The local anaesthetic activity of metiamide a histamine H_2-receptor antagonist

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Many of the conventional antihistamines (antagonists of histamine H_1-receptors) are also potent local anaesthetics (Dutta, 1949). In this study metiamide, a histamine H_2-receptor antagonist (Black, Duncan & others, 1973), has been examined for local anaesthetic activity using the guinea-pig wheal test of Bülbring & Wajda (1945) and by studying its effect on the conduction of action potentials in the isolated frog sciatic nerve. In both systems procaine hydrochloride has been used as a standard local anaesthetic.

Male guinea-pigs, 400–500 g, were shaved and depilated on their backs the day before the test. Irritation caused by the depilatory (Nair) disappeared overnight. Intradermal injections of 0·25 ml of the test compounds were given into allocated sites and the area of the resultant wheal was marked. The test for anaesthesia was then applied to the injected area six times at 5 min intervals. Each test consisted of applying six pricks with a surgeon's needle (Size 6) and a record was taken of how many of these pricks failed to elicit a contraction of the surrounding skin (a flinch). The animal's normal reaction to a pinprick was observed by applying the stimulus outside the injection site. The number of times the prick failed to induce a flinch was then summed, out of a possible 36, to give an indication of the degree of anaesthesia of the site.

A preliminary experiment was made to determine the most suitable injection sites. Ten guinea-pigs were used for four days. Eight injection sites were chosen, three on each flank and two on the middle of the back. Each site was injected with 1 % procaine hydrochloride dissolved in 0·9 % saline and the test for anaesthesia performed as described. A total of 320 test-scores was therefore amassed and the frequency characteristics of this population were analysed.

Metiamide was used as 2 and 4 % solutions and procaine hydrochloride as 0·5 and 1 % solutions. The procaine was dissolved directly in the appropriate volume of 0·9 % saline whereas metiamide was dissolved in an equivalent volume of 0·1 N hydrochloric acid before dilution. Only the two dorsal midline sites were used for the assay and a random incomplete blocks experimental design was therefore necessary (Finney, 1964). The design was such that 24 guinea-pigs were needed to allow for: (a) each combination of two doses from the four possible ($_4C_2 = 6$) (b) a reversal of each of the dose pairs to correct for forward/rear site differences and (c) one replication of the 12 units.

To measure the effect of metiamide on action potential conduction, the sciatic nerve from a frog (*Rana pipiens*) was dissected from the lumbar region to approximately 1 cm below the knee, both the peroneal and tibial branches being removed. The nerve was then mounted over five stainless steel electrodes in a nerve bath. This allowed impulses from a stimulator (Grass S8) to be applied at 1·5 times threshold to the proximal end of the nerve, whilst the evoked action potential could be differentially recorded at the distal end and displayed

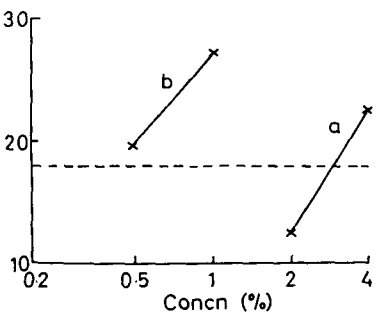

FIG. 1. The four point assay of metiamide (a) against procaine (b) using the number of no-responses to the stimulus (a prick) in selected dorsal skin sites of guinea pigs receiving intradermal drug. Each point is a mean of 12 observations. Broken line indicates 50% of maximum score. Ordinate—No-response scores.

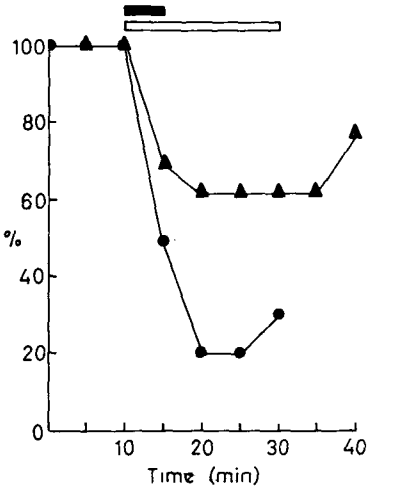

FIG. 2. Graph of action potential amplitude (expressed as a percentage of the original amplitude) against time. The open bar indicates the duration of superfusion with metiamide (0·1 M) and the closed bar indicates the duration of superfusion with procaine (0·01 M). ▲—amplitude during metiamide superfusion, ●—response during procaine superfusion.

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on an oscilloscope. The electrode array was such that a length of nerve could be superfused with any desired solution. The nerve was initially superfused with frog Ringer solution until the action potential amplitude (read at 5 min intervals) remained constant for 3 successive readings. The nerve was then superfused with a 0·1 M solution of metiamide in frog Ringer for 20 min with readings every 5 min. The recovery of the nerve, superfused with frog Ringer alone, was also followed. The nerve was then superfused with a 0·01 M solution of procaine in frog Ringer until action potential amplitude was reduced by 50% when the superfusion was continued with frog Ringer until recovery was seen.

In the preliminary investigation of the guinea-pig wheal test there was not a normal frequency distribution of the no-response scores taken from all the sites. When only the mid-line sites were considered, however, a normal distribution of scores was found. The local anaesthesia test was therefore restricted to these sites.

In the assay, the dose response lines for the two drugs did not differ significantly from parallel as determined by an analysis of variance. The analysis revealed an EC50 for procaine hydrochloride of 0·45 g per 100 ml and for metiamide 3·0 g per 100 ml (Fig. 1). In this test, therefore, metiamide has 15 % of the local anaesthetic activity of procaine.

The potency of metiamide relative to procaine was similar in the experiment on action potential amplitude. The result is shown in Fig. 2, where metiamide has 6 % of the activity of procaine when estimated by the time taken to achieve 20 % blockade.

The results from the guinea-pig wheal test give an EC50 for procaine which lies between the values published by Dutta (1949) and Bülbring & Wajda (1945), 0·31 and 0·61 g per 100 ml respectively. Dutta (1949) found that the H_1-receptor antagonists diphenhydramine and antazoline had relative potencies of 320 and 230 % compared with procaine. The results from the tests described here indicate that the histamine H_2-receptor antagonist metiamide does not share these local anaesthetic properties. Preliminary studies on a second H_2-receptor antagonist, cimetidine, have revealed a similar lack of local anaesthetic activity (Brimblecombe, Duncan & others, 1975).

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Influence of endosulfan on pentobarbitone sleeping time and blood and brain concentrations in male rats

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The chlorinated insecticide endosulphan (6,7,8,9,10, 10-hexachloro-1,5,5a,6,9,9a-hexahydro-6,9-methano-2,4,3-benzodioxathiepine-3-oxide), is of relatively recent introduction. Related insecticides are known to influence the activity of drug metabolising enzymes (Cram, Juchan & Fouts, 1965; Peakall, 1967) but to our knowledge no report has been made of the induced enzyme activity of endosulfan in rats. We have therefore examined the influence of endosulfan on organ weights and pentobarbitone-induced hypnosis.

Male albino rats, 190–203 g, with free access to commercial diet and water were used.

Rats in groups of eight received 0, 1·0, 2·5 or 5·0 mg kg^{-1} endosulfan in corn oil orally daily for 7 or 15 days. They were weighed initially and on the 8th or 16th day of the experiment before death after which liver, testes and adrenals were weighed. The experiment was in a room with the temperature varying from 25 to 27°. The interaction between endosulfan and sodium pentobarbitone was investigated by measuring the sleeping time (ST) after 50 mg kg^{-1} of drug given intraperitoneally 24 h after the final administration of endosulfan. The duration of ST was measured as the elapsed time from the loss of the righting reflex to the return and the induction time as the time between injection of drug and the loss of righting reflex.

The concentration of pentobarbitone was also measured in blood and brain of control and endosulfan-

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