ANTIHISTAMINIC ACTION OF ANTIMALARIALS

By

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Number of antimalarial drugs, though structurally different, share the same type of pharmacological actions. In the present paper three chemically different compounds namely the quinine, mepacrine and chloroquine are shown to have antihistaminic effect. This effect was studied on the isolated guineapig ileum, guineapig tracheal chain, dog's blood pressure and on the capillary permeability in guineapig skin. It was observed that chloroquine is the most potent drug in antagonising the effect of histamine on guinea-pig ileum and tracheal chain.

Antimalarial drugs though dissimilar in their chemical structure, resemble each other in most of their pharmacological actions. For example they simulate each other in their, depressant action on skeletal muscle (Oster and Maske 1953; Ravin, 1940, Harvey, 1939 ; Jindal *et al*, 1960, and Grewal and Sharma, 1960) ; antiveratrinic actions (Arora, 1955a) ; antiarrhythmic action on heart (Arora *et al*, 1955b and 1956, Gertle and Yohalem, 1947 and 1949 and Hess and Schmidt 1959), hypotensive action (Dawes and Mott, 1950), local anaesthetic action (Jindal and Patel, 1960) and stimulant action on uterus (Joseph and Jindal, 1957). Recently the antihistaminic property of chloroquine and mepacrine on guinea-pig lung have been reported (Bend and Miravet 1958). From the literature it appears that though the actions of antimalarials are extensively investigated, their action on smooth muscle particularly in relation to histamine is not well studied. Therefore, it was considered worthwhile to explore some of the common antimalarials for their antihistaminic action on different smooth muscle preparations.

METHOD

The effect of quinine, mepacrine and chloroquine is studied on the following preparations. The concentrations mentioned are of the base of these drugs.

Guinea-pig ileum.—A piece of guinea-pig ileum was suspended in a bath of 25 ml. capacity containing Kreb's solution at 28°C, and bubbled with a mixture of 0_2, 95% and CO_2 5%. By using different concentrations a suitable dose of

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histamine ($2{\cdot}5 \times 10^{-5}$) was selected a standard dose to produce a strong spasm of ileum. The effect of quinine, mepacrine and chloroquine on this histamine spasm of ileum was observed by keeping the ileum in contact with different concentrations of antimalarials for a period of 90 secs. The following concentrations of antimalarials were used; quinine—$2{\cdot}5 \times 10^{-5}$, 5×10^{-6}, 1×10^{-4} mepacrine—$2{\cdot}5 \times ^{-6}$, 5×10^{-5}, 1×10^{-5} chloroquine—$2{\cdot}5 \times 10^{-7}$, 5×10^{-7}, 1×10^{-6}.

Guinea-pig Tracheal chain preparations.—The method followed is that of Castillo and de Beer (1949). From the trachea of a freshly killed guineapig eight tracheal rings were prepared. The rings were cut anteriorly and were tied by a fine silk thread to prepare a chain. It was then suspended in a bath of 25 ml capacity containing Kreb's solution at 28°C and bubbled with a mixture of 95% O_2 and 5% CO_2. A satisfactory response was obtained by 2×10^{-6} concentration of histamine. The effect of antimalarials was observed qualitatively by keeping the tracheal chain in contact with the desired concentrations of antimalarial drugs for 90 secs. and thereafter recording the contraction with the histamine in their presence. Six experiments were done for each of the antimalerial drugs.

Blood pressure in dog —Dogs were anaesthetised by pentobarbitone 40 mg/kg given intraperitoneally and were set for recording blood pressure. Blood pressure was recorded from carotid artery by mercury manometer. After recording the initial hypotensive response to a dose of 2·5 μg/kg of histamine, a perfusion of antimalarial drug was started at a rate of 1 mg/min. Response of histamine 2·5 μg/kg was repeated at the completion of the perfusion of 10 mg, 20 mg and 40 mg of antimalarials. Six experiments were done with each drug.

Capillary permeability in guinea-pig skin.—Back of guinea-pigs was clean shaved, 2 ml of 2 per cent Evan's blue solution was injected I.V. through one of the marginal ear veins. After 45 min histamine was given intradermally (5 μg in 0·1 ml) and a standard response was noted. Modification of this response was observed by giving antimalarials intradermally in doses of 25 μg 50 μg, 100 μg 15 min before the injection of histamine. Each experiment was accompanied by the control experiments including the intradermal injections of normal saline on the other half of the back of the same guinea-pig. These observations are tabulated in Table II.

RESULTS

Guinea-pig ileum.—All the three antimalarials used in this experiment block the action of histamine on this preparation. Quantitatively on the basis of

ED_{50} calculated from the log dose response curve, chloroquine is about 10 times powerful than mepacrine and 100 times than quinine. The effect of

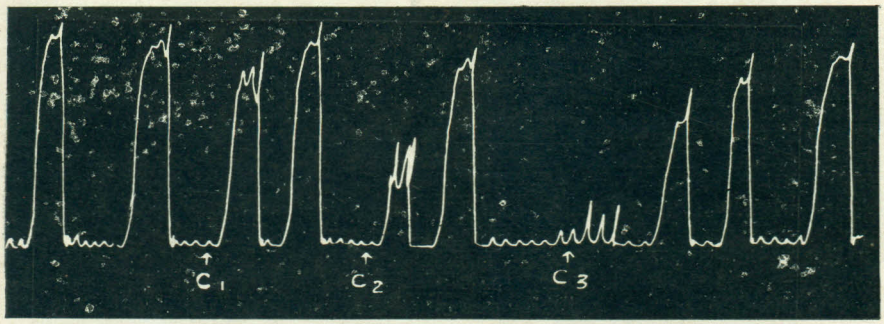

Fig. 1. Showing the effect of caloroquine on the histamine induced spasm in guinea-pig ileum. Concentrations of histamine used $2{\cdot}5 \times 10^{-5}$. At C1; C2; and C3—ileum exposed to chloroquine in $2{\cdot}5 \times 10^{-7}$; 5×10^{-7} & 1×10^{-6} concentrations respectively for 90 secs before repeating histamine response.

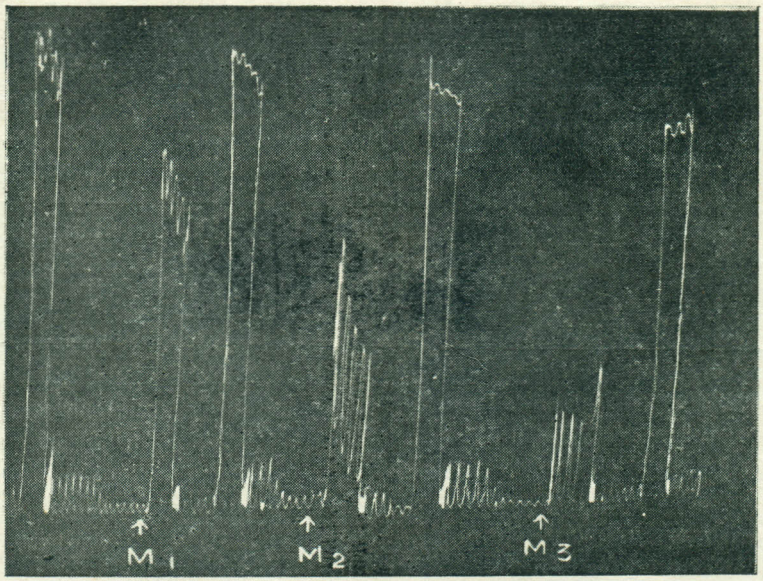

Fig. 2. Showing the effect of mepacrine on the histamine induced spasm in guinea-pig ileum. Concentration of histamine used —$2{\cdot}5 \times 10^{-5}$. At M1; M2 and M3 —ileum exposed to mepacrine in $2{\cdot}5 \times 10^{-6}$; 5×10^{-6} and 1×10^{-5} concentrations respectively for 90 secs, before repeating histamine response.

antimalarials on histamine response is shown in Fig. 1, 2 and 3, and dose response in Table I. In Fig. 4 antiacetylcholine action of antimalarials is shown.

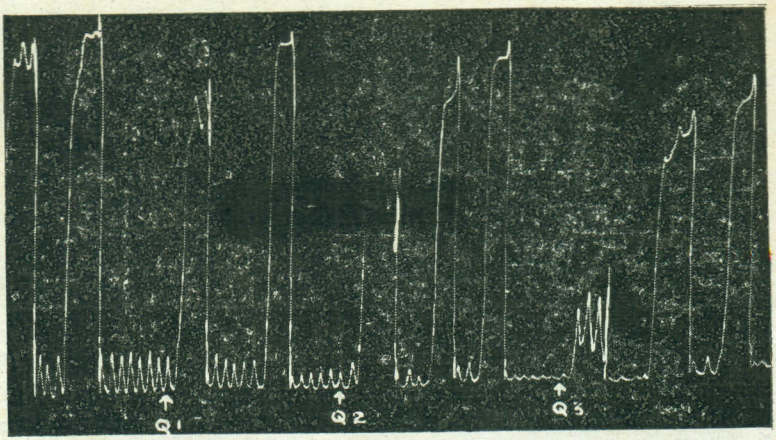

Fig. 3. Showing the effect of quinine on the histamine induced spasm in guinea-pig ileum. Concentrations of histamine used —2·5 x 10^{-5}. At O1; O2; and O3 —Ileum exposed to quinine in 2 5 x 10^{-5}; 1x10^{-4} concentrations respectively for 90 secs before repeating histamine response.

TABLE I.

Showing the average percentage reduction of histamine (2·5 x 10^{-5}) response on guinea-pig ileum by antimalarials

Drug	Concentration as base	Contraction height in cms. before	Height in cms. after exposure to antimalarial drugs	Per cent reduction
Chloroquine	2 x 10^{-7}	7·7	6·6	14·2
	5 x 10^{-7}	8·4	3·8	54 7
	1 x 10^{-6}	8·1	0 5	95 0
	2 x 10^{-6}	8·2	—	100
Mepacrine	2·5 x 10^{-6}	7·4	5·9	20·2
	5 x 10^{-6}	7·3	4·0	45·0
	1 x 10^{-5}	7·2	0·4	94·5
	2 x 10^{-5}	7·8	—	100
Quinine	2·5 x 10^{-5}	6·4	5·3	17·1
	5 x 10^{-5}	6·8	4·0	41·1
	1 x 10^{-4}	6·6	1·3	80·3
	2 x 10^{-4}	7·8	—	100

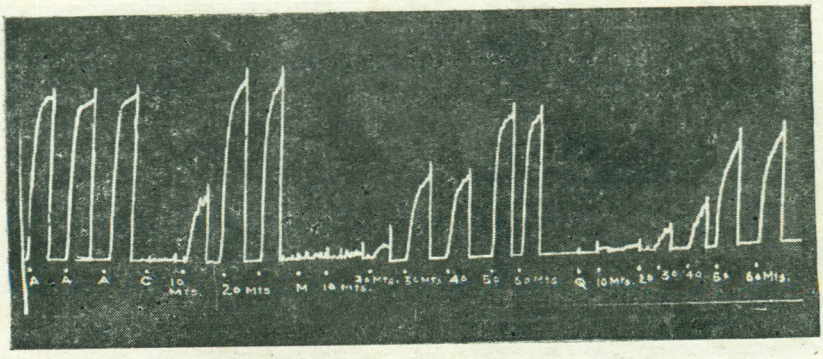

Fig. 4. Showing the effect of C—chloroquine; M—mepacrine and Q—quinine on acetylcholine ($2{\cdot}5 \times 10^{-5}$) induced contractions of guinea-pig ileum.

Guinea-pig tracheal chain preparation.—It is seen that antihistaminic potency of these drugs follow the same pattern as is seen on guinea-pig ileum chloroquine being the most powerful and quinine the least (Fig. 5).

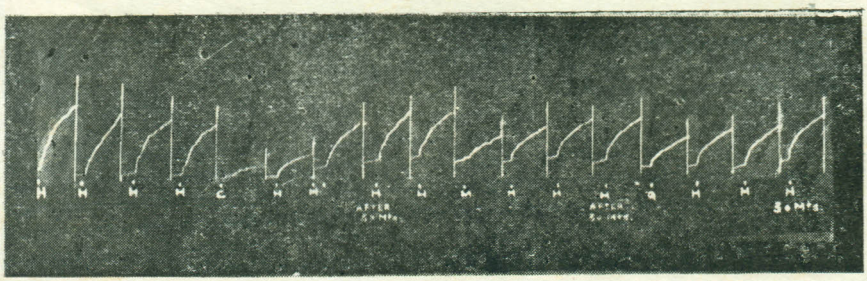

Fig. 5. Guinea-pig tracheal chain; at H—histamine 1×10^{-4}, at C—chloroquine 1×10^{-4}, at M—mepacrine 1×10^{-4}, at Q—quinine 1×10^{-4}, Note chloroquine is most active and quinine the least.

Blood pressure in dog.—Antimalarials by themselves lower the B.P. but with the rate of perfusion used in these experiments no hypotensive action was observed. Unlike the effects of the antimalarials on guinea-pig intestine and tracheal chain they do not block the action of histamine on blood pressure. The effect is shown in Figs. 6, 7 and 8.

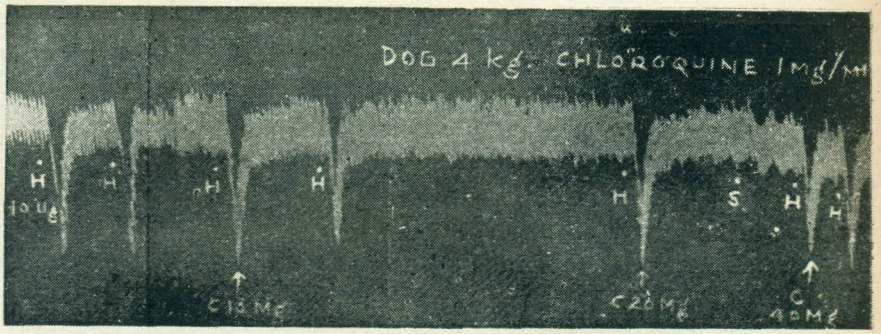

Fig. 6. Dog blood pressure. Effect of chloroquine perfusion on the histamine hypotensive response. H—histamine, C—chloroquine, S—Stopping of kymograph, Perfusion of chloroquine 1 µg/min.

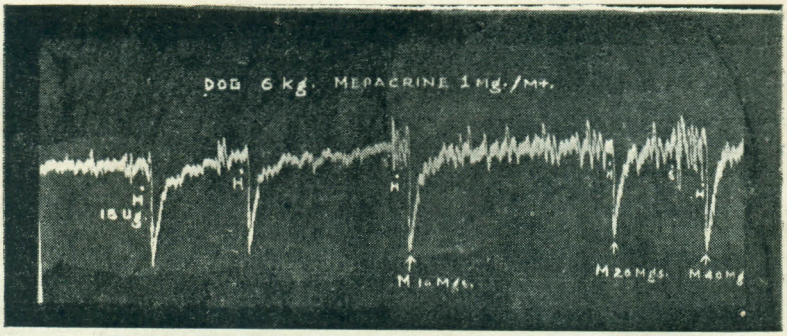

Fig. 7, Dog blood pressure. Effect of mepacrine perfusion on the histamine hypotensive response. H—histamine 2·5 µg/kg. M—mepacrine. Perfusion of mepacrine 1 µg/min.

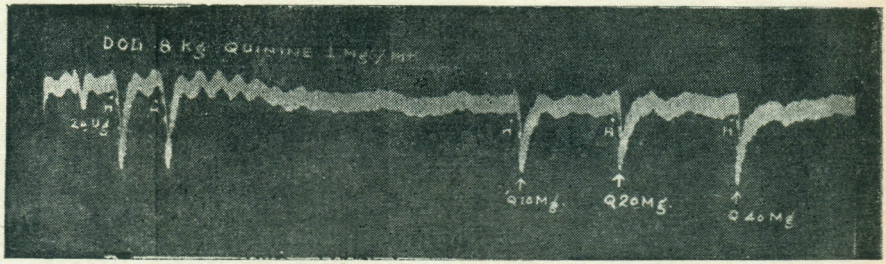

Fig. 8. Dog blood pressure. Effect of quinine perfusion on the histamine hypotensive response. H—histamine 2·5 µg/kg. Q—quinine. Perfusion of quinine 1 µg/min.

Capillary permeability in guinea-pig skin.-Antimalarials themselves increase the capillary permeability as was seen by the appearence of blue colouration at the site of their intradermal injections. This was seen with 100 μg. doses. Blue colouration was more in the control histamine intradermal tests, when histamine was given at the site where intradermal injection of these antimalarials were made in 25, 50 and 100 μg. doses. Intradermal response of histamine was also positive after the intraperitoneal injections of antimalarials (Table II).

TABLE II

Showing the effect of antimalarials on capillary permeability tests by intradermal injections of histamine in guinea-pigs.

Intradermal procedure	Doze	Blue colouration
Control histamine	5 μg/ml	+
Control normal saline	0·1 ml	—
Chloroquine	100 μg/01 ml	+
Mepacrine	100 μg/01 ml	+
Quinine	100 μg/01 ml	+
Chloroquinine followed by	25 μg/50 μg or 100 μg in. 05 ml	+ +
Histamine	5 μg/ ·05 ml	
Mepacrine followed by	25 μg 50 μg, or 100 μg in 05 ml	+ +
histamine	5 μg/ 05 ml	
Quinine followed by	25 ug 50 μg or 100 μg in ·05 ml	+ +
histamine	5 μg/·05 ml	
Chloroquine, mepacrine or quinine intraperitoneally followed by histamine after 30 mins.	5 μg/0·1 ml 5 μg/0·1 ml	+ +

DISCUSSION

From our findings it is clear that quinine, mepacrine and chloroquine effectively block the actions of histamine on guineapig ileum and tracheal chain and thus qualitatively exhibit the same type of action. This finding again proves the important fact that though these drugs belong to the different chemical groups they simulate each other, in most of their pharma-

cological actions. Quantitatively calculated on the basis of ED_{50} from the log dose response curve, chloroquine is most potent followed by mepacrine and quinine respectively. This observation is significant and interesting as the same degree of potency is observed in other pharmacological actions of these drugs. To quote a few examples, in the depressant action on skeletal muscles (Grewal *et al*, 1960), antiveratrinic action (Arora *et al*, 1955), antiarrhythmic action (Arora *et al*, 1955b) antimalarial action and antihexokinase activity (Fraser *et al*, 1950) chloroquine is most potent followed by mepacrine and quinine.

Antimalarial drugs of the present investigation also blocked the action of acetylcholine. It is well known that some of the antihistaminic drugs do possess the antiacetylcholine action. It is, therefore, possible that chloroquine, mepacrine and quinine may be having a specific antihistaminic action However, further investigations on these lines are necessary to elucidate the exact nature of the action of antimalarial drugs on histamine responses.

These drugs are not shown to antagonise the action of histamine on blood pressure and capillary permaeability. The cause of such failure of antagonism to histamine on the vasomotor system would require further investigation.

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