimmed away.

MUCHIRI, TABITHA WANJIKU

A DISSERTATION SUBMITTED IN PARTIAL
FULFILMENT FOR THE AWARD OF THE DEGREE OF BACHELOR
OF PHARMACY

DEPARTMENT OF PHARMACY
FACULTY OF MEDICINE
UNIVERSITY OF NAIROBI
KENYA.

JULY, 1982

UNIVERSITY OF NAIROBI
LIBRARY

University of NAIROBI Library



0390489 3

DEDICATION

To my loving father and late mother who first saw the need
for education and took me to school.

To my brother and sisters

To my husband and our son Eric, whose love inspires me
to work harder.

ACKNOWLEDGEMENTS

1. I'm greatly indebted to my supervisor Dr. G. Muriuki without whose guidance this work would not have been realised.
2. To Mrs. Gwantai of the pharmacology section
3. To the technical staff of the pharmacology section especially Mrs. Munenge whose assistance was most invaluable, and to Mr. Wangai for supplying all the animals used.
4. Last but not least to Miss Rosemary Matathia for typing the manuscript.

SOME PHARMACOLOGICAL ACTIONS
OF OXAMNIQUINE ON WHOLE
ANIMALS AND ISOLATED
TISSUES

TABLE OF CONTENTS

CONTENT	PAGE
ABSTRACT	1
INTRODUCTION	3
EXPERIMENTS AND RESULTS	8
DISCUSSION OF RESULTS	24
Conclusion	26
References	27

ABSTRACT

From the experiments carried out, oxamniquine was found to produce drowsiness in mice. This may be due to some of the oxamniquine reaching the central nervous system or due to an active metabolite of the drug which brings about the effects.

Oxamniquine was also found to potentiate pentobarbitone's central nervous system depressant effects in mice. Since pentobarbitone causes enzymes induction, Oxamniquine may be potentiating pentobarbitone by inhibiting the enzymes necessary for pentobarbitone destruction. It may also act by reducing pentobarbitone excretion.

Oxamniquine also reduced the blood pressure of an anaesthetised rat. The fall in blood pressure was prolonged.

Oxamniquine may be producing this prolonged fall in pressure by either slowing the heart, dilating the blood vessels or by its central nervous system depressant effect. Urethane which was used to anaesthetise the rat is related to barbiturates and since oxamniquine was found to potentiate a barbiturate centrally, it may be acting through the central nervous system.

When injected into the perfused heart, oxamniquine was found to cause myocardial depression. The rate of contraction was not affected but the force of contraction was significantly reduced. This however was short lived and the myocardium quickly recovered. Oxamniquine also reduced the force of contraction of the atria but the rate of contraction was not affected. High doses of the drug produced a complete block of articular contraction. Oxamniquine was also found to produce a blockade on phrenic nerve diaphragm preparation of the rat .

The inhibition on the phrenic nerve was not reversed by physostigmine so was not curare-like. Oxamniquine did not possess any local anaesthetic effects.

Oxamniquine was found to inhibit the barium induced contractions on the guinea pig ileum like nifedipine so is probably a calcium antagonist.

INTRODUCTION

Oxamniquine is used in the treatment of schistosomiasis caused by *Schistosoma mansoni*. The enthusiasm for oxamniquine in the treatment of *Schistosoma mansoni* infections stems from its effectiveness and apparent innocuousness⁽¹⁾. It is usually given by a deep intramuscular injection but oral doses have also been tried. Among the toxic effects observed are pain at the injection site, which may be accompanied by induration and fever and this frequently occurs within 48 hours of a deep intramuscular injection and lasts for 2-7 days. Other side effects include abdominal and muscular pains, headache, dizziness, somnolence, nausea, diarrhoea, skin eruptions and insomnia⁽²⁾. Slight liver toxicity and ECG changes have also been observed.

The efficacy and acceptability of oral oxamniquine was tested in Sudanese patients infected with *Schistosoma mansoni*. Cure rates were determined by the absence of viable eggs in stools six months after treatment. These were found to be 94.9% in patients treated with a total of 60mg/kg, 78.8% in those patients treated with 40mg/kg and 68.9% in those treated with 30mg/kg of oxamniquine. All treatment regimens considerably reduced the egg count even in those patients who were not cured. The drug was well tolerated and the side effects were minimal and transient, the most common being dizziness. Although 60mg/kg was the most effective dose in form of cure rates, the low doses considerably reduced the egg counts and could therefore be used in low cost programmes in reducing transmission of *Schistosoma mansoni* infections⁽³⁾.

Most of the patients noticed a reddish discolouration of their urine which was probably caused by a metabolite of the drug. In those patients treated with 60mg/kg there was a transient rise in eosinophil count and in serum amino transferase concentration. The parasitological findings of this study showed that oxamniquine produced a 95% cure rate six months after treatment when given in doses of 15mg/kg twice daily for two days (a total of 60mg/kg). The morbidity of the disease in Sudan may however, be different from that in other regions. In South America Da-silva et al ⁽⁴⁾ reported 100% cure in patients treated with 15mg/kg body weight of the drug. The differences which occur even within Sudan itself where the study was conducted may be due to previous antischistosomal treatment in which repeated and often incomplete courses of drugs were given leading to cross resistance. Other factors may affect the absorption and consequent concentration of oxamniquine.

Chemotherapy of infected persons with oxamniquine protected the community as a whole from high worm burdens for almost 3 years although at this point prevalence began to rise towards pretreated levels.

In chemotherapy of schistosomal colonic polyposis with Oxamniquine was found effective and safe. A total dose of 40mg/kg was found to be effective. No toxic effects were observed on the heart and no haematologic changes or the liver cells dysfunction was noted ⁽⁵⁾. In other studies, there was a rise in SGPT levels suggesting either a transient hepatic toxicity caused by the drug or a shift of worms to the liver ⁽⁶⁾.

Oxamniquine was in fact found to cause a shift of worms to the liver from the mesentric veins. In the liver, they were destroyed (7)

Effort was made to compare oxamniquine with nifedipine which is a vasodilator. Vasodilators act directly to relax vascular smooth muscle. The distinction between vasodilators and antihypertensives is made from the point of view of clinical use rather than from the mechanism of action. The mechanism of action of nifedipine is not well understood but some broad hypothesis may be made from available evidence.

The contractile mechanism of smooth muscle like that of skeletal muscle and the cardiac muscle is dependent on a calcium activated myosin ATPase. The intracellular stores of calcium in smooth muscle are relatively sparse and consequently much of the calcium necessary to activate the contractile mechanism enters the cell during the action potential. The vasodilators seem to act by depriving the contractile mechanism of calcium and this may be brought about in one or more of three possible ways:-

1. Cyclic AMP appears to stimulate a calcium binding process in smooth muscle thereby reducing the concentration of free myoplasmic calcium available to trigger contraction. Drugs that activate adenylate cyclase e.g. Isoprenaline or inhibit phosphodiesterase may therefore induce relaxation of the smooth muscle in that way.
2. Drugs may block the transport of calcium through the plasma membrane of the smooth muscle cells. Such drugs include Nifedipine and verapamil. These drugs also block the transport of calcium

into cardiac muscle cells and therefore depress the myocardium.

3. Drugs may block an active saturable reuptake process that transports adenosine in some cells including heart cells and erythrocytes. Since adenosine is a powerful vasodilator, blocking its reuptake results in more being available to produce coronary vasodilation.

Nifedipine and verapamil dilated peripheral arterioles and coronary arterioles. They selectively depress the secondary slow current component of the action potential but do not affect the initial fast sodium current or the conduction velocity. They seem to block all slow ion channels including the slow sodium channels. The main effect of these compounds is their ability to block calcium channels. The unwanted side effects of nifedipine are headache, flushing reflex, tachycardia due to hypotension, verapamil causes nausea, vomiting, dizziness and flushing (8). The drugs are contraindicated in cardiogenic shock, recent myocardial infarction, arterio-ventricular block and heart failure.

In the normal heart of a conscious animal, the direct action of nifedipine is neutralised by a reflex sympathetic - adrenergic activation since it has been shown that calcium antagonists do not interfere with the responsiveness of the heart to - adrenergic catecholamines (9).

Nifedipine has also been found to produce severe headache, hot flashes followed by severe chest pains. These side effects are probably due to increased cardiac output and heart rate plus a decreased peripheral resistance (10).

There have also been other studies on oxamniquine e.g. in

an experimental evaluation of Log p of oxamniquine,
< the log p value found agreed with that for antiparasitic
compounds. The side effects reported in clinical

practice include central nervous system stimulating
effects such as dizziness, drowsiness, headache and
nausea indicating that the drug is capable of
penetrating the central nervous system in appreciable
amounts or that there is an active metabolite which
brings up the effects (11).

In the use of oxamniquine, there has been transient
behaviour disturbances. In one case, an old alcoholic
with a history of lapses of consciousness suffered
a generalised ~~and~~ convulsion one hour after oxamniquine
ingestion. There was no previous history of such
convulsions or psychic disturbance and it would
therefore seem prudent to consider such history a
contraindication to oxamniquine therapy.

Several experiments were carried out here to help find
a possible mechanism of action for oxamniquine.

EXPERIMENTAL:

1. EFFECT OF OXAMNIQUINE ON MICE

Materials and Methods:

Eight mice equally divided in sex were injected intraperitoneally with 40mg/kg of body weight of 2.0 mg/kg solution of oxamniquine. Observation were made for 2 hours.

RESULTS

Table 1

Sex	Weight(g)	Dose of Oxamniquine	Effect on mouse
Male	21.0	0.42	Drowsy, altered respiratory movements
Male	30.0	0.6	Drowsy Loss of pedal reflex
Male	15.4	0.308	Drowsy
Male	19.8	0.396	No change
Female	24	0.48	Drowsy, respiration depressed
Female	16.5	0.33	Drowsy
Female	18.3	0.366	No change
Female	20.2	0.4	No change

Oxamniquine produced drowsiness in most of the mice so may have CNS depressant effects. Respiration was depressed and therefore it may have skeletal muscle paralytic effects. The animals however did not lose the righting reflex.

2. EFFECT OF PENTOBARBITONE ON MICE

Materials and Method:

Eight Mice equally divided in sex were injected with 35mg/kg body weight of a 2.5 mg/ml solution of pentobarbitone sodium.

Time taken to loose and to regain the righting reflex was noted. Other behaviour changes such as loss of corneal reflex were also observed.

RESULTS

Table 2

Sex	Weight (g)	Dose (ml)	Time taken to Lose Righting Reflexes (min)	Time taken to Regain Righting Reflexes (min)	Other Behaviour changes observed
Male	18.0	0.252	40	21.0	
Male	30.5	0.427	6.3	32.0	Shivering
Male	15.7	0.219	9.5	21.5	
Male	15.0	0.210	No loss of righting reflex	—	Drowsy
Male	20.5	0.287	7.5	21.5	Loss of corneal reflex
Male	16.0	0.224	3.0	29.0	
Male	27.0	0.378	5.0	1	
Male	15.4	0.215	4.0	18.0	Loss of Corneal reflex.

lag time between injection and loss of righting reflex was 3.0-9.5 min. animals had a sleeping time of between 18-32 min.

3. EFFECT OF OXAMNIQUINE ON THE PENTOBARBITONE INDUCED IN SLEEP IN MICE

Materials and Method

Eight mice equally divided in sex were injected with 40mg/kg body weight of oxamniquine followed by 35mg/kg body weight of 20mg/ml of oxamniquine. concentration of oxamniquine was also 2.0mg/ml. Time taken to loose righting reflex and the sleeping time was noted:

RESULTS

SEX	WEIGHT (g)	DOSE		TIME TO LOOSE RIGHTING REFLEX (MIN)	SLEEPING TIME (MIN)
		OXM (ml)	PENTOBARB (ml)		
Male	20.5	0.41	0.287	5.5	120
Male	35.5	0.71	0.497	3.0	.80
Male	22.0	0.44	0.308	2.0	Died
Male	17.0	0.34	0.238	3.5	-120
Female	24	0.336	0.336	4.0	19 hours
Female	17.0	0.238	0.238	2.5	63.5
Female	19.2	0.267	0.38	3.5	120
Female	17.0	0.238	0.238	3.5	60

The lagtime between injection and loss of righting reflex was 2.0 - 5.5 min. This is a shorter lagtime when compared to 3.0 - 9.5 min for animals injected with pentobarbitone alone. The sleeping time in mice injected with pentobarbitone alone was 18-32 min - a short time since pentobarbitone is a short acting barbiturate. The average sleeping time for those injected with both oxamniquine and pentobarbitone was 120 min showing some potentiation of pentobarbitone centrally by oxamniquine.

Oxamniquine may be acting by inhibiting the enzymes necessary for pentobarbitone destruction since pentobarbitone induces enzymes for its own destruction. It may also be acting by reducing the excretion of pentobarbitone or by producing synergistic effects with pentobarbitone. Oxamniquine should therefore not be used concurrently with pentobarbitone unless the dose of pentobarbitone is reduced. This applies to related barbiturates.

UNIVERSITY OF
LIBRARY

4. EFFECT OF OXAMNIQUINE ON THE BLOOD PRESSURE OF AN ANAESTHETISED RAT

Materials and Methods

A rat weighing 371g was anaesthetised using 0.6ml of urethane per every 100 grams of animal. The concentration of urethane was 25% w/V and therefore the rat was injected with 2.2 ml of solution intraperitoneally.

The anaesthetised rat was fasted onto the operation table. The legs were fastened using an adhesive tape and the head by passing a string across the upper jaws.

An incision was made in the midline from slightly back of the chin to the upper part of the thorax. The skin was pulled aside to expose the trachea which was cannulated with a plastic cannula and the cannula tied firmly with a thread.

The carotid artery was located and separated from the vagus, the cervical sympathetic nerves and the small jugular vein. The carotid cannula was connected to a pressure trans-ducer and the whole unit filled with heparinised saline taking alot of care to exclude air bubbles. The femoral vein through which the drugs were injected was also cannulated, oxamniquine was injected through the cannula in the femoral vein and its effects observed. The same was repeated with nifedipine.

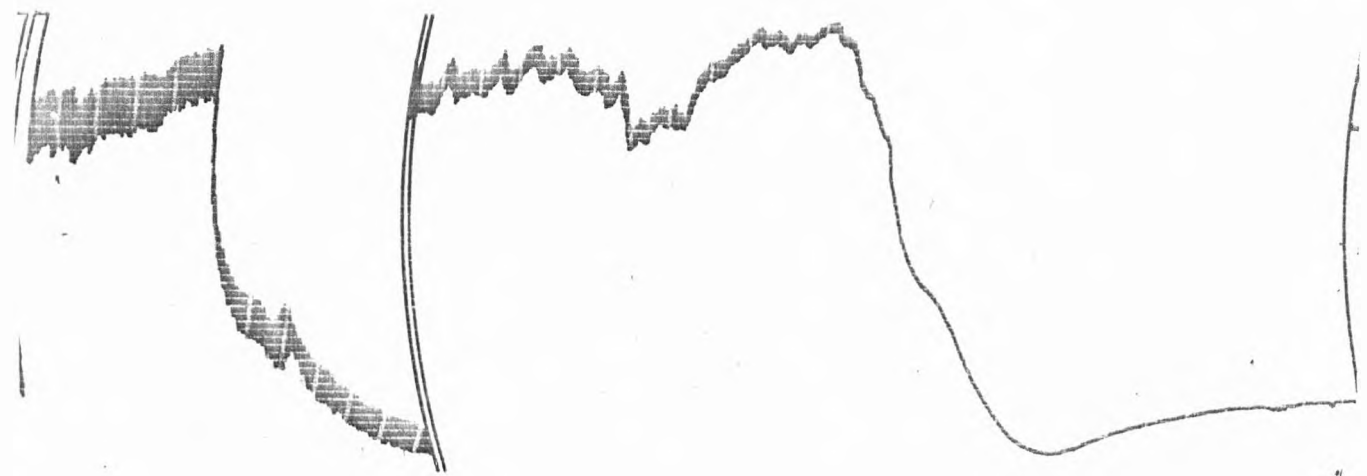
RESULTS

As seen in figures 1 and 2, both oxamniquine and nifedipine produced a prolonged fall in blood pressure. Since the fall in blood pressure was prolonged then oxamniquine and nifedipine do not act like acetylcholine or histamine which produce a fall in blood pressure and a rapid rise. Oxamniquine may be acting in one of three ways to reduce the blood pressure.

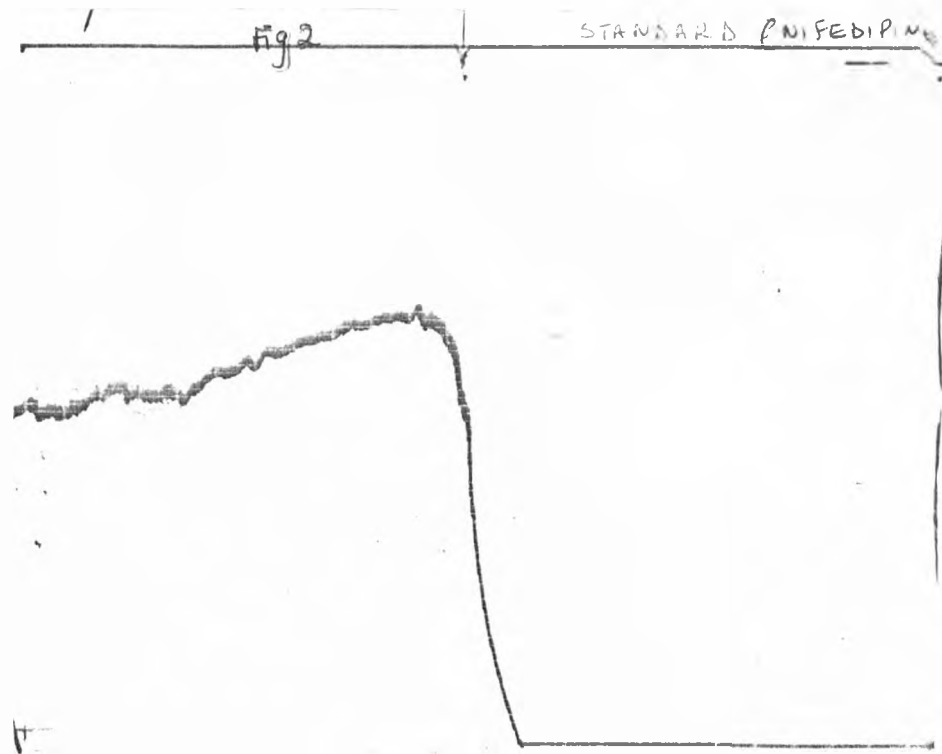
- a. by reducing force and rate of contraction of the heart i.e. negative chronotropic and ionotropic pressures
- b. It may be dilating blood vessels to reduce peripheral resistance and thereby cause a hypotensive action.

OXAMNIQUINE ON THE BLOOD PRESSURE OF AN ANAESTHETISED RAT

↓
(OXAMNIQUINE)
UNKNOWN 1/2 ml. Fig 1



NIFEDIPINE ON THE BLOOD PRESSURE OF AN ANAESTHETISED
RAT



- c. It may be acting by depressing the central nervous system.
- d. It may be causing respiratory block.

EFFECT OF OXAMNIQUINE ON THE ISOLATED PERFUSED RABBIT HEART

Materials and Method

A rabbit was killed by a blow on the head and cutting the throat. The heart was removed at least 1 cm of aorta attached. This was done as quickly as possible. The heart was placed in a dish of Ringer-Locke solution at room temperature.

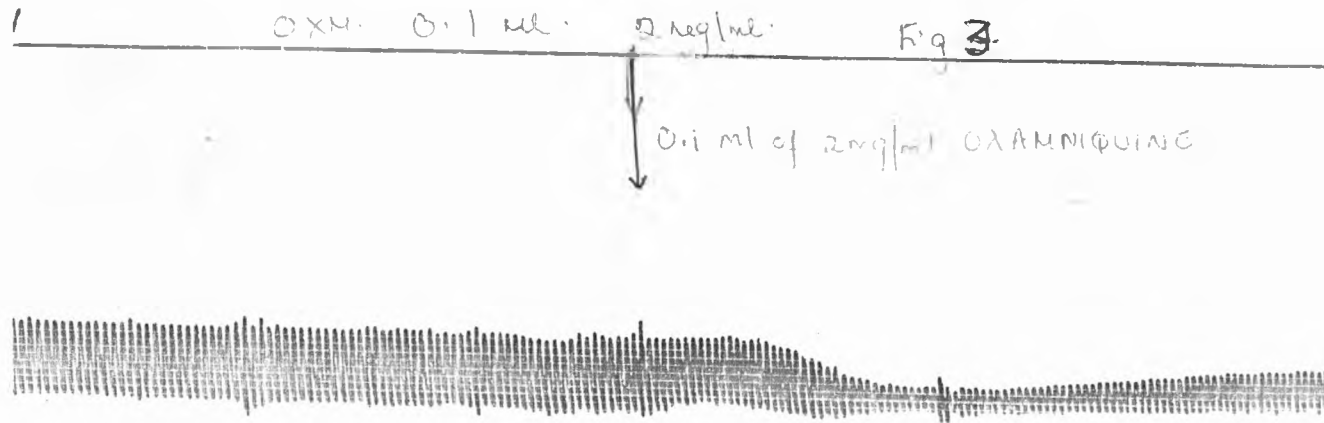
The heart was squeezed several times when first placed in the Ringer-Locke solution so as to remove as much blood as possible. The aorta was located and dissected free. All other vessels attached to the heart are trimmed away.

The aorta is cut just below the point where it divides and the heart is transferred to the perfusion apparatus where the aorta is tied onto a glass cannula. Great care was taken to ensure that no air bubbles entered the aorta and any bubbles present in the cannula were first removed. This was done by use of a long thin polythene pipette. The perfusion fluid, which was Ringer-Locke solution bubbled with pure oxygen which was passed from the reservoir at a constant pressure. It was warmed by water circulated in a thermostat at 37°C. The pressure of the perfusion fluid closes the aortic valve so that fluid passes only through the coronary vessels and escapes from the inferior vena cava.

Threads were attached to the ventricle by a hook and to the atria by a small spring clip. These threads are connected to spring levers to record the size of contractions on a force displacement transducer.

Oxamniquine was added to the preparation by injection through the rubber tubing. The effects of oxamniquine can be seen in figure 3 and 4. Oxamniquine could inhibit the contractions of the heart but once it had been washed off by the perfusion fluid, the contractions returned back to normal.

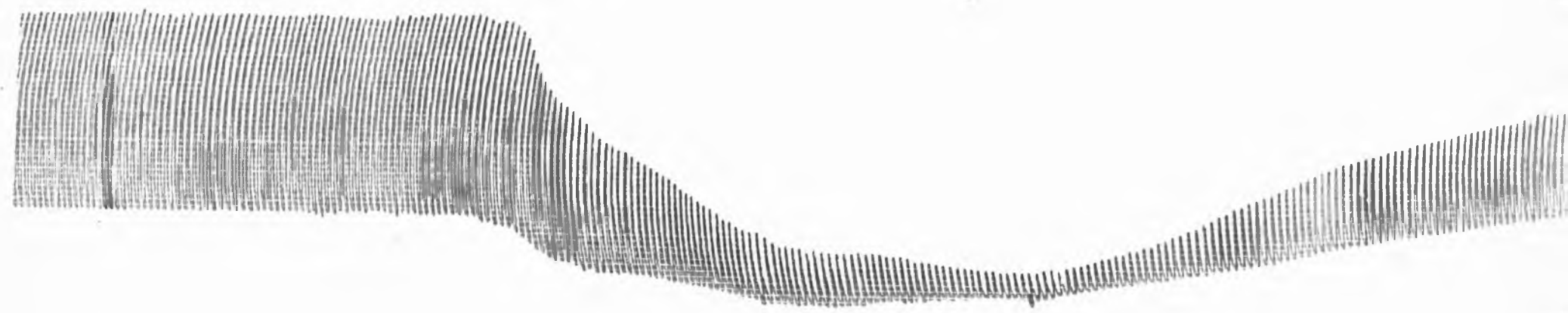
OXAMNIQUINE ON THE ISOLATED PERFUSED RABBIT HEART



OF
EFFECT OF A HIGHER DOSE OF OXAMNIQUINE ON THE ISOLATED PERFUSED RABBIT HEART

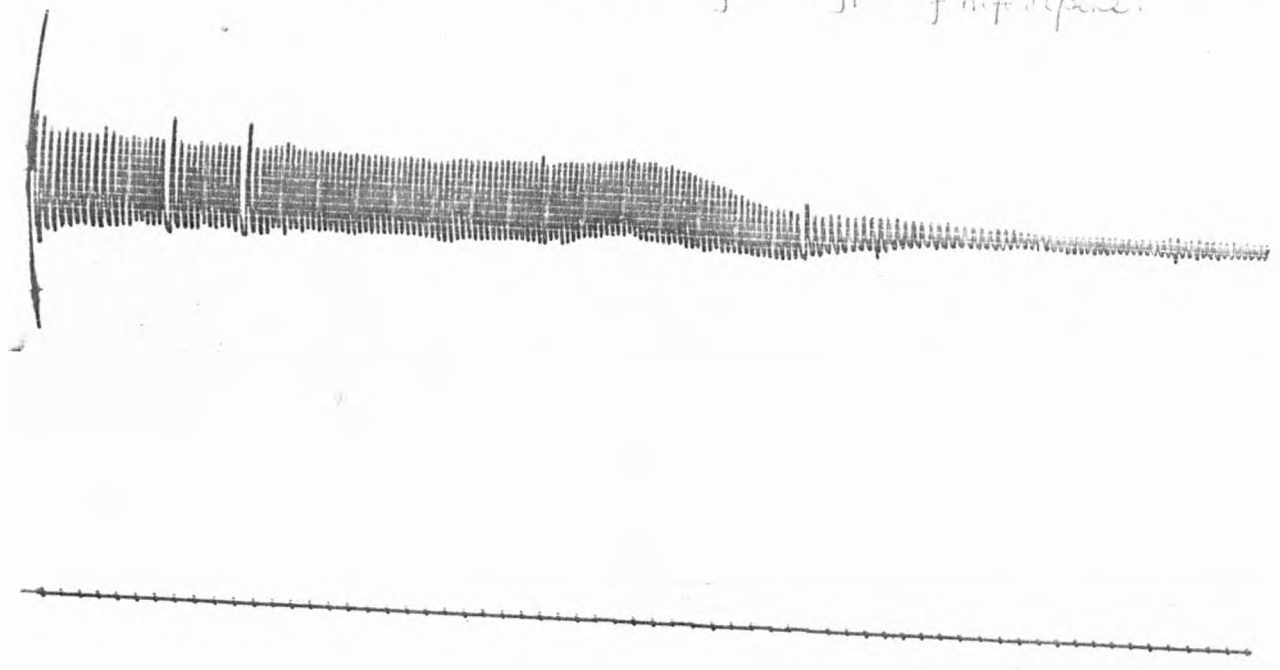
0.4 ml of 2 mg/ml OXAMNIQUINE

Figure 4



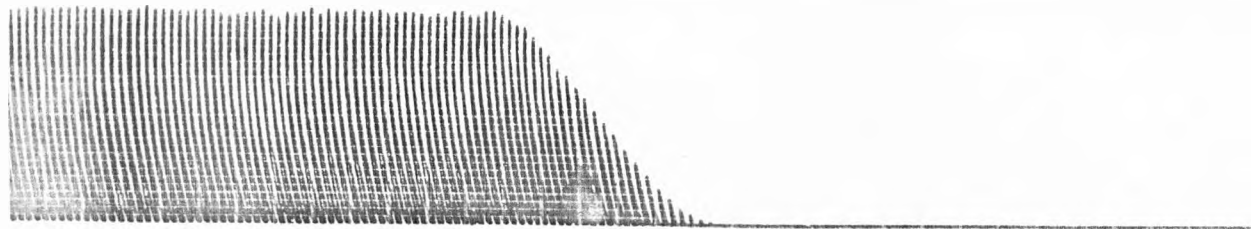
NIFEDIPINE ON THE ISOLATED PERFUSED RABBIT HEART

nifedipine 0.6ml 0.1mg/ml. Fig 5
0.6ml of 0.1mg/ml of nifedipine.



EFFECT OF A HIGHER DOSE OF NIFEDIPINE ON THE ISOLATED PERFUSED RABBIT HEART

nifedipine 1.0 mg/ml (complete block) 0.1 ml Fig. 6
↓
0.1 mg/ml nifedipine response



0.2mM Nifedipine (0.2 μ M of 0.1mg/ml) Fig 17

NIFEDIPINE ON THE ISOLATED AB221A



Nifedipine was also injected and found to have the same effect. This can be seen in figures 5, 6 and 7. In figures 6 there was complete inhibition for some time and later the heart started contracting normally. Both drugs therefore depress the myocardium.

The movements of the atria were very difficult to see because they were masked by the more powerful movements of the ventricles. Another experiment on the isolated atria was therefore set.

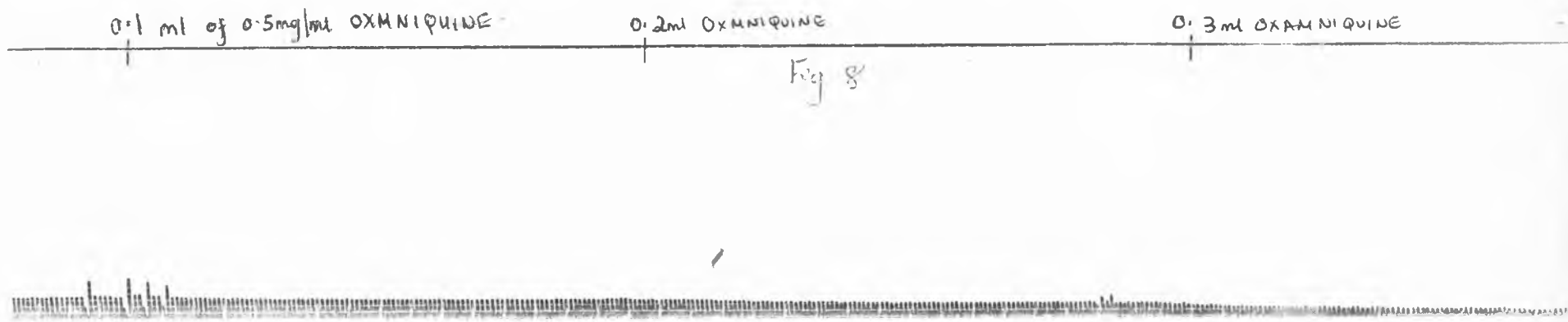
OXAMNIQUINE ON THE ISOLATED RABBIT ARTRIA

Materials and Method

A rabbit was killed by a blow on the head and cutting the throat. The chest was opened and the heart removed and quickly as possible and placed in Ringer-Locke solution at room temperature. All other tissue was cut away until nothing was left except the atria. A lot of care was taken during the dissection not to damage the pacemaker. Threads were then tied, one to each end of the atria and the preparation was mounted in an organ bath containing Ringer-Locke solution at 30°C through which a brisk flow of pure oxygen was blown.

One thread was attached to a fixed hook in the bath and the other to a force displacement transducer connected to an electrical amplifier and recorder. The volume of the organ bath was 20ml. The atria were allowed to beat spontaneously for some time and then oxamniquine was added to the organ bath. After recording the effects of oxamniquine and allowing the tissue to go back to normal, nifedipine was added to the organ bath and its effects also recorded.

EFFECT OF OXAMNIQUINE ON THE ISOLATED ATRIA



EFFECT OF NIFEDIPINE ON THE ISOLATED ATRIA

0.1 ml of 1.0 mg/ml nifedipine

0.2 ml NIFEDIPINE

0.3 ml NIFEDIPINE

0.4 ml NIFEDIPINE

Fig 9



0.1 mg/ml Nifedipine

RESULTS

Both drugs, oxamniquine and nifedipine were found to reduce the force of contraction of the artria as seen in figures 8 and 9. High doses of these drugs produced a complete block on articular contraction.

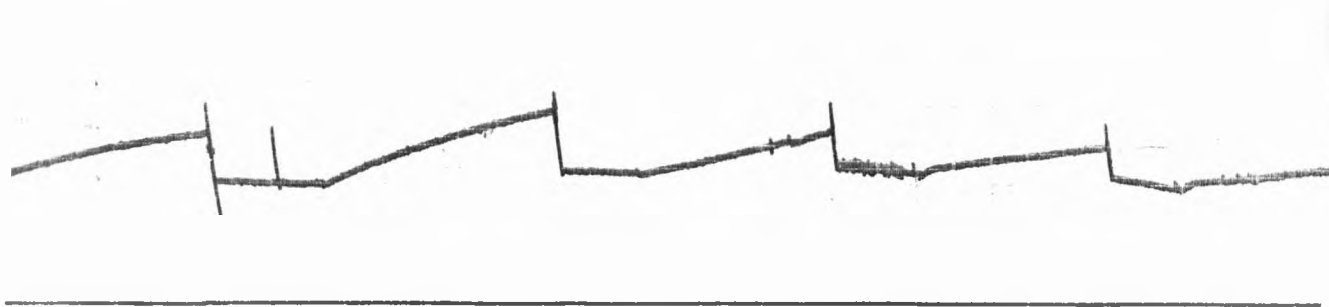
OXAMNIQUINE AND THE AORTIC STRIP

Materials and Method

A rabbit was killed by a blow on the head and cutting the throat. The chest was opened and the aorta cut through as near to the heart as possible and dissected free for as long a distance as possible. It was transferred to a dish containing Krebs Henselleit solution and cut spirally so as to produce a continuous strip of approximately 4mm wide and 4cm long. A thread was attached at each end and the preparation was mounted in Kreb's solution at 37°C, aerated with a mixture of carbon dioxide (5%) and oxygen (95%). one end of the strip was attached to a fixed pin in the bath and the other to a lever writing on a force displacement transducer. The preparation responds only rather slowly and therefore a long time cycle was necessary. The tissue also takes long to recover. An eight minute cycle was used. Isotonic contractions of the aortic strip were induced by a 10% solution of potassium chloride. Doses of 0.2ml and 0.3ml of potassium chloride were used. This gave contractions which were recorded, 1.0ml of 0.5mg/ml oxamniquine was then added to the organ bath followed by 0.3ml of potassium chloride. The tissue was left for about 5½ minutes to recover after which 0.6ml of the potassium chloride was injected.

EFFECT OF OXAMNIQUINE ON THE POTASSIUM INDUCED CONTRACTIONS OF THE
AORTIC STRIP

Fig 10



↑
0.2 ml
KCl

0.8 ml KCl

1 ml OXU ↑
0.3 ml KCl

↑
0.6 ml potassium chloride
(KCl) (10%)

RESULTS:

Oxamniquine caused some inhibition on the potassium induced contractions of the aortic strip. 1.0ml of a 0.5mg/ml solution of oxamniquine caused about 40% decrease in the contraction. Even/doubling the dose of potassium chloride, complete recovery of the tissue could not be achieved. Infact as the drug was given more time to act, on the tissue a complete blockade was achieved. This is seen on figure 10. These are all characteristics of compounds which block slow ion channels. Nifedipine also has this ability although the main effect is to block calcium channels.

OXAMNIQUINE ON THE RABBIT VAS DEFERENS

Materials and Method

A male rabbit was killed by a blow on the head and later cutting the throat. The abdomen was opened and the gut lifted aside. The testis were pushed back into the abdominal cavity by applying pressure on the scrotum. By lifting the terminal end of the colon, the hypogastric nerves were seen running on each side of the mesentery. A ligature was tied round one of the nerves about 5cm from the vas-d ferens and the nerve was dissected free to within about half a centimeter of the point where they join.

The corresponding vas deferens was cut just above the epididymus and also at the point where it joins the urethra and threads were tied to each end. The preparation was dissected free from connective tissue and mounted in Krebs's Henselleit solution aerated with carbogen. The thread attached to one end of the vas deferens was tied to a fixed pin and the other to a lever with a load of 1g. pontaneous contractions were recorded after which oxamniquine was added. The procedure was repeated but nifedipine was added instead of oxamniquine.

RESULTS:

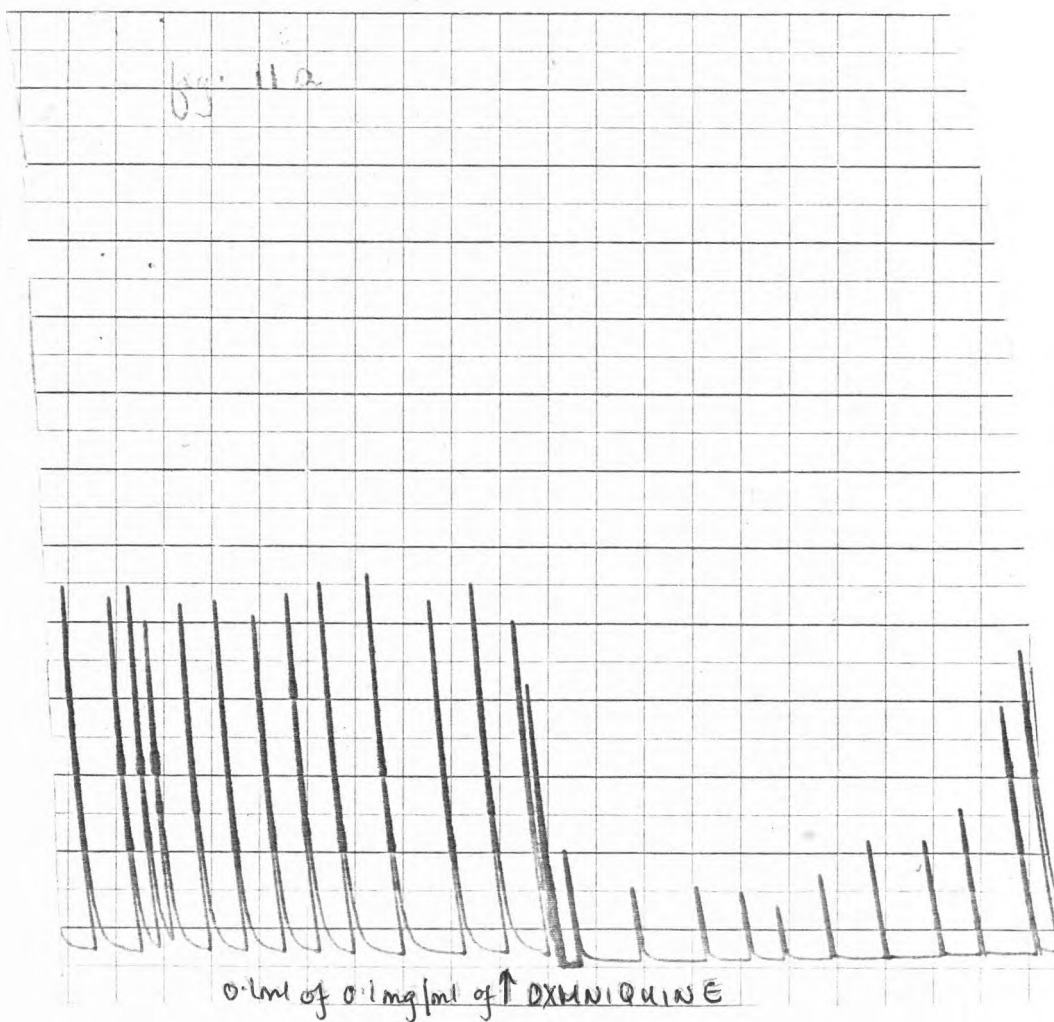
0.1ml of 0.5mg/ml of oxamniquine was found to inhibit the spontaneous contractions of the vas deferens by about 80%. The inhibition was short lived and the vas deferens quickly recovered.

0.1 ml of 0.1mg/ml of nifedipine produced almost complete blockade on the vas deferens but the vas deferens later recovered.

Nifedipine was found to be more potent than oxamniquine in this respect.

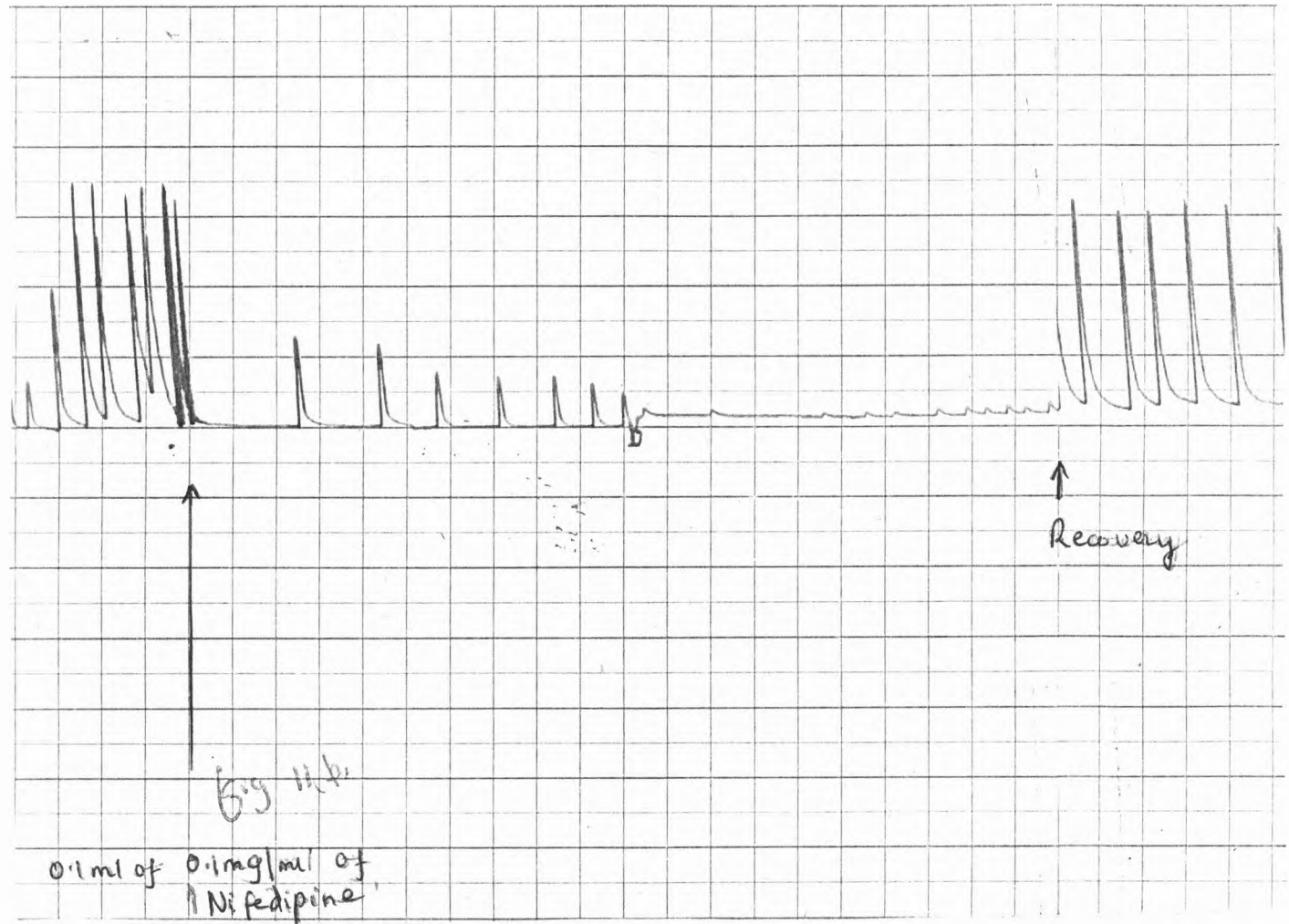
The results can be seen in figure 11a and 11b.

EFFECT OF EXAMNIQUINE ON THE RABIT VAS DEFERENS



EFFECT OF NIFEDIPINE ON RABBIT VAS DEFERENS

No. 1021



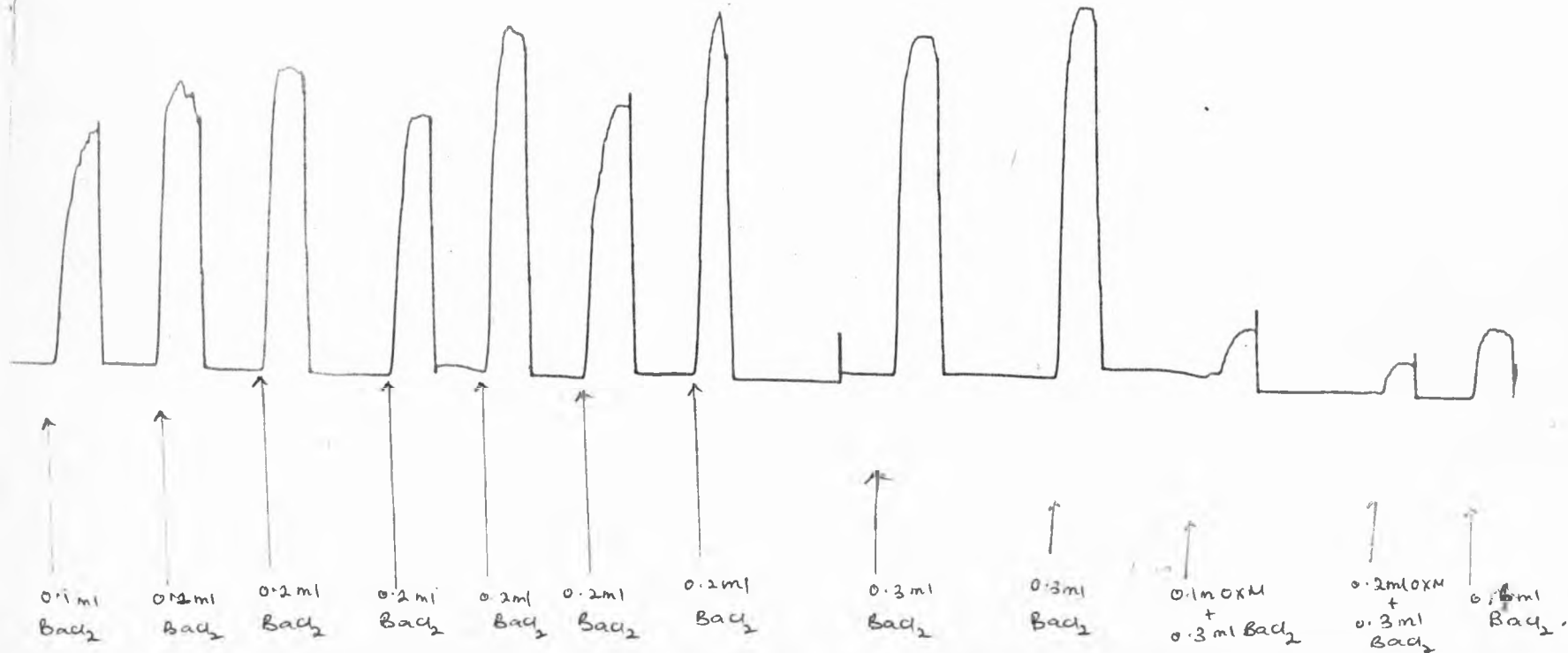
OXAMNIQUINE ON THE GUINEA PIG ILEUM

A female guinea pig weighing 240g was killed by a blow on the head, cutting the throat and bleeding the animal. A length of the ileum was removed from about 15cm above the ileocecal junction and suspended in a petridish containing tyrodes solution. Threads were tied to each end of the ileum. Great care was taken to avoid damaging the gut muscle. The guinea pig had been starved overnight to ensure the gut muscle was clean and free of spontaneous activity. The small section of ileum was suspended in an organ bath containing Tyrodes solution at 37°C and bubbled with a mixture of 95% oxygen and 5% carbon dioxide. Isotonic contractions of the ileum were induced every four minutes using a 2% solution of barium chloride. The four minute cycle used was as follows. At zero time, the Kymograph was started at 30 seconds, the barium chloride solution was added to the organ bath. At 1 minute, the Kymograph was stopped and the tissue washed immediately by running in more of the Tyrodes solution from reseivor. The tissue was then allowed to rest until the 4th minute when the cycle was replated. Increasing amounts of barium chloride were used untill the maximum contractions were got. The contractions induced by barium could be antagonised by addition of oxamniquine. They were also antagonised by nifedipine. Results are seen on figure 12 and 13.

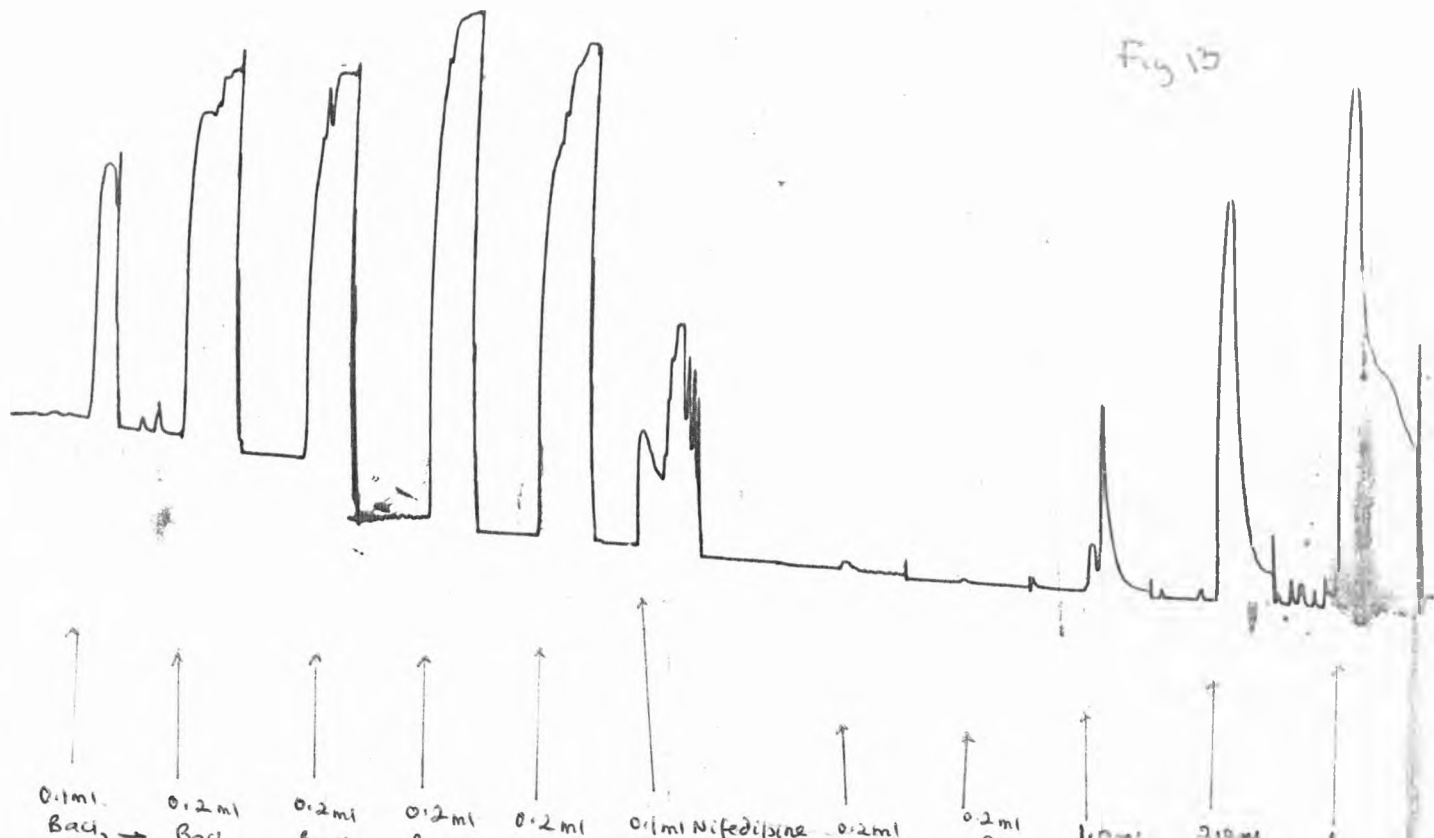
EFFECT OF OXAMNIQUINE ON BaCl₂ INDUCED CONTRACTION ON GP ILEUM

Fig. 12

BaCl₂ = barium chloride
OXM = oxamniquin
C.P. = Guinea pig.



EFFECT OF NIFEDIPINE ON GUINEA PIG ILEUM



EFFECT OF OXAMNIQUINE ON THE PHRENIC NERVE-DIAPHRAGM

PREPARATION OF THE RAT

Procedure

A rat was killed by a blow on the head and its throat was cut. It was left to bleed for as much as possible to ensure that the thorax was free of blood. The skin is removed in the middle of the chest. The muscles are freed from the chest wall right round towards the animals franks by inserting blunt scissors between the two and opening them. The phrenic nerve was dislodged from the membrane adhering to the inside of the chest wall. The ribs were cut through towards the animals frank. The upper part of the thorax was removed completely and the phrenic nerve could be seen running from the diaphragm to the thymus gland. The nerve was cut just below the thymus and transfered to a dish containing Kreb's solution.

A thread was attached securely to the apex of the piece of diaphragm and another thread to the cut end of the nerve. The preparation was lowered into the organ bath where the thread from the muscle was attached to the lever and that from the nerve to a pair of electrodes. The preparation was well aerated with a mixture of carbondioxide (5%) and oxygen (95%). The temperature was maintained at 37°C by water recirculating in a thermostat.

Contractions of the muscle were recorded with a light spring loaded lever with a side ways writing point.

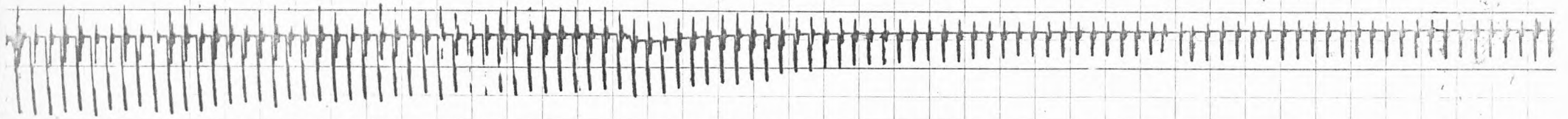
Oxamniquine and nifedipine were tested on the preparation. Both were found to reduce the contractions. Physostigmine was later injected into the solution to test whether it would reverse the effects of oxamniquine and nifedipine.

RESULTS

When 0.2ml of 0.5mg/ml of oxamniquine was added to the bath, there was more than 50% reduction in the force of contractions but the rate of contractions was not altered. Addition of 100 µg of Physostigmine did not reverse oxamniquine effects so the blockade was not like that of curare. Nifedipine also produced a blockade which was not reversed by physostigmine. The results may be seen in figures 14 and 15.

EFFECT OF OXAMNIQUINE ON PHRENIC NERVE DIAPHRAGM PREPARATION OF THE RAT

fig 14



0.2 ml (0.5 mg/ml) Oxamniquine

100 µg Physostigmine

EFFECT OF NIFEDIPINE ON THE PHRENIC NERVE DIAPHRAGM PREPARATION OF THE RAT

fig. 15

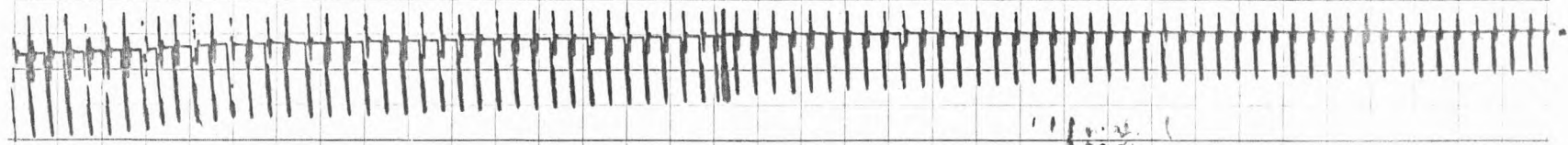


CHART No. 1021 0.1 ml of 0.1 mg/ml Nifedipine

↑ Physostigmine

From the results it can be seen that procaine and Lignocaine caused an immediate onset of anaesthesia with long duration of action.

Oxamniquine like normal saline had no local anaesthetic effects. There was no loss of pain reflex at the site of injection.

metabolism. Oxamniquine may act by causing enzymatic

DISCUSSION

Oxamniquine was found to cause drowsiness in mice. It was also found to potentiate pentobarbitone central nervous system depression. Oxamniquine may produce this depression by either

- a. direct central nervous system effects
- b. by producing a metabolite which produces the CNS depressant effects.
- c. Since pentobarbitone induces the enzymes for its own metabolism, Oxamniquine may act by causing enzymatic inhibition of these enzymes.

Oxamniquine is therefore contraindicated in barbiturate therapy. It is also contraindicated in epilepsy since it may also cause convulsions.

When Oxamniquine was given to an anaesthetised rat, there was a prolonged fall in pressure. This is not histamine or acetylcholine like which produce a sharp fall in blood pressure followed by quick recovery. The fall in blood pressure may be due to:-

1. Oxamniquine's central nervous system depressant effects
2. The drug may be producing a heart block
3. It may be causing respiratory block which in turn lowers blood pressure.

This prolonged fall in pressure was also observed with nifedipine. When administered to the isolated perfused rabbit heart oxamniquine caused cardiac depression. This was also found true with nifedipine. The two drugs only affected the force of contraction and not the rate of contraction i.e. they had negative inotropic effects. This however was short lived and the heart quickly recovered. A high dose of nifedipine produced a complete blockade on the heart.

On the isolated perfused rabbit heart, oxamniquine decreased the force of contraction but the rate of contraction was not altered. The inhibition however was short lived and the heart quickly recovered. Nifedipine had the same effects but a higher dose of nifedipine produced a complete block on the heart which recovered after about two hours. The two drugs oxamniquine and nifedipine were also tested on the isolated atria. They were found to produce complete blockade but the atria recovered after about half an hour. On this two tissues, the perfused heart and the atria, the two drugs had similar effects and therefore oxamniquine may be producing its effects by calcium antagonism. When oxamniquine was tested on an aortic strip where isotonic contractions had been induced with potassium chloride, it was found to produce about 50% inhibition on these contractions. The aortic strip is a tissue that does not recover soon and was therefore allowed nearly 6 minutes to recover. When double the initial dose of potassium chloride was later added to the organ bath, the aortic strip was found not to produce the initial amplitude of contraction showing that oxamniquine was producing prolonged effect on the aortic strip. This is a characteristic of other calcium antagonists and therefore oxamniquine too may be a calcium antagonist. On the phrenic nerve diaphragm preparations of the rat, oxamniquine was found to inhibit the contractions. It reduced the amplitude of contraction i.e. force of contraction but did not affect the rate of contraction. Since the diaphragm is involved in respiration oxamniquine may be producing respiratory blockade through inhibition on contractions of the diaphragm. In this muscle too calcium is involved in contraction and therefore oxamniquine may be a calcium antagonist.

When the local anaesthetic activity of oxamniquine was assessed by the guinea pig wheal method for infiltration anaesthesia, it was found to possess no anesthetic potency. This is why patients who have received deep intramuscular injections of oxamniquine have complained of pain at the injection site.

CONCLUSION

In all experiments done, oxamniquine was compared with nifedipine as a standard and in all it was found to exert effects very similar to nifedipine although in most cases nifedipine was more potent. Oxamniquine acts like a calcium antagonist.

R E F E R E N C E S

1. A.C. SLEIGH et al
A three year follow up of chemotherapy with oxamniquine
in a Brazilian community with Endemic Schistosomiasis
Mansoni.
Transactions of the Royal Society of Tropical Medicine
and Hygiene 1981 Vol.75 No.2 Pages 234-8
2. A. WADE, J.E.F. REYNOLDS (EDITORS)
Martindale extra pharmacopoea, 27th Edition Page 1376
3. A.H.S. OMER 15th July 1978
Oxamniquine for treating schistosoma Mansoni Infection in
Sudan
British Medical Journal, 1978, 2, 163-165
4. Da Silva et al
Revista do Instituto de Medica Tropica de
Sao Paulo 1974, 16, 103
5. H.H. ABASA N.HAMMOUDA, H. ABDRARBO AND A.Z. SHAFEI
Chemotherapy of schistosoma colonic polypsis with
oxamniquine
Transactions of the Royal Society of Tropical Medicine
and Hygiene, Vol. 72, No.6 1978 pages 602-604
6. Journal of Tropical Medicine and Hygiene January 1979
82(1) 18-20
7. N. KATZ et al
Reuta Institute
Med. Trop. S. Paulo 1973 (15) supplement 1
8. W.C. BOWMAN and M.D. RAND
TEXTBOOK OF PHARMACOLOGY, 2ND EDITION
CHAPTER 22:7-9, 22:13-14, 22:16, 22:61, 22:67, 22:70
9. ARZNEIM for schools 1979 29(9) 1368 - 73

10. SHILOMO KEIDAR, ALON MARMOR, EHUD GRENAIDER and
AURHAH PALANT
Nifedipine and prinzmetal's Angina
Circulation 59(1) 195 Jan 1979

11. KOFI TSEKPO W.M.
An Experimental evaluation of Log p value of
oxamniquine, a new schistosomicide
DRUGS EXPTL.CLIN.RES.6(5) 421-426 (1980)

12. S. BASSILY, Z. FARID, G.I. HIGASHI AND R.H. WATTEN
Treatment of complicated schistosomiasis mansoni
with oxamniquine
American journal of Tropical medicine and Hygiene
27(6) 1284-6 No.78

13. CHURCHILL LIVINGSTONE, 2ND EDITION
Pharmacological Experiments on isolated preparation

14. Pharmacology practicals manual
Department of pharmacy, Faculty of Medicine
University of Nairobi, KENYA