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SOME PHARMACOLOGICAL ACTIONS OF 2-PHENYLQUINOLINE METHIODIDE*

BY

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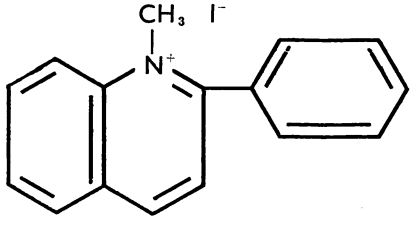
2-Phenylquinoline drugs have been used in clinical practice as antimalarials (Wiselogle, 1946), uricosurics (Hueper, 1948), and more recently for their effectiveness against infections due to flukes (Campbell & Cuckler, 1963). During the course of a synthetic programme the quaternized analogue of 2-phenylquinoline was made. It was found to possess considerable ganglionic blocking and anticholinergic activity and it is a description of these findings which forms the basis for this report.

2-Phenylquinoline methiodide was synthesized in our laboratory as described by Doebner & von Miller (1886). It is a yellowish-red crystalline powder with a melting point of 199–200° C which agrees with the value reported in Heilbron & Bunbury (1953). It is soluble in water and insoluble in nonpolar solvents such as chloroform, benzene and ether. The structure of this compound is shown below.



METHODS

In vitro *studies*

The isolated frog heart was prepared according to the method of Straub-Fuehner, as described by Sollmann (1922) and used at room temperature. The heart was perfused with frog Ringer solution and its contractions were recorded on a smoked drum with a seven-times magnification isotonic lever.

The frog rectus abdominis (3 cm in length) was used in an oxygenated 5 ml. organ bath containing frog Ringer solution at room temperature. The contractions were recorded on a smoked drum with a nine-times magnification isotonic lever. Before the addition of drugs the muscle was allowed to relax for approximately 30 min.

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Rat ileum preparations, 3 cm in length and taken from the terminal ileum, were placed in an oxygenated 5 ml. organ bath with Tyrode solution. The rat ileum was used at room temperature, because this tissue gave accurate and reproducible results over long periods of time at this lower temperature. The contractions were recorded with an isotonic lever of nine-times magnification. The muscle was allowed to equilibrate with the Tyrode solution for 30 min before addition of drugs. All *in vitro* experiments were repeated in triplicate and the mean values reported. Individual results did not deviate by more than 10% from their mean. Guinea-pig ileum preparations were prepared in a similar manner.

In vivo *studies*

The blood pressure experiments were performed on cats, weighing 2 to 3.5 kg, anaesthetized with a mixture of sodium diallylbarbitone and urethane (Dial, 0.6 mg/kg, intraperitoneally). After tracheal cannulation, the blood pressure was recorded from a cannulated femoral artery by a Bourdon type photoelectric transducer connected to a model IV physiograph. All drug injections were made into a catheterized femoral vein.

The nictitating membrane experiments were performed on cats, weighing 2 to 3.5 kg, anaesthetized as described above. The trachea was cannulated low in the neck, and the upper end of the trachea, together with the larynx, the oesophagus and the overlying muscles, were removed. The superior cervical ganglion on either side was exposed together with the pre-ganglionic, and post-ganglionic trunks. A thread was tied through the free cartilaginous border of the membrane, which was loaded with a 5 g weight. The contractions were recorded on a model IV physiograph with a type A myograph transducer. The preganglionic and post-ganglionic trunks were placed on platinum electrodes and stimulated with an American Electronics square wave stimulator. Supra-maximal stimuli were applied to the preganglionic trunk, 0.7 to 3 V, while the post-ganglionic trunk was stimulated submaximally, 2 to 5 V. Both were stimulated at a frequency of 20 p/sec with a duration of 0.5 msec for 5 to 10 sec, every 2–3 min. The drug injections were made either into the femoral vein or lingual artery. The blood pressure was simultaneously recorded as described in the previous paragraph.

Solutions and drugs

The frog Ringer solution consisted of the following (g/l.): NaCl 6.0, KCl 0.75, $CaCl_2$ 0.1 and $NaHCO_3$ 0.1. The Tyrode solution containing the following constituents (g/l.): NaCl 8.0, KCl 0.2, $CaCl_2$ 0.1, $NaHCO_3$ 1.0, $MgCl_2$ 0.1, NaH_2PO_4 0.05 and dextrose 1.0.

The drugs used in the *in vitro* experiments were made up in the solutions used to perfuse the tissues, whereas the drugs used in the *in vivo* experiments were prepared in 0.9% w/v NaCl solution. The drugs used were acetylcholine chloride (Merck), atropine sulphate (M.C. & B.), bradykinin (Sandoz), dimethylphenylpiperazinium iodide (Aldrich), d-tubocurarine chloride (Squibb), furtrethonium iodide (S.K. & F.), histamine phosphate (Lilly), methylhomatropine bromide (Henley), serotonin creatine sulphate monohydrate (Aldrich), tetraethylammonium chloride (Eastman). The doses stated were in terms of their free bases.

RESULTS

Frog heart preparation

2-Phenylquinoline methiodide in concentrations ranging between 1×10^{-6}M to 1×10^{-2}M did not cause any significant effects on the frog heart. However, 2-phenylquinoline methiodide antagonized the effects of acetylcholine on the heart (Fig. 1). A control dose of acetylcholine (5×10^{-6}M) caused a 77% depression of the height of contraction, but in the presence of 4×10^{-5}M and 8×10^{-5}M, 2-phenylquinoline methiodide, the negative inotropic effects of acetylcholine were reduced to 22 and 0% respectively. Also, when acetylcholine was administered first, its negative inotropic effects could be reversed by the administration of 8×10^{-5}M 2-phenylquinoline methiodide. Comparison

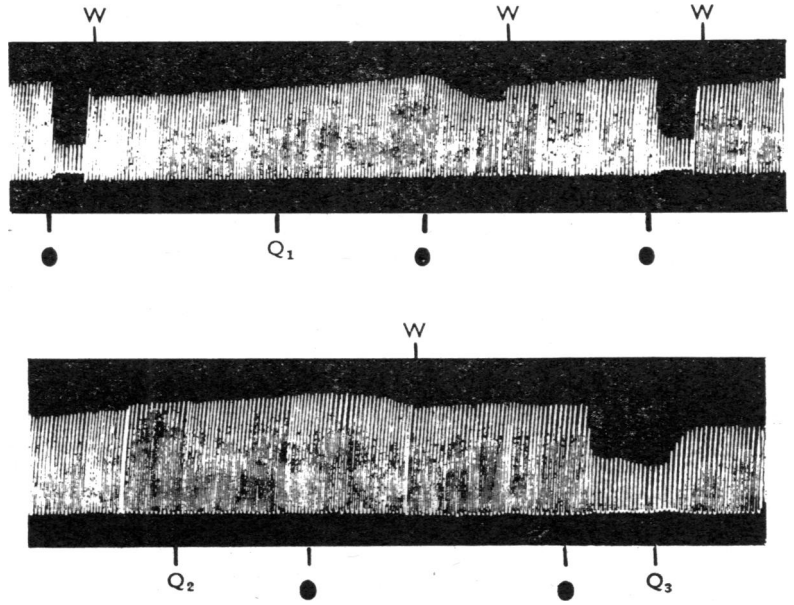

Fig. 1. Frog heart. Effect of 2-phenylquinoline methiodide (Q_1, 4×10^{-5}M ; Q_2, 8×10^{-5}M ; and Q_3, 8×10^{-5}M) on the depressor responses to acetylcholine (●, 5×10^{-6}M). Acetylcholine controls were obtained before each dose of 2-phenylquinoline methiodide. Q_1 and Q_2 were given one min before acetylcholine, whereas Q_3 was given at the peak depressor effect of acetylcholine. W, washing out.

of the antagonistic potency of 2-phenylquinoline methiodide with some standard anticholinergics showed that atropine (1×10^{-7}M), methylhomatropine (2×10^{-7}M), and tetraethylammonium ($>1\times10^{-3}$M) were equipotent with 8×10^{-5}M 2-phenylquinoline methiodide.

Rat ileum preparation

Furtrethonium, a potent cholinergic compound (Fellows & Livingston, 1942), was used to determine whether 2-phenylquinoline methiodide could cause antagonism on the rat ileum (Fig. 2). The contractions induced by furtrethonium (1×10^{-5}M) were found

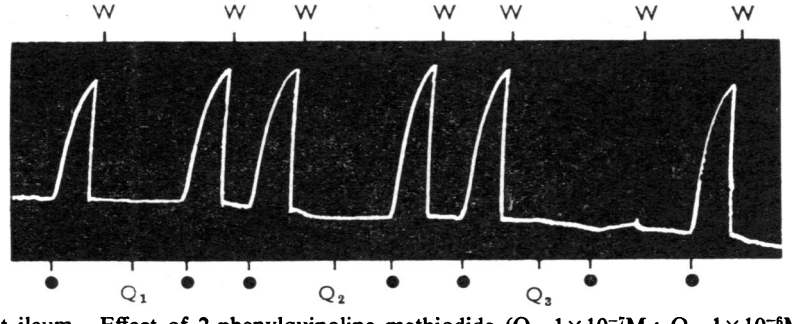

Fig. 2. Rat ileum. Effect of 2-phenylquinoline methiodide (Q_1, 1×10^{-7}M ; Q_2, 1×10^{-6}M ; and Q_3, 1×10^{-5}M) on the stimulating responses of furtrethonium (●, 1×10^{-5}M). Control contractions induced by furtrethonium were obtained before and after each dose of 2-phenylquinoline methiodide. Q_1, Q_2 and Q_3 were given 30 sec before furtrethonium. W, washing out.

to be antagonized by 2-phenylquinoline methiodide (1×10^{-5}M). Weaker concentrations of this quinolinium compound (1×10^{-7}M and 1×10^{-6}M) caused potentiation of the furtrethonium contractions. Similar antagonistic effects were also demonstrated on the guinea-pig ileum. However, contractions caused by serotonin (1×10^{-5}M, 1×10^{-6}M and 1×10^{-7}M), bradykinin (1×10^{-7} g/ml. and 1×10^{-8} g/ml.) on the rat ileum, and histamine (1×10^{-5}M, 1×10^{-6}M and 1×10^{-7}M) on the guinea-pig ileum were not antagonized by 2-phenylquinoline methiodide (1×10^{-5}M). In comparing potencies on the rat ileum with 2-phenylquinoline methiodide, atropine (2×10^{-7}M), methylhomatropine (6×10^{-7}M), and tetraethylammonium ($>1 \times 10^{-3}$M) caused an equivalent degree of blockade on the furtrethonium induced contractions.

Frog rectus abdominis preparation

The antagonistic effects of 2-phenylquinoline methiodide were also determined on the acetylcholine stimulated rectus (Fig. 3). 2-Phenylquinoline methiodide, concentrations of 2.8×10^{-4}M, 5.6×10^{-4}M and 1.1×10^{-3}M, antagonized the acetylcholine (5×10^{-6}M)

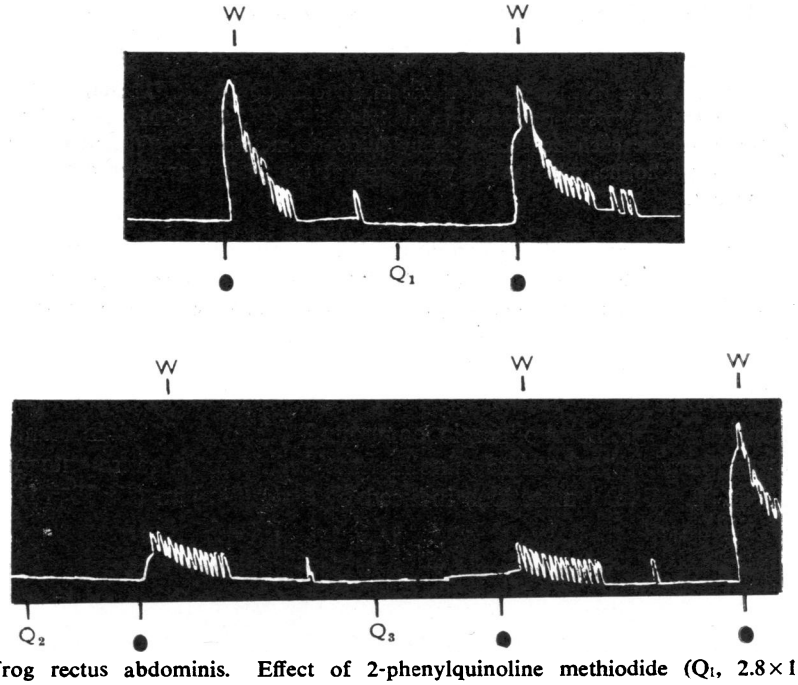

Fig. 3. Frog rectus abdominis. Effect of 2-phenylquinoline methiodide (Q_1, 2.8×10^{-4}M ; Q_2, 5.6×10^{-4}M ; and Q_3, 1.1×10^{-3}M) on the stimulating response of acetylcholine (●, 5×10^{-6}M). Acetylcholine controls were obtained at the beginning and end of the experiment. Q_1, Q_2 and Q_3 were given 1 min before acetylcholine. W, washing out. The contractions seen in the relaxing phase were due to movement of the muscle on repeated washing out.

induced contractions by 33, 73 and 100% respectively. As was observed in the previous preparation, lower concentrations of the quinolinium compound caused potentiation of the cholinergic contractions. The concentration of 2-phenylquinoline methiodide which caused 50% antagonism was compared with equipotent concentrations of some standard

blocking compounds. The compounds and concentrations were: d-tubocurarine (1×10^{-6}M), methylhomatropine (9×10^{-5}M) and tetraethylammonium ($>1 \times 10^{-3}$M).

Cat blood pressure preparation

Without causing any significant effects on heart rate, 2-phenylquinoline methiodide, intravenously, depressed the cat's blood pressure. Doses of the quinolinium compound ranging between 0.6 mg/kg to 6.4 mg/kg lowered the blood pressure between 17/20 mm Hg to 67/47 mm Hg. This hypotensive effect was brief; a dose of 6.4 mg/kg caused a maximal duration of action of only 10 min. Doses greater than 6.4 mg/kg produced shock level blood pressures which were not suitable for comparative assay. The administration of atropine (0.5 mg/kg) before the quinolinium compound did not prevent the blood pressure fall and this suggested a ganglionic rather than a peripheral mechanism.

Cat-cervical ganglion–nictitating membrane preparation

After obtaining control contractions of the nictitating membrane (Fig. 4), induced by stimulation of the pre- (A) and post-ganglionic (B) fibres, the quinolinium compound (3.2 mg/kg) was injected intravenously. The preganglionic induced nictitating membrane contractions were reduced, while the post-ganglionic induced contractions were unaffected. The preganglionic block coincided with the fall in blood pressure, as did recovery of both preganglionic contractions and blood pressure. When 2-phenylquinoline

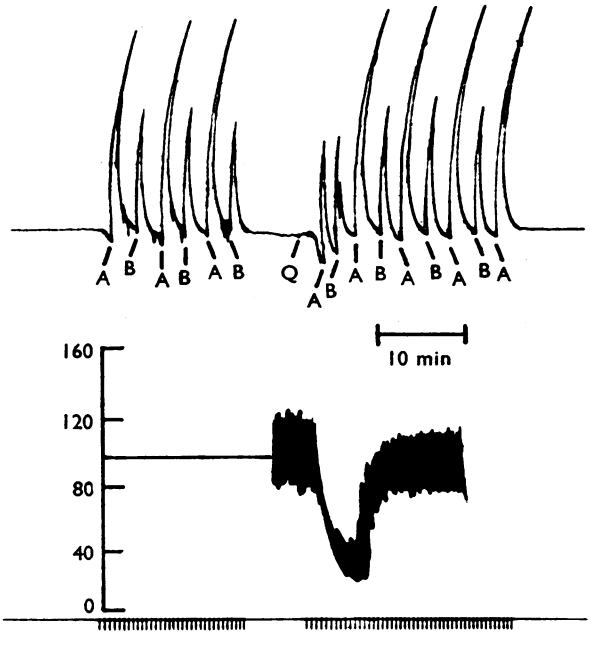

Fig. 4. Effect of 2-phenylquinoline methiodide (Q, 3.2 mg/kg; intravenously) on the cat's blood pressure (bottom) and nictitating membrane contractions (top) induced by preganglionic (A) (1 V, supramaximal) and post-ganglionic (B) (3 V, submaximal) stimulations. The drug was administered after obtaining three preganglionic and post-ganglionic contractions, and at peak hypotensive effect the stimulations were repeated until control levels were again obtained.

methiodide (0.01 mg/kg to 0.1 mg/kg) was injected into the lingual artery, the preganglionic induced nictitating membrane contractions were reduced from 0.7% to 95% with no significant effects on either the post-ganglionic induced contractions or blood pressure. Thus the results confirmed the impression that 2-phenylquinoline methiodide blocked ganglionic transmission, and that this was the cause of the fall in blood pressure. The percentage inhibition of the nictitating membrane contractions due to ganglionic blockade varied from 7 to 98% for the quinolinium compound, for intravenous doses ranging from 2.6 to 13.8 mg/kg (Table 1). The post-ganglionic induced contractions were unchanged.

TABLE 1

EFFECT OF 2-PHENYLQUINOLINE METHIODIDE ON THE CAT SUPERIOR CERVICAL GANGLION

Doses of 2-phenylquinoline methiodide were administered intravenously and the percentage inhibition of the nictitating membrane contractions, induced by stimulation of the superior cervical ganglion's preganglionic and post-ganglionic fibres, were calculated, correspondingly, the falls in blood pressure were recorded

		Nictitating membrane contraction		
Expts. (no.)	Dose (mg/kg)	Preganglionic stimulation (% inhibition)	Post-ganglionic stimulation (% inhibition)	Fall in blood pressure (mm Hg)
3	2·6	7±1·1	0	$\frac{35\pm5}{26\pm7}$
3	3·2	46±4·5	2±0·9	$\frac{48\pm13}{48\pm9}$
3	6·4	62±3·1	0	$\frac{67\pm8}{47\pm11}$
3	13·8	98±2·0	10±1·1	

A comparison of the ganglionic blocking potency of 2-phenylquinoline methiodide with standard ganglionic blocking compounds were made by comparing the mean doses necessary to reduce the maximal preganglionic stimulated nictitating membrane contractions by 50%. The mean doses were based on three experiments for each compound, and the individual doses did not deviate from their mean by more than 10%. The compounds and their mean doses were: hexamethonium (0.46 mg/kg), methylhomatropine (0.14 mg/kg), tetraethylammonium (1.3 mg/kg) and 2-phenylquinoline methiodide (3.2 mg/kg). The equipotent molar ratios were calculated and summarized in Table 2.

TABLE 2

COMPARISON OF THE EQUIPOTENT MOLAR RATIOS

Equipotent molar ratios of 2-phenylquinoline methiodide (PQM), methylhomatropine (MHA) and tetraethylammonium (TEA) were compared to atropine, d-tubocurarine, and hexamethonium on the frog heart, rat ileum, frog rectus abdominis, and cat nictitating membrane. Cat's nictitating membrane molar ratios were obtained by comparing the mean doses which reduced the maximal contraction of the nictitating membrane due to preganglionic stimulation by 50%. The molar ratios were calculated from the mean doses which were based on three experiments for each compound.

Compounds	Atropine frog heart	Atropine rat ileum	d-Tubocurarine frog rectus abdominis	Hexamethonium cat nictitating membrane
PQM	800	50	420	6·5
TEA	>1,000	>5,000	>1,000	3·5
MHA	2·0	3·0	90	0·2

The interaction of 2-phenylquinoline methiodide on the chemically stimulated sympathetic ganglion were studied using dimethylphenylpiperazinium iodide (DMPP), a potent ganglionic stimulant (Chen, Portman & Wickel, 1951) (Fig. 5). Three control doses of DMPP (25 μg/kg) were administered intravenously, and the resulting stimulatory effects on blood pressure and nictitating membrane were recorded. However, when the quinolinium compound was administered first, these stimulating effects of DMPP were blocked completely. Once the effects of the quinolinium compound had dissipated, the DMPP effects returned to normal. Identical results on the nictitating membrane were observed when 2-phenylquinoline methiodide (11 μg/kg) was injected into the lingual artery followed by DMPP (1.2 μg/kg).

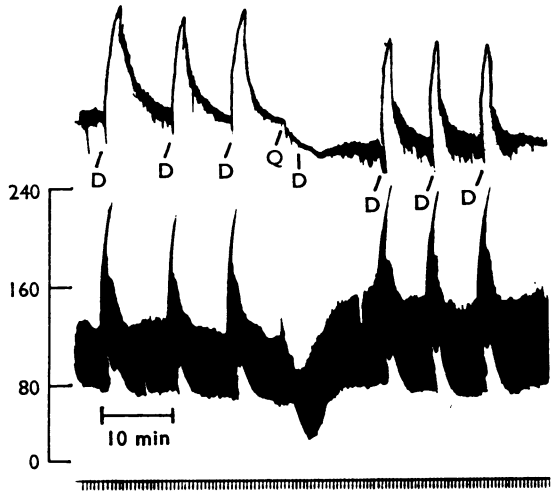

Fig. 5. Effect of 2-phenylquinoline methiodide (Q, 3.2 mg/kg, intravenously) on the stimulating effects of dimethylphenylpiperazinium (D, 25 ug/kg) on the cat's nictitating membrane (top) and blood pressure (bottom). After obtaining three stimulatory responses of D, Q was administered and at its peak hypotensive effect four doses of D were repeated.

In Table 2, the equipotent molar ratios of the quinolinium compound are compared with tetraethylammonium and methylhomatropine to atropine, d-tubocurarine, and hexamethonium on the previously mentioned preparations. On the frog heart, rat ileum and frog rectus abdominus, 2-phenylquinoline methiodide is more potent than tetraethylammonium but less potent than methylhomatropine. On the superior cervical ganglion the quinolinium compound is less potent than tetraethylammonium and methylhomatropine.

DISCUSSION

The ability to block transmission across autonomic ganglia is a property that is found among a wide variety of chemical compounds. The onium group is most ubiquitous and the agents which have been frequently explored are the monoquaternary ammonium compound, tetraethylammonium (Acheson & Pereira, 1946), and the biquaternary compound, hexamethonium (Paton & Zaimis, 1951). A wide variety of cyclic compounds have also been described by Plummer, Trapold, Schneider, Maxwell & Earl (1955). It would seem reasonable to expect that the monoquaternary, 2-phenylquinoline methiodide,

possesses some ganglionic blocking activity. In this study, 2-phenylquinoline methiodide blocks the electrically stimulated cervical ganglion and this block correlates both in degree and duration to its hypotensive effect. The ganglionic stimulatory properties of dimethylphenylpiperazinium iodide (DMPP) on the blood pressure and nictitating membrane are blocked by previous administration of 2-phenylquinoline methiodide. This indicates an identical ganglionic receptor site for DMPP and the quinolinium compound, and puts it in the same class of ganglionic blockers as hexamethonium (Aviado, 1965).

Since it is commonly known that most ganglionic blocking agents possess some weak neuromuscular blocking effects, it is not surprising that 2-phenylquinoline methiodide has antagonistic effects on the acetylcholine stimulated frog rectus abdominis. This finding is also supported by the works of Barlow & Ing (1948) who have shown that two polymethylene bisquinolinium compounds (trimethylene bis-quinolinium and pentamethylene bis-quinolinium), could elicit potent neuromuscular blocking effects.

Bhattacharya & Sen (1962) have shown that a polymethylene bisquinolinium compound (eikosamethylene bis-quinolinium) is capable of blocking the effects of acetylcholine on the isolated guinea-pig ileum, similar to the effects seen with 2-phenylquinoline methiodide. Although the structural relationships between 2-phenylquinoline methiodide and standard anticholinergic compounds appear unrelated, there are, however, similar functional groups found in both compounds. Long, Luduena, Tullar & Lands (1956) consider that some of the likely structural groups in anticholinergic compounds, which are mainly responsible for their blocking activity, are the ester carbonyl groups, the benzene ring, and the ionized amino group, surrounded by a large tropyl group. The receptor binding the ionized amino group is considered to be identical with the binding of the quaternary nitrogen in acetylcholine. The function of the benzene ring has been described by Lands & Luduena (1956) as an umbrella which masks the receptor, thus inhibiting acetylcholine from attaching. The ester carbonyl group appears to increase the affinity of the compound to the receptor. Since 2-phenylquinoline methiodide contains a benzene ring and a onium group, surrounded by a large molecule, then this quinolinium compound could possess weak anticholinergic activity. On the frog heart, rat ileum, and guinea-pig ileum, 2-phenylquinoline methiodide has been shown to antagonize the response of acetylcholine and furtrethonium. This quinolinium compound did not antagonize spasmogenic effects of serotonin, histamine and bradykinin on the ileum.

The antagonistic properties of 2-phenylquinoline methiodide were compared with known compounds having similar properties, such as methylhomatropine and tetraethylammonium. Cahen & Tvede (1952) have demonstrated that the quaternized analogue of homatropine, methylhomatropine, not only possesses potent anticholinergic properties, but also potent ganglionic blocking properties. Also, Feldberg (1951) has shown that tetraethylammonium ion has weak anticholinergic properties in addition to its ganglionic blocking activity. As a ganglionic blocking agent, 2-phenylquinoline methiodide is less potent than methylhomatropine and tetraethylammonium. As an anticholingeric and curare agent, the quinolinium compound is more potent than tetraethylammonium, but less potent than methylhomatropine.

The potentiating effects of 2-phenylquinoline methiodide, seen on the cholinergic induced contractions of the frog rectus abdominis and rat ileum, have not been extensively investigated. With the method of Ettinger (1966), preliminary experiments on

human serum esterase have indicated to us that this quinolinium compound can antagonize the hydrolysis of procaine by this enzyme. The potentiation of acetylcholine action on the rectus by low doses of 2-phenylquinoline methiodide might be explained in this way, but would not explain the potentiation of furtrethonium on the rat ileum. Therefore it appears that the potentiating effects of 2-phenylquinoline methiodide is due to an effect other than cholinesterase inhibition.

Thus the hypotensive action of 2-phenylquinoline methiodide appears mainly to be due to a direct blocking action on sympathetic ganglia. Since this ganglionic agent could antagonize the effects of dimethylphenylpiperazinium iodide on the superior cervical ganglion, one can assume that this quinolinium compound belongs in the hexamethonium class of ganglionic agents. *In vitro* the quinolinium compound possesses weak anticholinergic and curare effects, similar to methylhomatropine and tetraethylammonium, but in addition it may possess a cholinergic potentiating effect on rat ileum and frog rectus.

SUMMARY

1. On the frog heart, 2-phenylquinoline methiodide was found to antagonize the negative inotropic effects of acetylcholine.

2. On the rat ileum, 2-phenylquinoline methiodide was found to antagonize the furtrethonium induced contractions, but not the contractions induced by either serotonin or bradykinin. On the guinea-pig ileum the quinolinium compound also blocked the furtrethonium contractions, but not the histamine contractions. Concentrations of the quinolinium compound which did not cause antagonism, however, potentiated the furtrethonium contractions.

3. On the frog rectus abdominis 2-phenylquinoline methiodide was found to antagonize the acetylcholine induced contractions. Lower concentrations also potentiated the acetylcholine effects.

4. The administration of 2-phenylquinoline intravenously in a cat caused a transient lowering of blood pressure. This hypotensive effect was not blocked by atropine.

5. 2-Phenylquinoline methiodide induced an impairment of ganglionic transmission on the superior cervical ganglion, which was stimulated electrically and chemically (dimethylphenylpiperazinium). The ganglionic blocking effects of this quinolinium compound is less potent than methylhomatropine and tetraethylammonium.

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REFERENCES

ACHESON, G. H. & PEREIRA, S. A. (1946). The blocking effect of tetraethylammonium ion on the superior cervical ganglion of the cat. *J. Pharmac. exp. Ther.*, **87**, 273–280.

AVIADO, D. M. (1965). *Drill's Pharmacology in Medicine*, Editor. J. R. DIPALMA, 3rd ed., p.532. McGraw-Hill, New York.

BARLOW, R. B. & ING, H. R. (1948). Curare-like action of polymethylene bis-quaternary ammonium salts. *Br. J. Pharmac. Chemother.*, **3**, 298–304.

BHATTACHARYA, B. K. & SEN, A. B. (1962). The action of BQ20, a polymethylene bisquinolinium compound on the isolated guinea pig intestine. *Arch. int. Pharmacodyn. Ther.*, **139**, 109–119.

CAHEN, R. L. & TVEDE, K. (1952). Homatropine methylbromide: a pharmacological re-evaluation. *J. Pharmac. exp. Ther.*, **105**, 166–177.

CAMPBELL, W. C. & CUCKLER, A. C. (1963). Efficacy of a 2-phenylquinoline agonist against experimental Schistosoma mansoni infections in mice and monkeys. *J. Parasitol.*, **49**, 528.

CHEN, G., PORTMAN, R. & WICKEL, A. (1951). Pharmacology of 1,1-dimethyl-4-phenylpiperazinium iodide, a ganglion stimulating agent. *J. Pharmac. exp. Ther.*, **103**, 330–336.

DOEBNER, O. & VON MILLER, W. (1886). Über derivate des x-phenylchinolins. *Ber. dt. chem. Ges.*, **19**, 1194–1200.

ETTINGER, M. J. & GERO, A. (1966). Interactions of narcotics and their antagonists with human serum esterase. *Archs int. Pharmacodyn. Ther.*, **164**, 96–110.

FELDBERG, W. (1951). Effects of ganglion-blocking substances on the small intestine. *J. Physiol.*, **113**, 483–505.

FELLOWS, E. J. & LIVINGSTON, A. E. (1942). The comparative physiological action of analogous trimethyl ammonium iodides of benzene and furane. *J. Pharmac. exp. Ther.*, **74**, 65–70.

HEILBRON, I. & BUNBURY, H. M. (1953). *Dictionary of Organic Compounds*, Vol. 4, p. 170. Eyre and Spottiswoode, London.

HUEPER, W. C. (1948). Cinophen. *Medicine*, **27**, 43–103.

LANDS, A. M. & LUDUENA, F. P. (1956). The cholinolytic action of substituted dialkylaminoalkanes and dialkylaminoalkanols. *J. Pharmac. exp. Ther.*, **116**, 177–190.

LONG, J. P., LUDUENA, F. P., TULLAR, B. F. & LANDS, A. M. (1956). Stereochemical factors involved in cholinolytic activity. *J. Pharmac. exp. Ther.*, **117**, 29–38.

PATON, W. D. M. & ZAIMIS, E. J. (1951). Paralysis of autonomic ganglia by methonium salts. *Br. J. Pharmac. Chemother.*, **6**, 155–168.

PLUMMER, A. J., TRAPOLD, J. H., SCHNEIDER, J. A., MAXWELL, R. A. & EARL, A. E. (1955). Ganglionic blockade by a new bisquaternary series including chlorisondamine dimethochloride. *J. Pharmac. exp. Ther.*, **115**, 172–184.

SOLLMANN, T. (1922). *A Laboratory Guide in Pharmacology*, 1st ed., p. 190–193. Saunders, London.

WISELOGLE, F. Y. (1946). *A Survey of Antimalarial Drugs*, 3 vols. Edwards, Ann. Arbor, Mich.