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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Table 1. *Pentobarbitone sleeping time and blood and brain concentrations of male albino rats receiving endosulfan orally daily for 7 or 15 days.*

Dose mg kg^{-1}	Induction time[a] (min)	% change	Sleeping time[b] (min)	% change	Pentobarbitone, concn μg ml^{-1} or g 30 min Blood	30 min Brain	Upon awakening Blood	Upon awakening Brain
			8th day					
0·0	5·11 ± 0·12 (8)	—	118·41 ± 6·31	—	192 ± 16	117 ± 7	46 ± 3	29 ± 2
1·0	4·32 ± 0·02 (8)	5·67 (—)	108·21 ± 9·04	8·61 (—)	179 ± 18	109 ± 9	52 ± 7	31 ± 5
2·5	6·17 ± 0·11[b] (7)	20·74 (+)	74·21 ± 7·80	37·32 (+)	92 ± 11[d]	53 ± 6[d]	45 ± 5	27 ± 4
5·0	5·56 ± 0·07[c] (8)	8·80 (+)	69·26 ± 10·02	41·50 (+)	115 ± 9[d]	65 ± 13[d]	38 ± 6	26 ± 3
			16th day					
0·0	4·43 ± 0·13 (8)	—	112·51 ± 11·30	—	205 ± 13	137 ± 5	53 ± 7	34 ± 5
1·0	5·11 ± 0·19[c] (8)	5·34 (+)	122·13 ± 9·14	8.53 (+)	151 ± 11	125 ± 13	47 ± 5	28 ± 3
2·5	6·16 ± 0·32[d] (8)	41·26 (+)	77·26 ± 4·60[d]	31·33 (—)	76 ± 6[d]	76 ± 18[d]	56 ± 9	31 ± 4
5·0	5·57 ± 0·19[c] (8)	25·73 (+)	69·43 ± 9·30[d]	39·68 (—)	96 ± 4[d]	57 ± 4[d]	42 ± 13	29 ± 3

The figures in parenthesis indicated no. of animals.
a. Time from pentobarbitone injection to loss of righting reflex.
d. Pentobarbitone (50 mg kg^{-1}) was given 24 h after the final endosulfan administration.
c. Significantly different from control values $P < 0.01$.
d. Significantly different from control values $P < 0.001$.

treated rats. Groups of 16 rats were injected with sodium pentobarbitone 24 h after last treatment. Eight rats of each group were killed 30 min after the injection and the remainder upon awakening. Blood was collected in tubes containing potassium and ammonium oxalate and brain was removed immediately and frozen. Pentobarbitone in blood and brain was measured according to Goldbaum (1952).

All but one of the rats given 1, 2·5 or 5·0 mg kg^{-1} survived the treatment. There was no significant change in body weights of control and treated rats. The liver weights (g per 100 g) of rats receiving 2·5 or 5 mg kg^{-1} were respectively 3·53 ± 0·21 and 3·21 ± 0·10 ($P < 0.001$) (8 days) and 3·38 ± 0·04 ($P < 0.001$) and 3·11 ± 0·12 ($P < 0.01$) (16 days) which were significantly heavier than the control animals (2·79 ± 0·11; 8 days and 2·79 ± 0·02; 16 days). No change in absolute or relative weights of testes and adrenals of control and endosulfan treated rats was observed.

Mean values of pentobarbitone, ST and blood and brain concentrations of rats receiving endosulfan orally daily for 7 or 15 days are given in Table 1. The pentobarbitone induction and ST of rats given 1·0 mg kg^{-1} of endosulfan was not significantly changed. With higher doses (2·5 to 5·0 mg kg^{-1}) significant increase ($P \leqslant 0.001$) in induction time and decrease ($P \leqslant 0.001$) in ST was observed. The increase in induction time varied from 9 to 41% and decrease in ST from 31 to 41%. At 30 min, the blood and brain pentobarbitone concentrations of rats receiving 2·5 or 5 mg kg^{-1} endosulfan for 7 or 15 days were significantly decreased (53 and 58% respectively) as compared to control rats. Upon awakening no significant change in pentobarbitone concentrations in either blood or brain was observed.

Thus there was no significant change in pentobarbitone concentrations in blood and brain of control and endosulfan-treated rats, probably indicating endosulfan is not acting by altering the sensitivity of the brain to the barbiturate. The inhibitory effect on pentobarbitone-induced ST observed could be due to enhanced metabolism of the pentobarbitone since there is a decrease in the pentobarbitone concentrations in the blood and brain of endosulfan-treated rats.

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