THE EFFECT OF CHLOROQUINE ON THE SMOOTH CARDIAC AND SKELETAL MUSCLES: A RE-EVALUATION

BY

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A dissertation submitted in partial fulfilment for the award of the degree of Bachelor of Pharmacy, Under the Supervision of

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DEDICATION

This research work is dedicated to my beloved mother, Mrs Qaballe Waqo, whose unfailing commitment to my education has been a source of inspiration and hope and to my late father Mr. Waqo Sama who has always taken pride in his son's endeavors.

In addition this piece of work is dedicated to my brothers and sisters and to all those friends who have given me unwavering moral support during the trying times of my education.
ACKNOWLEDGEMENT

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The help of the technical staff of the Pharmacology Department is highly appreciated. Special words of thanks go to Mrs. R.W. Mumenge without whose help this work would not have been completed in time.

Unparalleled appreciation also goes to Miss Jemima Odari for meticulously typing the manuscript and to all those who have contributed in one way or another to completion of this piece of work in time.
KNOWLEDGE IS THE KNOWING THAT WE DO NOT KNOW.
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ABSTRACT:

The effect of chloroquine on the responses of smooth, cardiac and skeletal muscles to various drugs have been investigated using small laboratory animals such as guinea pigs, rats and rabbits. In all cases, isolated tissues were used. In addition, the effect of intraperitoneal (IP) administration of chloroquine on pregnant rats was undertaken, to investigate its alleged abortifacient action. In this investigation, the dose-response relationship, the possible mechanism of action and its implication are discussed.

Chloroquine was found to have the following properties:

a) Relaxes the tracheal smooth muscles and opposes the constrictor effect of acetylcholine (Ach), histamine, nicotine and barium chloride on the guinea pig tracheal smooth muscles.

b) Causes short-lived relaxation of rabbit ileal muscles and antagonizes the spontaneous contraction induced by acetylcholine, nicotine and barium chloride possibly by membrane stabilization and local anaesthetic properties.

c) Exhibits negative inotrophic and chronotropic effects on the isolated rabbit heart and opposes the positive chronotropic responses due to adrenaline and isoprenaline probably by β1-adrenergic blocking activity. It also antagonizes the cardiotensile action of caffeine and barium chloride. The negative chronotropic action could be the basis of its well known antiarrythmic property.

d) In addition to causing depression of neuromuscular transmission, chloroquine potentiates the neuromuscular blocking effect of tubocurarine succinylcholine and lignocaine probably by a non-specific interference with ionic conductance.
e) Chloroquine has no uterotonic activity of its own, but inhibits the contractions of rat uterine smooth muscles induced by carbachol, oxytocin, and prostaglandin E$_{20}$ (PGF$_{2a}$) (prostin) probably by extensive, non-specific interference with calcium conductance. The dose of chloroquine needed to totally inhibit oxytocin-induced contractions of rat uterine smooth muscles was 4mg. This was equivalent to both concentration of 200µg/ml.

f) Chloroquine may exert its alleged abortifacient action by causing sudden changes in intrauterine pressure. Due to its well known toxicity, caution is urged in the use of chloroquine than it is at present and reconsideration of the proposed chloroquinization of salt to counter malaria menace in developing countries is suggested before implementation.

**KEY WORDS**

- Antagonism
- Potentiation
- Inhibition
- Relaxation
- Contraction
- Antiasthmatic
- Antiadrenergic
- Antiarrhythmic
- Membrane stabilization
- Ionic conductance
- Intrauterine pressure
Evidence has accumulated in the literature concerning the unusual parallelism between chloroquine, amodiaquin, atabrine, quinine and quinidine, an isomers of quinine. In spite of their totally different chemical structures, they all show antimalarial, antiveratrinic and negative inotropic and antiarrhythmic activity. In 1975, Famaey, Fontaine and Reuse showed that chloroquine inhibits the isometric contractions of guine pig ileum induced by electrical coaxial stimulation in the same way as do non-steroidal and steroidal antiinflammatory drugs. The antiarrhythmic action of chloroquine and other 4-aminoquinolines had been reported by many researchers. Chloroquine and amodiaquin were shown to have more powerful action in the prevention of experimental auricular arrhythmias than quinidine (Aroora et al., Aroora, Madan and Pathak 1956).

Chloroquine had been reported to partially block the cardioinhibitory action of the vagus nerve in doses of 7mg to 10mg/Kg, the vagal block being reduced by 50% (Agarwal et al., 1956.) whereas Jindal M.N. (1970) reported that chloroquine partly abolished the adrenergic components of trachealis nerve muscle preparation from guinea pigs without affecting the cholinergic component or the noradrenaline response. That chloroquine and amodiaquin have an adrenergic neurone blocking properties have been reported (Jindal M.N. 1970) Both chloroquine and amodiaquin antagonise the spasms of rabbits' tracheal muscles (chain preparation) caused by acetylcholine, the antagonism being more with amodiaquine (Agarwal, S.L. and Aroora R.B, 1956).

The antifibrillatory action of chloroquine following chloroform-induced ventricular fibrillation and its antiasthmatic property have been reported (Aviado et al. 1970, Engeset, 1957). Chloroquine has also been found to reduce the histamine content of the lung to half the control level following the treatment of male rats with 5mg/Kg of the drug.
for three weeks (Agarwal et al., 1963), although it has also been reported to release histamine in the rat, but not in humans or the cat or the rabbit (Lecomte, 1955). Further, Cohn (1965) had reported that chloroquine inhibits the methylation of histamine in the male rat. Chloroquine potentiates the pressor effects of certain catecholamines (Jindal, 1956; Jindal and Joseph, 1958) also potentiates the effect of tyramine on the blood pressure of anaesthetized dogs (Jindal, Pandya and Kelkar, 1968).

The uterotonic action of prostaglandins (PGs) have been investigated and highlighted by many researchers. Karim et al. (1968) and Embrey (1969) showed in small series of experiments that labour could easily be induced with IV infusions of PGE$_2$ and PGF$_{2\alpha}$. PGF$_{2\alpha}$ have proved to have a potent uterotonic action on human myometrium (Bygdeman 1964, 1967). Karim et al. (1968) has further shown that PGF$_{2\alpha}$ appears in the maternal venous blood in variable amounts during labour and that the concentration of this PG was highest immediately before a uterine contraction. Prostaglandins bind to and release calcium from liver mitochondria (Malstrom et al., 1975) and from heart mitochondria and sarcoplasmatic reticulum from uterus (Tsuyoshi et al. 1979 Carsten et al. 1977). The prevention and reversal of heart rhythm disturbances caused by low concentrations of PGs by physiological levels of copperions and therapeutic levels of chloroquine has been demonstrated (Swift, et al. 1978) PGs may exert their effect via an ionophore-like action (Carsten M.E. and Miller D.J. 1977) and/or by a non-ionophoretic action on mitochondrial calcium movement. (Mcnamara et al. 1980).

The present research is intended for the re-evaluation of the already known effects of chloroquine on the smooth muscles of the trachea, heart, ileum and the uterus and the skeletal muscle. In addition, the dose-effect
relationship of chloroquine on the responses of the muscles to various exogenously added drugs is investigated since the review of the current literature showed that this has not been adequately investigated.
The antimalarial activity of the 4-aminoquinoline type of compounds was first described by Russian workers and later by Prech and German workers. During the second world war, many members of the 4-aminoquinoline series were synthesized and tested in the U.S.A. chloroquine, whose structure is shown below, is the most extensively used compound, though hydroxychloroquine and amodiaquin are also used.

![Chemical structure of chloroquine](image)

Chloroquine has a rapid schizonticidal action against the erythrocytic forms of all types of malarial parasites with the exception of resistant strains of *P. falciparum* in South America and S.E. Asia (Bowman W.C., Rand M.J. 1980). It is also effective against the gametocytes of *P. ovale*, *P. vivax* and *P. malaria* but not against those of *P. falciparum*. Besides the chemotherapy of malaria, chloroquine has been used in the past in the treatment of rheumatoid arthritis and systemic lupus erythematosus (S.L.E.) because of its antirheumatic properties. (Thomson and Werbel, 1972, and Rollo 1975). These properties were different from those of the classical steroidal and non-steroidal anti-inflammatory drugs mainly as they appear only after several months of treatment. (Famaey et al, 1977).

In 1975, Famaey, Fontaine and Reuse showed that chloroquine inhibits the isometric contractions of the guinea pig ileum induced by electrical coaxial stimulation in the same manner as do the non-steroidal and steroidal anti-inflammatory drugs. This inhibition was reversed by small concentrations of prostanoid (PGs), as also happens with inhibition by non-steroidal anti-inflammatory drugs.
of isotonic contractions of the guinea pig ileum caused by exogenously added acetylcholine (Ach), nicotine, histamine (Famaey, Fontaine and Reuse 1977a) and 5-hydroxytryptamine (5-HT) (Famaey et al., 1977c). It was also demonstrated that high concentrations of steroidal and non-steroidal anti-inflammatory drugs were able to specifically antagonize guinea pig ileum contractions to PGE\(_1\) and PGF\(_2\alpha\) (Famaey, Fontaine and Reuse 1977b). Chloroquine and amodiaquin have been reported to reduce the height of spontaneous contractions of the rabbit’s ileum and that amodiaquin was more potent in this respect than chloroquine (Agarwal et al., 1956). Both drugs diminished the responses to 10\(\mu\)g of Ach, the inhibition being more with amodiaquin than with chloroquine.

The antiarrhythmic action of chloroquine and other 4-aminooquinolines had been investigated by many researchers (Hiatt et al., 1945, Arora et al., 1955, 1956; Agarwal et al., 1956). Chloroquine and amodiaquin were shown to have more powerful action in the prevention of experimental auricular arrhythmias than quinidine (Arora et al., 1955, Arora, Madan and Pathak, 1956). It was also reported (Agarwal et al., 1956) that chloroquine in doses of 7mg to 10mg/kg partially blocked the cardioinhibitory action of the vagus nerve, the vagal block being reduced by 50%. With further increase in doses up to 20mg/kg, the reduction in vagal block was 67%. In the same investigation, amodiaquin was found to be less potent in blocking the cardioinhibitory action of the vagus nerve. The block in no case could be reduced by more than 50% with doses up to 20mg/kg.

In 1970, Jindal M.N. demonstrated that chloroquine partly abolished the adrenergic components of trachealis nerve muscle preparation from guinea pigs without affecting the cholinergic component or the noradrenaline response. In an earlier experiment, it has been reported that transmural stimulation of the trachealis muscles involves both the cholinergic and adrenergic components (Paterson, 1967). Chloroquine has no effect on tracheal muscles whereas amodiaquin produced very slight constriction of young rabbits tracheal muscles.
However, both drugs antagonized the spasms induced by Ach, the antagonism being more with amodiaquin.

In investigating the cardiopulmonary effects of two 4-aminoquinoline anti-malarials, chloroquine and quinetholates \([4(4\text{-dimethylaminoethylamino})-6\text{-methoxy-quinoline}]\), (Aviado et al. 1970), demonstrated that chloroquine reduced the incidence of fibrillation following chloroform inhalation and that chloroquine injection protected mice from ventricular fibrillation induced by chloroform inhalation.

The use of chloroquine in asthmatic patients was first reported by Engeset (1957). A daily dose of 100 - 250mg administered orally for two weeks caused an amelioration of the respiratory difficulties in 75% of 32 patients. Sylvio de Camargo (1958) described his experience with 20 patients whose condition improved under chloroquine treatment. The antiasthmatic property of chloroquine has also been reported by Aviado et al. (1970). They also reported that 6 to 8 weeks of chloroquine administration to rabbits did not influence the content of histamine, serotonin (5HT), noradrenaline and dopamine in the lung. It did not also appear to exert any protective action against anaphylaxis. Treatment of male rats with chloroquine 5mg/kg administered orally for 3 weeks resulted in the reduction of the histamine content of the lung to half the control level (Agarwal et al. 1963). However, chloroquine has been shown to release histamine in the rat but not in human, the cat or the rabbit (Lecomte, 1955). Furthermore, Cohn (1965) reported that chloroquine inhibits the methylation of histamine in the male rat. In the rabbit, chloroquine has no effect on the histamine content of the lung (Agarwal, S. L and Arora R.B. 1956).

Chloroquine and amodiaquin have been reported to have adrenergic neurone blocking properties (Jindal M.N. 1970). At low concentration \((10^{-6} - 5\times10^{-6} \text{ g/ml})\) both drugs disproportionately antagonized the effects of transmural stimulation of adult rabbit aortic strips without affecting the responses to noradrenaline.
With higher concentration such as $10^{-2}\text{mg/ml}$, both the responses were abolished. In lower concentrations ($10^{-2}\text{mg/ml}$) both chloroquine and amodiaquine potentiated the cumulative dose response curves of noradreneline while higher concentrations such as $5 \times 10^{-3}\text{mg/ml}$ depressed it.

Paterson (1965) demonstrated that transmural stimulation of aortic strips can be blocked by guanethidine without affecting the response to catecholamines. Thus chloroquine and amodiaquine have actions similar to those of guanethidine on adrenergic neurones. It was further shown (Jindal M.N. 1970), that the blockade caused by chloroquine was antagonized by dexamphetamine just as with guanethidine. The adrenergic neurone blocking action of both chloroquine and amodiaquine was suggested to be an extension of the local anaesthetic action reported for both compounds (Jindal, et al 1960). However, the paradox or contradiction was that the concentrations needed to cause adrenergic neurone blockade was lower than those needed to produce local anaesthesia. Jindal et al (1960) also drew the parallelism between the pharmacological actions of 4-aminoquinolines on the one hand and guanethidine and bretylium on the other. These include adrenergic neurone blockade, supersensitivity to catecholamines, local anaesthetic activity and neuromuscular junction blocking activity.

Jindal (1956) and Jindal and Joseph (1958), reported potentiation of the pressor responses of certain catecholamines following I.V administration of chloroquine concurrently. While investigating the mechanism of this supersensitivity, Jindal, et al (1960), found that both chloroquine and amodiaquine potentiated the effect of tyramine on the blood pressure of anaesthetized dogs. It was also found that the two drugs induced hypertension in amphetamine pretreated animals which was demonstrated to be due to release of catecholamines. These effects were reminiscent of those produced by acute I.V. administration of reserpine (Yelnosky, 1966).
Prostaglandins (PGs) are highly active, 20-carbon, modified unsaturated hydroxy fatty acids with uterotonic activity. The original work indicated that of the naturally occurring PGs, only two - PGE2 and PGF2α - are clinically important in reproduction. Using a few patients, Karim et al (1968) and Embrey (1969) showed that labour could readily be induced with I.V infusions of both PGs. PGF2α has a potent uteronic action on isolated strips of pregnant human myometrium. (Bygdeman 1964, 1967). Karim (1968) has further shown that PGF2α appears in the maternal venous blood in variable amount during labour and that the concentration of this PG is highest immediately before a uterine contraction. Due to the successful induction of labour with PGF2α and the appearance of this substance in maternal blood during labour and in close relation to uterine contraction, Embrey (1969) suggested that PGF2α has a physiological role to play in parturition.

Prostaglandins bind to and release calcium from liver mitochondria (Malstrom et al 1975). PG-induced calcium release from heart mitochondria and sarcoplasmic reticulum (SR) from the uterus has been reported (Tsuyoshi et al 1979, Carsten et al 1977). Intracellular - free calcium is thought to regulate the contraction/relaxation process in smooth muscle. It has been proposed that a subcellular mode of action of PGs may be the release of calcium from uterine sarcoplasmic reticulum (Carsten et al 1977).

PGs can also release calcium from bovine intrapulmonary vein and increase tension development in helical strips of the same tissue (Mcnamara et al 1980). It has been suggested that PGs exert their effect via an ionophore-like action on calcium movement, (Carsten ME and Miller J.D 1977). However, the possibility that PGs may also exert their effect by a non-ionophoretic action on mitochondrial calcium movement has also been suggested (Mcnamara et al, 1980).

The cardiotonic effect of PGE2 and PGF2α is concentration-dependent. Low concentrations consistently caused cardiac rhythm irregularities whereas high concentrations had no effect themselves and stabilized hearts made unstable by low concentrations. Copper ions (in the form of the sulphate salt) stabilized hearts made unstable by PGs and when present prior to the PGs prevented PG - induced heart rhythm disturbances. Chloroquine also reversed PG-induced rhythm disturbances.
SUGGESTED MECHANISMS OF ACTION OF CHLOROQUINE

Chloroquine and related drugs exert their antimalarial action by intercalating between the stacked base pairs of the DNA double helix by interacting with the purine bases (adenine and guanine). In this way, they prevent nucleic acid synthesis and consequently protein synthesis in the actively dividing erythrocytic schizonts and in the gametocytes. The parasitized erythrocytes concentrate chloroquine much more than other tissues and this probably accounts for the selective toxicity of the drug against erythrocytic schizonts and gametocytes (Bowman W.C. and Rand M.J. 1980).

It has been suggested that chloroquine acts in S.L.E. by binding to nucleic acids, preventing DNA repair, blocking DNA unwinding and inhibiting DNA and RNA polymerase, Rollo 1975). It has also been shown to inhibit PG synthesis but only in certain experimental conditions (Greaves and Macdonald-Bibson 1972, Collier, 1974). Further chloroquine has been shown to act as a PG antagonist in a rat mesenteric vasculature preparation (Manku and Horrobin 1976a,b).

It has also been suggested (Famaey et al 1977a) that the chloroquine inhibition of guinea pig ileum contractions induced by Ach, histamine, nicotine and electrical stimulation could be due to inhibition of endo-genous ileal synthesis of PGE as this inhibition was antagonized by small doses of exogenously added PGE.

The overall inhibition induced by chloroquine could in this case be related to its well known membrane stabilising properties (Weismann, 1965) which might affect the smooth muscle membrane reactivity.

On investigating the effect of Quinine, proguanil and chloroquine on cardiovascular responses to adrenaline and Ach in dogs, Jindal (1956) demonstrated that chloroquine potentiated the vasopressor response of adrenaline. He further hypothesized that this action of chloroquine could be due to its effect on the amine-oxidase system concerned with the inactivation of adrenaline and other catecholamines.

The mechanisms, involved in the antiasthmatic action of chloroquine, has not been fully elucidated. Four mechanisms have been suggested viz:
a) An anti-inflammatory effect analogous to the action responsible for the relief of inflammation in joints (Carminati, 1965).

b) An antihistaminic effect demonstrable in the isolated guinea pig ileum (Benda and Miravet, 1958).

c) An anti-serotonin effect observed in the isolated guinea pig ileum and rat uterus (Okegawa et al., 1965a, b).

d) Release of corticosteroids into the blood, which in turn exert an antihistaminic effect;

e) Reduction in the synthesis of histamine (Agarwal et al., 1963).

However, since chloroquine does not appear to exert any protective action against anaphylaxis and does not alter the content of histamine, serotonin and catecholamines (Aviado et al., 1970), hypotheses (b) and (c) can be excluded.

It was suggested by Aviado, sadavongvivad and Cambar (1970) that possibly an antihistaminic effect is exerted by chloroquine on the lung, as may be noted by comparing the increase in pulmonary resistance to histamine before and after administration of 4-aminquinolines. After administration of chloroquine, the response to histamine was reduced. It was probably this anti-histaminic effect that was responsible in part for the antihistaminic effect of the 4-aminquinolines. Since ordinary antihistaminics do not possess any antiasthmatic property, it was proposed that the 4-aminquinolines has access to the histamine to which antihistamines could not get access to (Aviado, et al 1970).

PGs bind to and release calcium from liver mitochondria (Mastrom et al 1975), heart mitochondria and uterine sarcoplasmic reticulum (Tsuyoshi et al. 1979 and Carsten et al. 1977). It has been proposed that a subcellular mode of action of PGs may be the release of calcium from uterine sarcoplasmic reticulum (Carsten et al. 1977).

Suggestion has been advanced that PGs exert their effect via an ionophore-like action on calcium movement (carsten M E and Miller J.D. 1977). However, the possibility that PGs exert their effect by a non-ionophoretic action on mitochondrial calcium movement has also been proposed (Monamara et al. 1980).
Chloroquine and the other 4-aminoquinolines are less toxic than quinine and mepacrine (quinacrine) in the doses used in the treatment of malaria. However, they can cause dizziness, headache, difficulty in accommodation, itching, vomiting and skin rash in the doses used for the treatment of an acute attack of malaria. With higher doses used in the treatment of amoebiasis, rheumatoid arthritis and S.L.E., toxic effects are more likely viz: skin eruptions, photosensitivity, alopecia, bleaching of the hair, leucopenia and blurring of vision that may progress to severe retinopathy and blindness.

The toxicological properties of chloroquine have been documented for a long time especially with doses used in the treatment of rheumatoid arthritis and S.L.E. In 1969, Chapman et al reported a case of generalized muscle weakness due to prolonged chloroquine ingestion, in a 64 year old woman who had been taking nivaquin (Chloroquine phosphate) 400mg daily for about 7 years, as an empirical therapy for a non-specific rash of the face. It was believed that chloroquine was responsible for the vascular myopathy reported and that muscular injury was due to inhibition of glycolysis since there was glycogen accumulation in the vacuoles (Chapman R S et al 1969). Loftus L R (1963) documented a case of four patients who developed similar episodes of peripheral neuropathy following prolonged treatment with chloroquine phosphate. All the four patients had complaints and findings consisting of weakness of quadriceps muscles accompanied by the loss of patellar and Achilles tendon reflexes bilaterally. One also had paraesthesia of the thighs and loss of vibratory sensation in both legs. All the four patients were treated for rheumatoid arthritis. Chloroquine can also cause foetal abnormalities. For instance, chloroquine caused congenital deafness with instability of the gait, choriocenteritis, hemihypertrophy and Wilms Tumour (Hart C.W. and Naunton R.F. 1964) in children whose mother had been given chloroquine during four out of her eight pregnancies. Complete cochlear damage (Matz and Naunton 1968) and embryonic death and eye abnormalities (Udalova, 1967) were observed when chloroquine was administered to
Cardiac arrest and hypotension are the main cause of death in chloroquine overdose. Death resulting from doses of chloroquine within the normal range either through cardiac arrest or hypotension have been reported (Michael T.A and S. Aiwazzadeh, 1970).

Here in Kenya itself, chloroquine has caused a number of deaths especially among young ladies who use it illegally for the procurement of abortion. Often the doses used were outside the therapeutic range and the victims die probably from cardiac arrest or hypotension (Michael et al 1970). However, experience has shown that chloroquine and quinine are effective abortifacients, though the method by which they bring about abortion is still obscure. One of the objectives of this research project was to investigate whether chloroquine has oxytocic activity of its own, or whether the abortifacient effect was due to a different mechanism.
EXPERIMENTAL

APPARATUS

Student Kymogram
Washington 400MD 2C Oscillograph
Langendorff apparatus
Heating bath
Organ bath
Manometer
Starling heart lever
Havard recorder.

DRUGS AND CHEMICALS:

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<th>MANUFACTURER</th>
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<tr>
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<td>Lab. chemicals</td>
<td>Howse &amp; McGeorge ltd.</td>
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**PHYSIOLOGICAL SALT SOLUTIONS**

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<td>Sodium dihydrogen phosphate</td>
<td>0.05</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Potassium dihydrogen phosphate</td>
<td>-</td>
<td>-</td>
<td>0.16</td>
<td>-</td>
</tr>
<tr>
<td>Sodium bicarbonate</td>
<td>1.0</td>
<td>0.2</td>
<td>2.10</td>
<td>0.5</td>
</tr>
<tr>
<td>Glucose</td>
<td>1.0</td>
<td>0.1</td>
<td>2.00</td>
<td>0.5</td>
</tr>
</tbody>
</table>
The quantities shown are for making one litre of solution. All the solutions are prepared freshly. Calcium chloride was dissolved separately and added slowly to the rest of the solution, to avoid the formation of calcium carbonate, which makes the solution cloudy.

**PROCEDURE**

**AGONISM OF CHLOROQUINE TO DRUG INDUCED CONSTRICITION OF INTACT GUINEA PIG TRACHEAL SMOOTH MUSCLES:**

Chloroquine inhibits the isometric contractions of the guinea pig ileum induced by electrical coaxial stimulation in the same manner as do the steroidal and non-steroidal antiinflammatory drugs and inhibits the height of the spontaneous contractions induced by Prostaglandin E₁ (PGE₁) and PGF₂α (Famaey et al., 1975). Chloroquine also inhibits the response of rabbits ileum to acetylcholine (Agarwal et al., 1956). Chloroquine has been used in the past for the treatment of asthma (Røgeset, 1957; Ivio de Camargo, 1958). It was therefore felt worthwhile to investigate whether chloroquine has a smooth muscle relaxing action on the guinea pig tracheal smooth muscles.

**Animals and Method:**

Adult guinea pigs weighing about 360g were killed by a blow on the head, cutting the throat as near the head as possible. The trachea was dissected out to a dish of prewarmed (95% O₂, 5% CO₂) tyrode solution freed from extraneous tissues and set up as shown in fig. 1. The tyrode solution was then drawn up through the trachea and into the graduated pipette (1mm internal bore), care being taken to exclude air bubbles from the system.

The set up was placed in a 20ml organ bath maintained at 37°C, containing tyrode solution and aerated with a mixture of 95% O₂ and 5% CO₂. After stabilizing for 3 minutes, the scale on the pipette was recorded and the drugs under investigation were added into the organ bath following a set order and maintaining drug-tissue contact time of 3 minutes. The change in pipette fluid volume was
noted on each occasion. Increased pipette fluid volume denotes bronchoconstriction whereas a decrease denotes relaxation of the tracheal smooth muscles.

A recovery time of 5 minutes was allowed after each drug response. Initially, each drug was added alone to observe and record the normal response of the tracheal smooth muscles to it. After recording the normal volume changes, chloroquine was added to the organ bath simultaneously with the agonists (acetylcholine, nicotine, barium chloride and histamine) in increasing doses and the volume changes recorded.

The drugs used were as follows:

<table>
<thead>
<tr>
<th>DRUG</th>
<th>Dose</th>
<th>Concentration in 20ml organ bath</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylcholine</td>
<td>10μg</td>
<td>0.5 μg/ml</td>
</tr>
<tr>
<td>Histamine</td>
<td>20μg</td>
<td>1.0 μg/ml</td>
</tr>
<tr>
<td>Nicotine</td>
<td>20μg</td>
<td>1.0 μg/ml</td>
</tr>
<tr>
<td>Barium chloride</td>
<td>4Mg</td>
<td>0.2 Mg/ml</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>2-8μg</td>
<td>0.1 -5.4μg/ml</td>
</tr>
</tbody>
</table>
The effect of chloroquine on the drug-induced spontaneous contractions of rabbit ileal muscles

Preamble:

Chloroquine antagonizes the contractions of guinea pig ileum induced by
acetylcholine, nicotine and histamine (Famney et al. 1977a) and of rabbit ileum induced by acetylcholine (Agarwal et al., 1956). In this investigation, an attempt is made to elaborate on the effect of chloroquine on rabbit ileal muscles and the possible mechanism underlying this antagonism.

MATERIALS AND METHOD:

A rabbit was killed by a blow on the head and immediately the stomach wall was opened up and a piece of jejunum removed at least 10 cm from the jejunum. A section of jejunum (1-1.5 cm long) was isolated, washed in fresh aerated tyrode solution and set up in a 20 ml organ bath containing tyrode solution and aerated with a mixture of 95% \( \text{O}_2 \) and 5% \( \text{CO}_2 \) and maintained at 37°C. After recording the normal contractions, three reproducible contractions induced by each agonist (acetylcholine, nicotine and barium chloride) were recorded. Using a constant dose of the agonists, the effect of varying dose of the test drug (chloroquine) on the contractions of the rabbit ileum was studied.

A time cycle of 5 minutes and drug-tissue contact time of 3-5 minutes was adhered to throughout the experiment. After recording the tissue response to each drug, the tissue was washed or rinsed at least three times with fresh tyrode solution before the next drug addition. The apparatus used is shown in Fig. 2.

The drugs used and their final bath concentrations were as follows:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Final Bath Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylcholine</td>
<td>0.2 ( \mu \text{g} )</td>
<td>0.01 ( \mu \text{g/ml} )</td>
</tr>
<tr>
<td>Nicotine</td>
<td>5 ( \mu \text{g} )</td>
<td>0.25 ( \mu \text{g/ml} )</td>
</tr>
<tr>
<td>Barium chloride</td>
<td>1 ( \text{mg} )</td>
<td>0.05 ( \text{mg/ml} )</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>2 - 8 ( \mu \text{g} )</td>
<td>0.1 - 0.4 ( \mu \text{g/ml} )</td>
</tr>
</tbody>
</table>
G. 2 - Apparatus used to investigate the effect of chloroquine on rabbit ileum
The effect of Chloroquine on the rabbit heart (Langendorff preparation)

Preamble:

Chloroquine and amodiaquin have a powerful action in the prevention of experimental auricular arrhythmias (Arona, et al; 1955, 1956). Further works have shown that chloroquine has a cardioinhibitory effect on the vagus nerve (Agarwal et al; 1956), antifibrillatory action (Aviado et al, 1970) and antiadrenergic (β-blockade) action (Cao et al; 1970). Its myocardial depressant action has also been reported (Michael et al, 1970). Literature survey have shown that whereas the negative inotropic effect of chloroquine have been well documented, its chronotropic effect have not been clearly established. The present experiment therefore attempts to establish the effect of chloroquine on the rate and force of myocardial contractility and also to elucidate the possible mechanism by which it exerts its effect.

Materials and Method

A rabbit was killed by a blow on the head and immediately the chest wall and the rib cage were quickly opened to expose the heart. The heart was removed with at least 1cm of aorta attached. It was then placed immediately in a dish of warm oxygenated Locke physiological solution, washed several times, squeezing gently to remove blood that might otherwise clot inside.

The heart was then freed from extraneous tissues and immediately attached through the aorta onto the cannula at the base of the langendorff apparatus ensuring that no air bubbles were trapped in the system. The temperature of the perfusing fluid (Locke solution) was maintained at 37°C. The rate of perfusion and aeration (95% O₂, 5% CO₂) was adjusted until the heart was beating satisfactorily. The apex of the heart was then hooked by a thread to a sterling heart lever via a pulley system. Normal contractions were recorded over a two minute period using a Havard recorder (BIOSCIENCE, USA). A bolus dose of each drug was given just above the cannula, and this was washed down by the perfusion fluid (Locke solution) into the heart via the aorta. After recording the response of the heart to individual drugs (both inotropic and chronotropic), the effect of the standard doses of these drugs in the presence of varying
doses of chloroquine were investigated. The Langendorff apparatus used in this is shown in fig. 3 below.

Drugs used:
- Adrenaline 0.2μg
- Isoprenaline 50ng
- Caffeine 4mg
- Barium chloride 2mg
- Chloroquine 2 - 10μg

**FIG. 3** - The Langendorff apparatus used in the investigation of the effect of chloroquine on the isolated rabbit heart.
The effect of Chloroquine on drug-induced contractions of rat uterine smooth muscles

Preamble:

Prostaglandin F2α (PGF2α) has a potent uterotonic action on isolated strips of pregnant human myometrium (Bygdeman 1964, 1967). Karim (1968) has further shown that PGF2α appears in the maternal venous blood in variable amount during labour and that the concentration of this prostaglandin is highest immediately before a uterine contraction. Due to the successful induction of labour with PGF2α and the appearance of this substance in maternal blood during labour and in close relation to uterine contraction, it has been suggested that PGF2α may have a physiological role to play in parturition (Embrey, 1969). It has also been demonstrated that chloroquine inhibits the height of spontaneous contraction of guinea pig ileal smooth muscles induced by PGE1 and PGF2α (Famaey et al., 1975, 1977b). The review of the literature have not shown whether chloroquine has its own intrinsic uterotonic activity. It was therefore thought worth investigating whether chloroquine has its own intrinsic uterotonic activity and further elucidate the possible mechanism of its alleged abortifacient property.

Materials and Method:

Young virgin female rats weighing between 125–145g, previously (24–48 hours) injected intraperitoneally (IP) with 0.1mg/kg stilboesterol to increase uterine sensitivity were used. The animals were killed by a blow on the head and the uterine-horns carefully dissected into a dish of de Jalon physiological solution. After cleaning off the extraneous tissues, about 3cm of the uterus was set up in a 20ml organ bath containing de Jalon solution gassed with 95% O2 and 5% CO2. The organ bath was thermostatically maintained at 32°C in order to minimize the spontaneous activity of the uterus since the activity of uterine myometrium increases with temperature. The tissue was allowed to stabilize for about 30 minutes, after which three reproducible contractions induced by either PGF2α, carbachol or oxytocin were recorded. The tissue was then challenged with an
increasing dose of chloroquine in the presence of PGF2α, carbachol and oxytocin. The effect of chloroquine alone on the uterine smooth muscles was also investigated.

After each drug addition, the tissue was rinsed three times with fresh de Jalow solution. The drug-tissue contact time of about 50 seconds and a recovery time of about 8 minutes was maintained throughout the experiment. The apparatus used is shown in fig 4.

Drugs used:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Final Bath Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxytocin</td>
<td>0.1I.U</td>
<td>0.005 I.U/ml</td>
</tr>
<tr>
<td>PGF2α</td>
<td>0.1μg</td>
<td>0.005μg/ml</td>
</tr>
<tr>
<td>Carbachol</td>
<td>6μg</td>
<td>0.3μg/ml</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>1 - 4000μg</td>
<td>0.05 - 200μg/ml</td>
</tr>
</tbody>
</table>

In another set of experiment, the effect of intraperitoneal (IP) injection of chloroquine on pregnant rats (gestation period unknown) was investigated. Ten pregnant rats were divided into five groups of two rats each. To each group, chloroquine was administered IP as follows:

Group A  - 5Mg/kg IP
Group B  - 8Mg/kg IP
Group C  - 10Mg/kg IP
Group D  - 20Mg/kg IP
Group E  - 30Mg/kg IP

After administration of the drug, each group of animals was placed in different cages to avoid mistaken identity. The animals were then observed for 48 hours for abortion, convulsions, ataxia, dyspnea etc.
The effect of Chloroquine on the transmission of neuromuscular junction

Preamble:

Chloroquine depresses and finally blocks the neuromuscular transmission which was attributed to depression of the sodium conductance mechanism in the axonal terminals (Chinyanga et al 1972). Chloroquine myopathy following prolonged use of the drug for the treatment of arthritic conditions have been reported.
(Chapman et al 1969; Hughes et al 1971). This was attributed to inhibition of glycolysis evidenced by accumulation of glucose (Chapman et al 1963) and degeneration of muscle fibres (Hughes et al 1972). Review of the literature have not revealed at what level(s) of the neuromuscular junction, chloroquine exerts its depressant action. It was therefore deemed necessary to establish at what level(s), chloroquine might exert its action, and consequently postulate the possible mechanism of action.

Materials and Method

A rat weighing about 130 g was killed by a blow on the head and the carotid arteries quickly cut out. The skin over the chest region and around the pectoral muscles were removed. The thorax was opened along one side, and the ribs cut close to the thoracic vertebrae to expose the left phrenic nerve. The latter was tied with thread and cut some distance away from the diaphragm. The left part of the diaphragm with the nerve was attached onto an electrode and then placed in a 40 ml organ bath containing Krebs-Henseleit physiological solution gassed with a mixture of 95% O₂ and 5% CO₂ and maintained at 37°C. The preparation was stimulated at one pulse per second and 5 Volts on addition of each drug. The effect of the standard dose of tubocurarine, succinylcholine and lignocaine was recorded and thereafter the tissue was challenged with varying doses of chloroquine in the presence of the above substance.

After each drug response was noted, the tissue was rinsed with fresh Krebs-Henseleit solution before addition of the next drug. The recovery time was between 30-60 minutes. The apparatus used is shown in Fig. 5.

Drugs used

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DOSE</th>
<th>FINAL LABTH CONCENTRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tubocurarine</td>
<td>1mg</td>
<td>0.025 mg/ml</td>
</tr>
<tr>
<td>Succinylcholine</td>
<td>5mg</td>
<td>0.125 mg/ml</td>
</tr>
<tr>
<td>Lignocaine</td>
<td>5mg</td>
<td>0.125 mg/ml</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>10μg</td>
<td>0.050 μg/ml</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.25 μg/ml</td>
</tr>
</tbody>
</table>
FIG. 5 Set up of the apparatus used to investigate the effect of Chloroquine on neuromuscular junction transmission
RESULTS:

ANTAGONISM OF CHLOROQUINE TO DRUG-INDUCED CONSTRICTION OF INTACT GUINEA PIG TRACHEAL SMOOTH MUSCLES:

Chloroquine, at a dose of 2µg caused relaxation of the smooth muscles of the guinea pig trachea by 2% and antagonized the constrictor effect of Ach (10µg), nicotine (20µg), histamine (20µg) and barium chloride (4mg), the extent of antagonism differing for each agonist. The antagonism was found to be dose-dependent. 4µg of chloroquine inhibited Ach (10µg)-induced constriction by 70% and further increase in the dose of chloroquine could not produce more than 50% inhibition. With histamine (20µg) 50% inhibition was effected by 4µg of chloroquine and further increase in the dose of chloroquine could not produce greater inhibition. Nicotine (20µg) and barium chloride (4mg) were found to be more sensitive to the action of chloroquine than histamine and Ach. 4µg of chloroquine completely inhibited the constrictor effect of 20µg of nicotine whereas 6µg of chloroquine completely inhibited the constrictor effect of 4mg of barium chloride and actually caused 33.3% and 25% relaxation respectively i.e. 133.3% and 125% inhibition respectively.

The result is summarized in table 1 below. Note that the response is 'RISE' when constriction occurs and 'FALL' when relaxation takes place. Fig. 6 shows a plot of % inhibition vs dose of chloroquine used.

TABLE I: Antagonism of chloroquine to drug-induced constriction of

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DOSE</th>
<th>INITIAL READING (ml)</th>
<th>FINAL READING (ml)</th>
<th>RESPONSE</th>
<th>% INHIBITION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ach</td>
<td>10µg</td>
<td>0.0500</td>
<td>0.0400</td>
<td>RISE</td>
<td></td>
</tr>
<tr>
<td>Histamine</td>
<td>20µg</td>
<td>0.0500</td>
<td>0.0410</td>
<td>RISE</td>
<td></td>
</tr>
<tr>
<td>Nicotine</td>
<td>20µg</td>
<td>0.0500</td>
<td>0.0470</td>
<td>RISE</td>
<td></td>
</tr>
<tr>
<td>BaCl2</td>
<td>4mg</td>
<td>0.0500</td>
<td>0.0460</td>
<td>RISE</td>
<td></td>
</tr>
<tr>
<td>Chloroquine(CQ) 2µg</td>
<td>0.0500</td>
<td>0.0510</td>
<td>FALL</td>
<td>20% relaxation</td>
<td></td>
</tr>
<tr>
<td>Ach + CQ</td>
<td>10µg+2µg</td>
<td>0.0500</td>
<td>0.0450</td>
<td>RISE</td>
<td>50.0%</td>
</tr>
<tr>
<td>DRUG</td>
<td>DOSE</td>
<td>INITIAL READING (ml)</td>
<td>FINAL READING (ml)</td>
<td>RESPONSE</td>
<td>% INHIBITION</td>
</tr>
<tr>
<td>------------</td>
<td>---------------</td>
<td>----------------------</td>
<td>--------------------</td>
<td>----------</td>
<td>--------------</td>
</tr>
<tr>
<td>Ach + CQ</td>
<td>10 µg + 4 µg</td>
<td>0.0500</td>
<td>0.0470</td>
<td>RISE</td>
<td>70.0</td>
</tr>
<tr>
<td></td>
<td>&quot; + 6 µg</td>
<td>0.0500</td>
<td>0.0450</td>
<td>RISE</td>
<td>50.0</td>
</tr>
<tr>
<td></td>
<td>&quot; + 8 µg</td>
<td>0.0500</td>
<td>0.0450</td>
<td>RISE</td>
<td>50.0</td>
</tr>
<tr>
<td>Histamine + CQ</td>
<td>20 µg + 4 µg</td>
<td>0.0500</td>
<td>0.0450</td>
<td>RISE</td>
<td>44.5</td>
</tr>
<tr>
<td></td>
<td>&quot; + 4 µg</td>
<td>0.0500</td>
<td>0.0455</td>
<td>RISE</td>
<td>50.0</td>
</tr>
<tr>
<td></td>
<td>&quot; + 6 µg</td>
<td>0.0500</td>
<td>0.0440</td>
<td>RISE</td>
<td>33.3</td>
</tr>
<tr>
<td>Nicotine + CQ</td>
<td>20 µg + 2 µg</td>
<td>0.0500</td>
<td>0.0495</td>
<td>RISE</td>
<td>83.3</td>
</tr>
<tr>
<td></td>
<td>&quot; + 4 µg</td>
<td>0.0500</td>
<td>0.0500</td>
<td>NONE</td>
<td>100.0</td>
</tr>
<tr>
<td></td>
<td>&quot; + 6 µg</td>
<td>0.0500</td>
<td>0.0510</td>
<td>FALL</td>
<td>133.3</td>
</tr>
<tr>
<td>BaCl₂ + CQ</td>
<td>4 µg + 2 µg</td>
<td>0.0500</td>
<td>0.0460</td>
<td>RISE</td>
<td>50.0</td>
</tr>
<tr>
<td></td>
<td>&quot; + 4 µg</td>
<td>0.0500</td>
<td>0.0485</td>
<td>RISE</td>
<td>62.5</td>
</tr>
<tr>
<td></td>
<td>&quot; + 6 µg</td>
<td>0.0500</td>
<td>0.0510</td>
<td>FALL</td>
<td>125.0</td>
</tr>
</tbody>
</table>

In each case, the % inhibition was calculated as follows:

\[
\text{% Inhibition} = \frac{(0.0500 - A) - (0.0500 - B)}{(0.0500 - A)} \times 100
\]

Where A = Volume change due to standard drugs

B = Volume change due to standard drugs + chloroquine.
FIGURE 6: % Change in drug-induced constriction of guinea pig tracheal smooth muscles by chloroquine.
FIG. 7a - Antagonism of Chloroquine to Ach-induced contractions of rabbit ileal muscles.
FIG. 7b Antagonism of chloroquine to BaCl$_2$-induced contractions of rabbit muscles.
FIG. 7c. Antagonism of nicotine to drug-induced contractions of rabbit ileal muscles.
FIGURE 3: Dose-dependent % inhibition of barium chloride-induced spontaneous contractions of rabbit ileal muscles by chloroquine.

Dose of chloroquine
in presence of a standard dose of BaCl$_2$ (1mg)
THE EFFECT OF CHLOROQUINE ON DRUG-INDUCED SPONTANEOUS CONTRACTION OF RABBIT ILEAL MUSCLES

Chloroquine, in doses of 2 μg and above caused slight short-lived relaxation of rabbit ileal smooth muscles which appeared to be dose-dependent. When co-administered with the agonists (Acetylcholine, nicotine and barium chloride), chloroquine, still caused an initial but reduced smooth muscle relaxation with the agonistic stimulant effect still evident but reduced. The dose dependent manner in which chloroquine inhibits the spontaneous contractions induced by barium chloride was more defined than with the other agonists. 8 μg of chloroquine reduced the height of spontaneous contractions induced by barium chloride (1 mg) and nicotine (5 μg) by 68.69% and 35.19% respectively. With acetylcholine (0.2 μg), the inhibition by chloroquine was not well defined; though dose-dependency was nevertheless evident.

The results are shown in table 2 and the tracings in fig. 7a, b, c. Fig. 8 shows the dose-dependent % inhibition of barium chloride induced contractions by chloroquine.

TABLE 2 % inhibition of drug induced spontaneous contractions of rabbit ileal muscles by chloroquine.

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DOSE</th>
<th>% INHIBITION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barium chloride</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+ chor.</td>
<td>1 mg + 2 μg</td>
<td>14.14</td>
</tr>
<tr>
<td></td>
<td>1 mg + 4 μg</td>
<td>21.21</td>
</tr>
<tr>
<td></td>
<td>1 mg + 6 μg</td>
<td>42.42</td>
</tr>
<tr>
<td></td>
<td>1 mg + 8 μg</td>
<td>68.69</td>
</tr>
<tr>
<td>Nicotine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+ chor.</td>
<td>5 μg + 2 μg</td>
<td>27.78</td>
</tr>
<tr>
<td></td>
<td>5 μg + 4 μg</td>
<td>14.81</td>
</tr>
<tr>
<td></td>
<td>5 μg + 6 μg</td>
<td>53.70</td>
</tr>
<tr>
<td></td>
<td>5 μg + 8 μg</td>
<td>35.19</td>
</tr>
<tr>
<td>Acetylcholine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+ chor.</td>
<td>0.2 μg + 2 μg</td>
<td>38.53</td>
</tr>
<tr>
<td></td>
<td>0.2 μg + 4 μg</td>
<td>21.10</td>
</tr>
<tr>
<td></td>
<td>0.2 μg + 6 μg</td>
<td>25.69</td>
</tr>
</tbody>
</table>
Chloroquine was found to cause dose-dependent negative inotropic and chronotropic effects on the isolated rabbit heart. The drug antagonized the positive chronotropic response induced by adrenaline and isoprenaline with no effect but sometimes enhancing the inotropic response. The same kind of response was observed with the use of other cardiac stimulants such as caffeine and barium chloride. This is obviously a paradoxical result in view of the fact that chloroquine itself has been shown to have a negative inotropic effect.

The results are summarized in table 3 whereas the tracings are shown in fig. 9a, b, c.
<table>
<thead>
<tr>
<th>DRUG</th>
<th>DOSE</th>
<th>Average % change in inotropic response</th>
<th>Average % change in chronotropic response</th>
<th>Average % change in inotropic response due to chloroquine</th>
<th>Average % change in chronotropic response due to chloroquine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenaline</td>
<td>0.2μg</td>
<td>55.34</td>
<td>50.53</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Isoprenaline</td>
<td>50ng</td>
<td>45.80</td>
<td>40.63</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>caffeine</td>
<td>4μg</td>
<td>48.33</td>
<td>28.79</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Barium chloride</td>
<td>2μg</td>
<td>69.06</td>
<td>10.59</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>chloroquine</td>
<td>2μg</td>
<td>0.00</td>
<td>-5.56</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>4μg</td>
<td>-5.00</td>
<td>0.00</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>6μg</td>
<td>-7.69</td>
<td>-4.76</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Adrenaline + chloroquine</td>
<td>0.2+2μg</td>
<td>42.86</td>
<td>15.84</td>
<td>-12.48</td>
<td>-34.69</td>
</tr>
<tr>
<td></td>
<td>&quot;+6μg&quot;</td>
<td>112.72</td>
<td>22.80</td>
<td>57.38</td>
<td>-27.73</td>
</tr>
<tr>
<td></td>
<td>&quot;+8μg&quot;</td>
<td>95.84</td>
<td>9.00</td>
<td>40.50</td>
<td>-50.53</td>
</tr>
<tr>
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<td>&quot;+10μg&quot;</td>
<td>58.33</td>
<td>8.34</td>
<td>2.99</td>
<td>-42.19</td>
</tr>
<tr>
<td>Isoprenaline + chloroquine</td>
<td>50ng+2μg</td>
<td>153.34</td>
<td>31.82</td>
<td>107.54</td>
<td>-8.81</td>
</tr>
<tr>
<td></td>
<td>&quot;+4μg&quot;</td>
<td>62.06</td>
<td>26.67</td>
<td>16.26</td>
<td>13.96</td>
</tr>
<tr>
<td></td>
<td>&quot;+6μg&quot;</td>
<td>95.84</td>
<td>25.75</td>
<td>50.04</td>
<td>-14.88</td>
</tr>
<tr>
<td></td>
<td>&quot;+8μg&quot;</td>
<td>78.95</td>
<td>109.09</td>
<td>33.15</td>
<td>68.96</td>
</tr>
<tr>
<td></td>
<td>&quot;+10μg&quot;</td>
<td>58.82</td>
<td>8.33</td>
<td>13.02</td>
<td>-32.30</td>
</tr>
<tr>
<td>caffeine + chloroquine</td>
<td>4μg+2μg</td>
<td>62.34</td>
<td>20.00</td>
<td>14.01</td>
<td>-5.79</td>
</tr>
<tr>
<td></td>
<td>&quot;+4μg&quot;</td>
<td>60.00</td>
<td>-</td>
<td>11.67</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>&quot;+6μg&quot;</td>
<td>28.57</td>
<td>5.56</td>
<td>-19.76</td>
<td>-23.23</td>
</tr>
<tr>
<td></td>
<td>&quot;+8μg&quot;</td>
<td>60.00</td>
<td>41.67</td>
<td>11.67</td>
<td>12.88</td>
</tr>
<tr>
<td></td>
<td>&quot;+10μg&quot;</td>
<td>61.54</td>
<td>76.92</td>
<td>13.31</td>
<td>48.13</td>
</tr>
<tr>
<td>Barium chloride + chloroquine</td>
<td>2μg+2μg</td>
<td>153.64</td>
<td>2.31</td>
<td>84.58</td>
<td>-8.28</td>
</tr>
<tr>
<td></td>
<td>&quot;+4μg&quot;</td>
<td>84.85</td>
<td>6.90</td>
<td>15.79</td>
<td>35.77</td>
</tr>
<tr>
<td></td>
<td>&quot;+6μg&quot;</td>
<td>74.45</td>
<td>46.36</td>
<td>5.39</td>
<td>35.77</td>
</tr>
<tr>
<td></td>
<td>&quot;+8μg&quot;</td>
<td>127.27</td>
<td>36.36</td>
<td>59.21</td>
<td>25.77</td>
</tr>
<tr>
<td></td>
<td>&quot;+10μg&quot;</td>
<td>108.22</td>
<td>122.22</td>
<td>39.27</td>
<td>111.63</td>
</tr>
</tbody>
</table>
FIG. 9a Response of the isolated rabbit heart to chloroquine.

4µg chloroquine

6µg chloroquine

8µg chloroquine
FIG. 9b Response of isolated rabbit heart to isoprenaline and adrenaline co-administered with chloroquine

Adrenaline 0.2μg

chloroquine 2μg

Adrenaline 0.2μg

chloroquine 4μg

Isoprenaline 50ng

chloroquine 2μg

Isoprenaline 50ng

chloroquine 4μg

Isoprenaline 50ng

chloroquine 10μg
FIG 9o  The effect of chloroquine on the response of isolated rabbit heart to caffeine and barium chloride.

- Caffeine 4mg
- Chloroquine 2μg
- Caffeine 4mg
- Chloroquine 8μg
- Caffeine 4mg
- Chloroquine 10μg
- Barium chloride 2mg
- Chloroquine 2μg
- Barium chloride 2mg
- Chloroquine 4μg
- Barium chloride 2mg
- Chloroquine 5μg
FIGURE 10: % change in chronotropic response of rabbit heart following co-administration of agonists and chloroquine.

- Adrenaline 0.3µg
- Isoprenaline 50µg
- Barium chloride 2mg
- Caffeine 4mg

Dose of chloroquine in presence of standard dose of agonists.
Although chloroquine had no uterotonic activity of its own, it was found to oppose the contractions of rat uterine smooth muscles induced by carbachol, oxytocin and PGF2α (Prostin). At doses below 0.3mg, chloroquine could not antagonize the contractions induced by 0.1 I.U of oxytocin. However, much lower doses were required to antagonize contractions induced by carbachol and PGF2α. While 4mg of chloroquine completely inhibited the contractions induced by 0.1 I.U of oxytocin, only 0.05mg was required to completely inhibit contractions induced by 6μg of carbachol. Though the inhibition of PGF2α-induced rat uterine smooth muscle contractions showed dose-dependency, complete inhibition was not produced. 100μg of chloroquine caused 90.48% inhibition, whereas 150μg caused 61.90% inhibition.

The attempt to procure abortion by intraperitoneal administration of chloroquine to pregnant rats (gestation period unknown) was unsuccessful. The rats in groups D and E died while those in group C manifested signs of ataxia and dyspnoea. Those in groups A and B behaved normally.

Table 4 shows the % inhibition of the height of spontaneous contractions of rat uterine smooth muscles induced by carbachol, oxytocin and PGF2α caused by chloroquine. Figs. 11a, b, c, shows the tracings of the contractions of rat uterine smooth muscles by drugs and figs. 12 and 13 shows a plot of the % inhibition versus the doses of chloroquine in presence of a standard dose of the reference drugs (carbachol, oxytocin and PGF2α). From figures 12 and 13 it can be noticed that as the dose of chloroquine is increased, the % inhibition increases accordingly.
<table>
<thead>
<tr>
<th>DRUG/DOSE</th>
<th>DOSE OF CHLOROQUINE (µg) AND THE CORRESPONDING % INHIBITION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbachol 6µg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>-35.71</td>
</tr>
<tr>
<td>PGF2α 0.1µg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-17.44</td>
</tr>
<tr>
<td>Oxytocin 0.1 I.U</td>
<td></td>
</tr>
<tr>
<td></td>
<td>9.62</td>
</tr>
<tr>
<td>Dose of chloroq./% inhibition (contd.)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>80</td>
</tr>
<tr>
<td>PGF2α(contd.)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-76.19</td>
</tr>
<tr>
<td>Oxytocin(contd.)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Antagonism of chloroquine to carbachol-induced contractions of rat uterine smooth muscles. Note the total inhibition caused by 50 µg of chloroquine.

**FIG 11a**

![Diagram showing the effect of chloroquine on carbachol-induced contractions of rat uterine smooth muscles. Noted the total inhibition caused by 50 µg of chloroquine.](image-url)
FIG. 11b Antagonism of chloroquine to prostin-induced contractions of rat uterine smooth muscles.
FIGURE 11c

Oxytocin 0.1 I.U  oxytocin 0.1 I.U  oxytocin 0.1 I.U  oxytocin 0.1 I.U  oxytocin 0.1 I.U
+ chloroq 1µg  + chloroq 2µg  + chloroq 4µg

Oxytocin 0.1 I.U  oxytocin 0.1 I.U  oxytocin 0.1 I.U  oxytocin 0.1 I.U  oxytocin 0.1 I.U
+ chloroq 6µg  + chloroq 8µg  + chloroq 10µg  + chloroq 200µg  + chloroq 400µg
FIGURE 11c (contd...) Antagonism of chloroquine to oxytocin induced contractions of rat uterine smooth muscles.

note the total inhibition caused by 4000µg (4mg) of chloroquine.

FIGURE 11c (contd..) Antagonism of chloroquine to oxytocin induced contractions of rat uterine smooth muscles.

note the total inhibition caused by 4000µg (mg) of chloroquine.
FIGURE 12: % inhibition of carbachol and PGP2α - induced contractions of rat uterine smooth muscles by chloroquine.

KEY

- Carbachol (6μg)
- PGP2α (0.1μg)

Dose of chloroquine in presence of a standard dose of carbachol (6μg) and PGP2α (0.1μg)
FIGURE 13: % Inhibition of oxytocin-induced contractions of rat uterine smooth muscles by chloroquine.

Dose of chloroquine in presence of a standard dose of oxytocin (0.1 U)
Using the isolated rat phrenic nerve-diaphragm preparation, chloroquine was found to have a neuro-muscular junction transmission blocking activity. It was found to potentiate the blocking of tubocurarine and succinylcholine which are typical non-depolarizing and depolarizing neuromuscular junction blockers, respectively. Lignocaine, a local anaesthetic. The neuromuscular transmission depression of chloroquine was found to be dose-dependent in that 1μg, 2μg and 10μg, caused 12.0%, 15.63% and 28.95% depression respectively (Table 5). Similarly 1μg of chloroquine potentiated the neuromuscular blocking action of tubocurarine (1mg), succinylcholine (5mg) and lignocaine (5mg) by 32.55%, 13.07% and 22.12% respectively (Table 5). Due to the long recovery time of the tissue after each drug response (except succinylcholine which is a short-acting muscle relaxant), no attempt was made to investigate the effect of alteration of the dose of chloroquine on the neuromuscular blockade caused by these drugs. However, since the depression appeared to be dose-dependent, it can be presumed that the potentiation is also dose-dependent. The results are summarised in Table 5. Figs 14a, b, c, and d show the actual tracings of the depression following addition of each drug.
<table>
<thead>
<tr>
<th>DRUG</th>
<th>DOSE</th>
<th>AVERAGE % NMJ BLOCKADE</th>
<th>AV. % POTENTIATION OF BLOCKADE BY CHLOROQUINE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloroquine</td>
<td>1μg</td>
<td>12.00</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>2μg</td>
<td>15.63</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>10μg</td>
<td>28.95</td>
<td>-</td>
</tr>
<tr>
<td>Succinylcholine</td>
<td>5mg</td>
<td>37.57</td>
<td>-</td>
</tr>
<tr>
<td>Succinylcholine + chloroquine</td>
<td>5mg+1μg</td>
<td>50.57</td>
<td>13.07</td>
</tr>
<tr>
<td>Lignocaine</td>
<td>5mg</td>
<td>47.65</td>
<td>-</td>
</tr>
<tr>
<td>Lignocaine + chloroquine</td>
<td>5mg+1μg</td>
<td>69.77</td>
<td>22.12</td>
</tr>
<tr>
<td>Tubocurarine</td>
<td>1mg</td>
<td>50.73</td>
<td>-</td>
</tr>
<tr>
<td>Tubocurarine + chloroquine</td>
<td>1mg+1μg</td>
<td>83.33</td>
<td>32.55</td>
</tr>
</tbody>
</table>
FIG. 14a The neuromuscular transmission depressing action of chloroquine at one pulse per second and 5 volts.

chloroquine 1μg

chloroquine 10μg
FIG. 14b The neuromuscular blocking action of succinylcholine and its potentiation by chloroquine (1μg)

Succinylcholine 5mg

Chloroquine 1μg
FIG 14d: The neuromuscular blocking action of tubocurarine and its potentiation by chloroquine (1μg)
FIG. 14d. The neuromuscular blocking action of lignocaine and its potentiation by chloroquine (1µg)

Lignocaine 4mg

Lignocaine 4mg
chloroquine 1µg
DISCUSSION

ANTAGONISM OF CHLOROQUINE TO DRUG-INDUCED CONSTRICION OF INTACT GUINEA-PIG TRACHEAL SMOOTH MUSCLES

Besides causing relaxation of the smooth muscles of intact guinea-pig trachea, chloroquine antagonized the constrictor effect of acetylcholine (10μg), nicotine (0.002mg), histamine (0.002mg) and barium chloride (4μg) on the tracheal smooth muscles. In this respect, the antagonism was found to be more pronounced with nicotine and barium chloride than with acetylcholine and histamine. With acetylcholine (10μg) only 70% maximum inhibition could be produced by 4μg of chloroquine and further increase in dose of chloroquine could not produce greater inhibition. Similarly, with histamine only 50% maximum inhibition could be produced, while with nicotine and barium chloride, the constrictor effect was converted to relaxant effect by 6μg of chloroquine.

Chloroquine has no effect on tracheal smooth muscles of young adult rabbits whereas amodiaquin caused very slight constriction. (Agarwal et al 1956) but reduced the content of histamine in the lung to half the control level (Agarwal et al 1963). Chloroquine may also release histamine in the rat, although not in human the cat or the rabbit (Lecomte, 1955) and also inhibits the methylation of histamine in the male rat (Cohn, 1965).

In the past, chloroquine has been used in the treatment of bronchial asthma (Engeset, 1957). The anti-asthmatic effect of chloroquine has also been reported (Aviado et al 1970). It has been proposed that probably, the anti-asthmatic property of chloroquine was due in part to its antihistaminic property (Aviado et al 1970).

Since chloroquine antagonizes the effect of acetylcholine, nicotine, histamine and barium chloride on tracheal smooth muscles of the guinea pig, the result favours the possibility that chloroquine has a non-specific action on the guinea pig tracheal smooth muscles, which may be attributable, to its well known membrane stabilizing property (Weissmann, 1965).
The results obtained from this investigation, suggests that Chloroquine may be of some value in the treatment of asthma. However, since better drugs are available, its use in this condition is not recommended. In any case, its use in the management of asthma will call for a long-term therapy which may undoubtedly be attended by serious consequences. Nevertheless, it is important to note that its use in asthmatics may be beneficial, no matter how slight and its use concurrently with other antiasthmatics is not contraindicated, and may indeed be synergistic.

**The Effect of Chloroquine on Drug Induced Spontaneous Contractions of Rabbit Ileal Muscles**

The inhibition of the spontaneous contractions of guinea pig ileal muscles induced by acetylcholine, nicotine and histamine have been reported (Famaey et al.; 1977a). This was attributed to inhibition of endogenous ileal synthesis of Prostaglandins and to non-specific sensitization induced by prostaglandins to any kind of stimulation and to membrane stabilizing property of chloroquine (Weissmann; 1965).

In this investigation too, chloroquine was found to cause short-lived relaxation of rabbit ileal smooth muscles and to inhibit the spontaneous contractions induced by acetylcholine, nicotine and barium.
chloride, the inhibition being dose-dependent. This inhibition occurred at a concentration known to inhibit both bacterial and mammalian cell growth (Rollo, 1975) and to affect prostaglandin synthesis (Greaves et al.; 1972, Collier 1974). This inhibition suggests that chloroquine behaves as a non-specific spasmolytic agent on rabbit ileal smooth muscles and its inhibition of barium chloride induced contractions suggests its role as a calcium antagonist. Thus it may exert its effect by extensive non-specific action on ionic conductance.

The Effect of Chloroquine on isolated rabbit heart (Langendorff preparation)

Propranolol (Inderal) and Chloroquine can oppose the positive inotropic and chronotropic effects of isoprenaline (isopretenerenol) on isolated rabbit heart and the isolated rat auricle diminishing also the aminophylline cardiostimulant action, but not that of Calcium (Cao et al. 1970). Chloroquine may also block the β-adrenergic receptors of the myocardium (Cao et al.; 1970).

Similarly, in the present investigation, Chloroquine was found to have a cardiac muscle relaxant action. In other words, it was observed to have both negative inotropic and chronotropic effects. It may also have an antiadrenaline and anti-isoprenaline action, besides opposing the cardiostimulant action of caffeine and barium chloride. With the latter two
substances, the effect seemed to be variable depending on the concentration of chloroquine used. Higher doses appeared to sensitize the heart to the action of these cardiostimulants. The effect of Chloroquine on the inotropic response of the above cardiostimulants was rather inconclusive, though the effect on the chronotropic response of the heart to adrenaline and isoprenaline was definitive. In general chloroquine opposed the positive chronotropic responses to these cardiostimulants but appeared to sensitize the heart to their inotropic effect. Chloroquine has an antifibrillatory (Aviado et al 1970), antiadrenergic (Jindal; 1970) and antivagal cardioinhibitory effects (Agarwal et al 1956).

Adrenaline acts on both α and β-receptors whereas isoprenaline is a potent activator of β-adrenergic receptors and has little effect on the α-receptors. The heart has mainly β1-receptors which on stimulation increase both the force of contraction (inotropic effect) and the rate of the heart (chronotropic effect). Caffeine, on the other hand acts directly on the myocardium to increase both the rate and force of contraction. Barium chloride also has both positive inotropic and chronotropic effects.

Since chloroquine opposed the positive chronotropic action of adrenaline and isoprenaline on the heart, it is probable that it competitively
blocks the interaction of these substances with the β-receptors. However, that chloroquine in the dose of 6 - 10µg, does not oppose the positive inotropic effects of adrenaline, isoprenaline, caffeine and barium chloride, is a paradox unless it has itself a positive inotropic effect but a negative chronotropic effect like digitalis preparations (eg digoxin) which are used in congestive cardiac failure. This paradox needs to be unravelled through further investigations. In addition to the β-adrenergic blockade of circulating catecholamines, β-blockers have two important pharmacological actions viz: intrinsic sympathomimetic activity (ISA) and membrane stabilizing action (MSA) (Grell G; 1983). It can therefore be submitted that in addition to the β-adrenergic blockade, MSA may also play a part since this is one of the ways through which the drug can oppose the cardiostimulant action of Caffeine and barium chloride.

Death occurring from chloroquine poisoning is due to cardiac arrest and hypotension (Michael et al; 1970). Since the drug reduces myocardial excitability and conductivity, death may be due to failure of myocardial contraction rather than respiratory failure. The hypotension may be due to peripheral vasodilation (Michael et al; 1970).

Death occurring from normal doses of chloroquine has also been reported (Michael et al; 1970). This
was also attributed to cardiac arrest and hypotension.

In view of the myocardial depressant action of chloroquine and possible occurrence of idiosyncratic response even with normal doses it is imperative that the use of chloroquine is closely monitored than is the case at present. In addition to the idiosyncratic reactions, the possibility of the existence of people with glucose-6-phosphate dehydrogenase (G-6-PD) deficiency in the population must be borne in mind. Ingestion of chloroquine, primaquine etc by such people may provoke severe haemolytic anaemia (Harper, H.A, 1973). It has been suggested that as a method of countering malaria menace particularly in developing countries, chloroquine should be added to salt (Anori et al, 1982)

Due to the difficulty in identifying people with G-6-PD deficiency and those prone to idiosyncratic reactions, it is important that the suggested chloroquinization of of common salt as a method of countering malaria menace not be implemented.

The effect of chloroquine on drug-induced contractions of rat uterine smooth muscles

Although it has no uterotonic activity of its own on rat interine smooth muscles, chloroquine antagonized the contractions induced by oxytocin carbachol and PGF2α (Prostin). The antagonism was dose-dependent and was more pronounced with some drugs than with others. Much lower doses were required to inhibit the carbachol (6μg) and PGF2α (0.1μg)
induced contractions whereas much higher doses (4mg) were required to inhibit the contractions induced by Oxytocin (0.1IU). Only 50μg was required to totally inhibit the contractions induced by 6μg of carbachol.

PGF2α has a potent uterotonic action on isolated strips of pregnant human myometrium (Bygdemann, 1964, 1967) and its concentration in maternal venous blood is highest immediately before a uterine contraction (Karim, 1968). This has led to the belief that it may have a physiological role to play in parturition (Embrey, 1969). Suggestion had been advanced that PGs exert their actions via an ionophore-like action on calcium movement (Malmström et al, 1975) although the possibility exists that they may also exert their effect by a non-ionophoretic action on mitochondrial calcium movement (McNamara et al; 1980).

The inhibition by chloroquine of guinea pig ileal contractions induced by actetylcholine, histamine, nicotine and 5HT has been demonstrated (Famaey et al 1977a) who attributed this to the membrane stabilizing action of chloroquine earlier reported (Weissmann, 1965). Chloroquine has also been reported to have a local anaesthetic property (Tindal et al; 1960).
In view of these findings, the result favours the possibility that chloroquine antagonism to the substances may be due to extensive, non-specific membrane stabilizing property due to its influence on ionic conductance.

The result does not justify the illegal use of chloroquine for the procurement of abortion especially by young women, since chloroquine has no uterotonic, activity of its own. However, it is possible that the drug may exert its alleged abortifacient action by other mechanism(s), since many women have confirmed that it works (personal communication) particularly in high doses.

There are many causes of abortion viz: acute episodes of hyperpyrexia, nephritis, syphilis, thyroid deficiency, inadequate levels of progesterone and use of drugs having an abortifacient action or toxic actions on the embryo or foetus (Bowman and Rand 1980). In recent years, it has been established that the conceptus, either the foetus or the placenta or a combination of both, serves as labour stimulant. Foetal adenohypophysis and adrenal cortices play a decisive part in determining the onset of parturition in sheep (Bowman and Rand, 1980).

Infusion of corticotrophins and glucocorticoids causes premature labour and this has been attributed to reduction in progesterone production and increase in the production of oestrogens and PGF2α (Bowman and Rand, 1980).
Although the volume of uterine content does not serve as an important stimulus for labour contractions, sudden change in intrauterine pressure resulting in an increase or decrease in length and tension of the smooth muscles may initiate rhythmic contractions leading to abortion (Bowman & Rand 1980).

Consequently, it can be inferred that chloroquine has no intrinsic uterotonic activity and unlike adrenal hormones does not increase the production of oestrogens and PGF2α. Hence this cannot be the basis of its abortifacient action. The possibility therefore exists that it may exert its abortifacient effect by toxic effect on the foetus or the embryo (Mats et al; 1968; Udalova, 1967, Hart et al 1964) or by causing drastic change in intrauterine pressure eventually leading to abortion. However, since none of the above researchers have reported the accompaniment of toxic effect by abortion, the drug may probably exert its action by effecting changes in intrauterine pressure.

The Effect of Chloroquine on the transmission of neuromuscular junction

Chloroquine has a neuromuscular junction transmission blocking activity and also potentiates the blockade caused by d-tubocurarine, succinylcholine and lignocaine. Besides depressing and finally blocking neuromuscular transmission, chloroquine also depresses the action potential in the axons
without changing their membrane potential (Chinyanga et al.; 1972). This blockade of neuromuscular transmission has been attributed to depression of the sodium conductance mechanism in the axonal terminals (Chinyanga et al., 1972).

Drugs acting at the neuromuscular junction (NMJ) exert their effect at various levels. The centrally acting muscle relaxants which are important anti-anxiety agents eg meprobamate, chlorpethin, benzodiazepines etc acts on the intermuncial spinal neurones and on the higher centres. Local anaesthetics such as lignocaine block axonal conduction. Drugs acting prejunctionally may interfere with the synthesis of acetylcholine eg hemicholinium or may interfere with its release eg aminoglycosides (eg streptomycin), high concentration of Calcium and botulinum toxin.

Postjunctionally acting drugs interact with the nicotinic receptors. They render the motor end-plate membrane of the NMJ incapable of responding to transmitter substance. Non-depolarizing NMJ blockers such as tubocurarine, competes with acetylcholine for the nicotinic receptors and prevent the depolarization of the postsynaptic membrane whereas the depolarizing NMJ blockers such as succinylcholine cause persistent depolarization by preventing repolarization. In other words, after an initial depolarization, the nicotine receptor become incapable of repolarization.
Since Chloroquine potentiated the action of tubocurarine, succinylcholine and lignocaine which cause neuromuscular blockade by different mechanisms, it is probable that it has a non-specific neuromuscular blocking action which could be due to interaction with the nicotinic receptors, membrane stabilization (Weissmann, 1965) and its local anaesthetic action (Jindal et al; 1960).

Chloroquine myopathy following prolonged use of the drug for the treatment of arthritic conditions has been reported (Chapman et al 1969, Hughes et al; 1971). This was attributed to inhibition of glycolysis evidenced by accumulation of glucose (Chapman et al; 1969) and degeneration of muscle fibres (Hughes et al; 1971).
CONCLUSION

The effect of Chloroquine on smooth, cardiac and skeletal muscles and the possible basis of its alleged abortifacient action has been discussed. In summary, chloroquine has been found to have the following properties:

(a) Relaxes the smooth muscles of intact guinea pig trachea and antagonizes the effect of acetylcholine, nicotine, histamine and barium chloride on guinea pig tracheal smooth muscles.

(b) Causes short-lived relaxation of rabbit ileal muscles and reduces the height of the spontaneous contractions induced by acetylcholine, nicotine and barium chloride.

(c) Causes relaxation of the cardiac muscles and has both negative inotropic and chronotropic effects. It also opposes the positive chronotropic effects of adrenaline and isoprenaline possibly by competitively interacting with the B1-adrenergic receptors of the heart. The drug also opposes the cardiostimulant action of Caffeine and barium chloride.

(d) Besides having an intrinsic neuromuscular blocking action, chloroquine potentiates the blockade caused by tubocurarine, succinyl choline and lignocaine possibly by membrane stabilization and local anaesthetic action.
(e) Chloroquine has no uterotonic action of its own, but inhibits the height of contractions induced by oxytocin, carbachol and PGF2\alpha probably by a non-specific interference with ionic conductance.

(f) By relaxing the tracheal smooth muscles and antagonizing the action of histamine on tracheal smooth muscles, chloroquine appears to have an antiasthmatic property which may be synergistic with the actions of standard antiasthmatic drugs when given concomittantly.

(g) Chloroquine may exert its abortifacient action by causing sudden change in intrauterine pressure.

Though Chloroquine is a non-prescription drug, its toxicological properties are well known. In particular, hypersensitivity, idiosyncratic reactions, fatal haemolytic anaemia in those with G-6-PD deficiency, cardiotoxicity, peripheral neuropathy, retinopathy, teratogenicity and myopathy following chloroquine ingestion are well known.

In recent times, there was a suggestion that Chloroquinization of salt could be adopted as a method of countering malaria menace particularly in developing countries. In view of the above drawbacks of this drug, it is imperative that this suggestion is not implemented.
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