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An analysis of the inhibitory effects of quinine and mepacrine in the guinea-pig isolated ileum

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Quinine is an antimalarial agent which has in addition antipyretic and analgesic actions. Its toxic effects include tinnitus, vertigo, visual disturbances as well as gastro-intestinal and respiratory disorders and even hypoprothrombinaemia.

Mepacrine is an antimalarial drug which is also used in the treatment of rheumatoid arthritis. Its anti-inflammatory properties might be related to its binding to various biological membranes (Lee 1971; Massari et al 1974) which, depending upon the membrane affected, promotes (i) lysosomal stabilization and inhibition of proteases extrusion in the inflamed tissue (Weissman 1968) (ii) inhibition of phospholipase A2 activity and reduction of the arachidonic acid concentration available for prostaglandin (PG) synthesis (Vargaftig & Dao Hai 1972; Flower & Blackwell 1976) (iii) inhibition of oxidative phosphorylation and mitochondrial ATPase activity (Hunter 1955; Whitehouse & Boström 1965). Both drugs are related in structure and properties to chloroquine, another antimalarial compound with antirheumatic properties (Famaey et al 1977a). All three antimalarials have been claimed to have in common a PG antagonist effect which might explain many of their properties (Manku & Horrobin 1976a, b; Horrobin et al 1977).

We have previously searched for this antagonistic effect of chloroquine in a guinea-pig isolated ileum preparation and we were unable to find any significant differences between the inhibitory effect of the drug on the contractile responses to several agonists including PG. We concluded that in that preparation chloroquine exhibits only a non-specific overall spasmolytic effect likely to be related to its membrane stabilizing properties (Famaey et al 1977a).

To check if this discrepancy between our results on the guinea-pig isolated ileum and those obtained in the rat vascular mesenteric bed by Horrobin et al (1977) was

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restricted to chloroquine, we have now extended our observations to quinine and mepacrine.

Contraction to PGE_1 (5 ng ml^{-1}, 45 s contact time, every 3 min), to histamine (30 ng ml^{-1}, 30 s contact time, every 6 min), to acetylcholine (20 ng ml^{-1}, 30 s contact time, every 3 min), to nicotine (0·5 μg ml^{-1}, 45 s contact time, every 6 min) and to 5-hydroxytryptamine (5-HT, 30 ng ml^{-1}, 45 s contact time, every 6 min) were elicited on guinea-pig isolated ileal segments of 4 cm length (removed at least 10 cm from the caecum) set up in Krebs Henseleit solution at 37 °C and gassed with a mixture of 5% CO_2 in oxygen. Similar ileal segments were set up in similar conditions and suspended under an initial load of 1 g. Isometric contractions (registered by a force transducer) were elicited by coaxial stimulation (pulse width 0·5 ms, pulse strength 5–25 V, frequency 0·1 Hz; Paton 1955).

At similar concentrations to those used previously with chloroquine (the lowest concentrations tested reducing both the electrically and the PG induced contractions by at least 50%; Famaey et al 1975, 1977a), quinine (5 μg ml^{-1}) or mepacrine (2·5 μg ml^{-1}) was added to the bath after 3 reproducible contractions of each agonist and the ileum was challenged again with the same agonists at the same intervals. When electrically induced contractions were used, the drug was added after 5 min of constant contractions. After 12 min contact time the antimalarial drug was washed from the bath and the ileum was again challenged at three consecutive intervals (during 6 min for electrical stimulations).

In another series of experiments, conducted simultaneously in a similar way, small amounts of PGE_2 or E_1 (2·5 ng ml^{-1}) were added to the bath 6 min after the antimalarial drug in an attempt to reverse the antimalarial inhibition. These were washed from the bath with the antimalarial drug 6 min later.

Finally, to determine the type of antagonism of the drugs dose response curves were constructed for acetylcholine, histamine and nicotine in the presence of quinine (5 μg ml^{-1}) or mepacrine (2·5 μg ml^{-1}).

Quinine and mepacrine diminished contractions to PGE_1 respectively by 60% (± 4.4) and by 67.3% (± 11.5) and this effect was reversed after washing out the antimalarials from the bath (mean $\pm$ s.e.m., n = 6, $P \leqslant 0.001$, Student's t-test for paired data).

Horrobin et al (1977) and Okpako (1978) have also described an antagonistic effect of mepacrine (at a similar concentration) against PGE_2 on the rat mesenteric vasculature and stomach strip.

Moreover the same concentrations of quinine and mepacrine diminished respectively the ileal responses to acetylcholine by 73.1% (± 7.8) and 85.2% (± 1.9), to histamine by 71.4% (± 4) and 77.9% (± 9.1), to nicotine by 78.3% (± 5.0) and 77.7% (± 7.7), to 5-HT by 78.3% (± 5.0) and 60.5% (± 4.9) and to electrical coaxial stimulations by 67% (± 6) and 76.3% (± 10.6) (mean $\pm$ s.e.m., n = 6, $P \leqslant 0.01$ for mepacrine on histamine and 5-HT and $\leqslant 0.001$ for the other experiments; Student's t-test for paired data).

No significant statistical differences (Student's t-test) were found between the various inhibitions including those on PG-induced contractions when studying either quinine or mepacrine. All these inhibitions were reversed by washing out the antimalarials from the bath and, as previously observed with chloroquine (Famaey et al 1975, 1977a), small amounts of PGE_1 or E_2 were able to restore the contractions to the control levels (except for quinine with acetylcholine and 5-HT).

It appears from these data that (i) like chloroquine, quinine and mepacrine exert no specific antagonism on PG-induced contractions in the guinea-pig isolated ileum but behave as overall spasmolytic agents (ii) the inhibitions by antimalarial drugs are reversed by PGE_2 or E_1. Similar observations were made previously by us with other compounds such as non-steroidal anti-inflammatory drugs (Famaey et al 1975, 1977b), steroidal anti-inflammatory drugs (Famaey et al 1975, 1979) and sex steroids (Seaman et al 1977a, b) and it was concluded that the observed inhibitions might be due to a non-specific smooth muscle desensitization related to the well known membrane-stabilizing effects of all these compounds. The PGs' reversal would be thus a non-selective sensitization of the smooth muscle induced by these compounds to any kind of stimulation (Bennett et al 1975; Schulz & Cartwright 1976; Famaey et al 1977b, 1979). Similar conclusions were made by us for chloroquine. It is likely that the overall inhibitions observed in the present study with quinine and mepacrine are also related to non-specific membrane proper-

ties which might affect the smooth muscle reactivity rather than to any specific antagonism.

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